

Rüdiger Rupp

Abstract

Neuroprostheses based on functional electrical stimulation (FES) are a means for compensation of lost motor functions such as grasping or walking. Many prerequisites need to be fulfilled for successful use of a neuroprosthesis, most importantly a low degree of lower motor neuron damage, an unrestricted passive joint motion, and a negligible spasticity.

For improvement of the grasp function, neuroprostheses with different degrees of complexity and invasiveness exist. The systems available for routine clinical application have demonstrated functional benefits and improvement of the users' independence and quality of life. Hybrid neuroprostheses combining FES with orthoses hold promise for restoring completely lost upper extremity function. Novel user interfaces integrating biosignals from different sources are needed to make full use of their many degrees of freedom. Brain-computer interfaces are an emerging technology that may serve as a valuable adjunct to traditional interfaces.

The main barrier for everyday use of lower extremity neuroprostheses solely based on FES is the occurrence of rapid muscle fatigue due to a non-physiological spatial and temporal activation by FES. However, their combined use with semi-active gait orthoses or robotic exoskeletons promises to overcome some of the current limitations.

R. Rupp
Spinal Cord Injury Center, Heidelberg University Hospital,
Schlierbacher Landstrasse 200a, 69118 Heidelberg, Germany
e-mail: ruediger.rupp@med.uni-heidelberg.de

Novel developments for more selective stimulation of neurons or for activation of the lumbosacral spinal pattern generator network may enhance the functionality of future neuroprostheses. It is likely that upcoming neuroregenerative therapies will be able to restore some motor functions. In these cases, modular, personalized, and patient-cooperative neuroprostheses will be needed for integration in and support of the residual body functions.

24.1 Introduction

The loss of motor function is the most obvious consequence of a spinal cord injury (SCI). Functional limitations resulting from SCI limit the affected individuals' ability to live independently and retain gainful employment post-injury [13, 49]. People with SCI also tend to report a lower quality of life compared to able-bodied persons [7]. Currently, 40–50 % of all individuals with an SCI are tetraplegic due to injuries of the cervical spinal cord with resulting life-long paralysis of the lower and upper extremities. While the majority of tetraplegic patients have a neurological level of lesion at C4 and C5 with loss of hand and finger function, the most common lesion level in paraplegic patients is Th12 with preserved trunk stability but loss of functions of the lower extremities [79].

Bilateral loss of the grasp function leads to a substantial dependency of tetraplegic patients on caregivers. Therefore, one of the main priorities of these patients is to improve a missing grasping and reaching function [2, 101]. Paraplegic patients rate the restoration of walking as very important [16]. If there is sufficient voluntary control of muscles caudal to the level of lesion, surgical procedures such as muscle and tendon transfers, tenodeses, and arthrodeses can be successfully applied for regaining a meaningful upper and lower extremity function [39, 48, 97]. However, if no voluntary motor functions are present or an individual is unwilling to undergo surgery with the associated extended postsurgical rehabilitation period, neuroprostheses on the basis of functional electrical stimulation (FES) may represent a valid alternative for functional restoration [87]. In general, neuroprostheses are technical systems that use electrical impulses to compensate for the loss of motor functions after lesions of the central nervous system.

The aim of this chapter is to provide the background to understand the physiological principles of and clinical prerequisites for the application of neuroprostheses, their possibilities and challenges for compensation of lost upper as well as lower extremity function, and the promises of future developments.

24.2 Electrical Activation of Nerves and Muscles

The transfer of information within the nervous system is based on the generation of action potentials and their transmission between excitable cells. In the physiological condition, an action potential on an axon is triggered by temporal and spatial

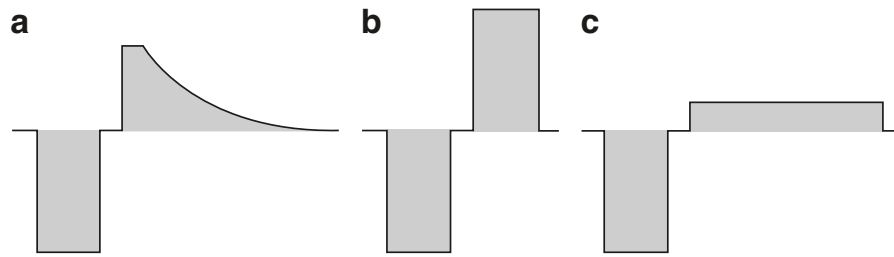


Fig. 24.1 Typical FES stimulation waveforms. (a) Rectangular pulse with exponential charge balance pulse. (b) Biphasic rectangular pulse. (c) Biphasic, rectangular pulse with reduced amplitude, but increased width of charge balance pulse

summation of electrical potentials on postsynaptic membranes. However, it is also possible to depolarize the membrane voltage of a nerve at a certain location by external electrical impulses to such a degree that a physiological action potential originates from there. From an electrical viewpoint, the nerve membrane mainly represents a capacitor, whose voltage is proportional to the injected charge. To guarantee a robust generation of action potentials despite time-varying and unknown skin tissue and inner tissue impedances, constant-current impulses are applied.

In electrical stimulators intended for FES applications, the initial stimulation impulse is followed by a charge balance pulse (charge = current \times time, gray area in Fig. 24.1) to avoid a net transmission of charged ions in the tissue under the electrodes. By this the coagulation (anode) and colliquation (cathode) necrosis, which typically occurred in prolonged application of FES with the technology available in the mid 1970s, can be effectively avoided. A low amount of charge injection is tolerated by the tissue as long as the effective direct current density at the electrode stays below $35 \mu\text{A}/\text{mm}^2$ [95].

From a technical viewpoint, the exponential charge balance pulse (Fig. 24.1a) can be implemented in the simplest way by adding a series capacitor to the stimulation circuit. The generation of rectangular pulses is technically more complex but allows for a higher pulse repetition rate (= stimulation frequency in Hz) (Fig. 24.1b). In case of pulse widths below $300 \mu\text{s}$, a short pause of approx. $100 \mu\text{s}$ is inserted between the stimulation and charge balance pulse. Without this pause the activation effect of the stimulation pulse is partly reduced due to the steep rise of the charge balance pulse [110]. If the amplitude of the charge balance pulse is substantially lower compared to the stimulation pulse (Fig. 24.1c), the pause can be omitted without any detrimental effect.

Basically, by FES an action potential can be triggered at any location of the nerve fiber – from the neuron via the axon to the motor end plate – which is then transmitted like in the physiological condition to the effector organ. It does not make a difference, if the stimulation impulses triggering the action potential are applied via surface electrodes, percutaneous wire electrodes, or fully implanted electrodes, which are places on a muscle or directly at the nerve's axon.

Usually, for stimulation of innervated muscles, biphasic, charge-balanced rectangular impulses with a stimulation pulse width between 50 and $500 \mu\text{s}$ are used.

If innervated muscles are activated by electrically induced nerve action potentials, a relatively small amount of charge is needed (curve 4 in Fig. 24.2). A much higher charge is needed in case of direct stimulation of denervated muscle fibers, because the motor threshold of muscle membranes is 500–1000 times higher than the activation threshold of nerve membranes [5]. Even in the case of needle electrodes inserted directly into an innervated muscle, it is always the nerve and not the muscle fibers that are electrically activated. This is the reason why the term “muscle stimulation,” which is clinically often used in the context of innervated muscles, is misleading.

With a larger extent of and longer time after denervation, more charge is needed to directly activate denervated muscles (curve 3 and 2 in Fig. 24.2). In case of a completely denervated muscle, impulses with high amplitude and pulse width need to be injected to generate contractions (curve 1 in Fig. 24.2) with the danger of exceeding the maximum permissible current density for surface electrodes of 2 mA/cm² and the associated risk for local burns [50]. In any case, stimulated denervated muscles do not produce the same amount of force than innervated ones. Therefore, a careful screening for the presence of denervated muscles is mandatory to estimate the potential of a user for successful application of a neuroprosthesis. In Europe, a few stimulators are commercially available capable of generating short (<1 ms) impulses for stimulation of innervated muscles and long impulses (>100 ms) for

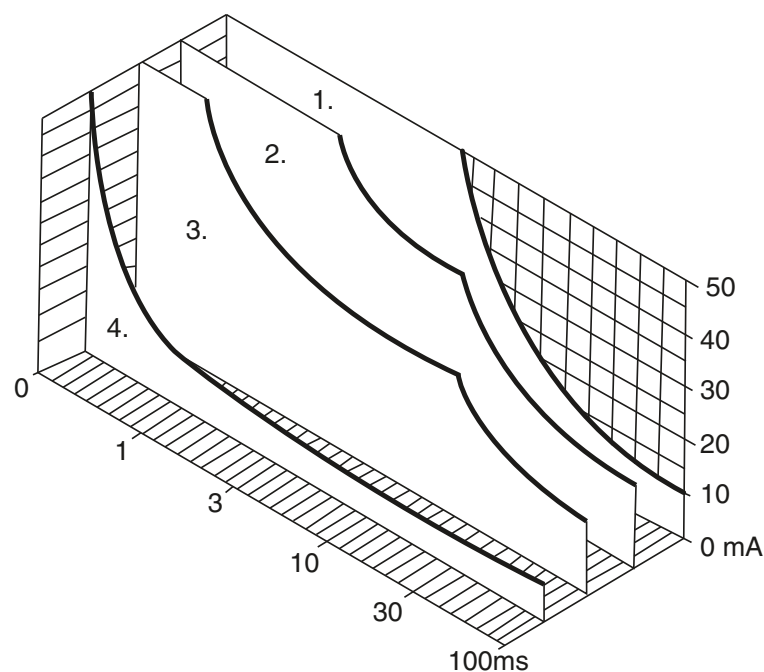


Fig. 24.2 Strength-duration curves of rectangular pulses for completely innervated (4.), decreasingly innervated (3., 2.), and completely denervated muscles (1.) [28]. The strength-duration curve shows the minimal current amplitude at a given pulse width, which is necessary to elicit a muscle twitch

direct muscle stimulation. With these devices, a precise testing of the innervation status of muscles and a training of denervated muscles to prevent muscle degeneration can be performed. Examples of such devices are the portable, single-channel Parestestim FES system from Medel GmbH, Hamburg, Germany, and the two-channel system stimulette den2x from Dr. Schuhfried Medizintechnik GmbH, Vienna, Austria.

The strength-duration curve for neural and muscle membrane flattens out with long stimulus durations, reaching an asymptote called rheobase. When the stimulus strength is below the rheobase, stimulation is ineffective even when stimulus duration is very long. The minimum pulse width needed to elicit a muscle contraction with a current of two times of the rheobase is defined as chronaxie. Both the rheobase and chronaxie are useful to document the degree of denervation and the course of reinnervation of a muscle.

Although electrically induced action potentials basically comply with physiological activation mechanisms, there are relevant differences between the physiological and artificial generation of muscle contractions [102]: In the physiological condition, if low muscle forces are generated, mainly thin fibers are activated. With increasing force, more thick fibers are recruited (Fig. 24.3). In case of external electrical stimulation, thick nerve fibers are first activated due to their higher electrical field and voltage gradient, and with increasing force, also smaller fibers get involved.

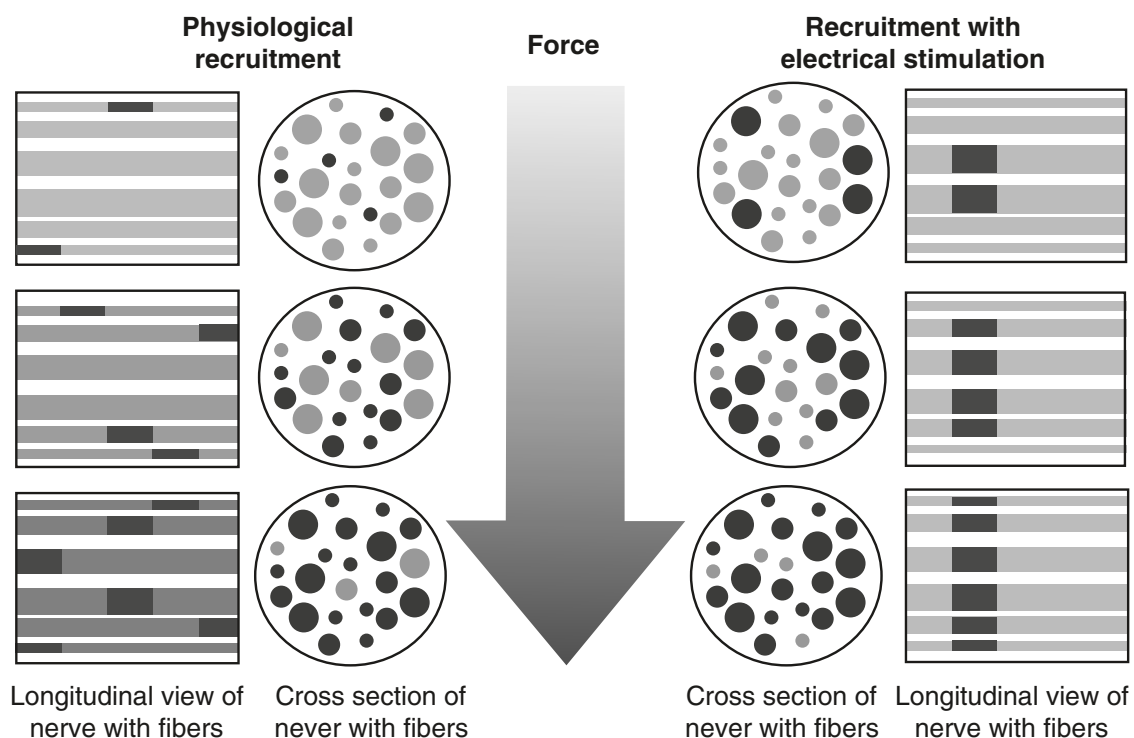


Fig. 24.3 Recruitment of nerve fibers under physiological conditions and by electrical stimulation. *Dark areas* represent activated parts of nerves; *light gray areas* indicate inactive parts

However, thick nerve fibers end at fast-fatiguing muscle fibers, while thin fibers innervate more fatigue-resistant muscle fibers. This phenomenon is called “inverse recruitment” [82] and represents one of the main causes why stimulated muscles fatigue relatively fast compared to the physiological condition. In addition, all nerve fibers get activated nearly at the same time, which results in an almost synchronous activation of all muscles fibers of the corresponding motor units. Furthermore, each electrical impulse activates the same motor units. The inverse recruitment together with the synchronous activation of the same motor units causes a rapid fatigue of stimulated muscles. Basically, muscle fatigue occurs more quickly with higher rates of pulse repetition. Therefore, in practical FES applications, where tetanic contractions are needed, relatively low stimulation frequencies in the range of 16–20 Hz are used that allow for generation of a sufficient amount of force without having too much tremor. Nevertheless, continuous tetanic stimulation contractions at high force levels, e.g., needed for standing and walking, can only be generated over a short time period of 15–30 min depending on the amount of training. Additionally, the movements and forces generated by FES are less graduated when compared to the physiological condition. This is especially the case when low forces for fine control of hand and finger movements are needed.

In patients with chronic SCI, paralyzed muscles consist to a large extent of fast-fatiguing muscle fibers with the associated severely decreased fatigue resistance and capability for force generation. The disuse atrophy of paralyzed muscles can be reversed through FES training even many years after SCI. Additionally, FES training converts the fiber composition of muscles in the direction of slow fatiguing muscles [94].

24.3 SCI-Associated Conditions Limiting Neuroprosthetic Applications

In general, FES may not be applied in individuals with metal implants in the stimulated areas of the body or if active implants such as cardiac pacemakers or medication pumps are present. Besides these non-SCI-related exclusion criteria, a lot of secondary side effects associated with SCI may prevent the successful use of a neuroprosthesis. A thorough initial screening is mandatory to set up a realistic roadmap for each prospective neuroprosthesis user.

In individuals with paraplegia due to a lesion of the conus or cauda equina, damage to the lower motor neurons and/or their axons occurs. The presence of denervated muscles may prevent a successful application of neuroprosthesis. As stated before, stimulated denervated, flaccid muscles do not produce enough force to effectively contribute to a functional restoration sufficient for everyday use [50].

Individuals with a cervical SCI have a very heterogeneous neurological and functional status depending on the level, completeness, and type of lesion [11, 105]. Additionally, in about 30–50 % of individuals with tetraplegia, denervated muscles

are present to a more or less extent due to the damage of motor neurons directly at the lesion site [26, 74].

Within the first 2 weeks after SCI, spasticity develops in many patients. Spasticity or clonus may be triggered by electrical stimulation in particular at the beginning of the FES training and each FES session. However, after some FES sessions, the muscle tone may be successfully reduced by the training [63].

If motor impairments persist, they lead to other negative effects. Immobility may lead to a reduction of the passive range of motion of affected joints, which may result in severe contractures with totally immobile joints due to calcified capsules. In such cases, even a strongly stimulated muscle is not able to generate joint movements. Intensive physical therapy may help to prevent some of these negative side effects on the musculoskeletal body structures.

In the chronic stage, profound disuse atrophy of the permanently paralyzed muscles is present. This may be reversed in innervated muscles by an FES-based training; however, if the SCI persists over a long time, it may take some months to achieve a fatigue resistance and force sufficient for neuroprosthetic applications [33].

Autonomic dysreflexia (AD) is a potentially dangerous clinical syndrome that develops in individuals with SCI, resulting in acute, uncontrolled hypertension. Briefly, AD develops within the first 6 months after injury in individuals with a neurologic level at or above the sixth thoracic level (T6). The occurrence of AD increases as the patient evolves from spinal shock. AD prevalence rates vary, but the generally accepted rate is above 50 % of all individuals with injuries at T6 and above. Patients with a sensorimotor complete injury have a much higher incidence of AD (91 % with complete injury vs. 27 % with incomplete injury) [22]. AD is caused by the damage of sympathetic spinal fibers and the resulting imbalanced innervation of the autonomous nervous system. Episodes of AD can be triggered by any strong stimulus below the level of injury [62]. AD may also be triggered by electrical stimulation of the lower extremity [4], but has also been seen by the author in very high lesioned patients during the application of a grasp neuroprosthesis.

Pain is a major problem after SCI and most of the patients report to have pain. In the acute phase after an SCI, it is mainly nociceptive pain due to trauma or spasm [30]. Usually within the first year after the injury, neuropathic pain develops in about 40–50 % of the patients and tends to become chronic [99]. Paresthesia in the stimulated dermatomes may restrict the application of a neuroprosthesis particularly systems based on surface electrodes.

24.4 Upper Extremity Neuroprostheses

Over the past 30 years, FES systems for restoration of upper extremity function with different levels of complexity and degree of invasiveness have been developed. While a handful of systems for restoration of a lost or restricted grasping function

have reached a level of maturity sufficient for routine application in end users with tetraplegia [85], none is available for restoration of a lost reaching function suitable for everyday use.

24.4.1 Grasp Neuroprostheses

When using FES in a compensatory setup, the easiest way to improve a weak or lost grasp function is to apply multiple surface electrodes. Generally, their major advantages are their simple and safe application and that they can be offered to patients for temporary application at a very early stage of rehabilitation. During this phase the electrode setup has often to be adapted to the changing neurological condition due to spontaneous recovery. Additionally, costs of noninvasive systems are much lower than those of invasive neuroprostheses, and they can be applied by physical medicine and rehabilitation specialists without the need for surgical expertise [21]. Examples of noninvasive grasp neuroprostheses are (1) the commercially available NESS H200 System (formerly known as Handmaster, Bioness Inc., Valencia, CA, USA), which is mainly intended for training purposes, but can also be used as an assistive device for support of activities of daily living [1], and (2) the formerly commercially available Bionic Glove for improving the strength of a tenodesis grip in SCI individuals with preserved strong voluntary wrist extension [84]. Other more sophisticated prototypes in terms of control capabilities were successfully evaluated in the clinical setting, but are not available for home-based application [69, 106].

The main aim of the application of a grasp neuroprosthesis is to generate two grasp patterns, namely, the lateral grasp, also called key or pinch grasp, and the palmar grasp, also called cylinder or power grasp. The lateral grasp provides the ability to pick up flat objects between the flexed fingers and the flexing thumb, while the palmar grasp, in which the thumb is positioned in opposition to the index finger, permits larger objects to be handled. To generate these grasp patterns, electrodes on the thenar eminence and inside the hand are typically needed, which, however, tend to fall off or shift easily due to the extended skin and soft tissue movements in these areas [29]. However, with seven self-adhesive gel electrodes placed on dedicated positions on the forearm (Fig. 24.4a), the pinch and power grasp patterns can be restored without the need for electrodes on the hand [92]. The pinch grasp can be achieved by stimulation of the finger (ext. digitorum communis muscle, electrode pair (EP) 1 in Fig. 24.4a) and thumb (ext. pollicis longus, EP 2 in Fig. 24.4a) extensor muscles for hand opening, the finger flexors (flex. digitorum superficialis, flex. digitorum profundus) for hand closing and the thumb flexor (flex. pollicis longus) for grasping. In many SCI end users, it is possible to stimulate the flexor muscles of the fingers and the thumb with a common electrode pair (EP 3 in Fig. 24.4a). By implementation of a dedicated stimulation profile into a universally programmable, multichannel FES stimulator available from different vendors (e.g., Motionstim 8, Medel GmbH, Hamburg, Germany), it is possible to use co-contractions of the thumb flexor and extensor muscles to achieve a state, in which the fingers are sufficiently flexed and the thumb is still in an extended position. For the power grasp,

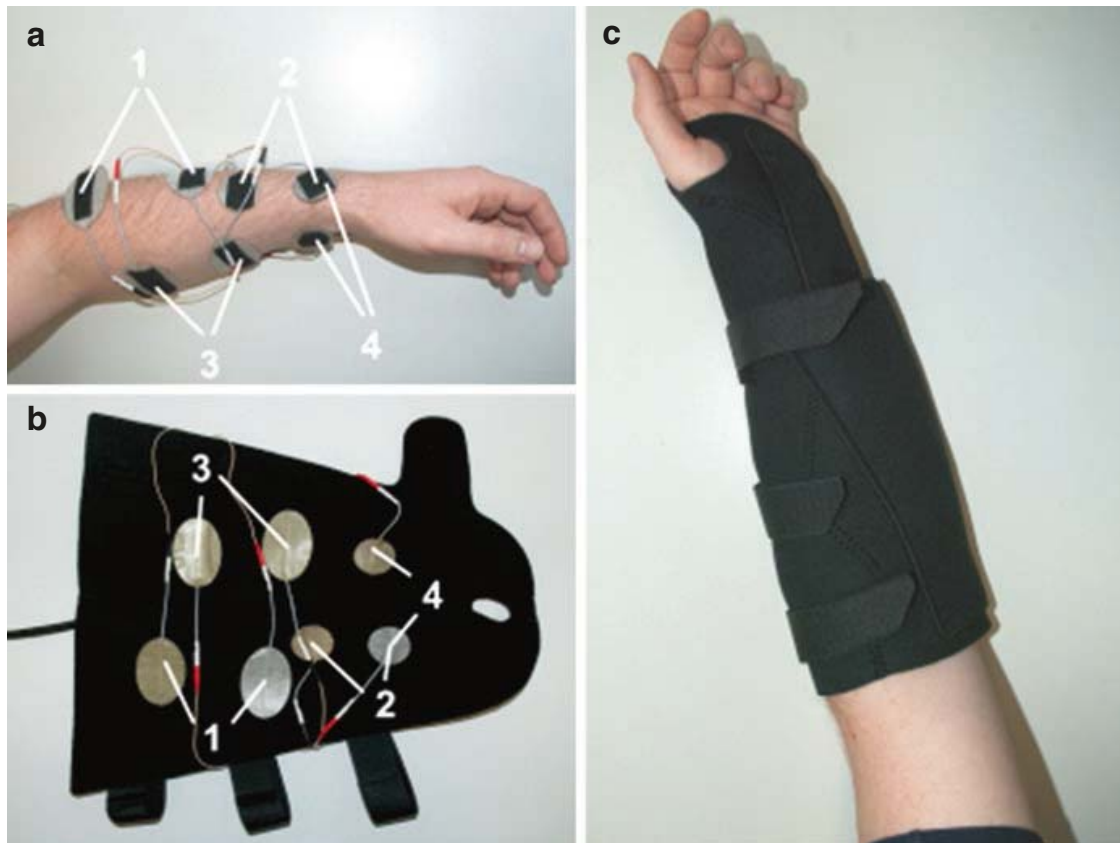


Fig. 24.4 (a) Electrode positions together with the assigned channel numbers of the stimulator. Due to space limitations, *channel 2* (ext. pollicis muscle) and *channel 4* (opponens pollicis muscle) share a common electrode. (b) Electrodes fixed with a velcro strap in a personalized forearm sleeve for easy and quick electrode mounting. (c) Mounted forearm sleeve. To stabilize the wrist, a bent metal splint is integrated into the volar part of the sleeve

a branch of the median nerve innervating the opponens pollicis muscle can be selectively stimulated with an electrode pair (EP 4 in Fig. 24.4a) placed on the medial side of the forearm.

Apparent disadvantages of grasp neuroprostheses based on surface electrodes include difficulties with daily reproduction of the desired grasping movements and limited selectivity in stimulating deeper or small muscles. Additionally, patients consider the placement of the electrodes to be complicated [54]. Some of these limitations may be overcome by an adjunct fixation mechanism in the form of an orthosis or a sleeve. After the appropriate electrode positions have to be defined, a self-adhesive velcro strip is stuck on the top of the electrodes, which are then covered by a neoprene sleeve. This sleeve is manufactured according to the individual anatomy (proximal and distal diameter, length, position of the thumb) of the forearm (Fig. 24.4b). The velcro strips hold the electrodes in a fixed position in the sleeve, which dramatically reduces the time for donning. The sleeve contains a hole for the thumb and a mark sign at the proximal end, which facilitates the correct positioning of the sleeve on a daily basis (Fig. 24.4c).

As a precondition for a functional grasp, the wrist needs to be stabilized in neutral position during flexion of the fingers. In individuals with preserved elbow



Fig. 24.5 (a) Individual with cervical SCI and absent finger and thumb function writes with an ordinary ball pen. (b) Individual moves glass cylinder (120 g). (c) Eating a cookie. (d) Grasping a coin. (e) Holding a matchbox to light a match. (f) Manipulating a can

flexion, the wrist extensor muscle is often weak or denervated. In these cases, it is not possible to achieve a stable dorsal extension of the wrist by stimulation, and a fixation splint made of aluminum is integrated into the sleeve to maintain the wrist in neutral position during grasping. With this setup, a variety of activities of daily living (ADLs) can be performed by the users (Fig. 24.5).

Another problem of noninvasive grasp neuroprostheses is the huge variation of the grasp patterns in dependence of the wrist rotation angle. In addition, defining the optimal size of stimulation electrodes during initial setup is often time-consuming. A promising concept for faster determination of the desired electrode positions and the dynamic compensation of position-dependent relocation of electrodes is the use of electrode arrays, in which small electrodes can be selectively activated and dynamically merged to virtual electrodes [41, 68, 83]. However, the clinical value of this newly introduced concept needs to be evaluated in future studies involving a larger number of end users.

Despite the technological progress made over the last two decades, some of the disadvantages of noninvasive neuroprostheses persist, among them are limited excitability of deeper muscle groups, painful sensations in case of paresthesia in the stimulated parts of the body, and handling problems. As a consequence, implantable neuroprostheses have been developed with different degrees of complexity: the BION [46, 67], a small single-channel microstimulator that can be injected through a cannula; a stimulus router system [31], an implantable electrode that picks up the current from surface electrodes; a multichannel implantable stimulator [100]; as well as a modular, networked, and wirelessly controlled system for stimulation and sensing [113]. In contrast to cardiac pacemakers, implants for restoration of complex motor functions need to deliver large amounts of energy to reanimate paralyzed limbs. This energy is typically provided through an inductive link either during operation (Freehand) or for charging batteries inside the implant (BION 3). Therefore, external coils need to be placed on the skin over the implant, and users of implanted motor neuroprostheses usually need to carry external components with them (Fig. 24.6c).

One of the implantable grasp neuroprostheses – the Freehand system – achieved commercialization in 1997 and was successfully used throughout the world by over 300 individuals with an SCI at C5/C6. It is therefore the most widespread implantable neuroprosthesis for restoration of the grasp function [47]. The first version of the Freehand system consisted of an implantable electrical stimulator, whose metal housing serves as a common anode (Fig. 24.6a, b), with eight stimulation channels and an external control unit, which contains the central processing unit and the batteries. In the early years, it used epimysial electrodes, which needed to be sutured to the muscle surface, but later it was possible to use intramuscular electrodes, which were directly inserted into a muscle and self-secured themselves with hooks. In the most recent revision, it is equipped with 12 stimulation channels and provides four channels for registration of myoelectric signals for control purposes [37].

The results of a multicenter trial including 51 Freehand users impressively demonstrated its high level of functional efficacy, end user satisfaction [80], and economic benefits [21]. Despite the proven clinical success, its commercialization stopped in 2001. This fact clearly demonstrates the difficulties industry encounters in sustained transfer of technology due to the small number of prospective end users and the few institutions providing the infrastructure for successful implantation of invasive neuroprostheses and for postoperative rehabilitation.



Fig. 24.6 (a) X-ray of internal components of the Freehand neuroprosthesis in the right arm of an end user. (b) Implantable electrical stimulator with connectors, leads, and epimysial electrodes. (c) User eating with the Freehand system. The external shoulder joystick (left shoulder) and induction coil (right chest) are visible. The external control unit containing the microprocessor and batteries is not shown

Besides their high costs, implantable systems inherently harbor the risk of infections and general surgery-related risks. Complex revision surgeries are necessary in case an implanted component fails. Although it has been shown that these events occur rather rarely [53], this risk has to be clearly communicated to patients who decide to receive an implant. Due to the fact that implantable neuroprosthesis and systems based on surface electrodes have distinct advantages and disadvantages, they represent alternative rather than competitive devices to surface electrode based systems.

Despite all the technical progress achieved, it has to be clearly stated that the degree of functional restoration by the currently available neuroprostheses based either on surface or implantable electrodes is rather limited. Even with the most sophisticated systems, it is only possible to restore one or two grasp patterns, and this does not include independent activation of single fingers or joints [52, 113]. Nevertheless, despite all their restrictions, grasp neuroprostheses represent a proven method for improving quality of life of end users with preserved shoulder function and elbow flexion, but missing hand and finger function.

24.4.2 Hybrid Neuroprosthesis for Grasping and Reaching

Most of the current neuroprostheses for the upper extremity are foreseen for individuals with preserved shoulder function and elbow flexion. In case of completely lost upper extremity function, meaningful restoration of a reaching and grasping function for activities of daily living by means of neuroprosthesis has not yet been demonstrated. The feasibility of using percutaneous electrodes for restoration of elbow extension and shoulder flexion/abduction was investigated only in an experimental setting [20, 45]. Recently, two advanced Freehand stimulators providing in total 24 stimulation channels connected to either epimysial, intramuscular, or nerve cuff electrodes were successfully implanted in two individuals with an SCI above C4 [71]. Although shoulder, elbow, forearm, wrist, and hand movements were achieved in both subjects by this highly invasive and complex surgical approach, only one individual was able to perform two activities of daily living (scratching nose, shaking hands).

In general, a major problem in restoration of a completely lost upper extremity function is the rapid muscle fatigue of continuously stimulated shoulder and elbow muscles. To assist weak voluntary or stimulated shoulder forces, a mobile, passive, spring-based antigravity arm support system mounted on the wheelchair may be used [71, 81]. To avoid fatigue of stimulated muscles, so-called hybrid neuroprostheses consisting of a combination of FES and orthoses are proposed. In general, an orthosis is a mechanical device that fits to a limb and corrects a pathological joint function. An actively driven orthosis supports the joint movements with active electric or pneumatic actuators. The disadvantages of these exoskeletons are their mechanical complexity, limited possibility for home-based use in an ordinary everyday scenario, and their need for a sufficient power supply [96, 111]. Therefore,

these systems are mainly intended to be applied in users for whom sufficient movements cannot be generated by FES.

If sufficient joint movements can be generated by FES, the application of an orthosis with an electromechanically un-/lockable joint is a more efficient solution than a robotic exoskeleton. In its released state, this joint allows for free movements and keeps a fixed joint position in the locked state. This locked state helps to avoid fatigue of the stimulated muscles needed to maintain a stable joint position. Both types of FES-hybrid orthoses may expand the group of prospective users of an upper extremity neuroprosthesis in the future.

At this point, it must be emphasized that the neurological status and functional capabilities of individuals with SCI, even with the same level of injury, vary to a large degree. As a consequence, an upper extremity neuroprosthesis necessarily has to consist of several modules that can be personalized according to the capabilities, needs, and priorities of an end user. Though this fact is well known among the neuroscience [9] and assistive technology community [44], very few technical solutions incorporate it [89].

For achieving a meaningful capability for object manipulation in individuals with an SCI at C4 or higher with only a few residual arm movements preserved, a mobile robot arm mounted on the wheelchair may be a cheaper, more robust, and better performing alternative than a full upper-arm neuroprosthesis based on FES. Some of these robot arms have been successfully tested in everyday scenarios in persons with tetraplegia, and some are commercially available, e.g., the iArm from Exact Dynamics, Didam, the Netherlands, and the Jaco arm from Kinova Robotics, Quebec, Canada. Whether these robotic arms are accepted by their users and an improvement of quality of life can be achieved in the long run, needs to be shown in future studies involving a larger number of end users.

24.4.3 User Interfaces for Control of Upper Extremity Neuroprostheses

The reliability and performance of the user interface of a neuroprosthesis have the same impact on the users' acceptance as the meaningfulness of the FES-generated movements. Therefore, a robust user interface is a highly important component of a neuroprosthetic system. While users may be satisfied with a switch-based control scheme for step initiation of a lower extremity neuroprosthesis, the need for a sophisticated user interface for autonomous control of grasping is much higher in upper extremity neuroprostheses. The individual selection of the control method is mainly depending on the nature and degree of preserved functions under voluntary control of a user. The following functions may be used as command sources:

1. Movements of mouth and tongue, including speech
2. Voluntary movements or electrical activity of muscles not directly related to the function to be restored, e.g., movements or myoelectric activities of the contralateral shoulder or head movements

3. Voluntary movements or electrical activity of muscles directly involved in the function to be restored, e.g., wrist extension or weak muscles of the forearm
4. Specific cortical electrical activities

Speech control has not gained wide acceptance for neuroprosthesis control due to slow speed, long delays, and maloperation in noisy environments [77]. The use of tongue movements [43] or tooth clicks [32] may restrict the users' ability to communicate. All user interfaces relying on mouth control are not appropriate if users wish to eat or drink with the help of the neuroprosthesis.

24.5 User Interfaces Using Functions Not Related to the Restored Movements

An established control method is the use of preserved movements not directly involved in the grasping function. Examples are the use of head orientation [115] or shoulder movements [100]. Command interfaces based on head movements or eye gaze may interfere with the user's natural eye movements. These may differ substantially from those of healthy subjects, since users with SCI need to compensate the loss of tactile and proprioceptive feedback by visual feedback. Nevertheless, head movements or eye gaze may be applied successfully when combined with other input modalities such as preserved myoelectric activities of the shoulder [19].

Shoulder movements recorded by a two-axis shoulder position sensor were chosen as the standard input modality of the user interface of the implantable Freehand neuroprosthesis [100]. The degree of hand opening/closing and the force of the closed hand are normally controlled by the user through forward/backward movements of the contralateral shoulder in a proportional manner. Locking of the grasping position is initiated by a quick shoulder upward movement. An additional switch button is integrated into the shoulder joystick, which permits the user to switch between grasp patterns through a short press and the in-/activation of the entire system through a long press. In case shoulder movements are restricted due to muscular weakness or joint contractures, also electromyographic (EMG) signals from voluntarily activated muscles can also be used for control [38]. The performance of EMG- and movement-based control is at least for short-term use in the same range.

24.6 User Interfaces Using Activities of Muscles Directly Involved in the Restored Movements

For bilateral grasp restoration, the use of shoulder movements for neuroprosthesis control is limited, because shoulder movements are needed to place the hand correctly in space and, in so doing, interfere with the control function. An alternative involves using muscles that do not interfere with any upper extremity task. In some users, muscular functions below the level of injury, e.g., from the lower extremities, that are not functionally relevant may be used for control [73]. A promising

way to set up a universal control interface involves selective activation of ear muscles [71, 109].

All of the control modalities mentioned above share the fact that the control is not “natural” for a user, i.e., it requires a substantial amount of training and special attention during use, particularly in the first weeks of use [38]. To overcome this limitation, the use of movements or muscle activities directly involved in the reaching or grasping function has been proposed. One of the first implementations of this approach was a proportional control of hand grasp by the degree of wrist extension measured either noninvasively [86] or by an implanted Hall-effect-based wrist angle sensor [8]. However, some users who are able to fully extend their wrist despite the presence of strongly stimulated finger flexors may not actually need a neuroprosthesis, if they use a natural tenodesis grip (passive flexion of finger and thumb flexors by active extension of the wrist) for everyday tasks.

A highly promising approach for a more natural and intuitive control involves monitoring the activity of weak muscles of the hand and arm. An example of this type of control is the use of the EMG activity of a weak brachioradialis or ext. carpi radialis longus muscle for proportional control of the grasp strength [51, 93, 106].

In individuals with high, complete SCI and the associated severe disabilities, too few residual functions may be preserved for setup of a reliable user interface. This has been a major limitation for the development of a reaching neuroprosthesis for individuals with a loss not only of hand and finger but also of elbow and shoulder function. Additionally, even end users who are basically able to use a certain interface may not be able to remain in control over an extended period of time due to physical and mental fatigue. Therefore, it is crucial for users to have a choice of options and for rehabilitation professionals to make them available, since each individual will find that some of the available options are more productive and work better than others. In this sense, brain-computer interfaces (BCIs) may serve as an alternative human-machine interface or may provide an additional control channel as an adjunct to traditional user interfaces.

24.7 Brain-Computer Interfaces for Control of Upper Extremity Neuroprostheses

BCIs are technical systems that provide a direct connection between the human brain and a computer. These kinds of systems are able to detect thought-modulated changes in brain activity and transform the changes into control signals. Most of the BCI systems rely on bioelectrical brain signals that are recorded noninvasively by electrodes on the scalp (electroencephalogram, EEG). A BCI system consists of five sequential components: (1) signal acquisition, (2) feature extraction, (3) feature translation, and (4) classification output, which interfaces to assistive devices and generates (5) a feedback to the user. These components are controlled by an operating protocol that defines the onset and timing of operation, the details of signal

processing, the nature of the device commands, and the oversight of performance [98]. At present, EEG-based BCI systems can function in most environments with relatively inexpensive equipment and therefore offer the possibility of practical BCIs in end users' home environment.

One type of EEG-based BCI exploits the modulation of sensorimotor rhythms (SMRs). These rhythms are oscillations in the EEG occurring in the alpha (8–12 Hz) and beta (13–30 Hz) bands and can be recorded over sensorimotor areas on the scalp. Their amplitude typically decreases during actual movement and similarly during mental rehearsal of movements (motor imagery, MI) [78]. It is known that people can learn to modulate the SMR amplitude by practicing MI of simple movements, e.g., hand/foot movements. This process occurs in a closed loop, meaning that the system recognizes, with the help of machine learning methods, the SMR amplitude changes induced evoked by MI, and these classification results are instantaneously fed back to the users. With the help of the feedback, users can adapt their mental modulation strategy to improve classification results. These neurofeedback-based procedure and mutual human-machine adaptation enable BCI users to control their SMR activity and use these modulations to control output device [15]. Although, most BCIs are used to generate binary control signals, MI-BCIs allow the detection of an intended movement based on brain signals, making them an exciting option for natural control of a grasping and reaching neuroprosthesis control, in particular in individuals with high SCI.

In the first pioneering work in BCI-controlled grasp neuroprosthesis, the BCI was used in a mainly digital manner (“brain switch”) as a substitute for the traditional neuroprosthesis control [76]. A novel development in BCI research is the introduction of the hybrid BCI concept [75]. A hybrid BCI (hBCI) consists of a combination of several BCIs or a BCI with other input devices. These input devices may be based on the registration of biosignals other than brain signals, such as EMG activities, or signals from traditional input devices like joysticks or mice.

In a first single-case study, a combination of an MI-BCI and an analog shoulder position sensor was proposed [90]. With upward/downward movements of the shoulder, the user was able to control the degree of elbow extension/flexion or of hand opening/closing. The selection, if the analog signal from the shoulder position sensor is used for elbow or hand control, and the access to a pause state were determined by the brain switch provided by the MI-BCI.

With this setup, a highly paralyzed end user who had no preserved voluntary elbow, hand, or finger movements was able to perform several activities of daily living, among them eating a pretzel stick, signing a document, and eating an ice cream cone (Fig. 24.7), which he was not able to perform without the neuroprosthesis. He used short imaginations of movements of the right hand to switch from hand to elbow control or vice versa. A longer imagination led to a pause state with stimulation turned off or reactivated the system from the pause state.

Despite research on the use of BCIs for neuroprosthesis control has seen tremendous progress in recent years, BCIs are not yet ready for independent home use. In general, setting up and handling current BCI systems is relatively complicated compared to traditional user interfaces and requires the (tele-)presence of technical



Fig. 24.7 Sequence of pictures showing the eating of an ice cream cone with the support of a FES-hybrid orthosis in a user with completely lost elbow, wrist, and hand function (a). The user starts in the hand control mode and lifts his left shoulder to open the right hand for grasping the ice cone (b, c). After successfully grasping the ice cone, the user emits a BCI command to switch from hand control to elbow control and lifts his shoulder to flex his elbow (d). Now, the user licks the ice. Finally, the user lowers his left shoulder to extend the elbow on (e), he puts the cone in its original place and switches back to hand mode to release the ice cream cone on (f)

experts. Thus, BCIs have to be improved to a stage at which end users together with their caregivers are able to apply the systems independently at home. A key component for achieving this goal is the availability of easier to handle, gel-less electrodes that provide a sufficient signal quality. Additionally, more studies with people in real need for a BCI such as individuals with high cervical SCI are needed to determine if research results obtained in able-bodied subjects also apply to neurologically impaired end users [91].

Initial human applications of invasive BCIs, in particular of intracortical electrode arrays for single-neuron recording, indicate that an intuitive brain control of robotic arms is possible without the need for extensive learning [17, 40]. However, this technology has not yet demonstrated its long-term stability over years. Additionally, due to the small number of study participants, the extent to which the results can be generalized remains unclear [103].

24.8 Lower Extremity Neuroprostheses

The first work reporting on the successful use of FES for restoration of foot dorsiflexion was already published in 1961 [66]. Since then a variety of FES systems have been developed and are commercially available for drop foot stimulation. While the use of FES for compensation of a limited movement of a single joint like the ankle is rather simple, the restoration of a completely lost lower extremity function is much more complicated, and many research groups worldwide have been working on the development of practical lower extremity neuroprostheses since decades.

24.8.1 Standing and Walking Neuroprostheses

A breakthrough in the development of lower extremity neuroprostheses using surface electrodes was achieved in 1970, where two Slovenian researchers used electrical stimulation of the peroneal nerve in individuals with complete paraplegia to elicit the withdrawal reflex with the associated flexion of the hip, knee, and ankle joints thereby simulating the swing phase of walking [59–61]. By this they overcame the problem that hip flexor muscles cannot be stimulated sufficiently directly by surface electrodes. If the stimulation of the withdrawal reflex is combined with the stimulation of the quadriceps and the glutei muscles, walking, standing up, and sitting down are possible with only six pairs of electrodes. Based on this knowledge, several devices have been developed, from which a few are commercially available, e.g., the Motionstim from Medel GmbH, Hamburg, Germany, and the Parastep FES system from Sigmedics Inc., Fairborn, Ohio, USA, which has been on the market for over 25 years. The Parastep system is used in combination with a walking frame with integrated push buttons for manual step initiation and has been tested so far in more than 750 individuals with complete thoracic injuries. The results of the Parastep applications show that performance in respect to walking in community is

rather limited [55] but that positive therapeutic benefits in terms of cardiovascular training and overall quality of life can be achieved [35].

After the feasibility of surface FES systems was shown, they were continuously improved: A higher number of stimulation channels were implemented for achieving a smoother standing up and sitting down, for combined antagonistic and agonistic stimulation to avoid hyperextension of the knees, and for stabilization of the trunk. Sensors were integrated for detection of gait phases and for automatic initiation of steps by recording of muscular activity of trunk muscles [34]. However, despite all these efforts, lower extremity neuroprostheses based on surface electrodes never made it to routine clinical use. One of the main reasons for this is the complicated and time-demanding setup of multiple stimulation electrodes, in particular the self-placements of electrodes on the glutei muscles.

To overcome the handling problems of surface FES systems, invasive neuroprostheses either based on percutaneous electrodes or fully implantable systems have been developed. At the end of the 1970s, up to 30 percutaneous electrodes were injected in each leg of volunteers with the aim of mimicking the physiological activation of lower extremity muscles [70]. With this overall high number of electrodes and the use of multiple electrodes in one muscle, a surprisingly smooth walking pattern was achieved. However, research in this direction was abandoned because of a missing perspective for everyday use and severe infections in some study participants due to broken wire electrodes. Over the last 40 years, different fully implantable systems were developed; however, none of them has become commercially available yet. Starting with the implantation of an 8-channel system for restoration of standing and walking in a few individuals with complete paraplegia in 1982 in Vienna, Austria [104], later a 16-channel system consisting of two Freehand implants [57] was used by the Cleveland group. In 2001, a 24-channel system was used from the European SUAW (stand-up-and-walk) consortium [112] in two paraplegic volunteers for the same purpose. With these implantations, it was successfully shown that the handling problems of neuroprostheses for walking based on surface electrodes can be overcome and a high reproducibility of movements can be achieved.

However, the main limitation of all lower extremity neuroprostheses independent from the technology and level of invasiveness is muscular fatigue. Due to the high forces needed to carry the full body weight and the co-contractions of agonistic and antagonistic muscles during standing, fast fatigue of stimulated muscles occurs allowing users only to walk very short distances of approx. 50–100 steps. The upright body position inherently bears the risk for falls. Therefore, the use of a walking frame, a walker, or crutches for stabilization of the trunk is mandatory, which restricts the use of the hands. In the early applications, lower forces were generated by stimulation that needed to be compensated by the users by carrying more weight on the crutches or the walker. However, on a long term, this led to shoulder pain, and as a consequence, the neuroprosthesis was sooner or later abandoned by the users.

At the current state of the art, lower extremity neuroprostheses do not represent an alternative to the wheelchair. Noninvasive FES systems are mainly used for therapeutic purposes to maintain joint mobility, muscle mass, and local vascularization.

The latter contribute effectively to the prevention of pressure ulcers. Fully implantable systems are used in everyday life mainly not for walking but for standing and transfers from and into the wheelchair. A good example for this paradigm shift is the VA/CWRU Standing System from the Cleveland group. This extremity neuroprosthesis evolved from the former 16-channel walking system and uses an 8-channel Freehand electrical stimulator with intramuscular electrodes in the quadriceps, glutei, and lumbar erector spinae muscles bilaterally for restoration of standing [108]. This system has been implanted in 15 users with paraplegia, who report a positive impact on their perceived quality of life [88]. However, studies are urgently needed to obtain quantitative information on the costs and implantation risks on the one hand and economic and personal benefit on the other. In any case, the technology of lower extremity neuroprostheses is after at least three decades of research and development still not mature enough to be broadly used for improvement of mobility in everyday life.

24.8.2 Hybrid FES Systems and Exoskeletons

During the last decade, neuroprosthesis for compensation of a lost lower extremity function was built solely on the basis of FES, because FES incorporates the body's own resources for energy-efficient activation of muscles. Additionally, the regular use of FES has positive therapeutic effects in regard to joint mobility, spasticity, cardiovascular training, and maintaining bone density. However, the two major technological challenges in solely FES-based lower extremity neuroprostheses are (1) the short application times due to the fast fatigue of muscles as a consequence of the need for continuous stimulation even during standing and (2) difficulties in generating precise kinematic patterns due to the nonlinear activation characteristics of muscles and the huge delays between onset of electrical stimulation and generation of force. To overcome these problems, a combination of FES with an external orthosis is proposed [24]. While these orthoses were fully passive in the early years, they are now either electromechanically un-/lockable [56], variably damped [12], or actively driven by electrical or pneumatic actuators [36]. The advantage of an orthosis is that a stable joint position can be maintained without the need for FES-induced co-contractions of agonists and antagonists. Additionally, joints can be linked with each other either mechanically or electrically, thereby allowing for simple generation of predefined multi-joint kinematics. While the first reciprocating gait orthoses of the 1950s looked very bulky and were very heavy, the field of orthotics has tremendously emerged throughout the last years. The introduction of new lightweight materials such as aluminum and carbon has led to customizable high-end solutions with an improved functionality and appearance. The latter is highly important for increased users' acceptance and compliance.

A technical challenge of hybrid neuroprostheses is the need for sophisticated control concepts, which are able to adequately manage the balance between the muscular forces generated by FES or by the actuators of the exoskeleton [23].

Although the beneficial therapeutic effects of FES are known, from a pure technical perspective, it is much easier to achieve ambulation in individuals with complete paraplegia by the use of robotic exoskeletons. The progress made in rechargeable battery technology over the last years, the availability of low-power, high-performance microprocessors, and the introduction of energy- and space-efficient electrical drives boosted the development of robotic exoskeletons for compensation of walking, standing, and partially also for stair climbing. Some robotic exoskeletons have become commercially available, among them the Ekso (Ekso Bionics, Richmond, CA, USA), the Hybrid-Assistive Limb (HAL) 5 (Cyberdyne, Tsukuba, Japan), the Indego (Parker Hannifin, Cleveland, OH, USA), the Rex (Rex Bionics, Auckland, New Zealand), and the ReWalk (ReWalk Robotics, Yokneam Ilit, Israel) systems [18]. Although some of them are intended to be used for gait training in a clinical setting, some are specifically designed to be used as personal assistive devices. Robotic exoskeletons are compared to hybrid neuroprostheses easier to handle by the users themselves. In particular, the setup time of the device and time for donning and doffing are much shorter. Nevertheless, even with the most sophisticated systems, users have to fulfill several requirements for a successful use. In any case users need to have sufficient trunk control. For most devices, the ability to hold crutches for additional stabilization and for turning needs to be preserved. The range of motion of the lower extremity joints must be unrestricted and the degree of spasticity must be low. Although data on the safe use of robotic exoskeletons are available for most devices, the long-term musculoskeletal complications and the level of users' acceptance need to be determined in future studies.

24.9 Future Developments and Challenges

The main restriction of lower extremity neuroprosthesis is the fast fatigue of muscles due to the synchronous stimulation of nerves and the limited ability to activate individual motor units. Also upper extremity neuroprostheses would profit from higher selectivity, because fine-graded movements of individual fingers may be possible. To achieve a more selective activation of nerves closer to the physiological condition, novel concepts for stimulation of peripheral nerves are developed. Another promising approach for improving the performance of neuroprostheses for walking and standing is the stimulation of the spinal circuitry called spinal or central pattern generator for locomotion located in the lumbar spinal cord. This network of interneurons is capable of interpreting afferent input from the lower extremities and of generating locomotor-like stepping movements [42].

24.9.1 Novel Concepts for Peripheral Nerve Stimulation

A higher selectivity in stimulating peripheral nerves can only be achieved by the use of nerve electrodes. As a general rule, a higher degree of selectivity is associated

with a higher level of invasiveness and as a consequence a higher risk for damage to neural structures [25]. Intramuscular or epimysial electrodes have a negligible risk for causing any harm during first-time implantations and revision surgeries. Multipolar nerve cuff electrodes, which are placed around a nerve, provide a higher selectivity than muscle electrodes, but with a higher risk for complications. This is in particular true, if the electrodes are not flexible and connective tissue grows in the space between the nerve and the electrode resulting in denervation of motor units. The highest level of selectivity is achieved with intrafascicular [64] or nerve-penetrating electrodes [14]. However, these electrodes cannot be used without causing damage to nerve structures during implantation. If such highly invasive electrodes are implanted at a location, at which the nerve is exposed to extensive mechanical stretching, additional mechanical damage or tissue reactions due to chronic inflammation are likely to occur over time. To avoid these problems, multi-channel electrodes might be placed more proximally, ideally at the ventral spinal roots, or even inside the gray matter of the ventral horn of the spinal cord. The latter is the basis for the promising concept of intraspinal microstimulation (ISMS) [6]. For ISMS, microwires are inserted near lower motor neurons, which are stimulated by microampere currents. While ISMS has been extensively tested in animal experiments, it still awaits its first human application.

With smaller dimensions of electrodes, the likelihood of exceeding a critical current density at the electrode-tissue interface is getting higher resulting in necrosis and chronic inflammation. While this may not be relevant for neural recording systems, it represents the major barrier for the use of micro- and ultraminiature electrodes for electrical stimulation. Due to a not perfect balancing of the injected charge, corrosion may occur at the surface of the electrodes degrading their electrical conductivity over time. In case of chronic inflammation, activated macrophages may additionally contribute to this effect.

A solution for overcoming the limitations of electrical activation of single axons or nerve cells may evolve from a relatively new method called optogenetics. This approach is based on the identification and functional characterization of several photoactivated ion channels, which have the remarkable property of being light gated [10]. Through introduction of a single gene-encoding channel rhodopsin-2 (ChR-2), a light-gated activation of neurons was realized. It was demonstrated that light-gated activity in ChR-2-positive neurons has a rapid onset in the millisecond timescale and is highly consistent while being phase locked to the stimulus frequency. Since photo-stimulation is noncontact and can be genetically targeted to specific cell populations using viral-vector gene therapy, a much higher spatial specificity in three dimensions can be achieved than in electrical stimulation opening up the possibility of large-scale spatial-temporal patterned stimulation for neuromodulation [58]. Optogenetics may also offer a seamless solution to the problem of cross talk generated by simultaneous electrical stimulation and recording. Although the perspective of human application of these methods is fascinating, the clinical translation of the combination of genetics and optics, including photonics, will face several challenges, in particular the unknown long-term effects of the genetically modified cell populations [114].

24.9.2 Spinal Cord Stimulation

Another very promising approach for restoration of the lower extremity function is the direct stimulation of the lumbosacral spinal cord either with epidural electrodes, typically used for pain relief, or by use of transversal surface stimulation [72]. It is assumed that the afferent fibers of the posterior roots are stimulated with both types of stimulation, thereby modulating the activity of the lumbosacral spinal circuitry [65]. It was demonstrated in the mid 1990s in individuals with clinically complete SCI that there is a stimulation frequency-dependent effect on the motor pattern of the spinal pattern generator [27]. High frequencies around 25–35 Hz facilitated a stepping-like motor pattern, while frequencies around 10–16 Hz produced extensor contractions similar to those that occur during standing. It has been recently shown in four individuals with an initially clinically motor complete SCI that voluntary motor function can recover after a combined application of epidural stimulation of different sites of the lumbosacral spinal cord and task-specific standing and locomotion training [3]. The study clearly shows that neuromodulation of the subthreshold motor state of excitability of the lumbosacral spinal networks was the key to recovery of intentional movement, because activity-based therapy applied over a month before the implantation of the epidural electrode did not lead to any improvement. However, since some input from the brainstem must be preserved to voluntarily trigger a stepping pattern and the exact mechanisms for the observed functional recovery are still unknown, it is not clear in how far the results obtained in four study participant can be generalized to a larger population. Additionally, more research is necessary to find ways for generation of stronger contractions in the lower extremities to allow for independent locomotion.

Conclusion

Over the past 30 years, about 25 neuroprostheses with different electrode technologies, degree of complexity, and level of invasiveness have been developed. Less than five of them have successfully applied in a larger group of end users, while others were only tested exemplarily with a few subjects. Lower extremity neuroprostheses for standing, walking, and stair climbing have not yet reached a level of usability sufficient for independent home use. Grasp neuroprostheses demonstrated in several clinical trials that they can greatly increase the quality of life of users with completely missing hand and finger function, in whom surgical options such as tendon transfers are not applicable.

From a technological viewpoint, scalable, modular neuroprostheses are a prerequisite for providing users with a personalized assistive device that is adapted to the residual capabilities, limitations, and needs of each individual end user. This issue of implementation of personalized and user-cooperative neuroprostheses will become more relevant in the future, if neuroregenerative therapies will succeed in increasing the number of individuals with preserved motor functions. With hybrid neuroprostheses combining orthotic and FES components, a further improvement in the functionality of neuroprostheses in particular for

compensation of the loss of the lower extremity function and an extension of the group of prospective users will be achieved. In this context, invasive and noninvasive neuroprostheses are companions rather than competitors, because a substantial percentage of individuals with SCI are unwilling to undergo implantation surgery. Prospective neuroprosthetic users need to be transparently informed about the additional benefits, risks, and long-term complications of implantable neuroprostheses compared to the noninvasive solutions.

During the development of neuroprostheses, it has become obvious that the functionality of the user interface has the same impact on the level of user acceptance than the actuator components. BCIs are a highly promising method for intuitive control of neuroprostheses, and research in this field has seen tremendous progress in recent years. The new concept of the hybrid BCI holds the promise that BCIs can be seamlessly integrated into traditional user interfaces such as switches, joysticks, EMG sensors, or eyetrackers and represents a major step toward user-cooperative neuroprostheses. Initial studies incorporating the hybrid BCI approach show that one configuration does not work with all end users. Similar to the orthotic and stimulation components of a neuroprosthesis, the possibility of a personalized configuration of the user control interface will be essential for its successful acceptance and integration in the users' everyday life. Long-term studies are needed with end users in real need of a BCI-controlled neuroprosthesis to demonstrate its reliability and usefulness.

Special care must be taken to correctly identify end users who may profit from a grasp neuroprosthesis. Spasticity, restrictions in joint mobility, and lower motor neuron damage are major obstacles for successful application of a neuroprosthesis. In general, the capabilities and limitations of the currently available systems need to be clearly communicated to users waiting for a "cure" and to be aligned with their needs and expectations to avoid disappointment and frustration.

During the last decade, a higher affinity to personal and wearable technology evolved in the general community due to the widespread utilization of smartphones, navigation systems, and augmented reality systems. This is also true for persons with motor impairments such as amputees. Nowadays, a sophisticated prosthesis or orthosis is perceived more as an expression of personal uniqueness rather than a device for compensation of a handicap. This change in attitude to assistive devices might help to overcome the complacency in individuals with SCI and professionals with the standard of care and may lead to a better compliance with and acceptance of high-tech solutions like neuroprostheses. Additionally, an integration of neurotechnology into educational curricula or training programs to certify health-care professionals like physicians or physiotherapist and occupational therapist is needed to increase knowledge about its possibilities and limitations.

In any case, an industrial uptake of the available technology is necessary to achieve a broad availability of neuroprostheses for routine clinical application and to guarantee long-term support for end users, including provision of spare parts and consumables. Together with the difficulties of regular reimbursement,

this seems to be one of the main barriers for widespread application of neuroprostheses in general, which have not been overcome during the last 20 years [107]. Multidisciplinary teams of engineers, health-care providers, consumers, and reimbursement agencies need to bring in their expertise and unique perspectives and keep up an intensive dialogue to remove the current barriers. Traditional rehabilitation team boundaries will need to be expanded to establish neuroprostheses as routinely used assistive technology.

References

1. Alon G, McBride K (2003) Persons with C5 or C6 tetraplegia achieve selected functional gains using a neuroprosthesis. *Arch Phys Med Rehabil* 84(1):119–124. doi:[10.1053/apmr.2003.50073](https://doi.org/10.1053/apmr.2003.50073)
2. Anderson KD (2004) Targeting recovery: priorities of the spinal cord-injured population. *J Neurotrauma* 21(10):1371–1383
3. Angeli CA, Edgerton VR, Gerasimenko YP, Harkema SJ (2014) Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. *Brain* 137(Pt 5):1394–1409. doi:[10.1093/brain/awu038](https://doi.org/10.1093/brain/awu038)
4. Ashley EA, Laskin JJ, Olenik LM, Burnham R, Steadward RD, Cumming DC, Wheeler GD (1993) Evidence of autonomic dysreflexia during functional electrical stimulation in individuals with spinal cord injuries. *Paraplegia* 31(9):593–605. doi:[10.1038/sc.1993.95](https://doi.org/10.1038/sc.1993.95)
5. Ashley Z, Sutherland H, Lanmuller H, Unger E, Li F, Mayr W, Kern H, Jarvis JC, Salmons S (2005) Determination of the chronaxie and rheobase of denervated limb muscles in conscious rabbits. *Artif Organs* 29(3):212–215
6. Bamford JA, Mushahwar VK (2011) Intraspinal microstimulation for the recovery of function following spinal cord injury. *Prog Brain Res* 194:227–239. doi:[10.1016/B978-0-444-53815-4.00004-2](https://doi.org/10.1016/B978-0-444-53815-4.00004-2)
7. Barker RN, Kendall MD, Amsters DI, Pershouse KJ, Haines TP, Kuipers P (2009) The relationship between quality of life and disability across the lifespan for people with spinal cord injury. *Spinal Cord* 47(2):149–155. doi:[10.1038/sc.2008.82](https://doi.org/10.1038/sc.2008.82)
8. Bhadra N, Peckham PH, Keith MW, Kilgore KL, Montague F, Gazdik M, Stage T (2002) Implementation of an implantable joint-angle transducer. *J Rehabil Res Dev* 39(3):411–422
9. Borton D, Micera S, Millan Jdel R, Courtine G (2013) Personalized neuroprosthetics. *Sci Transl Med* 5(210):210–212. doi:[10.1126/scitranslmed.3005968](https://doi.org/10.1126/scitranslmed.3005968)
10. Boyden ES, Zhang F, Bamberg E, Nagel G, Deisseroth K (2005) Millisecond-timescale, genetically targeted optical control of neural activity. *Nat Neurosci* 8(9):1263–1268. doi:[10.1038/nn1525](https://doi.org/10.1038/nn1525)
11. Bryden AM, Peljovich AE, Hoyer HA, Nemunaitis G, Kilgore KL, Keith MW (2012) Surgical restoration of arm and hand function in people with tetraplegia. *Top Spinal Cord Inj Rehabil* 18(1):43–49. doi:[10.1310/sci1801-43](https://doi.org/10.1310/sci1801-43)
12. Bulea TC, Kobetic R, Audu ML, Schnellenberger JR, Triolo RJ (2013) Finite state control of a variable impedance hybrid neuroprosthesis for locomotion after paralysis. *IEEE Trans Neural Syst Rehabil Eng* 21(1):141–151. doi:[10.1109/TNSRE.2012.2227124](https://doi.org/10.1109/TNSRE.2012.2227124)
13. Charlifue S, Gerhart K (2004) Community integration in spinal cord injury of long duration. *NeuroRehabilitation* 19(2):91–101
14. Christensen MB, Pearce SM, Ledbetter NM, Warren DJ, Clark GA, Tresco PA (2014) The foreign body response to the Utah Slant Electrode Array in the cat sciatic nerve. *Acta Biomater* 10(11):4650–4660. doi:[10.1016/j.actbio.2014.07.010](https://doi.org/10.1016/j.actbio.2014.07.010)
15. Cincotti F, Mattia D, Aloise F, Bufalari S, Schalk G, Oriolo G, Cherubini A, Marciani MG, Babiloni F (2008) Non-invasive brain-computer interface system: towards its application as assistive technology. *Brain Res Bull* 75(6):796–803

16. Collinger JL, Boninger ML, Bruns TM, Curley K, Wang W, Weber DJ (2013) Functional priorities, assistive technology, and brain-computer interfaces after spinal cord injury. *J Rehabil Res Dev* 50(2):145–160
17. Collinger JL, Wodlinger B, Downey JE, Wang W, Tyler-Kabara EC, Weber DJ, McMorland AJ, Velliste M, Boninger ML, Schwartz AB (2013) High-performance neuroprosthetic control by an individual with tetraplegia. *Lancet* 381(9866):557–564. doi:[10.1016/S0140-6736\(12\)61816-9](https://doi.org/10.1016/S0140-6736(12)61816-9)
18. Contreras-Vidal JL, A Bhagat N, Brantley J, Cruz-Garza JG, He Y, Manley Q, Nakagome S, Nathan K, Tan SH, Zhu F, Pons JL (2016) Powered Exoskeletons for bipedal locomotion after spinal cord injury. *J Neural Eng.* 13(3):031001. doi: [10.1088/1741-2560/13/3/031001](https://doi.org/10.1088/1741-2560/13/3/031001)
19. Corbett EA, Kording KP, Perreault EJ (2013) Real-time evaluation of a noninvasive neuroprosthetic interface for control of reach. *IEEE Trans Neural Syst Rehabil Eng* 21(4):674–683. doi:[10.1109/TNSRE.2013.2251664](https://doi.org/10.1109/TNSRE.2013.2251664)
20. Crago PE, Memberg WD, Uzey MK, Keith MW, Kirsch RF, Chapman GJ, Katorgi MA, Perreault EJ (1998) An elbow extension neuroprosthesis for individuals with tetraplegia. *IEEE Trans Rehabil Eng* 6(1):1–6
21. Creasey GH, Kilgore KL, Brown-Triolo DL, Dahlberg JE, Peckham PH, Keith MW (2000) Reduction of costs of disability using neuroprostheses. *Assist Technol* 12(1):67–75. doi:[10.1080/10400435.2000.10132010](https://doi.org/10.1080/10400435.2000.10132010)
22. Curt A, Nitsche B, Rodic B, Schurch B, Dietz V (1997) Assessment of autonomic dysreflexia in patients with spinal cord injury. *J Neurol Neurosurg Psychiatry* 62(5):473–477
23. Del-Ama AJ, Gil-Agudo A, Pons JL, Moreno JC (2014) Hybrid FES-robot cooperative control of ambulatory gait rehabilitation exoskeleton. *J Neuroeng Rehabil* 11:27. doi:[10.1186/1743-0003-11-27](https://doi.org/10.1186/1743-0003-11-27)
24. Del-Ama AJ, Koutsou AD, Moreno JC, De-los-Reyes A, Gil-Agudo A, Pons JL (2012) Review of hybrid exoskeletons to restore gait following spinal cord injury. *J Rehabil Res Dev* 49(4):497–514
25. del Valle J, Navarro X (2013) Interfaces with the peripheral nerve for the control of neuroprostheses. *Int Rev Neurobiol* 109:63–83. doi:[10.1016/B978-0-12-420045-6.00002-X](https://doi.org/10.1016/B978-0-12-420045-6.00002-X)
26. Dietz V, Curt A (2006) Neurological aspects of spinal-cord repair: promises and challenges. *Lancet Neurol* 5(8):688–694. doi:[10.1016/S1474-4422\(06\)70522-1](https://doi.org/10.1016/S1474-4422(06)70522-1), S1474-4422(06)70522-1 [pii]
27. Dimitrijevic MR, Gerasimenko Y, Pinter MM (1998) Evidence for a spinal central pattern generator in humans. *Ann N Y Acad Sci* 860:360–376
28. Edel H (1993) *Fibel der Elektrodiagnostik und Elektrotherapie*, 5th edn. Verlag Müller und Steinicke, München
29. Ferrari de Castro MC, Cliquet A Jr (2000) Artificial grasping system for the paralyzed hand. *Artif Organs* 24(3):185–188
30. Finnerup NB (2013) Pain in patients with spinal cord injury. *Pain* 154(Suppl 1):S71–S76. doi:[10.1016/j.pain.2012.12.007](https://doi.org/10.1016/j.pain.2012.12.007)
31. Gan LS, Prochazka A (2010) Properties of the stimulus router system, a novel neural prosthesis. *IEEE Trans Biomed Eng* 57(2):450–459. doi:[10.1109/TBME.2009.2031427](https://doi.org/10.1109/TBME.2009.2031427)
32. Gan LS, Ravid E, Kowalczewski JA, Olson JL, Morhart M, Prochazka A (2012) First permanent implant of nerve stimulation leads activated by surface electrodes, enabling hand grasp and release: the stimulus router neuroprosthesis. *Neurorehabil Neural Repair* 26(4):335–343. doi:[10.1177/1545968311420443](https://doi.org/10.1177/1545968311420443)
33. Gordon T, Mao J (1994) Muscle atrophy and procedures for training after spinal cord injury. *Phys Ther* 74(1):50–60
34. Graupe D (1989) EMG pattern analysis for patient-responsive control of FES in paraplegics for walker-supported walking. *IEEE Trans Biomed Eng* 36(7):711–719. doi:[10.1109/10.32103](https://doi.org/10.1109/10.32103)
35. Graupe D, Cerrel-Bazo H, Kern H, Carraro U (2008) Walking performance, medical outcomes and patient training in FES of innervated muscles for ambulation by thoracic-level complete paraplegics. *Neurol Res* 30(2):123–130. doi:[10.1179/174313208X281136](https://doi.org/10.1179/174313208X281136)

36. Ha KH, Quintero HA, Farris RJ, Goldfarb M (2012) Enhancing stance phase propulsion during level walking by combining FES with a powered exoskeleton for persons with paraplegia. *Conf Proc IEEE Eng Med Biol Soc* 2012:344–347. doi:[10.1109/EMBC.2012.6345939](https://doi.org/10.1109/EMBC.2012.6345939)
37. Hart RL, Bhadra N, Montague FW, Kilgore KL, Peckham PH (2011) Design and testing of an advanced implantable neuroprosthesis with myoelectric control. *IEEE Trans Neural Syst Rehabil Eng* 19(1):45–53. doi:[10.1109/TNSRE.2010.2079952](https://doi.org/10.1109/TNSRE.2010.2079952)
38. Hart RL, Kilgore KL, Peckham PH (1998) A comparison between control methods for implanted FES hand-grasp systems. *IEEE Trans Rehabil Eng* 6(2):208–218
39. Hentz VR, Leclercq C (2002) *Surgical rehabilitation of the upper limb*. W.B. Saunders, London/Edinburgh/New York
40. Hochberg LR, Bacher D, Jarosiewicz B, Masse NY, Simeral JD, Vogel J, Haddadin S, Liu J, Cash SS, van der Smagt P, Donoghue JP (2012) Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. *Nature* 485(7398):372–375. doi:[10.1038/nature11076](https://doi.org/10.1038/nature11076)
41. Hoffmann U, Deinhofer M, Keller T (2012) Automatic determination of parameters for multipad functional electrical stimulation: application to hand opening and closing. *Conf Proc IEEE Eng Med Biol Soc* 2012:1859–1863. doi:[10.1109/EMBC.2012.6346314](https://doi.org/10.1109/EMBC.2012.6346314)
42. Hultborn H, Nielsen JB (2007) Spinal control of locomotion – from cat to man. *Acta Physiol (Oxf)* 189(2):111–121. doi:[10.1111/j.1748-1716.2006.01651.x](https://doi.org/10.1111/j.1748-1716.2006.01651.x)
43. Huo X, Ghovanloo M (2010) Evaluation of a wireless wearable tongue-computer interface by individuals with high-level spinal cord injuries. *J Neural Eng* 7(2):26008. doi:[10.1088/1741-2560/7/2/026008](https://doi.org/10.1088/1741-2560/7/2/026008)
44. ISO (2010) *ISO 9241:2010 ergonomics of human-system interaction part 210: human-centred design for interactive systems*. ISO, Geneva
45. Kameyama J, Handa Y, Hoshimiya N, Sakurai M (1999) Restoration of shoulder movement in quadriplegic and hemiplegic patients by functional electrical stimulation using percutaneous multiple electrodes. *Tohoku J Exp Med* 187(4):329–337
46. Kane MJ, Breen PP, Quondamatteo F, OL G (2011) BION microstimulators: a case study in the engineering of an electronic implantable medical device. *Med Eng Phys* 33(1):7–16. doi:[10.1016/j.medengphy.2010.08.010](https://doi.org/10.1016/j.medengphy.2010.08.010)
47. Keith MW, Hoyen H (2002) Indications and future directions for upper limb neuroprostheses in tetraplegic patients: a review. *Hand Clin* 18(3):519–528, viii
48. Keith MW, Peljovich A (2012) Surgical treatments to restore function control in spinal cord injury. *Handb Clin Neurol* 109:167–179. doi:[10.1016/B978-0-444-52137-8.00010-3](https://doi.org/10.1016/B978-0-444-52137-8.00010-3)
49. Kennedy P, Lude P, Taylor N (2006) Quality of life, social participation, appraisals and coping post spinal cord injury: a review of four community samples. *Spinal Cord* 44(2):95–105. doi:[10.1038/sj.sc.3101787](https://doi.org/10.1038/sj.sc.3101787)
50. Kern H, Carraro U, Adami N, Hofer C, Loeffler S, Vogelauer M, Mayr W, Rupp R, Zampieri S (2010) One year of home-based daily FES in complete lower motor neuron paraplegia: recovery of tetanic contractility drives the structural improvements of denervated muscle. *Neurol Res* 32(1):5–12. doi:[10.1179/174313209X385644](https://doi.org/10.1179/174313209X385644)
51. Kilgore KL, Hoyen HA, Bryden AM, Hart RL, Keith MW, Peckham PH (2008) An implanted upper-extremity neuroprosthesis using myoelectric control. *J Hand Surg Am* 33(4):539–550. doi:[10.1016/j.jhsa.2008.01.007](https://doi.org/10.1016/j.jhsa.2008.01.007), S0363-5023(08)00011-7 [pii]
52. Kilgore KL, Peckham PH, Crish TJ, Smith B (2007) *Implantable networked neural system*. US Patent, 21 Aug 2007
53. Kilgore KL, Peckham PH, Keith MW, Montague FW, Hart RL, Gazdik MM, Bryden AM, Snyder SA, Stage TG (2003) Durability of implanted electrodes and leads in an upper-limb neuroprosthesis. *J Rehabil Res Dev* 40(6):457–468
54. Kilgore KL, Scherer M, Bobblitt R, Dettloff J, Dombrowski DM, Godbold N, Jatich JW, Morris R, Penko JS, Schremp ES, Cash LA (2001) Neuroprosthesis consumers' forum: consumer priorities for research directions. *J Rehabil Res Dev* 38(6):655–660
55. Klose KJ, Jacobs PL, Broton JG, Guest RS, Needham-Shropshire BM, Lebowhl N, Nash MS, Green BA (1997) Evaluation of a training program for persons with SCI paraplegia using the Parastep 1 ambulation system: part 1. Ambulation performance and anthropometric measures. *Arch Phys Med Rehabil* 78(8):789–793

56. Kobetic R, To CS, Schnellenberger JR, Audu ML, Bulea TC, Gaudio R, Pinault G, Tashman S, Triolo RJ (2009) Development of hybrid orthosis for standing, walking, and stair climbing after spinal cord injury. *J Rehabil Res Dev* 46(3):447–462
57. Kobetic R, Triolo RJ, Uhler JP, Bieri C, Wibowo M, Polando G, Marsolais EB, Davis JA Jr, Ferguson KA (1999) Implanted functional electrical stimulation system for mobility in paraplegia: a follow-up case report. *IEEE Trans Rehabil Eng* 7(4):390–398
58. Kos A, Loohuis NF, Glennon JC, Celikel T, Martens GJ, Tiesinga PH, Aschrafi A (2013) Recent developments in optical neuromodulation technologies. *Mol Neurobiol* 47(1):172–185. doi:[10.1007/s12035-012-8361-y](https://doi.org/10.1007/s12035-012-8361-y)
59. Kralj A, Bajd T, Turk R, Krajnik J, Benko H (1983) Gait restoration in paraplegic patients: a feasibility demonstration using multichannel surface electrode FES. *J Rehabil Res Dev* 20(1):3–20
60. Kralj A, Vodovnik L (1977) Functional electrical stimulation of the extremities: part 1. *J Med Eng Technol* 1(1):12–15
61. Kralj A, Vodovnik L (1977) Functional electrical stimulation of the extremities: part 2. *J Med Eng Technol* 1(2):75–80
62. Krassioukov A, Warburton DE, Teasell R, Eng JJ (2009) A systematic review of the management of autonomic dysreflexia after spinal cord injury. *Arch Phys Med Rehabil* 90(4):682–695. doi:[10.1016/j.apmr.2008.10.017](https://doi.org/10.1016/j.apmr.2008.10.017)
63. Kuhn D, Leichtfried V, Schobersberger W (2014) Four weeks of functional electrical stimulated cycling after spinal cord injury: a clinical cohort study. *Int J Rehabil Res* 37(3):243–250. doi:[10.1097/MRR.0000000000000062](https://doi.org/10.1097/MRR.0000000000000062)
64. Kundu A, Harreby KR, Yoshida K, Boretius T, Stieglitz T, Jensen W (2014) Stimulation selectivity of the “thin-film longitudinal intrafascicular electrode” (tLIFE) and the “transverse intrafascicular multi-channel electrode” (TIME) in the large nerve animal model. *IEEE Trans Neural Syst Rehabil Eng* 22(2):400–410. doi:[10.1109/TNSRE.2013.2267936](https://doi.org/10.1109/TNSRE.2013.2267936)
65. Ladenbauer J, Minassian K, Hofstoetter US, Dimitrijevic MR, Rattay F (2010) Stimulation of the human lumbar spinal cord with implanted and surface electrodes: a computer simulation study. *IEEE Trans Neural Syst Rehabil Eng* 18(6):637–645. doi:[10.1109/TNSRE.2010.2054112](https://doi.org/10.1109/TNSRE.2010.2054112)
66. Liberson WT, Holmquest HJ, Scot D, Dow M (1961) Functional electrotherapy: stimulation of the peroneal nerve synchronized with the swing phase of the gait of hemiplegic patients. *Arch Phys Med Rehabil* 42:101–105
67. Loeb GE, Davoodi R (2005) The functional reanimation of paralyzed limbs. *IEEE Eng Med Biol Mag* 24(5):45–51
68. Malesevic NM, Popovic Maneski LZ, Ilic V, Jorgovanovic N, Bijelic G, Keller T, Popovic DB (2012) A multi-pad electrode based functional electrical stimulation system for restoration of grasp. *J Neuroeng Rehabil* 9:66. doi:[10.1186/1743-0003-9-66](https://doi.org/10.1186/1743-0003-9-66)
69. Mangold S, Keller T, Curt A, Dietz V (2005) Transcutaneous functional electrical stimulation for grasping in subjects with cervical spinal cord injury. *Spinal Cord* 43(1):1–13. doi:[10.1038/sj.sc.3101644](https://doi.org/10.1038/sj.sc.3101644)
70. Marsolais EB, Kobetic R (1988) Development of a practical electrical stimulation system for restoring gait in the paralyzed patient. *Clin Orthop Relat Res* 233:64–74
71. Memberg WD, Polasek KH, Hart RL, Bryden AM, Kilgore KL, Nemunaitis GA, Hoyen HA, Keith MW, Kirsch RF (2014) Implanted neuroprosthesis for restoring arm and hand function in people with high level tetraplegia. *Arch Phys Med Rehabil* 95(6):1201–1211. doi:[10.1016/j.apmr.2014.01.028](https://doi.org/10.1016/j.apmr.2014.01.028) e1201
72. Minassian K, Hofstoetter U, Tansey K, Mayr W (2012) Neuromodulation of lower limb motor control in restorative neurology. *Clin Neurol Neurosurg* 114(5):489–497. doi:[10.1016/j.clineuro.2012.03.013](https://doi.org/10.1016/j.clineuro.2012.03.013)
73. Moss CW, Kilgore KL, Peckham PH (2011) A novel command signal for motor neuroprosthetic control. *Neurorehabil Neural Repair* 25(9):847–854. doi:[10.1177/1545968311410067](https://doi.org/10.1177/1545968311410067), 1545968311410067 [pii]
74. Mulcahey MJ, Smith BT, Betz RR (1999) Evaluation of the lower motor neuron integrity of upper extremity muscles in high level spinal cord injury. *Spinal Cord* 37(8):585–591

75. Müller-Putz GR, Breitwieser C, Cincotti F, Leeb R, Schreuder M, Leotta F, Tavella M, Bianchi L, Kreilinger A, Ramsay A, Rohm M, Sagebaum M, Tonin L, Neuper C, Millan Jdel R (2011) Tools for brain-computer interaction: a general concept for a hybrid BCI. *Front Neuroinform* 5:30. doi:[10.3389/fninf.2011.00030](https://doi.org/10.3389/fninf.2011.00030)
76. Müller-Putz GR, Scherer R, Pfurtscheller G, Rupp R (2006) Brain-computer interfaces for control of neuroprostheses: from synchronous to asynchronous mode of operation. *Biomed Tech (Berl)* 51(2):57–63. doi:[10.1515/BMT.2006.011](https://doi.org/10.1515/BMT.2006.011)
77. Nathan RH, Ohry A (1990) Upper limb functions regained in quadriplegia: a hybrid computerized neuromuscular stimulation system. *Arch Phys Med Rehabil* 71(6):415–421
78. Neuper C, Scherer R, Reiner M, Pfurtscheller G (2005) Imagery of motor actions: differential effects of kinesthetic and visual-motor mode of imagery in single-trial EEG. *Brain Res Cogn Brain Res* 25(3):668–677. doi:[10.1016/j.cogbrainres.2005.08.014](https://doi.org/10.1016/j.cogbrainres.2005.08.014)
79. NSCISC (2012) The 2012 annual statistical report for the model spinal cord injury care system. National SCI Statistical Center. www.uab.edu/NSCISC
80. Peckham PH, Keith MW, Kilgore KL, Grill JH, Wuolle KS, Thrope GB, Gorman P, Hobby J, Mulcahey MJ, Carroll S, Hentz VR, Wiegner A (2001) Efficacy of an implanted neuroprosthesis for restoring hand grasp in tetraplegia: a multicenter study. *Arch Phys Med Rehabil* 82(10):1380–1388. doi:[10.1053/apmr.2001.25910](https://doi.org/10.1053/apmr.2001.25910), S0003-9993(01)45286-5 [pii]
81. Pedrocchi A, Ferrante S, Ambrosini E, Gandolla M, Casellato C, Schauer T, Klauer C, Pascual J, Vidaurre C, Gfoehler M, Reichenfelser W, Karner J, Micera S, Crema A, Molteni F, Rossini M, Palumbo G, Guanziroli E, Jedlitschka A, Hack M, Bulgheroni M, DA E, Schenk P, Zwicker S, Duschau-Wicke A, Miseikis J, Graber L, Ferrigno G (2013) MUNDUS project: Multimodal neuroprosthesis for daily upper limb support. *J Neuroeng Rehabil* 10(1):66. doi:[10.1186/1743-0003-10-66](https://doi.org/10.1186/1743-0003-10-66)
82. Petrofsky JS (1978) Control of the recruitment and firing frequencies of motor units in electrically stimulated muscles in the cat. *Med Biol Eng Comput* 16(3):302–308
83. Popovic-Maneski L, Kostic M, Bijelic G, Keller T, Mitrovic S, Konstantinovic L, Popovic DB (2013) Multi-pad electrode for effective grasping: design. *IEEE Trans Neural Syst Rehabil Eng* 21(4):648–654. doi:[10.1109/TNSRE.2013.2239662](https://doi.org/10.1109/TNSRE.2013.2239662)
84. Popovic D, Stojanovic A, Pjanovic A, Radosavljevic S, Popovic M, Jovic S, Vulovic D (1999) Clinical evaluation of the bionic glove. *Arch Phys Med Rehabil* 80(3):299–304
85. Popovic MR, Popovic DB, Keller T (2002) Neuroprostheses for grasping. *Neurol Res* 24(5):443–452
86. Prochazka A, Gauthier M, Wieler M, Kenwell Z (1997) The bionic glove: an electrical stimulator garment that provides controlled grasp and hand opening in quadriplegia. *Arch Phys Med Rehabil* 78(6):608–614
87. Ragnarsson KT (2008) Functional electrical stimulation after spinal cord injury: current use, therapeutic effects and future directions. *Spinal Cord* 46(4):255–274. doi:[10.1038/sj.sc.3102091](https://doi.org/10.1038/sj.sc.3102091)
88. Rohde LM, Bonder BR, Triolo RJ (2012) Exploratory study of perceived quality of life with implanted standing neuroprostheses. *J Rehabil Res Dev* 49(2):265–278
89. Rohm M, Müller-Putz GR, von Ascheberg A, Gubler M, Tavella M, Millan JR, Rupp R (2011) Modular FES-hybrid orthosis for individualized setup of BCI controlled motor substitution and recovery. *Int J Bioelectromagn* 13:127–128
90. Rohm M, Schneiders M, Muller C, Kreilinger A, Kaiser V, Muller-Putz GR, Rupp R (2013) Hybrid brain-computer interfaces and hybrid neuroprostheses for restoration of upper limb functions in individuals with high-level spinal cord injury. *Artif Intell Med* 59(2):133–142. doi:[10.1016/j.artmed.2013.07.004](https://doi.org/10.1016/j.artmed.2013.07.004)
91. Rupp R (2014) Challenges in clinical applications of brain computer interfaces in individuals with spinal cord injury. *Front Neuroeng* 7:38. doi:[10.3389/fneng.2014.00038](https://doi.org/10.3389/fneng.2014.00038)
92. Rupp R, Kreilinger A, Rohm M, Kaiser V, Müller-Putz GR (2012) Development of a non-invasive, multifunctional grasp neuroprosthesis and its evaluation in an individual with a high

- spinal cord injury. *Conf Proc IEEE Eng Med Biol Soc* 2012:1835–1838. doi:[10.1109/EMBC.2012.6346308](https://doi.org/10.1109/EMBC.2012.6346308)
93. Rupp R, Müller-Putz GR, Pfurtscheller G, Gerner HJ, Vossius G (2008) Evaluation of control methods for grasp neuroprostheses based on residual movements, myoelectrical activity and cortical signals. *Biomed Tech (Berl)* 53(Suppl 1):2
 94. Salmons S, Sreter FA (1976) Significance of impulse activity in the transformation of skeletal muscle type. *Nature* 263(5572):30–34
 95. Scheiner A, Mortimer JT, Roessmann U (1990) Imbalanced biphasic electrical stimulation: muscle tissue damage. *Ann Biomed Eng* 18(4):407–425
 96. Schill O, Wiegand R, Schmitz B, Matthies R, Eck U, Pylatiuk C, Reischl M, Schulz S, Rupp R (2011) OrthoJacket: an active FES-hybrid orthosis for the paralysed upper extremity. *Biomed Tech (Berl)* 56(1):35–44. doi:[10.1515/BMT.2010.056](https://doi.org/10.1515/BMT.2010.056)
 97. Schweitzer KM Jr, Jones CP (2014) Tendon transfers for the drop foot. *Foot Ankle Clin* 19(1):65–71. doi:[10.1016/j.fcl.2013.12.002](https://doi.org/10.1016/j.fcl.2013.12.002)
 98. Shih JJ, Krusienski DJ, Wolpaw JR (2012) Brain-computer interfaces in medicine. *Mayo Clin Proc* 87(3):268–279. doi:[10.1016/j.mayocp.2011.12.008](https://doi.org/10.1016/j.mayocp.2011.12.008)
 99. Siddall PJ, McClelland JM, Rutkowski SB, Cousins MJ (2003) A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. *Pain* 103(3):249–257
 100. Smith B, Peckham PH, Keith MW, Roscoe DD (1987) An externally powered, multichannel, implantable stimulator for versatile control of paralyzed muscle. *IEEE Trans Biomed Eng* 34(7):499–508
 101. Snoek GJ, [IJzerman](#) MJ, Hermens HJ, Maxwell D, Biering-Sorensen F (2004) Survey of the needs of patients with spinal cord injury: impact and priority for improvement in hand function in tetraplegics. *Spinal Cord* 42(9):526–532. doi:[10.1038/sj.sc.31016383101638](https://doi.org/10.1038/sj.sc.31016383101638) [pii]
 102. Stieglitz T (2005) Diameter-dependent excitation of peripheral nerve fibers by multipolar electrodes during electrical stimulation. *Expert Rev Med Devices* 2(2):149–152
 103. Stone J, Landau W (2013) Neuroprosthetic control and tetraplegia. *Lancet* 381(9881):1900. doi:[10.1016/S0140-6736\(13\)61153-8](https://doi.org/10.1016/S0140-6736(13)61153-8)
 104. Thoma H, Frey M, Holle J, Kern H, Mayr W, Schwanda G, Stohr H (1987) State of the art of implanted multichannel devices to mobilize paraplegics. *Int J Rehabil Res* 10(4 Suppl 5):86–90
 105. Thorsen R, Binda L, Chiaramonte S, Dalla Costa D, Redaelli T, Occhi E, Beghi E, Ferrarin M (2014) Correlation among lesion level, muscle strength and hand function in cervical spinal cord injury. *Eur J Phys Rehabil Med* 50(1):31–38
 106. Thorsen R, Dalla Costa D, Chiaramonte S, Binda L, Beghi E, Redaelli T, Occhi E, Ferrarin M (2013) A noninvasive neuroprosthesis augments hand grasp force in individuals with cervical spinal cord injury: the functional and therapeutic effects. *Scientific World J* 2013:836959. doi:[10.1155/2013/836959](https://doi.org/10.1155/2013/836959)
 107. Triolo R, Nathan R, Handa Y, Keith M, Betz RR, Carroll S, Kantor C (1996) Challenges to clinical deployment of upper limb neuroprostheses. *J Rehabil Res Dev* 33(2):111–122
 108. Triolo RJ, Bailey SN, Miller ME, Rohde LM, Anderson JS, Davis JA Jr, Abbas JJ, DiPonio LA, Forrest GP, Gater DR Jr, Yang LJ (2012) Longitudinal performance of a surgically implanted neuroprosthesis for lower-extremity exercise, standing, and transfers after spinal cord injury. *Arch Phys Med Rehabil* 93(5):896–904. doi:[10.1016/j.apmr.2012.01.001](https://doi.org/10.1016/j.apmr.2012.01.001)
 109. Tuga MR, Rupp R, Liebetanz D, Mikut R, Reischl M (2013) Concept of a co-adaptive training environment for human-machine interfaces based on EMG-control. *Biomed Tech (Berl)*. doi:[10.1515/bmt-2013-4388](https://doi.org/10.1515/bmt-2013-4388)
 110. van den Honert C, Mortimer JT (1979) The response of the myelinated nerve fiber to short duration biphasic stimulating currents. *Ann Biomed Eng* 7(2):117–125
 111. Varoto R, Barbarini ES, Cliquet A Jr (2008) A hybrid system for upper limb movement restoration in quadriplegics. *Artif Organs* 32(9):725–729. doi:[10.1111/j.1525-1594.2008.00597.x](https://doi.org/10.1111/j.1525-1594.2008.00597.x)

112. von Wild K, Rabischong P, Brunelli G, Benichou M, Krishnan K (2002) Computer added locomotion by implanted electrical stimulation in paraplegic patients (SUAW). *Acta Neurochir Suppl* 79:99–104
113. Wheeler CA, Peckham PH (2009) Wireless wearable controller for upper-limb neuroprostheses. *J Rehabil Res Dev* 46(2):243–256
114. Williams JC, Denison T (2013) From optogenetic technologies to neuromodulation therapies. *Sci Transl Med* 5(177):177ps176. doi:[10.1126/scitranslmed.3003100](https://doi.org/10.1126/scitranslmed.3003100)
115. Williams MR, Kirsch RF (2008) Evaluation of head orientation and neck muscle EMG signals as command inputs to a human-computer interface for individuals with high tetraplegia. *IEEE Trans Neural Syst Rehabil Eng* 16(5):485–496. doi:[10.1109/TNSRE.2008.2006216](https://doi.org/10.1109/TNSRE.2008.2006216)