Gernot Müller-Putz
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Neuroprosthetics and Brain-Computer Interfaces in Spinal Cord Injury

A Guide for Clinicians and End Users

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Preface

An injury of the spinal cord caused by trauma or disease results in impairments of sensory, vegetative, and motor functions below the level of the lesion up to their complete loss. Regaining the ability to move, in particular arms and hands, is of utmost importance for people affected by spinal cord injuries. Unfortunately, despite substantial efforts in biological research, there is still no causal therapy available for the repair of damaged axons and cells within the spinal cord.

Assistive technology has always played a major role in the life of people with paralysis to achieve at least partial autonomy and to participate in society. However, common assistive devices such as wheelchairs, manipulation, or walking aids such as orthoses represent rather simple technological systems mainly designed for compensation of a lost motor function. However, novel innovative technologies interacting with the neuronal structures of the central nervous system hold promise to achieve a level of functional restoration in people with paralysis that no one would have expected years ago. Over the last decade, the interest in neurotechnology has tremendously increased and substantial progress has been made in this field. The reasons for this are manifold: First, the developments in hardware components, e.g., microelectronics, computing power, energy storage, and power efficiency, and in mathematical algorithms including machine learning methods have paved the way for innovative neurotechnological systems. Second, our understanding how neural networks located in the brain and the spinal cord contribute to and control coordinated movements has substantially increased. And finally, there is a growing interest of end users and clinicians in neurotechnology as an ad hoc means for improving independence in daily life activities until cure will eventually become a reality.

However, the successful translation of neurotechnology from the laboratory into clinical routine depends on the close cooperation and knowledge exchange between scientists, engineers, clinicians including surgeons and rehabilitation specialists, therapists, and end users. Among the most promising neurotechnological developments for functional restoration are neuroprostheses based on functional electrical stimulation and brain–computer interfaces. Based on our experiences, however, researchers on brain–computer interfaces are typically not familiar with the

possibilities and challenges of the application of neuroprostheses. On the other hand, developers and clinical users of neuroprostheses are not aware of the recent progress achieved in brain–computer interfaces and their potential use as a control interface. And finally, end users with spinal cord injury desperately searching for solutions to improve their situation often overestimate the capabilities of the current technology, partly due to sensational reports in the media raising high expectations.

Up to now, a comprehensive textbook about brain–computer interfaces and neuroprostheses has been missing. Therefore, this unique textbook aims at fostering the interdisciplinary exchange of knowledge by providing a thorough overview of the basics, the technology, and the clinical application of both technologies. In order to make the content and the main messages of the book chapters accessible to end users, special care was taken to use clear and understandable language.

The book starts with the basics about spinal cord injury and its specific challenges with respect to functional restoration by means of functional electrical stimulation such as the presence of upper vs. lower motor neuron damage. Based on this, the basic physiological principles regarding electrical stimulation of nerves and muscles are explained together with the technical specifications of stimulation devices.

The final introductory chapter presents the basics of brain electrophysiology, brain signal recording, and setup of brain–computer interfaces.

The next block of chapters focuses on noninvasive and invasive neuroprostheses for functional restoration. After brief insights into the history of neuroprosthetics and the lessons learned with respect to successful clinical translation, neuroprostheses for restoration of upper extremity function in people with high spinal cord injury and exoskeletons for improvement of walking are presented. The last chapter of this block describes the state of the art of an emerging neuroprosthetic approach, namely epidural and transcutaneous spinal cord stimulation, to enhance motor recovery after spinal cord injury.

The next series of chapters provide an overview of clinical noninvasive and invasive brain–computer interfaces starting with the introduction of an established electroencephalography-based brain–computer interface, which is the P300 BCI. The major advantage of brain–computer interfaces in contrast to traditional neuroprosthetic user interfaces is the possibility for decoding of the movement intention of an end user directly from brain signals. The first promising attempts in this direction by the use of invasive and recently noninvasive devices are thoroughly discussed.

An important part of this book is formed by the presentation of clinical use cases. Electrical stimulation can not only be used for functional restoration but also for therapy of secondary conditions associated with spinal cord injury such as muscle atrophy, spasticity, or trunk instability. The principles of this therapeutic application of electrical stimulation and its parameters are given. First promising results of clinical pilot studies aiming at enhancing functional recovery by the use of closed-loop electrical stimulation controlled by a brain–computer interface are presented. Finally, the current state of noninvasive brain–computer interface-controlled grasp neuroprostheses developed within the recent European MoreGrasp project and

applied in end users with spinal cord injury and missing hand but preserved elbow movements is shown.

The book ends with an outlook on future technologies of the next decade such as invasive microelectrodes and optogenetics. But rather than presenting a sheer technological description of these methods, the increasingly important ethical considerations of their use are critically reflected.

The editors wish to thank and congratulate all the contributing engineers, clinicians, therapists, and scientists, who have written such a comprehensive book. We are convinced that this unique compilation will provide new and valuable information to professionals and end users about neuroprostheses and brain–computer interfaces in a clinical and research context. We hope that this book will improve the understanding of the possibilities and challenges of neurotechnology for functional restoration and foster discussions between all involved stakeholders.

Graz, Austria — Gernot Müller-Putz
Heidelberg, Germany — Rüdiger Rupp

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Part I
Basics

Chapter 1
Spinal Cord Injury

Rüdiger Rupp

Abstract An injury of the spinal cord leads to impairments up to the complete loss of motor, sensory, and autonomous functions below the injury level. Worldwide, the prevalence of spinal cord injury (SCI) is 1:1000 and the incidence is between 4 and 9 new injuries per 100,000 people per year. Traffic accidents, falls, and violence represent the most frequent causes of traumatic SCI. Nowadays, the incidence of tetra- and paraplegia is similar. In industrialized countries, the proportion of non-traumatic injuries has significantly increased over the last two decades and so does the mean age at onset of SCI. In contrast to paraplegia, more than half of all people with tetraplegia have an incomplete SCI with preserved functions below the injury level. Patients with initially preserved motor functions have a good prognosis for recovery; however, only 25% of the cases with initially complete SCI convert to an incomplete injury. The SCI affects multiple organ systems and leads to typical complications such as spasticity, bladder and bowel problems, and musculoskeletal and neuropathic pain. The latter is reported to be associated with an SCI-induced structural and functional reorganization of the brain. In people with incomplete lesions particularly in the subacute phase after injury, the focus of rehabilitation is on restoration of functions by activity-based, task-specific therapies. In people with only a few functions preserved, compensatory techniques including the use of assistive devices are applied to achieve the highest possible level of independence. In any case, the rehabilitation aims and procedures need to be tailored to the individual needs and priorities of each person. For this, a precise characterization of the neurological and functional status of an individual with SCI together with documentation of factors impacting rehabilitation outcomes such as spasticity, autonomic dysfunctions, infections or the presence of pain is mandatory.

Keywords Spinal cord injury · Tetraplegia · Paraplegia · Lower motor neuron damage · Assessment · Neurological recovery · Functional improvements · Brain reorganization · Rehabilitation · Restoration · Compensation · User priorities

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1.1 Neurological Background of Spinal Cord Injury

A damage of the spinal cord with its descending and ascending longitudinal nerve fiber tracts at a defined level caused by, e.g., trauma, infections, tumor, or disc herniation, results in an impairment up to a complete loss of motor, sensory, and autonomous functions at and below this lesion level.

The spinal cord is located in the spinal canal surrounded by the bony parts of the spine and is longitudinally like the vertebrae of the vertebral column divided into segments. Between the segments, spinal nerve roots are exiting the spinal canal dorsally and ventrally. While each of the segmental dorsal nerve roots innervates a distinct sensory area of the skin (dermatome) (Downs and Laporte 2011), two or more ventral nerve roots innervate muscles of the upper or lower extremities (Schirmer et al. 2011). The spinal cord segments are named according to the level where the nerve roots leave the spinal cord: There are 8 cervical (C1–C8), 12 thoracic (Th1–Th12), 5 lumbar (L1–L5), 5 sacral (S1–S5) segments and one coccygeal, rudimentary segment. The more rostral (or higher) the spinal cord is injured, the more body segments are impaired (Fig. 1.1).

A cervical spinal cord injury (SCI) commonly results in impairments of sensory and motor functions of the arms, trunk, and legs, a condition called tetraplegia (the term quadriplegia is nowadays less used). Someone with a lesion level of C4 or higher may need respiratory support by an artificial ventilator. An SCI at the thoracic or lumbar level commonly results in paraplegia, i.e., impairments of sensory and/or motor functions of the legs and commonly the trunk. In all cases of SCI, bladder, bowel, and sexual functions are affected.

1.1.1 Upper Versus Lower Motor Neuron Damage

In general, an injury of the spinal cord does not only impact the correct function of the descending nerve fiber tracts (axons of the upper motor neurons (UMN) located in the motor cortex of the brain) within the white matter of the spinal cord at the lesion site, but also that of the cell bodies of the lower motor neurons (LMNs) in the gray matter. Therefore, a peripheral paralysis of the muscles formerly innervated by axons of these LMNs superimposes the central paralysis. While a missing central innervation normally results in a paralysis of muscles at and caudal (or below) to the level of injury, peripheral paralysis is only expected in muscles whose LMNs originate at and around the lesion epicenter (Grumbles and Thomas 2017). Spinal lesions of UMNs are characterized by a preserved structural integrity of LMNs below the injury including their axons and synapses to the innervated muscles. In contrast, damage to LMNs leads to a pattern of peripheral nerve degeneration with subsequent atrophy of the muscles formerly innervated by the damaged neurons or their axons. While a LMN damage does not become clinically apparent in thoracic lesions, where only intercostal or small spine muscles are affected, this may differ in

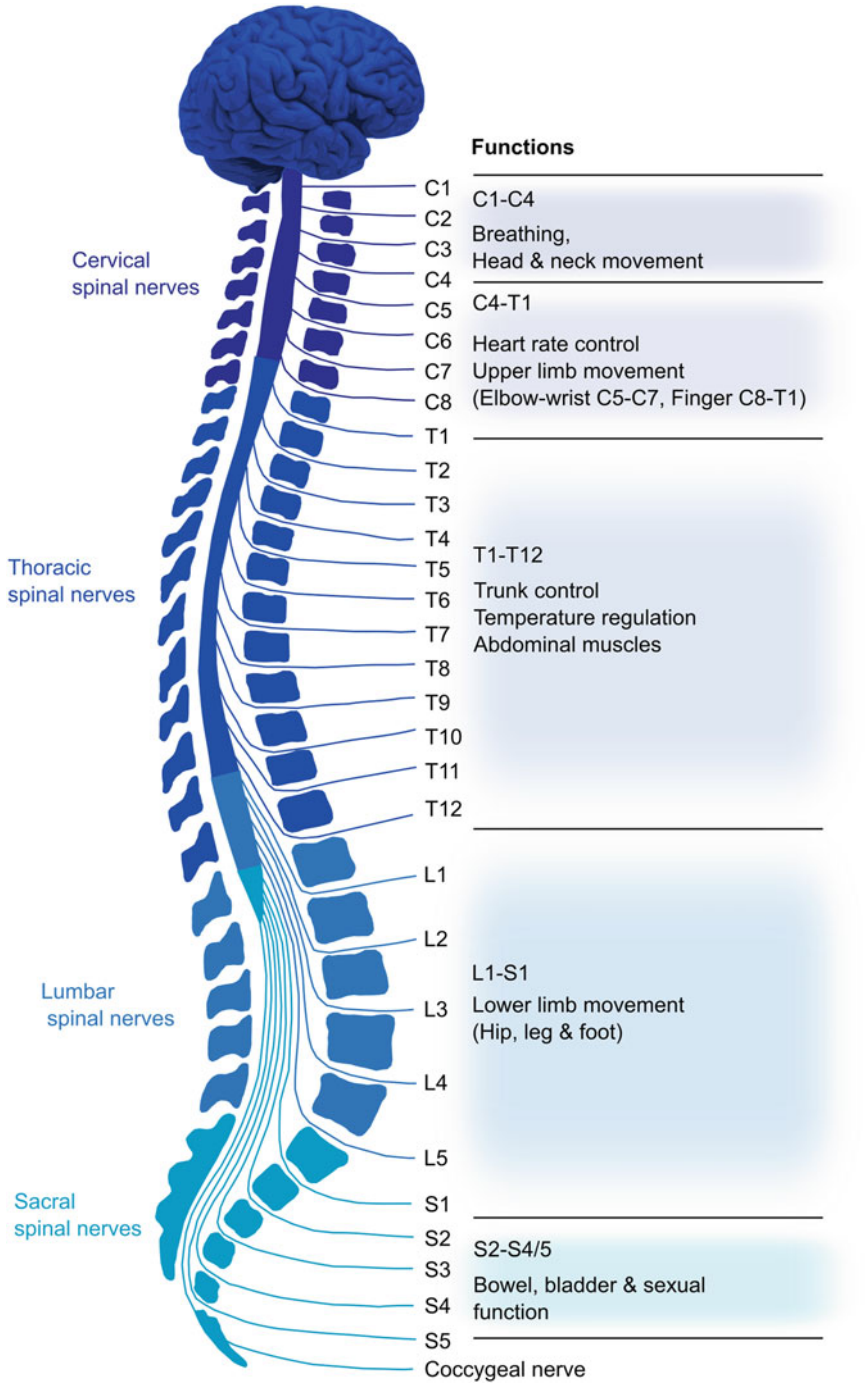

Fig. 1.1 Longitudinal, segmental organization of the spinal cord (with cervical, thoracic, lumbar, and sacral segments), vertebrae of the vertebral column, and spinal nerves and a broad representation of major segmental functions of the spinal cord (with permission from (Rupp 2020))

cervical lesions. In cervical lesions, the presence of denervation in upper extremity muscles shows high interindividual variability but may be up to 90% in some muscles such as the biceps (Mulcahey et al. 1999; Bersch et al. 2018).

At this point, it is important to recapitulate that the longitudinal nerve fiber tracts end at the conus medullaris of the spinal cord, which extends from the 12th thoracic down to the 2nd lumbar vertebrae. Caudal to the conus the spinal cord turns into the cauda equina purely consisting of peripheral nerve fibers (Fig. 1.2). A lesion of this part of the spinal cord always shows the characteristics of a LMN damage. Clinically, an SCI without substantial LMN damage most often results in spasticity due to preserved, hyperextensive reflex arcs, while LMN lesions lead to flaccid paralysis with missing reflex signs (Bryden et al. 2016).

The assessment of the presence of LMN damage and its degree is essential for clinical decision making, because people with paraplegia and extended LMN damage are of higher risk for developing pressure ulcers due to the massive atrophy of lower extremity muscles (Kern et al. 2008). Another complication that may arise in particular in patients with tetraplegia are contractures of upper extremity joints due to an imbalance of (voluntary) innervated agonists and denervated antagonists (Bryden et al. 2016). Additionally, denervated muscles cannot be activated by the short electrical impulses generated by a neuroprosthesis (Rupp 2017).

The clinical gold standard assessment to quantify LMN integrity is the needle electromyography (Benecke et al. 1983) or the activation of nerves and muscles with electrical impulses of different pulse durations and slopes (see Chap. 2) to determine the strength/duration (I/t)-curve (Lapicque 1907).

1.1.2 Assessment of the Level and Severity of a Spinal Cord Injury

The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) published by the American Spinal Injury Association (ASIA) represents the accepted gold standard for assessment of motor and sensory impairments, i.e., the level and severity of the injury (American Spinal Injury Association 2019). The ISNCSCI examination consists of two parts testing two sensory modalities as well as motor function of upper and lower extremities on both sides of the body (Fig. 1.3). Testing in supine position allows for assessment of the neurological function early after injury and for comparison of subsequent examination results.

The aim of the sensory examination is to test the integrity of afferent spinal fiber tracts responsible for transmission of touch and nociceptive sensations. For this, light touch (LT) and pin prick (PP) sensation is examined at key points in each of the 28 dermatomes located near bony anatomical landmarks on the left and right side of the body. The examination results are graded on a 3-point scale: 0 = absent, 1 = altered (impaired or partial appreciation, hyperalgesia), and 2 = normal. It needs to be mentioned that if an individual with SCI is not able to consistently

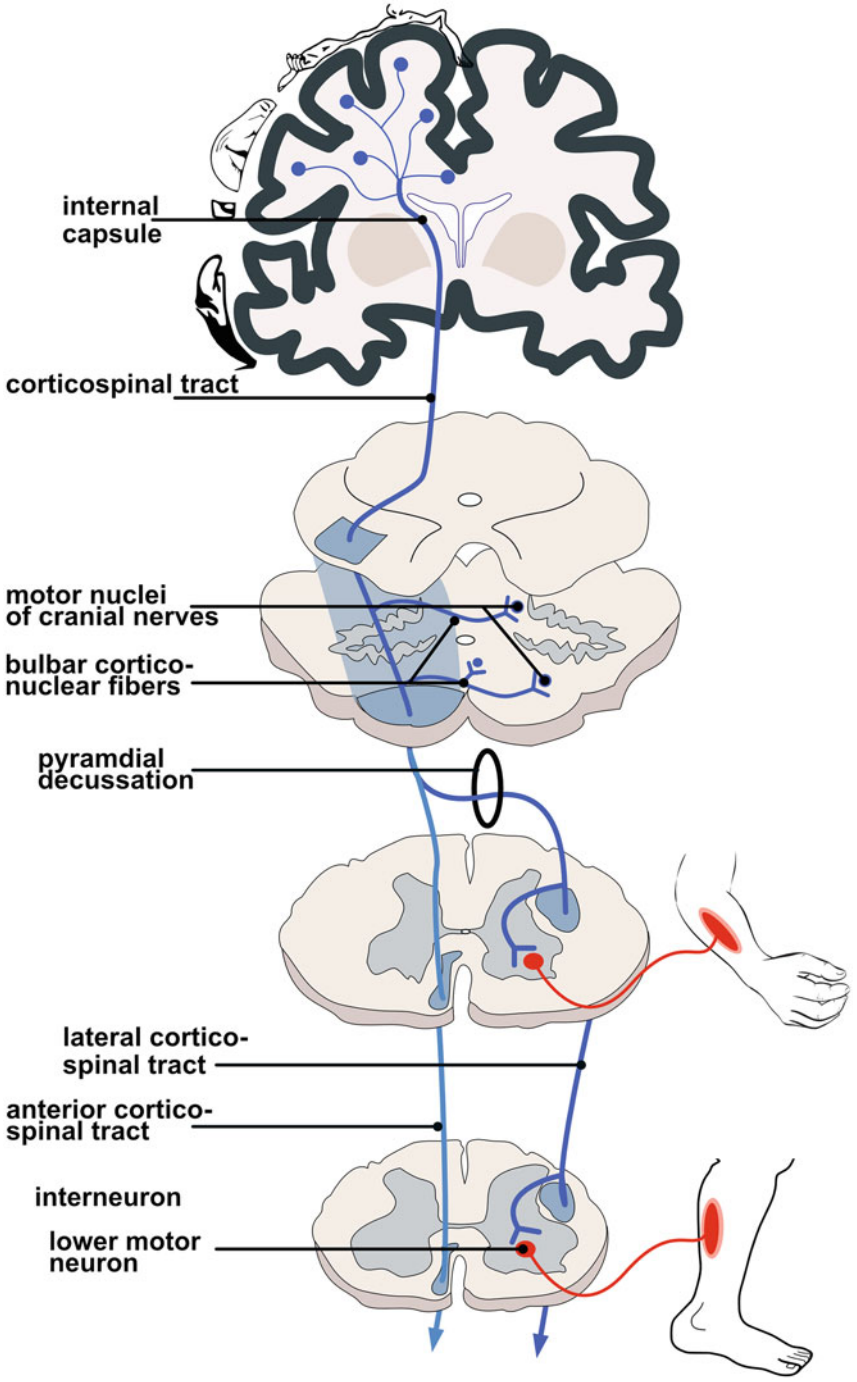

Fig. 1.2 Overview of the route of the corticospinal tract starting with cell bodies of upper motor neurons in the primary motor cortex, its descending axonal fiber tracts, its separation into the lateral (80% of the fibers) and the anterior (20%) tracts, and its connection to the lower motor neuron in the

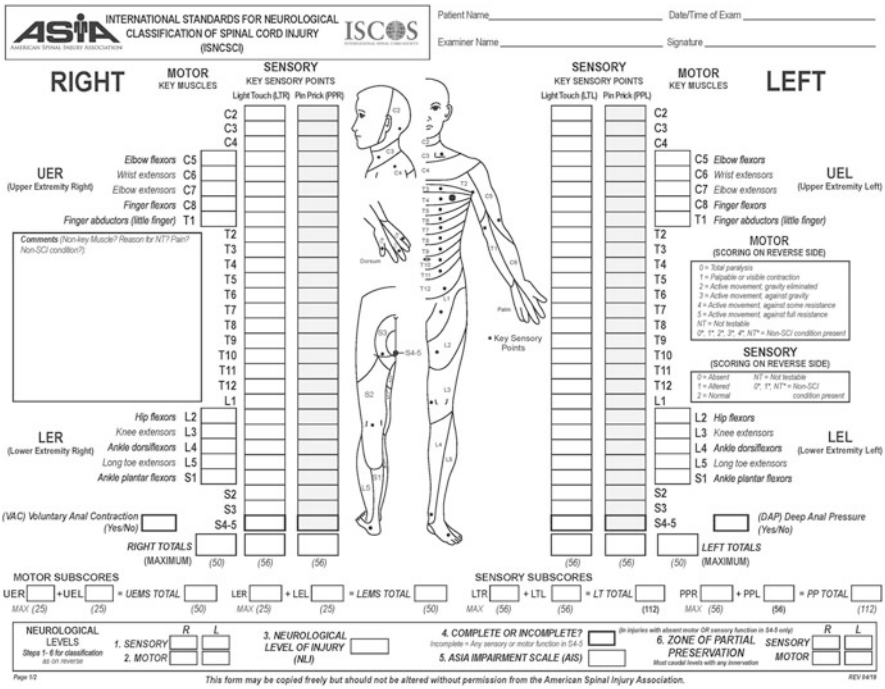

Fig. 1.3 The front side of the most recent ISNCSCI examination worksheet (revised April 2019). Freely available for download from the American Spinal Injury Association webpage http://www.asia-spinalinjury.org/elearning/ISNCSCI.php. With reprint permission from the American Spinal Injury Association (ASIA)

discriminate between sharp and dull sensation in a dermatome, this is recorded as an absent PP sensation of this dermatome. An important additional component of the sensory exam is the testing of the preservation of any sensation in the lowest sacral segments S4–5. This is done by testing the sensation of deep anal pressure (DAP) in side-lying position and grading it as being present or absent.

The motor examination consists of the testing of the strength of 10 key muscles of the right and left upper (myotomes C5–T1) and lower (myotomes L2–S1) extremities (Fig. 1.3). The rationale for the selection of the key muscles was the innervation from only two spinal segments. The strength of these key muscles is graded on a 6-point scale from 0 (absent) to 5 (full strength against resistance over the whole range of motion) (American Spinal Injury Association 2020). The total motor score is calculated as the sum of the motor scores from all examined myotomes; however,

Fig. 1.2 (continued) anterior horn of the gray matter of the spinal cord. The axons of the lower motor neurons then innervate fibers of skeletal muscles forming motor units

Table 1.1 ASIA Impairment Scale (AIS) definition (American Spinal Injury Association 2019)

ASIA Impairment Scale	Definition
A	Complete. No sensory or motor function is preserved in the sacral segments S4–S5
B	Sensory incomplete. Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4–S5 (light touch or pin prick at S4–5 or deep anal pressure) and no motor function is preserved more than three levels below the motor level on either side of the body
C	Motor incomplete. Motor function is preserved at the most caudal sacral segments for voluntary anal contraction (VAC) or the patient meets the criteria for sensory incomplete status (sensory function preserved at the most caudal sacral segments (S4–S5) by LT, PP, or DAP), and has some sparing of motor function more than three levels below the ipsilateral motor level on either side of the body (this includes key or non-key muscle functions to determine motor incomplete status). For AIS C, less than half of key muscle functions below the single NLI have a muscle grade $\geq$3
D	Motor incomplete. Motor function is preserved below the neurological level and at least half of key muscle functions below the NLI have a muscle grade of 3 or more
E	Normal. If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments and the patient had prior deficits

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it is recommended to provide upper (UEMS) and lower (LEMS) extremity motor scores separately.

Like in the sensory examination, the anorectal examination of motor function is a mandatory component. The presence of any voluntary anal contraction (VAC) is scored as present or absent (Kirshblum et al. 2016).

The results of the sensory and motor anorectal exam are extremely important, because an SCI is only classified as complete, when no voluntary function is preserved in the lowest sacral segments, i.e. LT, PP, DAP sensation and VAC are all absent (Table 1.1).

On the basis of the sensory and motor examination results, classifications are performed as part of ISNCSCI to determine additional variables important for characterization of the SCI (Schuld et al. 2013). This classification process includes the determination of sensory and motor levels as the most caudal segments with intact function, and the neurological level of injury (NLI) as the most caudal segment with both intact sensory and motor function. The most complex classification procedure is the determination of the ASIA Impairment Scale (AIS) (Table 1.1). The AIS categorizes the severity of the SCI ranging from A (complete SCI) to E (normal according to ISNCSCI) (Kirshblum and Waring 2014).

In a final step, the zones of partial preservation (ZPPs) are determined on each side of the body. The sensory/motor ZPPs are only given in individuals with missing sensory/motor function in the lowest sacral segments and refer to the most caudal dermatome and/or key muscle with any function (ASIA and ISCoS International Standards Committee 2019). The basic characteristics of the neurological status of

an individual with SCI are well characterized with provision of the UEMS, LEMS, NLI, AIS, and eventually ZPPs. Although the ISNCSCI represents the de-facto assessment of the neurological impairments of individuals with SCI, its standardized exam procedure and classification rules are quite complex. This results in the need for training to achieve consistency of examination results between different raters (ASIA International Standards Committee et al. 2018). To support self-training and classification accuracy, validated ISNCSCI computer algorithms represent valued complementary tools (Walden et al. 2016; Schuld et al. 2012).

1.1.3 Functional Assessments

According to the International Classification of Functioning, Disability and Health (ICF) published by the WHO in 2001, the functioning and disability of people with neurological impairments such as SCI are determined by a complex interaction between the health condition of the individual and the contextual factors of the environment as well as personal factors. The ICF is based on a biopsychosocial model and provides a coherent view of different perspectives of health: biological, individual, and social. In respect of outcome measures, the ICF argues that functioning and disability of people with SCI are described not only by the impairment of body functions but also by the impact of the SCI on activities of daily living and ultimately on participation in society (Dorjbal et al. 2016; Organization Organization 2001). Accordingly, the ICF recommends to characterize individuals with SCI by assessing their impairments in the body structure and function domain, in the activity domain, and on the participation level. In respect of ICF, ISNCSCI represents an assessment of body functions, namely the scoring of the segmental sensory and motor functions and classification of the severity of a single-level SCI. Although often misused, the UEMS, LEMS, and AIS were never intended to be used as functional assessments related to activities or even independence. For this purpose, the ISNCSCI assessment should be complemented with activity measures such as the Spinal Cord Independence Measure III (SCIM III (Itzkovich et al. 2007)). The Spinal Cord Ability Ruler (SCAR) combining parts of ISNCSCI and SCIM III represents a novel assessment with more unidimensional features than the SCIM III (Reed et al. 2017).

However, both the SCIM and the SCAR might not be responsive enough to quantify outcomes of specific rehabilitative interventions. For a more fine graded assessment of ambulation, it is recommended to add walking tests like the 10-m-walk test or the 6-min-walk test (van Hedel et al. 2007) and the Walking Index for Spinal Cord Injury (Ditunno et al. 2013) for categorization of the dependency on walking aids. For a more detailed assessment of arm and hand functions, the Graded and Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) version 2 represents a comprehensive assessment of the neurological and functional status of the upper extremities in individuals with tetraplegia (Kalsi-Ryan et al. 2019).

In the end, what matters most for people with any neurological impairment is their ability to fully participate in the society. This domain is assessed by structured interviews and questionnaires (Aquarone and Faro 2014), among them are the free-of-charge WHO quality of life measure (WHOQOL-100) (Skevington et al. 2004) and its short-form WHOQOL-BREF with 26 questions covering 4 domains (Lude et al. 2014).

The Spinal Cord Injury Research Evidence (SCIRE, www.scireproject.com) initiative summarizes evidence from validated assessments in the field of SCI and provides a web-based toolkit summarizing recommendable assessments based on expert consensus (Chan et al. 2017).

1.1.4 Prevalence, Incidence, and Etiology of SCI

According to the World Health Organization (WHO) 15% of the global population is affected by disability, 0.1% of the total population by SCI (WHO 2013). The worldwide prevalence of traumatic SCI is estimated to be 1000 per million people (Singh et al. 2014). The global incidence of SCI including traumatic and non-traumatic spinal lesions is estimated between 40 and 83 per million people per year resulting in an estimated number of 250,000–500,000 new cases per year (Wyndaele and Wyndaele 2006). While the worldwide incidence of only traumatic SCI is estimated to be between 10.4 and 83 per million people per year, the incidence of non-traumatic SCI varies between 12 and 76 per million population (Milicevic et al. 2012; New et al. 2014; Nijendijk et al. 2014; Noonan et al. 2012; O'Connor 2005). However, these numbers need to be interpreted very carefully, because they mostly represent an extrapolation from data obtained from a limited number of regional SCI centers. This might result in a substantial overestimation of the real numbers (GBD 2016 Traumatic Brain Injury Spinal Cord Injury Collaborators 2019). Additionally, huge regional differences in terms of hazard potentials and different levels of emergency treatment might have a strong impact on these numbers.

Road traffic accidents, falls, and violence are the most frequent global causes for traumatic SCI (Lee et al. 2014). The proportion of SCIs caused by road traffic accidents varies to a large degree for different regions of the world (Nwadinigwe et al. 2004; Smith et al. 2014; Hua et al. 2013; Obalum et al. 2009; DeVivo and Chen 2011). Traffic accidents are the most common cause of SCI in the subpopulation with an age below 45 years. After the age of 45, SCI results most frequently by falls (McCaughey et al. 2016). In industrialized countries, due to the increase of the society's mean age and the high number of fall-related SCIs in elderly persons, the mean age at injury is steadily increasing (DeVivo and Chen 2011; McCammon and Ethans 2011; NSCISC 2018).

In Europe, 11,000 new injuries occur per year and the total number of people with SCI is estimated to be 330,000 (Ouzký 2002; van den Berg et al. 2010). The numbers for the United States of America are similar (NSCISC 2018). Despite marked

regional differences across the globe, there has been a trend toward increasing prevalence rates of SCI over the past decades (Furlan et al. 2013). In industrial countries, there is an ongoing trend toward a higher proportion of non-traumatic lesions (Exner 2004; McCaughey et al. 2016; Thietje 2015). The fact that non-traumatic spinal cord damage affects people at an age above 55 years (Scivoletto et al. 2011) results in a continuous increase in the mean age of the SCI population. In regard to lesion level, there is a trend toward a higher number of cervical injuries resulting in tetraplegia (McCaughey et al. 2016). In recent years, at least half of all individuals with an acute SCI are tetraplegic. The NLI of the majority of patients with tetraplegia due to traumatic SCI is C4 or C5 (NSCISC 2018) (Fig. 1.7). In respect of upper extremity function, in lesions with an NLI of C5, typically only hand and finger functions are impaired, while in most C4 lesions, additionally wrist and elbow functions are limited. About 8% of all patients with a traumatic SCI have a NLI rostral to C4 resulting in sensorimotor impairments of both upper extremities including shoulder, elbow, and hand movements.

Epidemiological data on non-traumatic SCI are sparse. Non-traumatic SCI is attributed in 41% to degenerative spine diseases with consecutive spinal canal stenosis, 26% to tumors compressing the spinal cord, 20% to infectious diseases, and 16% to ischemia (Thietje 2015; Milicevic et al. 2012). Non-traumatic SCI results much more often in incomplete paralysis (AIS B-D) than traumatic lesions (Dahlberg et al. 2005; Hua et al. 2013; Milicevic et al. 2012; New et al. 2013; Nijendijk et al. 2014; Obalum et al. 2009; Thietje 2015; van den Berg et al. 2012).

1.2 Neurological and Functional Recovery After SCI

Reliable data about the course of neurological and functional recovery are only available from patients with traumatic SCI. In patients with non-traumatic spinal cord damage, the extent of recovery is highly heterogenous because of significant variations in the cause of the spinal cord damage and the presence of different concomitant complications.

After acute trauma, the majority (overall 47%; tetra-/paraplegia = 19%/27.5% of the total population) of patients with SCI are classified as AIS A.

While in most (49%) of the acute patients with tetraplegia motor functions are preserved (AIS C and D), in patients with acute paraplegia almost three-fourth (71%) are motor complete (Fig. 1.4). The reason for this is that the spinal canal is smaller in the cervical compared to the thoracic and lumbar region with the consequence that already a low-energy spine trauma results in damage to the cord.

Initially after the injury, patients are in the phase of the spinal shock, i.e., muscle tone and tendon tap reflexes are absent. The phase of the spinal shock typically ends within the first 2–4 weeks after injury with reappearing muscle tone and tendon reflexes (Boland et al. 2011). Simultaneously, neurological functions start to recover. The highest extent of neurological recovery occurs within the first 3 months after injury (Langhorne et al. 2011; Curt et al. 2004), while the highest functional

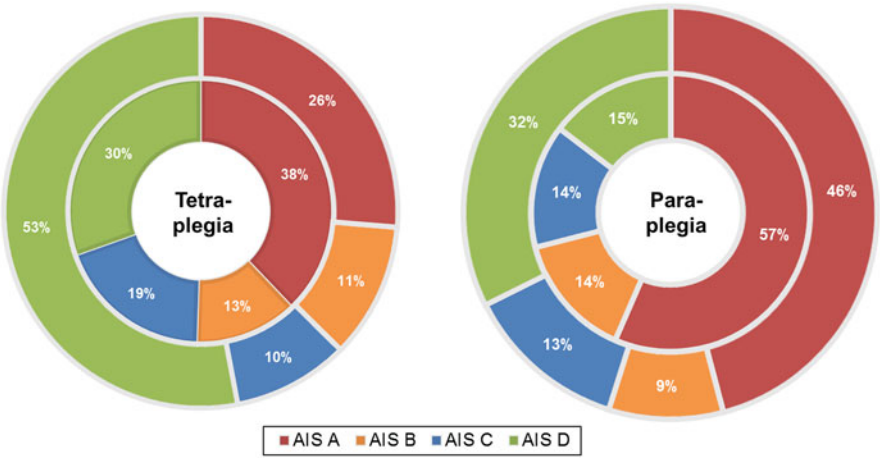

Fig. 1.4 AIS distribution of individuals with traumatic tetraplegia (left) and paraplegia (right). The inner ring represents the AIS distribution at the acute (15.1 ± 10.8 days after injury) and the outer ring at the chronic (328.2 ± 98.4 days after injury) stage after injury. The data shown originate from a representative European cohort (n = 2.660) of individuals with traumatic SCI included in the European multicenter study about human spinal cord injury (EMSCI, www.emsci.org)

improvements are delayed and can be observed within the first 6 months (Figs. 1.5 and 1.6) (Curt et al. 2008). In the chronic stage (>12 months after injury), neurological recovery reaches a plateau and sensorimotor deficits are likely to persist permanently.

In the first months after SCI, initially incomplete patients with preserved sensory and/or motor functions in the lowest sacral segments have a high potential for motor recovery, while three quarters of the patients with an initially sensorimotor complete SCI (AIS A) remain complete (Kirshblum et al. 2016; Spiess et al. 2009). Because the percentage of people with a complete SCI is higher in patients with acute paraplegia than with acute tetraplegia, the proportion of people with a persisting complete paralysis is higher in individuals with paraplegia (46% of all people with paraplegia) than with tetraplegia (26% of all people with tetraplegia) (Figs. 1.4 and 1.7).

Although three quarters of the patients with initially complete tetraplegia stay complete (AIS A), they still recover on average 10 motor points in their UEMS independent from the initial level of injury (Kramer et al. 2012; Steeves et al. 2011). An initial motor ZPP of two segments or more is associated with a gain of two or more motor levels 1 year after SCI (Marino et al. 2011). Functional recovery of upper extremity function is significantly greater for those individuals regaining two motor levels compared with those recovering only one or no motor levels. This is the case in 22% of the patients with an initial motor level of C4 and in 27% of the initially C5 patients (Kramer et al. 2012).

In an analysis of the database of the European Multicenter Study about Spinal Cord Injury (EMSCI, http://emsci.org) (Curt et al. 2004) it was found that the most

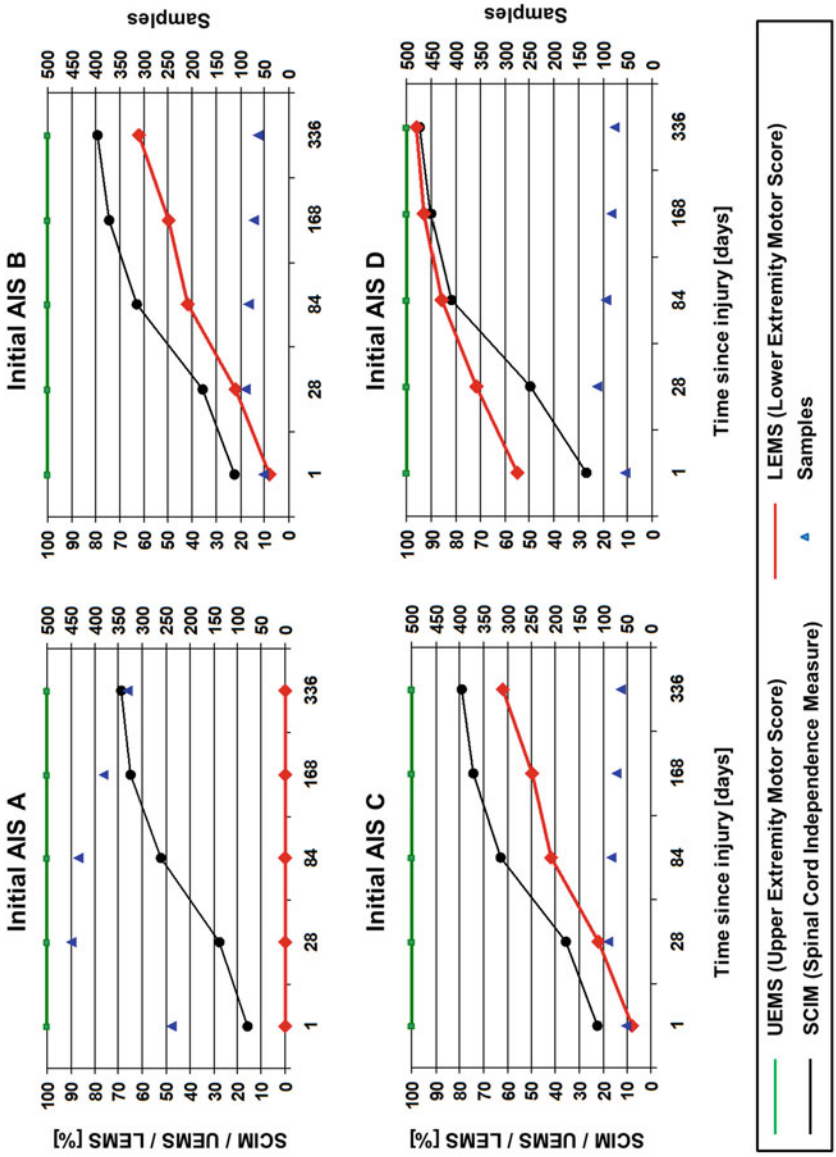

Fig. 1.5 Neurological and functional recovery profiles of individuals with paraplegia (initial NLI of T1–T12) within the first year after injury. The normalized median of UEMS, LEMS, and SCIM grouped by the initial AIS are shown. Data have been obtained within the European multicenter study about human spinal cord injury (EMSCI, www.emsci.org). The number of patients (samples) contributing to each data point is given as triangles with the corresponding ordinate on the right side of each graph (with permission from (Rupp 2020))

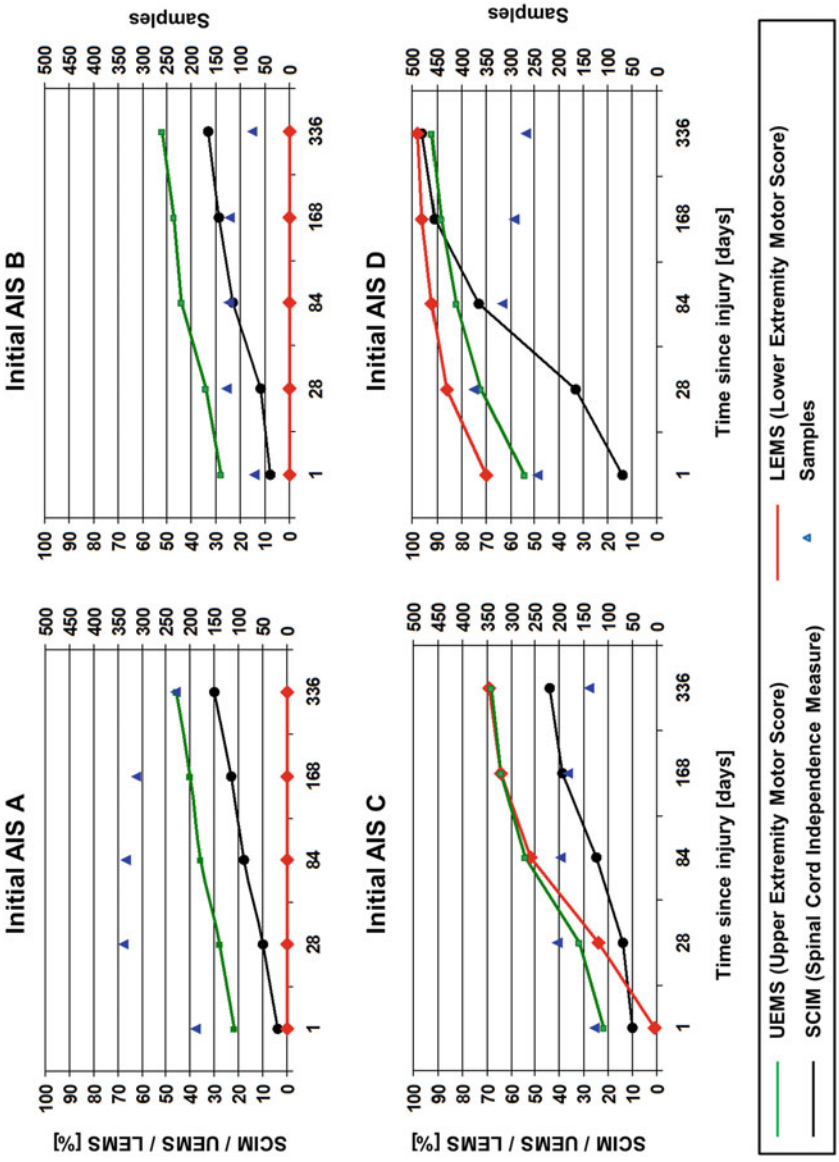

Fig. 1.6 Neurological and functional recovery profiles of individuals with tetraplegia (initial NLI of C1–C8) within the first year. The normalized median of UEMS, LEMS, and SCIM grouped by the initial AIS is shown. Data have been obtained within EMSCI. The number of patients (samples) contributing to each data point is given as triangles with the corresponding ordinate on the right side of each graph (with permission from (Rupp 2020))

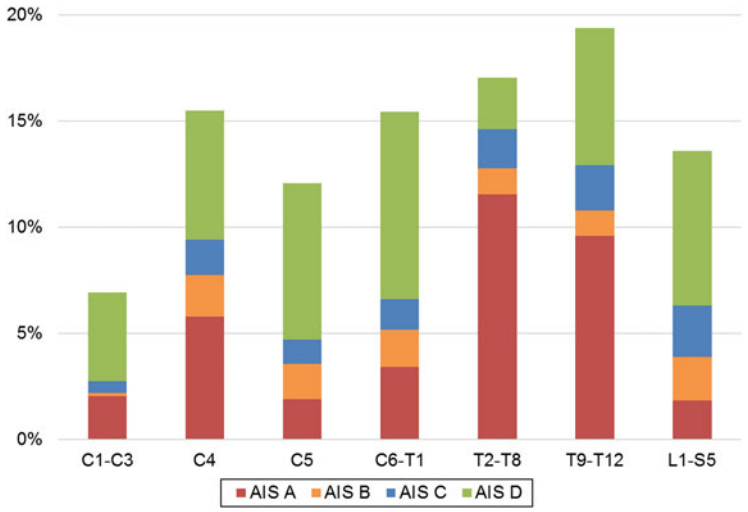

Fig. 1.7 Distribution of the AIS grouped by regions of NLIs of a cohort of patients ($N = 2.239$) with traumatic or ischemic SCI assessed at a late (328.2 ± 98.4 (standard deviation) days after injury) time point. The data have been collected within the European multicenter study about human spinal cord injury (EMSCI)

frequent NLIs in chronic patients with traumatic or ischemic SCI are C4 (15.5%) and C5 (12.1%). In the chronic stage, substantial motor functions (AIS D) are present in 53% of all patients with tetraplegia (Figs. 1.4 and 1.7).

1.3 Clinical Consequences of an Acute SCI

Because the spinal cord innervates multiple organ systems, its injury impacts almost all autonomous, sensory, and motor functions resulting in a variety of complications. The first weeks after the injury patients are in the phase of the spinal shock with very little motor functions below the level of lesion. The spinal shock typically ends within the first 2-4 weeks after onset of SCI with reappearing tendon reflexes and muscle tone. After spinal shock spasms, i.e., involuntary muscle contractions that cannot be suppressed or controlled by the patient, clinical signs of spasticity slowly show up (Hiersemenzel et al. 2000). Spasticity may result in abnormal joint positions and later in joint contractures in particular if LMNs damage of antagonistic muscles is present. An example is a fixed elbow joint in fully flexed position after a C4 lesion with a hyperactive biceps and a completely paralyzed triceps muscle.

A variety of autonomic dysfunctions develop after an SCI, among them are the paralysis of the bladder and the bowel and orthostatic hypotension due to venous pooling of the blood in the paralyzed legs. In individuals with lesions above the level of the sixth thoracic spinal cord segment additional cardiovascular complications

such as low systolic and diastolic blood pressure, bradycardia, and autonomic dysreflexia are present. Autonomic dysreflexia is a potential life-threatening complication with an uncontrolled increase of blood pressure in response to either noxious or non-noxious stimuli, resulting in sympathetic stimulation and hyperactivity. The most common causes include bladder or bowel over-distension from urinary retention and fecal compaction, respectively. After spinal shock ends, spastic activity may develop not only in skeletal muscles, but also in the detrusor muscle restricting the bladder capacity to store urine and resulting in incontinence. In the long run, complication may arise due to pathologically high detrusor pressures, which—if untreated—may result in renal complications.

Pain is a major problem after SCI and most of the patients report to have pain. In the acute and subacute phase after SCI it is mainly nociceptive pain due to trauma or spams (Finnerup 2013). Usually within the first year after SCI, neuropathic pain develops in about 40–50% of the patients and tends to become chronic (Siddall et al. 2003). Higher age and preserved sensory and motor functions below the NLI are the most important risk factors for developing neuropathic pain (Warner et al. 2019). Chronic pain has a negative impact on quality of life as it is often associated with depressive symptoms (Müller et al. 2017).

For the treatment of autonomic complications and pain, patients with SCI receive multiple medications in particular in the first months after injury. These medications are in many cases associated with negative clinical outcomes and have a detrimental influence on attention, memory, and concentration contributing to general tiredness and low compliance with rehabilitative measures, especially in patients with higher level and more severe injuries (Cadel et al. 2019).

In cases of severe SCI with loss of sensation and severe paralysis and the associated muscular atrophy, pressure injuries (older terms “pressure ulcers” or “pressure sores”) are among the most frequent complications (incidence 25–66%) after an SCI (Fuhrer et al. 1993). The most common sites of occurrence are the ischium (28%), the sacrum (17–27%), the trochanter (12–19%), and the heel (9–18%). In all these susceptible areas, pressure injuries occur when external pressure exceeds capillary pressure, and ischemia of tissue leads to damage of the skin and the underlying tissue. The incidence of pressure ulcers in the SCI population is 25–66% with patients with higher-level spinal cord injuries being more susceptible than those with lower-level lesions.

In cervical lesions respiratory problems are present due to impaired voluntary control of the diaphragm. This applies in particular to patients in the very acute phase, during which 6.5% of all patients are respirator dependent in the first weeks after the injury for at least some hours a day (NSCISC 2018). In complete lesions above the level of C3, permanent artificial ventilation is needed.

The most obvious impairment after SCI is the loss of motor functions resulting in limited mobility and, in particular in case of tetraplegia, in limited autonomy and the dependency on caregivers. In most patients, these restrictions lead to difficulties in social participation, and returning or gaining employment after SCI is a fundamentally difficult experience. Factors that predicted problems with social participation include a younger age, having more severe secondary medical complications like

bladder and bowel dysfunctions, a higher functional independence level, a lower cognitive capacity, perceiving one has less control (self-efficacy) over one's life and environment, and having lower perceived social support (Craig et al. 2015; Hilton et al. 2018).

1.4 Consequences of an SCI on Brain Structures and Function

While the consequences of an SCI on sensorimotor functions with spastic (intact LMNs) or flaccid (damaged LMNs) paralysis of muscles are well-known, the knowledge about the impact of the spinal cord injury leading to a cortical deefferentation and deafferentation on brain structures and functions is still limited (Tidoni et al. 2015). However, this knowledge is of utmost importance in order to identify factors that might prevent a successful use of a brain–computer interface (BCI).

1.4.1 Anatomical and Neurophysiological Changes of the Brain at Rest

Several studies investigated the anatomical and neurophysiological changes of the brain occurring after SCI: Wrigley et al. (2009) found a significant reduction of gray matter volume in the left primary motor cortex (M1), medial prefrontal and the anterior cingulate cortices in people with complete thoracic SCI. Two other studies confirmed these findings: The results of a structural MRI study using voxel-based morphometry (VBM) show that already after 4–12 weeks after a complete or incomplete SCI the motor and sensory cortices present gray matter atrophy affecting M1, the primary sensory cortex (S1), the supplementary motor area (SMA), and the thalamus (Hou et al. 2014). In particular, a positive correlation was found between the decreased M1 gray matter volume and the total summary ISNCSCI motor score as a measure of the overall neurological impairment. In the second study, a progressive volume reduction of the gray matter volume within M1 over the first year after acute SCI was found by applying magentization transfer maps which are sensitive to myelin-changes (Freund et al. 2013). It has been additionally found that a better neurological recovery over the first year after the injury is associated not only with increased cortical activation (Sabre et al. 2013) at the initial period after SCI, but also with a larger corticospinal tract integrity (Freund et al. 2013). However, it must be emphasized that the causal relationship between these changes is largely unknown, i.e. it is not known, whether they are the origin or the consequence of the neurological recovery.

In EEG studies, a reduction of brain wave activity in the range of 8–13 Hz (Tran et al. 2004) and an increase in the beta range (Herbert et al. 2007) during rest were found. This finding suggests that people with SCI have a generally increased neural processing, which might be interpreted as ongoing reorganization of brain structures after SCI.

While the above studies report on significant anatomical and neurophysiological changes of the brain after SCI, not all studies come to the same conclusion: Using both manual and automatic VBM procedures, no morphometric differences in gray and white matter volume within M1 were found between groups of non-disabled subjects and individuals with complete and incomplete cervical SCI (Crawley et al. 2004). A follow-up, more detailed analysis of the data obtained in this study revealed a reduction of the gray matter volume within S1 and parietal cortices (Jurkiewicz et al. 2006). The differences in the results of the two analyses show impressively the high dependency of the results on the methods used for image analysis, threshold definitions, and statistical approaches.

In general, discrepancies between the results of analyses of subpopulations within a single study and between different studies might be attributed to the high heterogeneity of the study participants investigated (Tidoni et al. 2015). This does not only refer to differences in motor, but also in sensory impairments. Even in clinically complete patients (AIS A with no preserved functions below the NLI), there still might be intact, but silent fibers present (McKay et al. 2004) with an impact on the integrity of brain structures.

Overall, the current evidence from the literature indicates that at least in a subpopulation of individuals with SCI, anatomical changes and functional reorganization take place immediately after the injury, but also at later stages, within brain and spinal regions (Huber et al. 2015).

It is widely accepted that chronic pain as one of the most frequent SCI-associated complications that is associated with cortical and subcortical reorganization (Pascoal-Faria et al. 2015). Tissue volumes of individuals with SCI with and without chronic, neuropathic pain were compared using structural MRI and structural changes in the primary somatosensory cortex, corticospinal tract and visual cortex were found (Mole et al. 2014). These changes were more pronounced in people with below-lesion level chronic pain and the amount of structural brain reorganization correlated with the reported intensity of the pain (Wrigley et al. 2009).

1.4.2 Functional Brain Reorganization

The first evidence on altered action-related cortical activity in individuals with SCI originates from EEG studies. A study involving subjects with complete paraplegia (time since injury <6 months) attempting a toe movement found that the readiness potentials reflecting motor cortical activity during motor programming are similar to non-disabled people who actually executed the movement (Castro et al. 2007). Interestingly, movement-related cortical potentials (MRCPs) reflecting brain activity

associated with movement preparation and execution showed a higher degree of similarity between the subjects with complete paraplegia and a group of non-disabled subjects who prepared, but did not perform the toe movements. This indicates that the parts of the motor cortex responsible for planning and execution of movements seem to be unaltered even in individuals with severe SCI, and that the observed changes in MRCPs might be more related to the impairments of tactile and proprioceptive sensations. This hypothesis is supported by a study also involving participants with chronic paraplegia, which found that the motor areas show an unaltered temporal and spatial pattern during preparation and execution of movements of the unimpaired hand (Mattia et al. 2006). A more recent investigation involving people with tetraplegia confirmed these findings (Ofner et al. 2019).

Contradictorily, other high-resolution EEG studies indicate that the origin of MRCPs elicited by executed feet or finger movements (and also attempted movements) is shifted toward the posterior direction at least in a subgroup of individuals with SCI compared to non-disabled subjects (Green et al. 1999).

Like in the EEG studies, the results from studies using functional neuroanatomical imaging techniques are also not fully conclusive. In a study using positron emission tomography (PET) an increased activation of cortical (contralateral sensorimotor cortex and ipsilateral superior parietal lobe) and subcortical areas (contralateral thalamus and bilateral cerebellum) having an important role in sensorimotor integration was shown in individuals with paraplegia during hand movements compared to non-disabled subjects (Curt et al. 2002b). Subjects with tetraplegia showed only an activation of the SMA during the same motor task. An expansion of the sensorimotor "hand area" toward the "leg area" was observed in both individuals with paraplegia and tetraplegia compared to controls without an SCI during execution of hand movements operating a joystick (Bruehlmeier et al. 1998). In a study using functional magnetic resonance imaging (fMRI) for investigation of individuals with tetraplegia, a shift of the area responsible for tongue movements in the direction of the deafferented area responsible for arm movements was reported, but no increase in activation volume was found (Mikulis et al. 2002). Additionally, it was found that the degree of this posterior shift was correlated with UEMS and NLI indicating a causal relationship between the cortical reorganization and the SCI. Following the same line, another fMRI study found that individuals with a complete paraplegia show a displacement of the areas responsible for elbow movements in the precentral gyrus toward the direction of the deafferented cortical thoracic representation (Lotze et al. 2006).

In contrast to these results, other fMRI studies show only minor reorganization of the sensorimotor brain areas after SCI: It was shown in individuals with complete paraplegia that the upper limb and tongue representations in M1 were somatotopically preserved without any shift of activation toward the deefferented and deafferented M1 foot area (Curt et al. 2002a). However, individuals with SCI showed an increased volume in M1 activation compared to non-disabled controls during finger movements. Increased activation was also found in non-primary motor and parietal areas, as well as in the cerebellum during upper extremity movements, whereas no changes were detected during tongue movements. These results indicate

that the cortical activation pattern during movements of the non-impaired upper limb is altered in individuals with paraplegia, though without any topographic reorganization in M1. Other fMRI studies confirmed the absence of a topographic reorganization of M1 and of non-primary sensorimotor cortical areas in individuals with cervical SCI during attempted movements of paralyzed limbs (Shoham et al. 2001). Interestingly, a single-case fMRI study with an individual with tetraplegia (NLI C4, AIS A) showed that all activation centers (M1, SMA, and cerebellum) remained unaltered compared to a group of non-disabled controls after imagined hand and foot movements (Enzinger et al. 2008). This individual, however, was special in that he was trained to use a brain–computer interface (Müller-Putz et al. 2006), for which he regularly performed imaginations (or attempts) of hand and feet movement over years.

Most of the studies cited so far represent cross-sectional studies not intended to investigate the changes in brain organization after the spinal lesion. In an fMRI study, six individuals with cervical SCI were followed over the first year after injury (Jurkiewicz et al. 2007). In the subacute period after SCI, during movements of impaired limbs, little task-related activation within M1 was present, whereas a higher activation in associated cortical sensorimotor areas was seen than in non-disabled controls. During motor recovery, a progressive enlargement of the volume of movement-related M1 activation and decreased activation in associated cortical sensorimotor areas were detected. When the movement could be performed almost or fully normal, the overall pattern of cortical activation was similar to the one of non-disabled controls. These results indicate that SCI-induced brain reorganization reverses as functions recover.

In summary, the conclusions from literature on SCI-induced changes of the topographic organization of primary sensorimotor brain areas are incongruent and sometimes conflicting. While some studies report on changes in the M1 topography of activation of areas responsible for movements of impaired as well as non-impaired body parts, others do not confirm these findings. As a bottom line, most of the studies agree that extended activity in the sensorimotor network is present in individuals with SCI reflecting a severe impairment of sensorimotor integration.

It can only be speculated on the reasons for the large differences in study results. One reason might be differences in data analysis techniques. Additionally, only a small number of participants are often included in the studies with the risk of a selection bias. The large heterogeneity of the SCI population with respect to time after injury, lesion level and severity, and other factors such as the presence of pain most probably contributes to the differing results (Tidoni et al. 2015). The impact of pain as one of the most frequent SCI-associated complications on structural and functional brain anatomy has been investigated quite intensively. It has been shown that areas activated during motor imagery tasks are connected to areas involved in pain and reward processing (Gustin et al. 2010a, 2010b). This suggests that chronic pain is associated with both cortical and subcortical changes in brain regions related to pain perception and pain modulation (Yoon et al. 2013). Chronic pain appears to

alter topographic brain organization and EEG signals in individuals with SCI. More specifically, people with SCI suffering from neuropathic pain show a greater slowing of EEG activity relative to those without or non-disabled subjects (Boord et al. 2008). Similarly, individuals with pain after SCI show a reduced peak frequency in the range of 6–12 Hz relative to individuals without pain (Wydenkeller et al. 2009). Interestingly, closed-eye patients with SCI and pain show reduced brain activity in the theta-alpha frequency band compared to non-disabled controls and patients with SCI, but without pain (Pascoal-Faria et al. 2015). Another study confirmed that people with paraplegia and chronic neuropathic pain show increased event-related desynchronization in the theta, alpha, and beta bands (16–24 Hz) during imagination of movements of both non-painful (arms) and painful limbs (legs). Contrarily, people with paraplegia with no pain showed a much reduced power in relaxed state and reduced event-related desynchronization during imagination of movements (Vuckovic et al. 2014). In a follow-up study, frequency-specific EEG signatures were identified that may be useful for prediction and monitoring of the development of neuropathic pain in the SCI population (Vuckovic et al. 2018).

Since individuals with SCI develop different degrees of spasticity (Sköld et al. 1999) and have a high risk for chronic pain (Störmer et al. 1997), they are often under medication. This medication includes spasmolytic drugs, anticonvulsants, and pain medication including antidepressants. It has been shown that spasmolytic medications such as anticholinergics for treatment of an overactive detrusor muscle, in particular oxybutynin, and other medication for treatment of spasticity of skeletal muscles such as baclofen, an agonist to GABA-β receptors, affect CNS activity. Thus, a decrease in alpha, beta, and theta activity of EEG spectral power distribution (Pietzko et al. 1994; Todorova et al. 2001; Kay and Ebinger 2008; Badr et al. 1983) and an increase in delta activity (Seyfert and Straschill 1982) have been observed. Pregabalin is an anticonvulsant binding to a subunit of the voltage-gated calcium channels in CNS tissues and by this reducing calcium influx at nerve terminals to inhibit the release of excitatory neurotransmitters. Individuals with SCI and intake of pregabalin show increase in theta and delta activity (Graversen et al. 2012). Opioids produce analgesic effects on neurons by directly acting on receptors located on neuronal cell membranes (Feng et al. 2012). It has been shown in non-disabled subjects that the intake of opioids caused an increase in delta activity and decrease in theta and alpha activity (Graversen et al. 2015).

In a nutshell, chronic neuropathic pain after SCI has a substantial influence on cortical topographic organization and the frequency distribution of EEG signals. In addition to the pain-associated changes, anticonvulsants and spasmolytic medications contribute to the altered EEG signatures. The increases in theta as well as delta activity caused by these medications are known to increase the level of mental fatigue (Borghini et al. 2014). This might result in a lower adherence and compliance to rehabilitation procedures. It is therefore important not only in research, but also in clinical practice to precisely document the presence of pain, its perceived intensity, and the type and dose of CNS activity altering medications.

1.5 Motor Rehabilitation After SCI

The overall goal of all rehabilitative interventions in patients with SCI is to achieve the highest level of autonomy as possible. For obvious reasons, in individuals with impairments of upper extremity functions the main focus of rehabilitation is on improving manipulation skills to perform typical everyday self-care activities such as dressing or grooming and to allow independent eating or computer operation. In individuals with impairments of lower extremity functions achieving mobility in indoor and outdoor environments has a high priority.

In this context, rehabilitation of motor functions is based on two fundamental therapeutic principles, namely recovery or restoration and compensation/substitution. The term *recovery* of motor functions related to the restoration of elemental motor patterns which were present prior to injury by training (Levin et al. 2009). *Compensation* is defined as the appearance or installation of new motor patterns resulting from the adaptation of remaining motor elements. *Substitution* as a special form of compensation describes an approach to replace, take over, or substitute functions by the application of assistive technology.

Compensatory rehabilitation interventions are mainly applied in individuals with a low chance for neurological recovery. This includes people with little or no spared sensorimotor functions below the level of injury and people with chronic injuries (>9–12 months after injury). Therapeutic interventions emphasizing on compensation include:

1. Surgical procedures such as muscle and tendon transfers, tenodeses and arthrodeses, and/or nerve transfers for re-gaining a meaningful grasp function (Hentz and Leclercq 2002; van Zyl et al. 2019; Friden and Lieber 2019). These procedures are preferably applied in patients with some level of preserved voluntary control of upper extremity muscles.
2. Strengthening of voluntarily activated muscles, emphasizing on muscles required to perform compensatory movements, e.g. shoulder muscles.
3. Training of compensatory movement strategies, e.g. compensation of a limited ability for plantar dorsiflexion (drop foot) by increased hip flexion or trunk movements or compensation of missing active elbow extension by shoulder and trunk movements.
4. Use of adaptive passive equipment like knee-ankle-foot orthoses, reciprocating gait orthosis, or wrist splints.
5. Neuroprostheses based on functional electrical stimulation (FES).
6. Providing assistive devices to support activities of daily living and participation, e.g. environmental control systems, adapted electronic aids, special tools such as forks, wheelchairs, or walking aids.

A restorative rehabilitative approach represents the other end of the continuum of motor rehabilitation measures with the aim to reinstall a normal movement pattern to the highest possible degree. During restorative trainings, compensatory movements are avoided or corrected by therapists. Over the last three decades, gain in scientific

knowledge about the neurobiology of the central nervous system (CNS) and its capacity for use-dependent neuroplasticity and reorganization has resulted in a widespread acceptance and intense application of task-specific therapies. Task-specific restorative therapies are based on principles of motor learning and are preferably used in individuals with a high potential for neurological recovery, i.e., people in the subacute phase (<3–6 months) after injury with an incomplete SCI. Therapeutic interventions emphasizing on restoration include:

1. Intensive, task-specific training such as body weight-supported locomotor training on a treadmill and/or overground, or training of activities of daily living with arm weight support. Assistance in task-specific training can be either manual or applied by a robotic device.
2. Conventional physiotherapy or occupational therapy interventions, e.g. practice of transfers from bed to wheelchair, wheelchair to toilet, practice of static and dynamic standing balance, stepping, and walking or practice of upper extremity functions in everyday tasks.
3. Strengthening of muscles emphasizing on physiological movement patterns.
4. FES therapy for muscle strengthening and functional training emphasizing on normal movement patterns.

At this point, there is no clinical algorithm available regarding the extent and timing of restorative therapies tailored to the neurological status of individuals with spared sensorimotor function.

As a general rule, the more acute an injury is and the more functions are preserved, the more the focus is on restorative therapies with the aim of translating neurological recovery into functional improvements (Fig. 1.8).

In contrast, the less sensorimotor functions are preserved and the more chronic the SCI is, the more compensatory interventions are applied to maximize functional ability. Due to the high variations of neurological recovery and priorities between individuals, it is often very hard for clinicians to decide which rehabilitation approach to follow. It is therefore of utmost importance to often track changes of neurological functions in each individual to be able to closely adapt the contents of the therapy. At the point in time, when neurological recovery plateaus and the time of admission into the home environment comes close, a compensatory approach or substitution by technical aids should be applied to achieve the highest level of functional ability as a prerequisite for leading an independent life.

It is important to emphasize that the therapeutic strategies of compensation and restoration are not mutually exclusive. Instead, functional improvements are often dependent upon compensation and compensatory or substitutive approaches might lead to a better outcome of task-oriented, restorative trainings, e.g. a hand stabilization orthosis or a grasp neuroprostheses may allow for retraining shoulder and elbow movements.

Because there are no general rules existing on when to use compensatory or restorative approaches, it is very important to agree upon realistic rehabilitative goals taking the patients' individual priorities and their social environment into account. This is mandatory to match expectations and to select the appropriate therapy methods to achieve them.

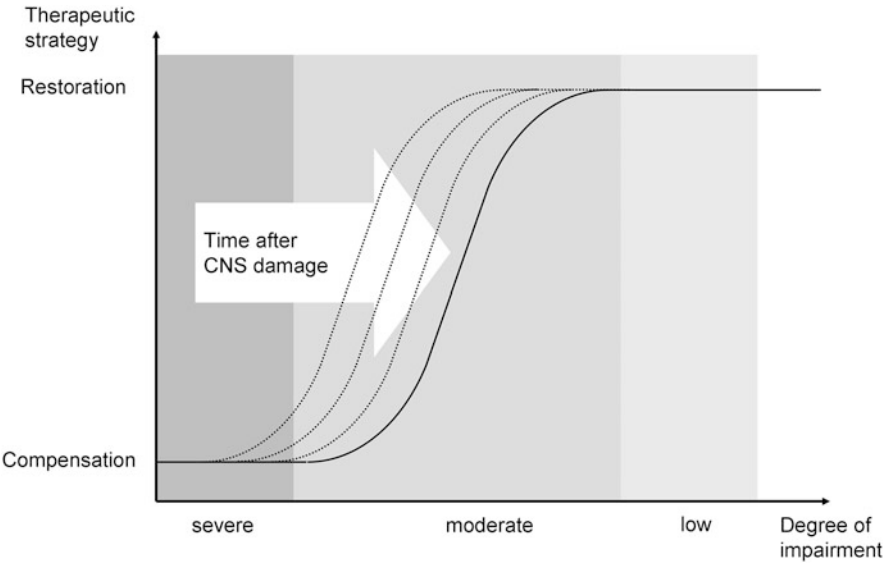

Fig. 1.8 Dependency between the therapeutic strategy, the severity of and time after SCI

Over the last two decades, the use of technology in the rehabilitation of motor impairments has constantly increased both in restorative therapies based on motor learning approaches and for compensation or substitution of permanently restricted or lost motor functions (Dietz and Fouad 2014; Prochazka 2015; Rupp et al. 2015b; Hensel et al. 2017; Nowak et al. 2017). Examples are body weight-supported treadmill training with or without the help of motorized gait orthoses that help to achieve a high number of repetitions—one of the key principles of motor learning—and grasp neuroprostheses on the basis of FES to compensate for the loss of upper extremity function (Rupp et al. 2015a). To allow individuals with very high SCI to participate in society, assistive devices are used enabling environmental control and computer, internet, and social media access. Examples for established human–machine interface to control assistive devices are—depending on the residual capabilities of the user—joysticks operated by the hand or the chin, suck-and-puff control, voice control or eye-tracking systems. In recent times, the technology of brain–computer interfaces has reached a state where they may serve as an alternative or adjunct user interface (see Chaps. 9, 10, and 13).

1.6 End User Needs and Priorities

For tailoring the rehabilitation process, for selection of therapies and assistive devices, and for defining future research and translational directions, it is important to put the needs and priorities of people with SCI in the center of all efforts.

In this respect, a milestone study conducted in 2004 found that the highest priority among individuals with tetraplegia is the improvement of hand function (Anderson 2004). The reason for this is somehow obvious, because a bilateral loss of grasp function negatively affects the individuals' ability to live independently and fully participate in society. Other studies confirmed these results (Collinger et al. 2013; Snoek et al. 2004). In people with paraplegia, improvement of autonomous functions such as bladder and bowel and sexual functions has highest priority. Compared to the importance of improvements of bladder and bowel functions, the need for better walking function is less clear and was rated incongruent (Anderson 2004; Collinger et al. 2013). This incongruence of different surveys shows that it is very hard to generalize the priorities of people with SCI. Even in a supposed homogeneous group of people with tetraplegia, the personal needs in respect of manipulation skills differ substantially (Kilgore et al. 2001). The personal health status, age, access to personal care and assistive technology, support by relatives, and accessibility of the private and professional environment have among others a high impact on end user needs and priorities. This explains why some people with SCI perceive a high need to improve their quality of life in some domains, while others do not.

Over the past decade, the digital transformation of the general society does also affect the needs of individuals with severe motor impairments including people with high SCI. Technologies enabling environmental control and computer, internet, and social media access are nowadays of utmost importance for people including those with manipulation limitations (Zickler et al. 2009).

Assistive technology plays an important role in the life of people with SCI and aims to augment function and increase independence. Although all people with SCI use some kind of assistive devices, surveys reveal a huge information deficit of end users and their caregivers as well as health professionals about the possibilities and limitations of new technologies (Letourneau et al. 2020; Collinger et al. 2013). The provision of objective information and non-commercial interest driven knowledge about assistive technology helps to overcome the serious problem of technology abandonment. Studies show that almost one-third of all devices are completely rejected by end users with mobility aids being most frequently abandoned. The abandonment rates were highest during the first year and after 5 years of use (Phillips and Zhao 1993). Different design criteria are significantly related to the acceptance of new technology: Independent operation, high functionality and performance of the device, ease of use, non-invasiveness and easy device procurement (Collinger et al. 2013; Phillips and Zhao 1993; Zickler et al. 2009). In any case, consumers need to be involved at all stages of the development of new technologies to enhance consumer satisfaction. This ensures that the technology fits to the end user and that not end users have to be identified that match the technical possibilities of an assistive device.

In recent years, our understanding of the neurobiological basis of movement control and the miniaturization and availability of novel technologies resulted in emerging interventions for people with neurological impairments icnluding those with SCI. However, their implementation into mainstream clinical practice represents a huge challenge. A recent study examining the potential for clinical translation

of novel interventions came to the conclusion that with two thirds of the studies examining emerging technologies, the likelihood of successful clinical implementation was questionable (Musselman et al. 2018). As the interventions being studied may not align with the preferences of clinicians and priorities of end users, the appropriateness of these interventions for the current health care environment was questioned. Meaningfulness and economic evidence were also identified as gaps since few studies included measures reflecting the perceptions of the participants or economic factors, respectively. The authors conclude that the identified gaps will likely impede the clinical uptake of many of the interventions currently being studied. In this context, the use of the FAME (Feasibility, Appropriateness, Meaningfulness, Effectiveness, Economic Evidence) framework is recommended to be applied in studies as useful taxonomy to evaluate the strengths and gaps of novel neurorehabilitation methods and devices with respect to likelihood of clinical implementation (Jordan et al. 2018; Pearson et al. 2005). Future research may lessen these gaps through a staged approach to the consideration of the FAME elements as novel interventions and technologies are developed, evaluated, and implemented.

1.7 Conclusion

The rehabilitative aims of individuals with SCI basically depend on the severity and the time after injury. However, to tailor therapies to the individual needs and priorities of each person with SCI, the precise characterization of the neurological status of a person with SCI together with documentation of secondary factors impacting rehabilitation outcomes such as age, spasticity, autonomic dysfunctions, infections, or the presence of musculoskeletal and/or neuropathic pain is mandatory.

The gold standard for classification of the level and the severity of an SCI is the ISNCSCI assessment. However, providing only the AIS and the NLI is not sufficient and information on the sensory and motor levels of each side together with the UEMS and LEMS need to be given. In cases with missing sensory and/or motor function in the lowest sacral segments, the sensory and/or motor ZPPs should be specified for evaluation of the caudal extent of preserved voluntary functions. For evaluation of the presence of neuropathic pain the Spinal Cord Injury Pain Instrument (SCIPI) represents a simple and fast assessment which can be administered also by non-clinicians (Bryce et al. 2014). This is in particular important, because chronic neuropathic pain has been reported to be associated with substantial brain reorganization. A couple of other SCI-related medical factors are known to influence brain function and it is important to check for their presence (Rupp 2014). In particular, spasmolytic and pain medication have an influence on EEG parameter and evoked potentials and it is therefore important to document the dose of these type of drugs. By this, the partly controversial results from imaging and neurophysiological studies on the SCI-associated changes in brain functions might be explained in the future.

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Chapter 2
Functional Electrical Stimulation

Rüdiger Rupp

Abstract The activation of excitable biological tissues such as nerves and muscles by external electrical stimulation follows well-studied neurophysiological principles. Similar to the physiological condition, the nerve membrane is depolarized by the stimulus until the activation threshold is reached and action potentials are triggered for generation of muscle contractions. The introduction of charge-balanced stimulation pulses has made it possible to activate nerves and muscles over substantial periods of time without causing tissue necrosis and skin damage. This paved the way for the restoration of lost motor functions by neuroprostheses based on Functional Electrical Stimulation (FES). While noninvasive systems based on surface electrodes are the preferred choice for muscle training and restorative interventions, implanted electrodes are better suited for permanent use in neuroprosthetic applications.

An essential prerequisite for the successful use of a neuroprosthesis is a preserved neural innervation of muscles. The strength-duration curve allows for quantitative evaluation of denervation of muscle fibers. A profound knowledge of the neurophysiological principles underlying electrical stimulation of nerves and muscles is needed to correctly select and parameterize the device for stimulation of innervated and denervated muscles.

One of the main problems of FES is the increased fatigue of stimulated muscles. The propensity to early fatigue can be reduced by proper muscle training and the associated transformation of fast- into slow-fatiguing muscle fibers. However, fatigue represents an inherent problem of FES and cannot be completely avoided.

From a technological perspective, most devices for electrical stimulation are quite simple, with few predefined stimulation programs designed for dedicated applications. For complex FES applications, however, programmable stimulators with a customizable control interface are needed.

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Keywords Action potential · Strength-duration curve · Rheobase · Chronaxie · Innervated muscle · Denervated muscle · Fatigue · Electrodes · Electrical stimulation parameters · Electrical stimulation technology

2.1 Introduction

While electrical stimulation was used over 2000 years ago by the Egyptians who used certain fish emitting electrical impulses to treat pain, the basics mechanisms of the effects of external electrical currents on excitable biological tissues were long unknown. In 1745, it was the German physician Altus Kratzstein who first described that muscles could be activated by electrical currents. Later that century, it was the Italian physician and physicist Luigi Galvani (1737–1798), who investigated the effects of bioelectricity in animals. He discovered with his famous experiments on spinalized frogs that electric currents are responsible for the activation of skeletal muscles (Galvani 1791). While Galvani still drew the wrong conclusion that the electricity came from the frog itself and called it "animal electricity," it was Alessandro Volta (1745–1827) who was able to show that excitability in the nervous system occurs with "normal" electric current (Volta and Banks 1800).

However, it took another 150 years until Hodgkin and Huxley put the ion theory of nerve conduction on a quantitative basis (Hodgkin et al. 1952). With their experiments on giant nerve fibers of squid they could show that an electrical resting potential is present at the nerve cell membrane, which changes characteristically in the activated state before it returns to the resting state. This change is called action potential and its generation by external electrical current forms the basis for every application of neuromuscular electrical stimulation (NMES).

The aim of this chapter is to provide the background knowledge to understand the physiological principles of NMES and the technical parameter for its application in particular for stimulation of paralyzed muscles.

2.2 Physiological Background

The core of neuronal function originated from the property of neurons for rapid change of the electrical potential difference across their membrane. This excitability of the nervous system represents the basis for the transmission, processing, and exchange of information in the human body. The rapid, reversible change of the membrane voltage is called action potential or nervous impulse.

2.2.1 Action Potential

When the membrane voltage of a neuron in its resting state is increased above a threshold of approximately −70 mV (inside vs. outside), a physiological action potential is triggered. The term action potential describes a change of the membrane voltage starting at the resting potential of −70 mV followed by a rapid increase up to a peak around +30 mV, and a final return to resting potential. A unique feature of the action potential is that each time a stimulus, e.g., originating from dendrites or axons of other neurons, depolarizes the membrane voltage above this threshold, the generated voltage change has always the same shape and size (Fig. 2.1). This means that an additional increase of the stimulus intensity above the threshold voltage of approximately −55 mV does not results in a higher amplitude of the action potential. This phenomenon is referred to as the "all-or-nothing law," and indicates that there is no "in-between" action potential. The neuron either does not respond at all in case of sub-threshold stimuli or it will generate a complete action potential as a reaction to any supra-threshold stimulus.

The temporal course of the action potential can be divided into five phases (Fig. 2.1): (1) resting state, (2) depolarization to threshold, (3) overshoot, (4) peak, (5) repolarization, and (6) hyperpolarization. The characteristic voltage changes of the action potential are caused by the activation of dedicated voltage-gated ion channels, namely Na^+ and K^+ channels, by membrane depolarization to or beyond the threshold voltage. In fact, all of the characteristics of the action potential can be explained by knowledge about the molecular mechanisms of these voltage-gated ion channels

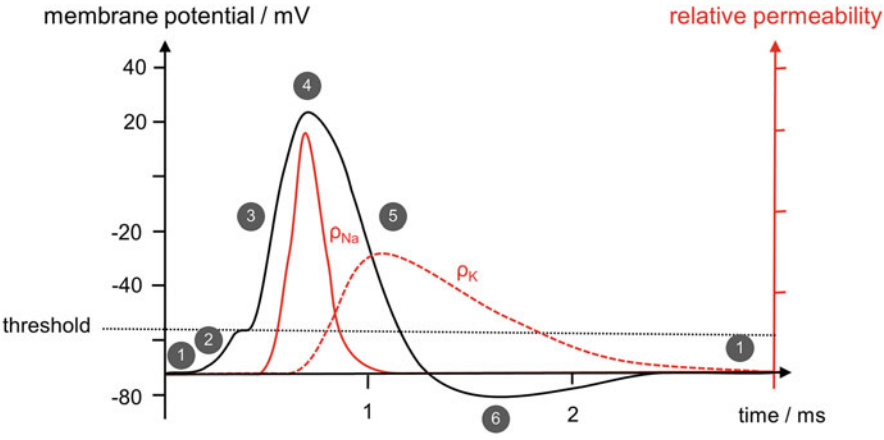

Fig. 2.1 The course of an action potential (solid black curve) with the changes in permeability of voltage-gated Na^+ (ρNa, solid red curve) and K^+ (ρK, dotted red curve) ion channels. The relative permeabilities for Na^+ and K^+ are not drawn to scale. At the peak of the action potential, ρNa is ~12 times larger than ρK. The numbers in dots indicate distinct phases of the action potential: (1) resting state, (2) depolarization to threshold, (3) overshoot, (4) peak, (5) repolarization, (6) hyperpolarization

together with the electrochemical gradients of Na^+ and K^+ ions across the nerve membrane. Initially, the voltage-gated Na^+ channels are activated by depolarization of the membrane voltage above the threshold of −55 mV (Phase 2 in Fig. 2.1). The activated Na^+ channels allow Na^+ ions to inflow into the cell, which, in turn, results in a further increase of the membrane voltage. The massive intracellular entry of Na^+ ions leads to rapid (<1 ms) depolarization of the neural membrane. Because rapid opening of Na^+ ion channels leads to a fast rise in membrane permeability to Na^+, the membrane potential goes from negative to positive and approaches the equilibrium potential for Na^+ of about +30 mV. This cycle is called the Hodgkin cycle and is responsible for the overshoot phase (Phase 3 in Fig. 2.1) of the action potential.

Voltage-gated Na^+ channels in the neuronal membrane can enter one of three different states: closed state, open state, and inactive state. The sequence of the Na+ channel states follows a well-defined pattern, starting with the resting state, in which Na + ion channels are all closed (non-conducting; $\rho_{Na} = 0$). When the membrane is depolarized by a stimulus to the threshold voltage, Na^+ ion channels open (channels conduct ions; $\rho_{Na} > 0$). After activation, the Na^+ ion channels spontaneously enter an inactive state (non-conducting state; $\rho_{Na} = 0$) before returning to the closed state. Channels do not directly change their state from open to closed without being inactive first, and channels in an inactive condition cannot open without closing first. The period of inactivity is a time- and voltage-dependent process and takes about 3–5 ms. Even though the Na^+ channel are non-conducting in either the closed or inactive state, the two states represent distinct and separate conditions of the channel.

When the action potential has reached its maximum voltage, the Na^+ channels begin spontaneously to very rapidly enter the inactivate state (Phase 4 in Fig. 2.1). Once the membrane voltage reaches its peak, Na^+ channels enter the inactivate state, and as a result ρ_{Na} falls rapidly and approaches its resting value. At this time, however, because of the delayed response of the voltage-gated K^+ channels to the initial membrane depolarization, ρ_K is still increasing. Now, much more K^+ ions are moving out of the cell than Na^+ ions are moving into it. Movement of K^+ out of the cell results in a rapid repolarization of the membrane voltage back to the resting value (Phase 5 in Fig. 2.1). However, ρ_K stays at an increased level for some time even after the membrane voltage has reached the resting value. Therefore, continued movement of K^+ out of the cell causes a membrane hyperpolarization (i.e., more negative than the membrane potential at rest). This phase is commonly referred to as hyperpolarization (Phase 6 in Fig. 2.1). Finally, ρ_K returns to its resting value, and at this time the membrane potential also returns to its resting value before activation of about −70 mV. It is important to mention that in contrast to Na^+ channels, K^+ channels do not enter an inactive state. They close simply because the membrane potential becomes more negative than the threshold potential (the potential at which Na^+ and K^+ channels become activated). Thus, the repolarization and hyperpolarization that is caused by outflow of K^+ ions through the voltage-gated K^+ channels causes a self-closing of these K^+ channels.

2.2.2 Refractory Periods

As mentioned in the last section, opening of the Na^+ channels spontaneously leads to their inactivation. At the maximum of the action potential, all Na^+ channels become inactivated. When Na^+ channels become inactivated, they cannot immediately open again. Recovery from inactivation is a time- and voltage-dependent process. It takes about 3–4 ms for all Na^+ channels to leave the inactivation state before being ready for activation (opening) again. The time from initiation of the action potential to immediately after the peak is referred to as the absolute refractory period (ARP). This is the time during which another stimulus given to the neuron—no matter how strong—will not have an effect in respect to generating another action potential. The reason for the inability to generate a second action potential during this time is the fact that Na^+ channels are in an inactive state.

After the ARP, Na^+ channels start to leave the inactive state spontaneously and if stimuli are given to the neuron, it may respond again with action potentials. However, during this time, the stimuli must be much stronger than was needed when the neuron was at rest. This situation will continue until all Na^+ channels have left the inactive state. The period during which a stronger than normal stimulus may lead to an action potential is called relative refractory period (RRP). During the RRP, since ρ_K remains higher than its resting value, continued K^+ outflow would tend to oppose any depolarization caused by opening of Na^+ channels that have recovered from inactivation.

Considering the refractory periods, it can be seen that the neuron is not excitable at all during the ARP, however, neuronal excitability recovers in a time-dependent (and also voltage-dependent) manner. As mentioned above, the period immediately following the ARP until neuronal excitability is similar to that for a resting neuron is the RRP. The neuron will only react to a slightly above threshold stimulus when the neuron is back to its resting state, meaning the neuron will only respond when the RRP is over. However, during the RRP, the neuron can be excited if a stimulus stronger than normal is applied. The strength of the stimulus needed to generate an action potential during the RRP is very high immediately after the end of the ARR, but decreases throughout the RRP until it reaches the at-rest threshold at the end of the RRP.

In summary, inactivation of Na^+ channels is solely responsible for the ARP. Na^+ channel inactivation as well as a ρ_K value higher than at rest are responsible for the RRP.

2.2.3 Information Transfer in the Nervous System

As already stated above, the generation of action potential follows an all-or-nothing law, meaning that every time the neural membrane is depolarized by a stimulus above the threshold, the resulting voltage change is always the same. If the stimulus

strength is further increased, the amplitude of the action potential will not get higher. If the size and shape of the action potential is always the same and independent of the intensity of the stimulus, the nervous system cannot code the stimulus intensity in an amplitude-modulated manner. Thus, another principle of coding of the intensity information needs to be used, which is frequency coding. This means that a neuronal cell reacts to a stronger stimulus by generating action potentials more rapidly. The maximum repetition rate (frequency) of action potentials is determined by the ARP. This maximum action potential frequency, in turn, has important physiological implications on how the nervous system can respond to high-frequency stimuli, and also for the ability of the nervous system to transmit high-frequency signals to effector organs such as muscles.

Because the ARP lasts at least 1–2 ms, the maximum repetition rate of action potentials is at maximum 500–1000 per second. This upper limit, however, is only achieved if a stimulus with is very large intensity is applied in order to overcome the RRP. Thus, the maximum frequency of action potentials is ultimately limited by the duration of the ARP. On the other hand, if the applied stimulus is only large enough to increase the voltage of the resting neuron above threshold, the maximum frequency of action potentials will now be determined by the total duration of the neuron refractory period (i.e., sum of the ARP and RRP). In a typical neuron, this is approximately 5 ms and thus, the maximum frequency of action potentials under normal conditions is around 200 Hz.

2.3 Artificial Stimulation of Electrically Excitable Tissue

In the physiological condition an action potential is triggered by temporal and spatial summation of electrical stimuli on postsynaptic membranes. However, it is also possible to depolarize the membrane voltage of a nerve at a certain location by external electrical currents above threshold so that a physiological action potential originates from there.

2.3.1 Physiological Foundations of Electrical Stimulation

Electrical stimulation of electrically excitable tissue is applied with the aim of changing the membrane potential of a nerve by an electrical field in such a way that the threshold for eliciting an action potential is reached. For this, an electrical field is applied to the tissue via electrodes (Fig. 2.2).

While in technical systems, electrical currents are based on free electrons, these are not present in biological tissues. Instead, positively charged ions such as Na^+ or K^+ or negatively charged ions such as large proteins or Cl^- ions are present and are the carriers of electrical current in biological tissues (Fig. 2.2a). When a voltage is applied to a biological tissue via electrodes, e.g., in case of noninvasive electrodes to

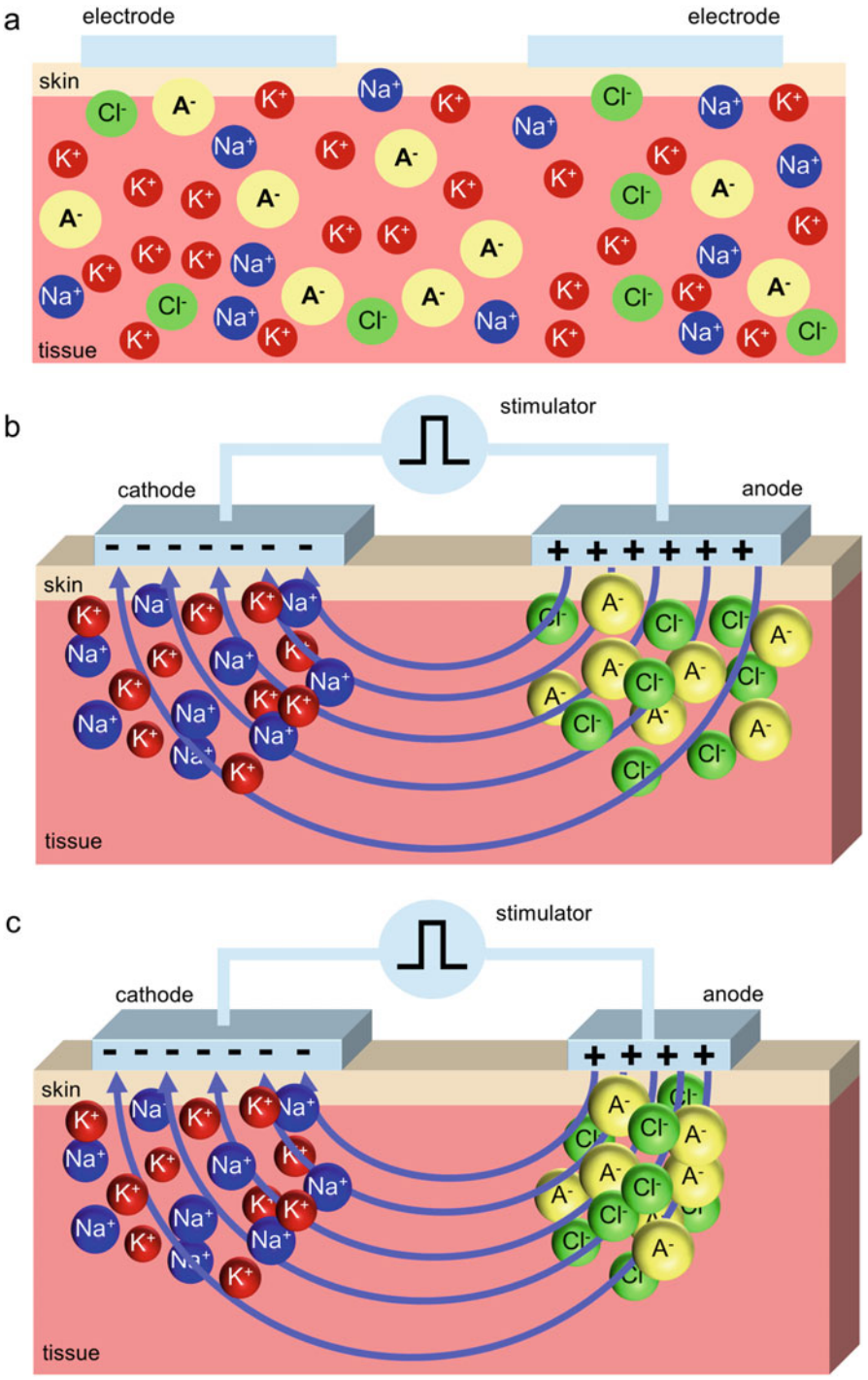

Fig. 2.2 Basic principle of external activation of excitable tissue. (**a**) Biological tissue contains negatively and positively charged ions, (**b**) An electrical field applied by surface electrodes causes

the skin, an electric field is generated between them causing electrically charged ions to move. While the negatively charged ions move to the positive electrode (anode), the positively charged ions migrate to the negative electrode (cathode) (Fig. 2.2b). The extraction of positively charged ions from the tissue to the area under the cathodic electrode result in an accumulation of negative ions at the outside of the nerve membrane leading to a depolarization of the voltage at the nerve membrane towards the positive direction (potential from inner to outer area of the nerve membrane).

When the field is strong enough so that a sufficient number of ions are collected, the threshold for triggering a physiological action potential is reached. Because the depolarization happens only under the cathodic electrode, it is the cathode under which an action potential is typically elicited. Basically, the injected charge which corresponds to the number of moved ions represents the relevant stimulation parameter. However, this is a rather simplistic view because also the area of charge injection plays an important role: When the size of the electrode becomes smaller, the electrical field is condensed and thus, the number of moving ions in the volume beneath the electrode increases (Fig. 2.2c). This results in a higher voltage shift, and therefore in a higher probability for depolarization of the nerve membrane. This means, that in biological tissue the parameter determining the final stimulation success is the charge density. In a two-electrode setup, the smaller electrode is called different electrode and the large indifferent electrode. The eliciting of an action potential normally happens under the different electrode due to the concentrated field and the larger shift of the membrane voltage. This effect can be used for selective stimulation of muscles by placing the small different electrode—no matter if cathode or anode—near the motor point of a muscle and the larger indifferent electrode at a body location with no excitable tissues, e.g., the muscle tendon area near joints. The motor point has been defined as the point where the motor nerve enters the muscle and represents the point with the lowest stimulation threshold for selective stimulation of this muscle. Some textbooks include maps showing the motor points of upper and lower extremity muscles (Kendall et al. 1993). While these maps provide some guidance during the initial placement of electrodes it is important to know that these maps were determined in a few non-disabled subjects with similar anatomical dimensions. In clinical practise, there are high interindividual variations of the locations of motor points and this does particularly apply to people with paralysis, where disuse muscle atrophy is present, and perfusion and composition (fat content) of skin and muscles are substantially different from non-disabled individuals. These changes lead to differences in conductivity of the tissues. In general, body tissue types differ in their specific conductivity (Table 2.1). Blood has a high conductivity and therefore, well-perfused tissues such as muscles or blood vessels are preferred current conductors. Fat, bone, or skin have a relatively low conductivity. This means

Fig. 2.2 (continued) the ions to move; negative ions move to the positive pole (anode), positive ions move to the negative pole (cathode), (**c**) The concentration of moving ions is higher at the electrode with the smaller size (different electrode) compared to the electrode with the larger area (indifferent electrode)

Table 2.1 Overview of the specific conductivity of different body tissues

Tissue	Specific conductivity in mS/cm
Non-flowing blood	6.6
Flowing blood	5.8–6.1
Brain tissue	2.5
Liver	3.3
Heart muscle	1.5–3.8
Skeletal muscle	0.8–6
Fat	0.23
Bone	0.06–0.2
Skin	0.0003–0.1

that in people with a substantial layer of subcutaneous fat or very dry skin, high charge densities are necessary to elicit an action potential.

On the other hand, if blood vessels are in direct vicinity of a motor nerve, action potentials are very easily elicited at this location. This might result in low gradeability of muscle contractions, because all nerve fibers are stimulated supramaximal already at low stimulation intensities. Additionally, unwanted contractions of muscles not intended to be activated may also occur in such a constellation.

Caution is required when very small electrodes are used. Due to the high current density in the tissue below the electrode, power is dissipated as heat resulting in a temperature increase of the tissue to a potentially dangerous level. In very high current densities, this may even lead to skin burns. These negative effects can be prevented by applying effective direct current (DC) densities below 35 $\mu A/mm^2$ (International Electrotechnical Commission 2015). It must be emphasized that this limit represents a mean value of the current meaning that peak currents which are only applied as short impulses can be much higher.

2.3.2 Technological Fundamentals of Electrical Stimulation

As mentioned above, in biological tissues no free electrons are available as charge carriers. This induces a chemical reaction at the surface of the electrodes, where charge is exchanged between the charge carrier in the technical system, which are electrons, and the biological system, which are ions. Beneath the cathode, Na^+ ions are recombining with free electrons and water to hydrogen and caustic soda (Eq. 2.1)

$$2Na^+ + 2e^- + 2H_2O = H_2 + 2NaOH \tag{2.1}$$

Beneath the anode, Cl^- ions are recombining with water to electrons, oxygen, and hydrochloric acid (Eq. 2.2).

$$2Cl^- + H_2O = 2e^- + 2HCl + ½\, O_2 \quad (2.2)$$

If stimulation currents are applied over an extended amount of time (15 min or more), the chemical products under the electrodes result in body reaction which might lead to tissue and skin damage, i.e., coagulation (anode) and colliquation (cathode) necrosis. Current-induced tissue damage ranging from skin redness to severe skin burns represented a serious problem in prolonged stimulation applications with the early FES technology available in the midst 1970s, where monophasic impulses with a net DC component were used.

To effectively avoid the DC-induced tissue damage, a net injection of charged ions in the tissue below the electrodes needs to be prevented. This means that the delivered charge needs to be removed from the tissue. From a technical perspective, this can be done by applying an impulse with the same number of injected ions but reversed polarity. The impulse with reversed polarity is called charge balance impulse, the impulse sequence consisting of a stimulation together with a charge balance impulse is called biphasic pulse. The DC-compensation does not need to be absolutely perfect, because a low amount of net charge injection is tolerated by the tissue (Scheiner et al. 1990).

2.4 Pulse Shape

In modern electrical stimulators intended for FES applications, biphasic pulses are used, i.e., the initial stimulation impulse is followed by the charge balance impulse with reversed polarity, but with the same amount of injected charge Q (gray area in Fig. 2.3). The charge (unit: fC) of an impulse is calculated as the product of the current amplitude (in mA) of the impulse and its duration (in µs). Typical shapes of stimulation pulses implemented in FES stimulators are composed of a rectangular stimulation impulse followed by different forms of charge balance impulses (Fig. 2.3).

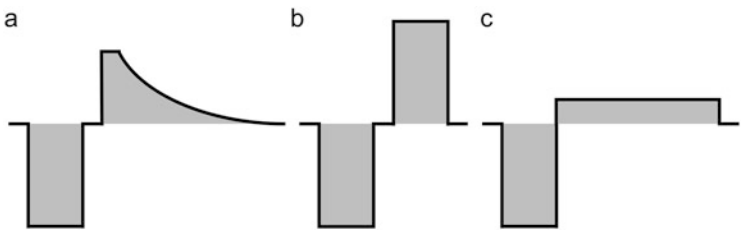

Fig. 2.3 Typical FES stimulation waveforms. (**a**) Rectangular impulse with exponential charge balance impulse, (**b**) Biphasic rectangular pulse with symmetric charge balance impulse, (**c**) Biphasic rectangular pulse with asymmetric (reduced amplitude, increased width) charge balance impulse (Rupp 2017)

From a technical viewpoint, an exponential charge balance impulse (Fig. 2.3a) can be implemented in a very simple way by adding a series capacitor to the stimulation circuit, which is de-charged by an electronic switch shortcutting the capacitor with the electrodes. The generation of rectangular charge balance impulses is technically more complex, because it needs either a negative supply voltage or an H-bridge current output stage. An H-bridge output stage basically consists of electronic switches, which alter the polarity of the electrodes between stimulation and charge-balancing impulse. On the other hand, rectangular charge balance impulses allow for the highest pulse repetition rate (frequency in Hz) (Fig. 2.3b). In case of stimulation impulse durations (also called pulse widths) below 1 ms a short pause of approx. 100 μs is inserted between the stimulation and charge balance impulse (Gorman and Mortimer 1983). Without this pause the activation effect of the stimulation impulse is partly reduced due to the steep slope of the charge balance impulse (van den Honert and Mortimer 1979). If the amplitude of the charge balance impulse is substantially lower compared to the stimulation impulse, its reduced amplitude does not trigger an action potential under the anode and thus, the pause can be omitted without any detrimental effect (Fig. 2.3c). In cases where both the stimulation and charge-balancing impulse have the same amplitude the pulses are called symmetric biphasic pulses. Pulses with reduced amplitude of the charge balance impulse are called asymmetric biphasic pulses. In asymmetric pulses, the lower amplitude of the charge balance impulse needs to be compensated by longer duration of the impulse to guarantee DC-neutrality (gray areas indicate equal amounts of charge in Fig. 2.3c).

Theoretically, a charge balance impulse can be omitted when the polarity of the stimulation pulse is alternating between each impulse. However, this might result in action potentials under both electrodes, which is particularly in FES applications neither desirable nor acceptable. Biphasic pulses ensure the long-term safety and integrity of the stimulated tissues, while making it possible to control exactly which electrode triggers an action potential generating the desired contractions. By adjusting the amplitude of the leading stimulation impulse to be sufficiently high to generate a desired muscle contraction and by selecting the amplitude of the trailing pulse to be sufficiently low not to trigger muscle contraction, one can deliver stimulation only to desired motor points with precision.

Usually, for stimulation of innervated muscles biphasic pulses with a stimulation impulse width between 50 and 500 μs are used. Short pulse widths are appropriate in cases were pain sensations needs to be prevented due to their inability to activate non-myelinated pain fibers.

Another way to stimulate muscles without causing pain sensations is to use low-frequency modulated alternating currents with carrier frequencies above 1000 Hz (Ward 2009). The reason to use higher frequency than 1000 Hz is that the impedances of skin decrease substantially at higher frequencies due to its capacitive electrical properties. Thus, less energy is dissipated to the surface of the epidermis and a larger proportion of energy reaches deeper tissues (Ward et al. 2002). However, the energy demands of alternating currents is much higher than of low-frequency biphasic rectangular pulses, which prevents their use in

battery-powered stimulation devices. This is the reason why interferential medium-frequency alternating stimulation currents have not been used in FES applications.

2.5 Constant-Current Versus Constant-Voltage Stimulation

From the previous subchapters, it can be concluded that electrically the nerve membrane mainly represents a capacitor, whose voltage is proportional to the injected charge. To guarantee a consistent generation of action potentials and the associated muscle contractions despite time-varying and unknown electrode-skin and body tissue impedances, constant-current pulses need to be applied (Fig. 2.4).

Although a constant-current amplifier stage adds substantial technical complexity to the stimulator, in constant-voltage stimulators the voltage amplitude has to be continuously adapted to the changing electrode-skin impedances. In FES applications, this represents a severe drawback because due to the prolonged application times electrode-skin and body tissue impedances alter substantially over time caused for example by sweating or changes in perfusion.

However, some safety measures need to be implemented in constant-current stimulators in case of a poor electrode contact or complete electrode drop-off. When the electrode has a poor contact the electrode-skin impedance increases. While a constant-voltage stimulator would not increase the stimulation voltage in this condition, the constant-current stimulator does so to keep the selected current constant. If the electrode contact improves from a sudden, e.g., by pressing the electrode onto the skin, the current control circuit might be too slow in reducing the stimulation voltage causing unwanted sensory and motor responses. To prevent such a potentially dangerous situation, constant-current stimulators need to continuously monitor the inter-electrode impedance between the electrodes to switch off the stimulation when a safety threshold is exceeded.

2.6 Electrical Stimulation Electrodes

Basically, by FES an action potential can be triggered at any location of a nerve fiber—from the cell body of the neuron to the axon to the motor end plate. It does not make a difference, if the stimulation impulses triggering the action potential are applied via electrodes over the skin or inside the body. Thus, electrical stimulation can be delivered using electrodes with different levels of invasiveness. They can be placed on the surface of the body (called transcutaneous or surface electrodes), or can be partially or completely implanted, known as percutaneous or implanted electrodes, respectively. Each type of electrode offers advantages and disadvantages

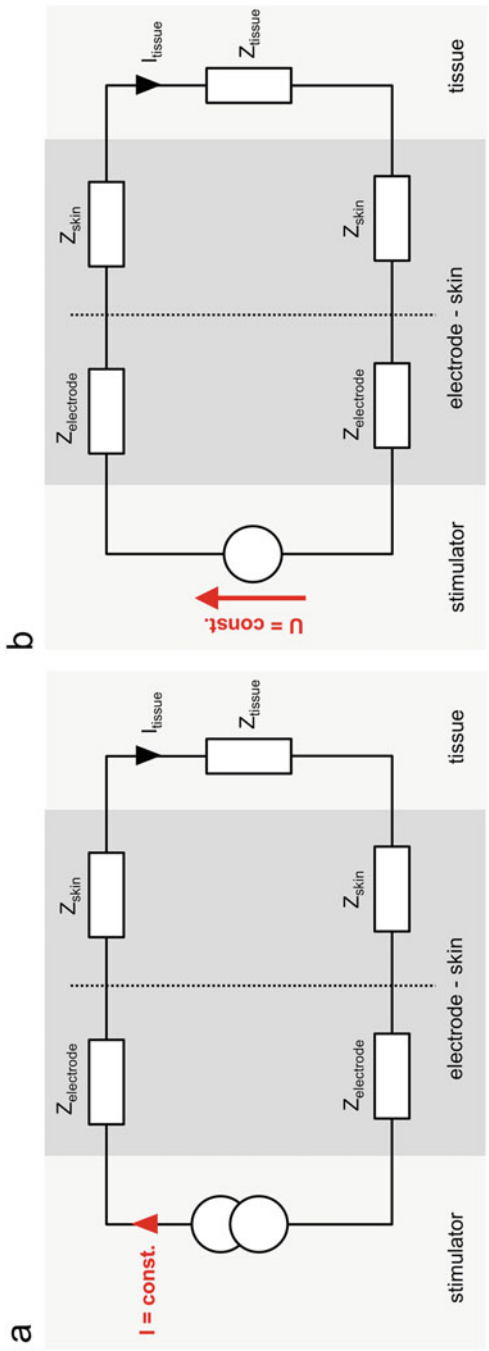

Fig. 2.4 Equivalent circuit diagram of constant-current versus constant-voltage stimulation of excitable tissue. (**a**) The constant current applied by the stimulator equals the current in the tissue independent from the electrode-skin impedance, (**b**) In a constant-voltage stimulator the current in the tissue varies with changing electrode-skin impedances

Table 2.2 Overview of the advantages/disadvantages of stimulation electrodes with different levels of invasiveness

Type	Typical current	Advantages	Disadvantages
Invasive			
Fully implantable	10–20 mA	• High spatial stimulation specificity • High temporal stimulation stability • Suitable for long-term use	• Require surgery • Placement cannot be modified after implantation
Percutaneous	10–20 mA	• High stimulation specificity • Suitable for short-term use	• Sometimes require surgery • Risk of infection at skin insertion point
Noninvasive			
Transcutaneous (surface)	2–120 mA	• Do not require surgery • Easy to reposition	• Selective stimulation of deep muscles not possible • Often require higher stimulation current

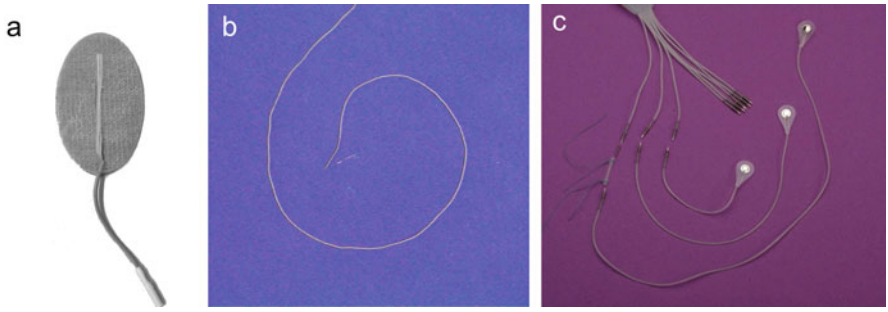

Fig. 2.5 Common types of stimulation electrodes. (**a**) Oval (4 × 6 cm) self-adhesive, gel-electrode for transcutaneous stimulation, (**b**) percutaneous fine spiral wire electrode (wire Ø 50 μm), (**c**) Fully implantable electrode (Ø 7 mm) embedded in silicone with integrated double helix-coiled wire and connector (Kilgore et al. 1990)

with respect to their spatial specificity, stability over time, usability, flexibility, and costs (Table 2.2).

2.6.1 Transcutaneous Electrodes

Transcutaneous electrodes are placed on the surface of the body. Most commonly, gel-electrodes are used due to their self-adhesiveness (Fig. 2.5a). Graphite-rubber electrodes represent a cheaper alternative, but are not self-adhesive and need to be

secured to the skin with adhesive tape or velcro straps. They can be used in combination with electrode gel to minimize electrode-skin impedances. For stimulation of muscle contractions via surface electrodes, the different electrode or both electrodes are placed over the motor point of the desired muscle. In addition to the fact that the use of transcutaneous electrodes does not require surgery, they can be repositioned immediately to ensure that the stimulation elicits the desired response. Changing the position of the electrodes (and hence their effect) may be of particular importance if the stimulation needs to be modified in response to the changing needs of an individual, as is often the case during the early rehabilitation phase with the greatest extent of neurological recovery (see Chap. 1). This makes them ideal for temporary use, such as when using electrical stimulation as part of a restorative, task-oriented neurorehabilitative intervention (see Chap. 11). The current used with transcutaneous electrodes (2–120 mA) is typically higher than that of implanted ones. Although the costs of surface electrodes vary substantially, they are low comparable to the price of implantable electrodes.

The main disadvantages of noninvasive electrodes are insufficient selectivity in respect to generate movements needed for fine motor tasks, difficulties with setup and daily reproduction of functionally relevant movement patterns, limited excitability of deeper (i.e., far below from the skin) muscle groups, and pain sensations in particular when high stimulation intensities are needed for stimulation of deep muscles. Additionally, patients describe the handling of the electrodes and the total system setup as complicated. The identification of the correct electrode positions for generation of the desired movement patterns represents a severe challenge for end users. In addition, defining the optimal size of stimulation electrodes during initial setup is even for experts often time consuming. In some end users, stimulation-induced or voluntary movements result in substantial shifts of the cutaneous location of the motor points of specific muscles resulting in the inability to generate the desired movement pattern. A promising concept for faster determination of the correct electrode positions and the dynamic, joint-position-dependent re-location of electrodes is the use of multi-pad electrode arrays, in which small electrodes can be selectively activated, dynamically merged to larger electrodes, and electronically shifted inside the array (Hoffmann et al. 2012; Malesevic et al. 2012; Popovic-Maneski et al. 2013). Array electrodes might substantially resolve the handling problem of end users of noninvasive neuroprostheses (see Chap. 13). However, the clinical value of this newly introduced concept needs to be evaluated in future studies involving a larger number of end users.

2.6.2 Percutaneous Electrodes

Percutaneous electrodes typically have the form of thin wires that penetrate the skin with a portion of them inserted in the body in close proximity to nerves or the end plates innervation region of muscles (Ajiboye et al. 2017; Buckett et al. 1988) (Fig. 2.5b). While the stainless steel wire is typically electrically isolated, both ends are

blank on a length of 5–10 mm. While the one end inserted in the body serves as electrode, the other end outside the body is connected to the electrical stimulator mostly via a clip mechanism. For better fixation inside the muscle, some percutaneous leads have a hook-shaped end. Percutaneous electrodes are typically inserted into the body with a small cannula. The stimulation current amplitude typically used with percutaneous electrodes is the same than in permanently implantable electrodes (<20 mA). Percutaneous electrodes are usually used together with a surface electrode as a common anode. Although initially intended for short-term applications, over the years these electrodes have proven their robustness for selected long-term applications (e.g., phrenic pacing, see Chap. 4). Most of the restrictions of noninvasive electrodes in respect to selectivity, stability of the generated movement patterns and pain sensations can be overcome by percutaneous, intramuscular electrodes. Their costs are relatively low, however, handling is complicated. For chronic FES-based reanimation of paralyzed limbs there are increased risks of mechanical failure of the thin wires at the insertion point and of inflammation (Marsolais and Kobetic 1988).

2.6.3 Implanted Electrodes

As the name suggests, implanted electrodes are surgically placed on nerves or muscles inside the body. They can be placed in close proximity to targeted nerve branches of specific muscles resulting in high spatial selectivity, i.e., it is easier to isolate specific muscles to stimulate. Implanted electrodes can be epimysial, intramuscular or electrodes around a nerve, the so-called nerve-cuff electrodes (Memberg et al. 2014).

Implanted electrodes are superior to all other types in respect to long-term stability of stimulation intensities and selectivity. Thus, they provide an excellent stability of stimulation and movement patterns and are the preferred choice for long-term use in neuroprosthetic applications over many years (see Chap. 5). In addition to the general risks of the surgery, there is an increased risk of infections in implanted systems. In extreme cases, infections might result in the explantation of all implanted components including electrodes, cables and the stimulation device. To prevent this, microstimulators with integrated stimulation electronics, batteries, inductive power supply and communication interface inside an electrode housing small enough to allow for injection into the tissue through a large cannula have been developed (e.g., the BION implants (Loeb and Davoodi 2005; Kane et al. 2011)). The main challenge of these systems is to guarantee a continuous power supply independent from the orientation of the implant and the thickness of the tissue between the implant and the extracorporeal energy transmission coil. In any case, microimplants can only be operated with additional external components.

The electrical current necessary to produce a muscle contraction with implanted electrodes is much lower than that of surface electrodes and is—depending on the size of the active electrode area—in the range of up to 20 mA (Kilgore et al. 2003). Once implanted, invasive FES systems require less preparation time for donning and

doffing compared to surface stimulation technology, despite implanted systems often go along with external components as part of the complete neuroprosthesis (e.g., a controller interface or an inductive power supply) that a user must put on. Due to their ease of use and stable operation over many years, end users show a high degree of satisfaction with implanted systems (see Chap. 5). Implantable electrodes have to undergo a substantial testing and certification process before regular use which results in high costs.

2.7 The Strength-Duration Curve

In respect to external electrical stimulation of nerves and muscles, the triggering of action potentials depends mainly on two variables: first, the strength of the stimulus, and second, the duration for which the stimulus is applied (Geddes and Bourland 1985). More than 100 years ago, Louis Lapicque, a French neuroscientist, systematically investigated the dependency of the excitability of nerves and other excitable tissue on the duration of an electrical stimulus (Lapicque 1907). This relationship is called strength-duration curve (often abbreviated in the literature as S-D curve) and represents one of the most important fundamentals of electrical stimulation of excitable biological tissues. It plots the minimal stimulus current (also called threshold current) required to trigger an action potential over the duration of a stimulus pulse (pulse width). In case of stimulation of muscle contractions, it provides quantitative information about the excitability of the nerve-muscle-unit. In case of rectangular stimulation impulses, the S-D curve is characterized by a hyperbola-like shape (Stämpfli 1971) (see Fig. 2.6). The use of strength-duration curves was developed in the 1930s, followed by the use of threshold current measurements for the study of human axonal excitability in the 1970s (Nodera and Kaji 2006).

Lapicque already introduced two characteristic parameters of the S-D curve, namely the rheobase b and the chronaxie t_{ch}. In Greek, the root "rhe" translates to "current or flow," and "basi" means "bottom or foundation". The rheobase b (in mA) is a measure of membrane potential excitability and represents the minimal current intensity with infinite duration (in reality, about 500 ms) that results in a depolarization of an excitable tissue such as nerve or muscle membranes (Lapicque 1907). The chronaxie t_{ch} (in ms) is the minimum stimulus pulse width to excite the nerve or muscle tissue for a stimulus pulse current of twice the amplitude of the rheobase (Geddes 2004).

Lapicque's equation for determining the threshold current I (in mA) equals to

$$I = b\left(1 + \frac{t_{ch}}{d}\right) \tag{2.3}$$

where b relates to the rheobase value (in mA) and t_{ch} related to the chronaxie value (in ms) over the impulse duration d (in ms).

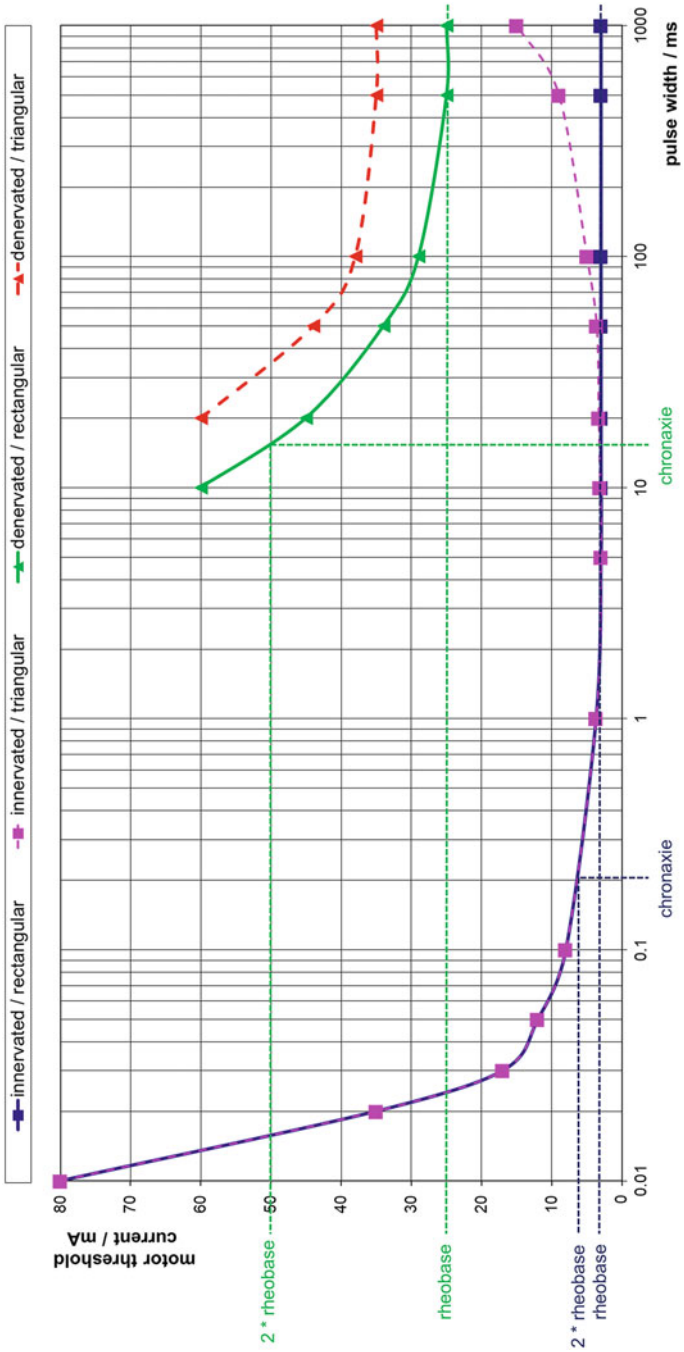

Fig. 2.6 Examples of strength-duration curves of the quadriceps muscle measured with rectangular stimulation electrodes of 5 × 9 cm. The vertical axis shows the minimal peak current in mA of the stimulation impulse for eliciting a muscle contraction. The logarithmical horizontal axis shows the pulse width in ms. The square-marked curves were measured in a healthy subject without any neurological disease, i.e., fully innervated quadriceps muscle. In pulse widths longer than 20 ms, an increase of the motor threshold current occurs (called accommodation effect). For triangular pulses with symmetrical slopes, the motor threshold current (peak pulse current) becomes higher for long pulse widths >20 ms due to the accommodation effect. The triangle-marked curves were measured in an individual with a complete (American Spinal Injury Association Impairment Scale A, no zones of partial preservation), chronic (2 years after injury) spinal cord injury at the conus level (neurological level of injury T11). The subject showed no reflexes in the lower extremities and the severe denervation of the quadriceps

Fig. 2.6 (continued) muscle was confirmed by neurophysiological measures including needle electromyogram. The S-D curve shows a 10 times increase of the rheobase and 100 times increase of the chronaxie in the denervated quadriceps muscle when stimulated with biphasic rectangular impulses. In contrast to the innervated quadriceps, the denervated muscle does not show an accommodation effect and the associated increase in the motor threshold current when stimulated with triangular pulses with pulse widths longer than 20 ms

Table 2.3 Comparison of parameters for stimulation of innervated and denervated muscles

Stimulation parameter	Innervated muscle	Denervated muscle
Stimulation pulse shape	Rectangular pulse	• Rectangular pulse • Triangular pulse with variable slope
Pause between stimulation and symmetrical charge-balancing pulse	100 μs	Not needed
Charge balance pulse	• Rectangular pulse • Exponential pulse	• Rectangular pulse • Triangular pulse
Pulse duration/width	0.05–1 ms	20–500 ms
Pulse repetition rate/frequency	1–100 Hz	0.5–20 Hz
Current amplitude	1–120 mA	1–150 mA
Size of stimulation electrodes	5–45 cm^2	45–100 cm^2

Lapicque's equation (Eq. 2.3) can be transformed into the equation established by Weiss in 1901 by multiplication with the impulse duration d. Weiss's equation equals to

$$I \times d = Q = b(d + t_{ch}) \tag{2.4}$$

with Q (in μC) relating to the charge injected into to the tissue.

Equation (2.4) indicates that the charge needed to elicit an action potential increases linearly with stimulus duration with the rheobase defining the slope. This means that the use of shorter pulse widths represents an efficient way to save energy in an electrical stimulator. Practically, pulse widths from 100 to 500 μs are used for stimulation of innervated muscles (Table 2.3). Stimulation threshold difference between different diameter motor nerve fibers increases with decreasing pulse width, the greatest effects are evident for pulses less than 100 μs (Gorman and Mortimer 1983).

Even though the diameters and conduction velocities of the motor and sensory fibers with the lowest excitation thresholds are in the same range, sensory fibers have significantly longer strength-duration time constants. As a result, sensory nerves have a lower rheobase than motor nerves meaning that they have a lower stimulation threshold (Daskalova and Stephanova 2001).

2.8 Indirect Versus Direct Electrical Stimulation of Muscles

Since Lapicque, studies have been published using strength-duration curves to differentiate between and central and peripheral nerve lesions. S-D curves show substantial changes depending on the degree of denervation (Edel 1993). After

peripheral nerve injury, the distal nerve, which under normal conditions could be excited with short stimulation impulses below 1 ms, will degenerate and thus action potentials are not transmitted to the muscles anymore. In people with spinal cord injury (SCI), damage to the lower motor neurons at the lesion site might occur with different degrees (see Chap. 1). This damage results in a denervation of the muscles which were formerly innervated from these spinal segments (Mulcahey et al. 1999). In case of a denervated muscle, contractions can only be generated by direct excitation of the membranes of the muscle fibers. However, to achieve this, much higher current amplitudes and longer pulse widths are needed compared to the stimulation of innervated muscles (Fig. 2.6). While the rheobase of the S-D curve of denervated muscles is up to 10 times higher, the pulse width is increased by factor 20–500 (see Table 2.3). The pulse widths used for stimulation of denervated muscles are in the range of 20–500 ms, depending on the training state of the muscle (Ashley et al. 2005). Due to the increase of rheobase and pulse widths, the S-D curve shifts to the upper right in long-term denervated muscles. This shift can be used diagnostically to differentiate between peripheral and central paralysis and to determine the degree of denervation. In case muscle fibers are innervated by a nerve, contractions induced by electrical stimulation—even when applied with implanted electrodes—are always triggered by action potentials on nerves due to their much lower stimulation threshold. The determination of the chronaxie for detection of denervation of muscles has a high interrater reliability (Schuhfried et al. 2005). Normally, the chronaxie is determined with rectangular pulses, but is also defined for triangular pulses (Fig. 2.6).

At the beginning of the nineteenth century, Ritter observed that a slow increase of a direct current attenuates or even suppresses the elicitation of an action potential on a nerve, while the same current amplitude applied with a steep slope triggers it (Ritter 1808). This accommodation effect can be quantified by using triangular stimulation impulses. With increasing pulse width, the steepness of the rising slope of the triangular stimulation impulse decreases. In pulse widths greater than 20 ms, the steepness of the slopes is becoming so low that an action potential on the nerve is only excited at stimulus currents higher than the rheobase (Fig. 2.6). A current increase in the S-D curve for pulse durations greater than 20 ms is therefore a sign for at least partially intact innervation of a muscle. Denervated muscles do not show an accommodation effect and the associated increase in the motor threshold current when stimulated with pulse widths larger than 20 ms. Therefore, the lack of the accommodation effect can be interpreted as a sign of denervation.

To quantify the effect of accommodation, the accommodation coefficient λ can be calculated (Eq. 2.5). It refers to the slope in the S-D curve for high pulse widths of triangular pulses and can be calculated by dividing the stimulation intensity at a pulse width of 500 ms by the rheobase:

$$\lambda = \frac{I(500\ \text{ms})}{b} \tag{2.5}$$

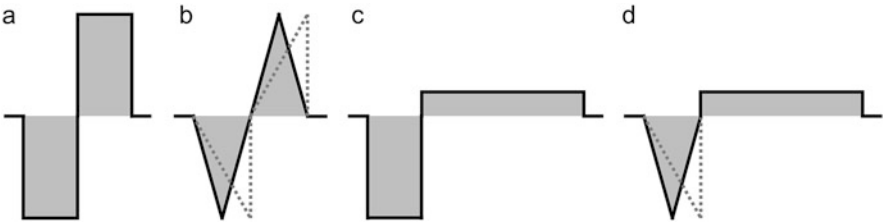

Fig. 2.7 Typical waveforms for stimulation of denervated muscles. (**a**) biphasic rectangular pulse with symmetric charge balance impulse, (**b**) biphasic triangular pulse with variable rising slope and symmetric charge balance impulse, (**c**) biphasic rectangular impulse with asymmetric (reduced amplitude, increased width) charge balance impulse, (**d**) biphasic triangular impulse with variable rising slope and asymmetric rectangular charge balance impulse

with I(500 ms) related to the motor threshold current at a pulse width of 500 ms of a triangular pulse and b being the rheobase as the minimal current needed to elicit an action potential.

Clinically, the accommodation effect can be effectively used to reduce stimulation-induced pain sensations caused by the high energy impulses used for direct stimulation of denervated muscles in patients with fully or partially preserved sensory functions. This situation might be present in cases of incomplete conus-cauda lesion of the spinal cord. By using triangular stimulation impulses with a low steepness of the slopes at high pulse widths (>20 ms), unpleasant sensations are reduced due to attenuation of action potentials on sensory nerves by the accommodation effect, while the denervated muscle fibers are activated by the long triangular pulses (Fig. 2.7b, d).

With a larger extent of and longer time after denervation more charge is needed to directly activate muscle fibers. In case of a completely long-term denervated muscle, impulses with high current amplitudes up to 150 mA and extended pulse widths up to 500 ms need to be applied to generate contractions (Fig. 2.6). This results in a high risk to exceed the maximum permissible current density for surface electrodes of 2 mA/cm^2 and to cause local skin burns (Kern et al. 2010). As safety measure, large electrodes preferably embedded into wet sponges or covered by conductive electrode gel should be used (Fig. 2.8).

In any case, stimulated denervated muscles do not produce the same amount of force than innervated ones. Therefore, a careful screening of the presence of denervated muscles is mandatory to estimate the potential for successful application of FES. 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 direct muscle stimulation. With these devices, a precise testing of the innervation status of muscles and eventually a training of denervated muscles to prevent muscle degeneration can be performed. Examples of such devices are the portable, single channel Paresestim FES system from Medel GmbH (Hamburg, Germany) and the 2-channel system Stimulette edition5 S2x from Dr. Schuhfried Medizintechnik GmbH (Vienna, Austria).

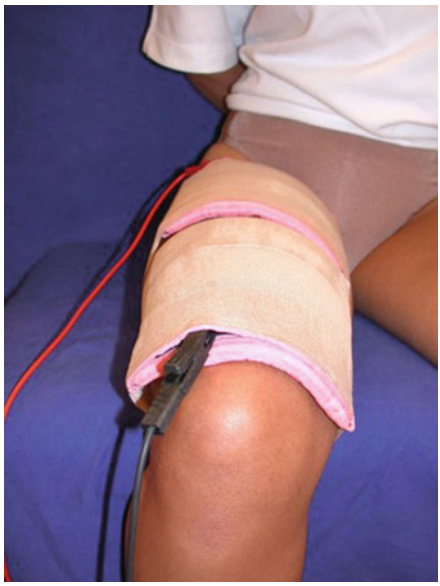

Fig. 2.8 Electrode setup in an individual with a conus-cauda spinal cord lesion for direct stimulation of denervated thigh muscles. Large electrodes (15 × 10 cm) are used together with wet sponges for decreasing the current density and electrode-skin impedance. These safety measures are applied to reduce the risk of skin burn due to the high stimulation intensities. Of note, in this individual with the electrodes over the quadriceps muscle, the hamstring muscles were activated simultaneously due to the high stimulation intensities

2.9 Selection of Stimulation Parameters

The stimulation result is determined by mainly three parameters: pulse amplitude, pulse duration, and pulse frequency. As outlined in the previous paragraphs, there are substantial differences in these parameters for stimulation of nerves in contrast to direct stimulation of muscles (Table 2.3).

2.9.1 Amplitude

The pulse amplitude refers to the magnitude of the stimulation current. It affects directly the type of nerve fibers that respond to the stimulation with large fibers in close proximity to the stimulation electrode being recruited first (Reilly 1998). Typical amplitudes for stimulation of nerves with small electrodes, e.g., round electrodes with a diameter of 3 cm for selective stimulation of finger and thumb muscles, are below 30 mA, while amplitudes for stimulation of large muscles such as the quadriceps muscles with large electrodes up to 5 × 9 cm may require stimulation currents up to 120 mA (at approx. 300 μs pulse width). Stimulation currents needed for direct muscle stimulation might be even higher (up to 150 mA). The sensory threshold is much lower than the motor threshold current and ranges from 3–8 mA (at 300 μs) in non-disabled people.

Basically, the pulse width and the pulse current are somehow interchangeable. They are inversely related so that an increase in pulse duration may result in a lower

pulse current amplitude to generate a response. Conversely, reducing the pulse duration may translate into the need to increase the amplitude of the stimulating pulse. In practical FES applications, current amplitudes can be adjusted by the end user to compensate for daily variations in the stimulation pattern, while the stimulation pattern itself is implemented as a predefined pulse width map (Rupp et al. 2012). However, users of FES systems need to be sufficiently trained in the details and consequences of amplitude adjustments to be able to make the right changes of amplitudes of individual channels to improve the quality and therefore usefulness of the FES-generated movements.

2.9.2 Pulse Width

The pulse duration (pulse width) is the time in which the stimulation pulse is present. As already outlined in the S-D curve subchapter, the selection of the right pulse width has a substantial impact on the current amplitude needed for eliciting a muscle contraction.

Typical pulse widths for stimulation of innervated muscles are in the range of 50 μs–1 ms with 200–300 μs representing typical durations. Shorter pulse widths are often used in cases where pain sensations are a problem. Pulses with shorter duration do not activate large unmyelinated sensory fibers and are therefore often perceived as less painful.

For direct muscle stimulation, much higher pulse widths above 20 ms are needed. During screening of potential FES users with SCI, it is of utmost importance to determine the degree of denervation caused by peripheral nerve lesions or lower motor neuron damage in the spinal cord. Therefore, muscles are often stimulated with short (300 μs) and long (200 ms) impulses to evaluate their excitability status.

2.9.3 Frequency

The frequency of stimulation is the rate at which stimulation pulses are delivered. It affects the strength of the muscle contraction as well as its quality. Each stimulation pulse with properly selected amplitude and duration produces a muscle twitch, characterized by a sharp increase in force followed by a slower return to a relaxed state (Kandel 2013). The application of subsequent stimulation pulses before the muscle is relaxed will produce additional muscle twitches. The force produced by each twitch is added so that the mean force of the contraction is greater than that produced by a single twitch. Further increase in the pulse frequency results in a sustained contraction, in which no individual twitches are visible, and instead replaced by a smooth movement. This so-called tetanic contraction is desired in FES applications.

Higher pulse frequencies generate stronger tetanic contractions, however, they can also result in faster muscle fatigue. Very high-frequency stimulation (greater than 70 Hz) will cause neuromuscular junction failure and rapid muscle fatigue (Petrofsky 1982; Petrofsky et al. 1981a). The optimum stimulation frequency is similar to the range of normal motor unit discharge frequencies generated during voluntary activity of 20–50 Hz (Petrofsky et al. 1981a, b). Lower frequencies cause a more unfused muscle contraction. In practical FES applications, the selection of the frequency is always a compromise between sufficiently smooth movements and force generation and reduction of muscular fatigue. Typical stimulation frequencies for FES application in people with SCI are 16–20 Hz (see Chap. 5 and 14).

In direct muscle stimulation applications, the frequency is quite limited due to the long pulse width needed to directly activate muscle fibers. In biphasic, symmetric, rectangular stimulation impulses with a stimulation pulse width of 200 ms, the theoretical maximum stimulation frequency is 2.5 Hz (=1/(200 ms + 200 ms)). However, with electrical stimulation training the pulse width needed to activate muscles directly can be reduced to approx. 20 ms or even lower, so that tetanic frequencies of up to 20 Hz become possible (Kern et al. 2010). With long-term training over many months, the ES-generated tetanic contractions might achieve a level of force which is sufficiently strong to allow for short-term functional use such as standing (Kern et al. 2010).

2.10 Muscular Fatigue Induced by Electrical Stimulation

A striated skeletal muscle is composed of rapidly contracting, but fatigue-prone fibers and slower contracting fibers for steady force generation. For a gradual development of muscle strength, nerve fibers are activated in different ways according to the type of muscle fibers they innervate: when muscle strength is low, thin fibers of a nerve are activated first, which innervate fatigue-resistant, slow muscle fibers (aerobic type-I fibers). With increasing strength requirements, more and more thick nerve fibers are activated, which end at quickly fatiguing muscle fibers (glycolytic type-II fibers) (Bigland and Lippold 1954; Olson et al. 1968).

Although electrically induced action potentials basically comply with physiological activation mechanisms, there are relevant differences between the physiological and artificial generation of muscle contractions (Stieglitz 2005): In the physiological condition, when low muscle forces are generated, mainly thin fibers are activated. With increasing force more thick fibers are recruited (Fig. 2.9). 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. However, thick nerve fibers end at fast-fatiguing muscle fibers, while thin fibers innervate more fatigue-resistant muscle fibers. This phenomenon called inverse recruitment is one of the main reasons, why stimulated muscles fatigue relatively fast compared to the physiological condition (Petrofsky 1978). In addition,

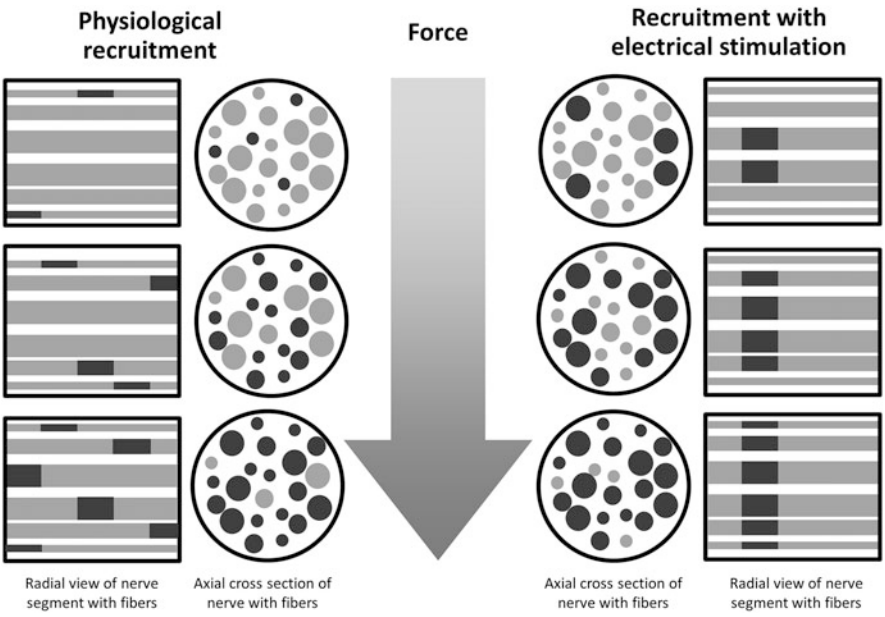

Fig. 2.9 Recruitment of nerve fibers under physiological conditions and by electrical stimulation. Dark areas represent activated parts of the nerve fibers, light gray areas indicate inactive parts. Nerve fibers with small diameter typically end at slow-fatiguing, type-I muscle fibers, while nerve fibers with larger diameter end at fast-fatiguing, type-II muscle fibers. With increasing force more fibers are activated in both conditions, however, with an increasing number of thick fibers in the physiological condition (left) and an increasing number of thin fibers in the electrical stimulation condition (Rupp 2017)

all nerve fibers get activated nearly at the same time, which results in a nearly synchronous activation of all muscles fibers of the corresponding motor units. Furthermore, each electrical pulse 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 people with chronic SCI, paralyzed muscles consist to a large extent of fast-fatiguing, type-II muscle fibers with the associated severely decreased fatigue resistance and capability for force generation (Burnham et al. 1997). The disuse

atrophy of paralyzed muscles can be reversed through FES training (see Chap. 14) even many years after SCI. Additionally, FES training converts the fiber composition of muscles in the direction of slow-fatiguing, type-I muscles (Salmons and Sreter 1976).

A way to generate higher levels of force is to use duplet or triplet impulses, where more than one stimulation impulse is applied shortly after each other (Karu et al. 1995; Mela et al. 2002). However, the additional force-generating effect of duplets and triplets are strongly depending on the actual stimulation setup and cannot be generalized. In small muscles, a slower fatigue has been determined using doublet impulses (Bigland-Ritchie et al. 2000).

2.11 Electrical Stimulators for FES

The electrical stimulator is the key component of any FES application. It is responsible for generating the electrical impulses on different channels in a timely manner to produce muscle contractions resulting in coordinated joint movements. Most FES applications are based on more than a single stimulation channel. Typical numbers are 4–8 stimulation channels each connected to a pair of electrodes. A multichannel programmable stimulator, which allows unique settings for activation of each channel, makes it possible to facilitate different functional movements. A programmable electrical stimulator consists of typical hardware components (Fig. 2.10): A microcontroller forms the heart of the stimulator. It controls high-level as well as low-level functions. The low-level functions are mainly related to the generation of the stimulation pulses. For this, the microcontroller needs to set the current amplitude of the stimulation pulse of each channel and precisely control the duration of its phases, namely the widths of the stimulation impulse, pulse pause, and the charge-balancing impulse. In most stimulators, the impulses for each channel are multiplexed sequentially. One way to generate the charge balance impulse is by reversing the polarity of the output connectors to the internal anode and cathode by an H-bridge driver. Another way to generate an exponential charge balance impulse is to discharge a series capacitor, which has been charged during the stimulation impulse, by an electronic switch.

For the generation of stimulation currents up to 120 mA in case of an electrode-skin-tissue impedance of up to 1 kOhm, voltages around 120 V are needed. These high voltages are generated from the internal battery by a high voltage DC/DC-converter.

Among the high-level control functions of the microcontroller is to provide feedback to the user via a small display about the main stimulation parameters such as set current amplitudes or on/off-state of each stimulation channel.

Another important high-level function is the evaluation of user inputs from the user interface. The complexity of this task may range from detecting a simple button press for increasing the amplitude to the real-time acquisition and processing of

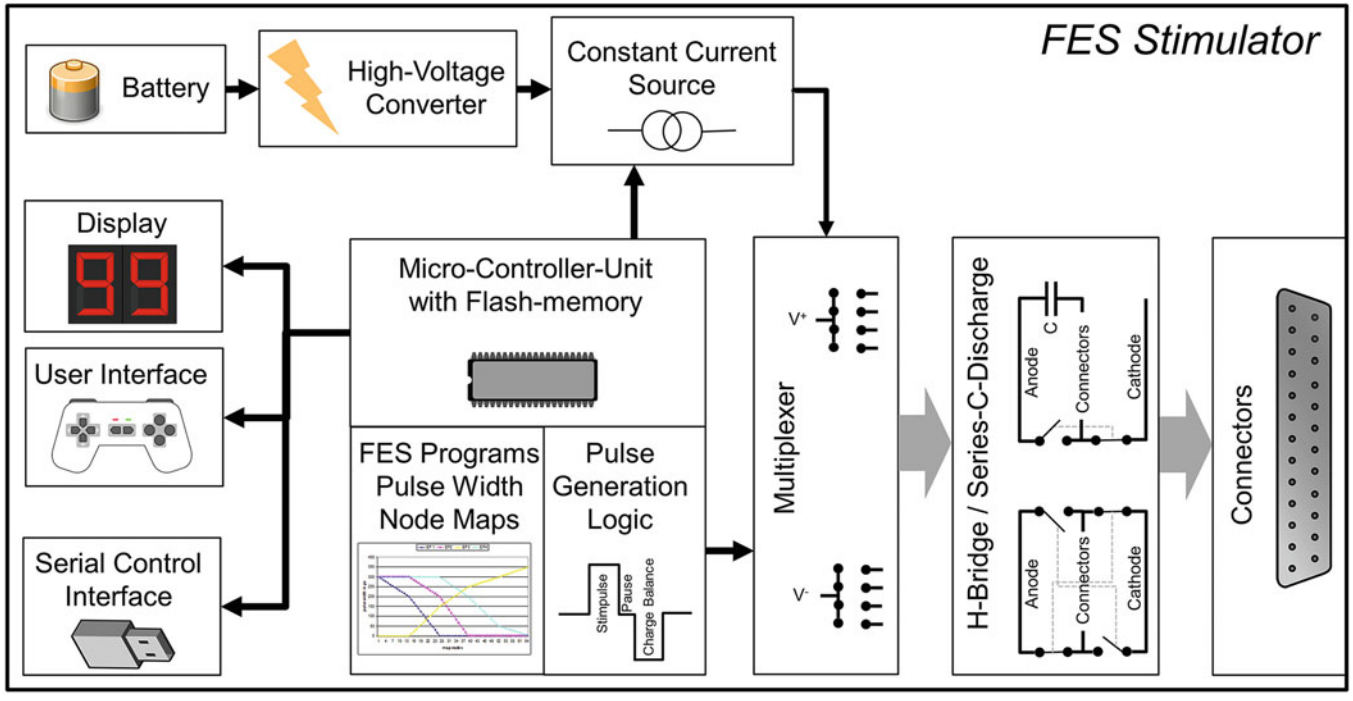

Fig. 2.10 Building blocks of a multichannel electrical stimulator for use with surface electrodes. The microcontroller represents the main control unit for generation of the stimulation impulses in a coordinated manner. The user is informed about the current stimulation state by a display and provides input via buttons and keys or externally connected sensors such as a shoulder joystick. Optionally, the stimulation can be controlled from a high-level control unit via transmission of serial commands and status feedback. A voltage converter generates the high voltage supplying the current source for the stimulation routing matrix consisting of multiplexer and H-bridge circuits

signals from external sensors. Ideally, the user interface of the stimulator offers the ability for customization.

Stimulators may accept commercially available accessible switches and, in some cases, it may also be possible to incorporate other specialized sensors allowing individuals with different abilities to command the device. For example, a two-axis angle sensor can be used to analogously control the degree of hand opening/closing in a grasp neuroprosthesis by detecting wrist or shoulder movements. Another possibility is a switch originating from a brain–computer interface (see Chap. 3) to select the basic grasp pattern or to switch through predefined phases of a grasp sequence (Rupp et al. 2015) (see Chap. 13). Very sophisticated FES stimulators allow for a transparent external control of the stimulation parameters via a—preferably wireless—serial interface. This allows the stimulator to be embedded in a complex neuroprosthesis setup. For safety reasons, real-time control of FES via a serial command stream is not done on a pulse-by-pulse basis but rather on a higher command level. For example, within a stimulator predefined stimulation phases with a unique setting of the stimulation parameters (amplitude, pulse width, frequency) of all channels could be selected by serial commands. By this, the bit rate of the serial data stream and the required bandwidth can be efficiently reduced. A special implementation of this concept is the use of pulse width node maps, with which pulse widths of different channels are assigned to a single command variable (e.g., 0–100). This concept can, for instance, be used to allow a user control of a predefined grasp pattern by a single command variable such as the output signal of a one-axis goniometer. Unfortunately, the number of available stimulation devices providing flexible programming capabilities together with transparent external serial control is low. A major drawback of all the externally controllable stimulation devices is the lack of standardization of the hardware specifications of the control interface and of the serial command protocol. This does not permit the interchange of devices and the sharing of software drivers and modules, which prevents the development of hardware- and vendor-independent applications.

2.12 Conclusion

The activation of electrically excitable biological tissues such as nerves and muscles by external stimulation currents follows well-studied neurophysiological principles. Similar to the physiological condition, the membrane is depolarized by the stimulus until the activation threshold is reached and action potentials are triggered for generation of muscle contractions. The introduction of biphasic, charge-balanced pulses has made it possible to activate nerves and muscles over substantial durations without causing tissue necrosis and skin damage. This paved the way for the restoration of lost motor functions due to SCI by neuroprostheses based on FES. While noninvasive electrical stimulation systems based on surface electrodes are the preferred choice for muscular training and restorative, neurorehabilitative

interventions, implanted electrodes provide a better selectivity, higher robustness, and easier handling for permanent use in neuroprosthetic applications.

An essential prerequisite for successful use of a neuroprosthesis is a preserved neural innervation of those muscles generating the movement patterns relevant for everyday activities. The strength-duration curve as a quantitative measure of the excitability of muscles allows for detection of substantial denervation of muscle fibers. Although it is possible to electrically stimulate denervated muscle fibers to contract, the amount of charge needed for direct activation of muscle fibers exceeds the one of nerve fibers by a factor of 500–1000. A profound knowledge of the neurophysiological principles underlying electrical stimulation of nerves and muscles is needed to correctly select and parameterize the stimulation device.

One of the main problems of FES is the increased fatigue of stimulated muscles in comparison with the physiological condition due to inverse recruitment of nerve fibers. The propensity to early fatigue can be reduced by proper muscle training and the associated transformation of fast- into slow-fatiguing muscle fibers. However, fatigue represents an inherent problem of FES and cannot be completely avoided. This limits the successful use of FES in neuroprosthetic applications where large forces need to be generated over substantial periods.

Most devices for electrical stimulation are quite simple, with predefined stimulation programs designed for single dedicated applications. For complex FES applications, programmable stimulators with a customizable control interface are needed. However, for this purpose neither generalized hardware specifications nor software standards have been established so far. This limitation needs to be addressed in the future to allow shared use of devices and software modules, thereby considerably reducing the resources needed for maintenance and adaption of existing neuroprosthetic solutions and development of new applications.

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Chapter 3
Electroencephalography and Brain–Computer Interfaces

Gernot Müller-Putz and Selina C. Wriessnegger

Abstract This chapter gives an overview on the foundation of the electroencephalogram (EEG), describes its phenomena, and explains how EEG recordings can be performed. This includes types of electrodes, amplifiers, and known artifacts. Further on, the term brain–computer interface (BCI) is introduced and its components and useful experimental paradigms get explained. With an outlook of application scenarios we build the basis for further chapters in this book.

Keywords Electrical brain activity · Electroencephalography (EEG) · Brain–Computer Interface (BCI) · Event-related potential (ERP) · Event-related desynchronization (ERD) · EEG frequency bands

3.1 Introduction

The electroencephalogram (EEG) has already been used to investigate and research brain activity for almost 100 years. A pioneer named Hans Berger, a German neurologist and psychiatrist, discovered the so-called alpha rhythm, a specific type of brain oscillations in 1924 (Berger 1929).

In neuroscience and in related fields EEG is one of the standard methods to measure brain activity and is the most important signal source for non-invasive brain–computer interfaces (BCIs). This chapter highlights the physiological foundation and properties of the EEG and different recording techniques including electrodes, amplifiers, and artifacts. Furthermore, this chapter gives an overview of BCIs, shows its components, and describes briefly the areas of applications.

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3.2 The EEG: Establishment and Components

3.2.1 Origin of the EEG

The human brain consists of an estimated 83 billion neurons. Each neuron has about 10,000 connections to other neurons. This huge neural network, which functions electrically and electrochemically, is made up of many sub-networks. Ion currents emanating from excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs) in these smaller networks cause local extracellular potential changes. The superposition of these potential differences has been named local field potential (LFP) (Buzsáki et al. 2012). Transforming LFPs into the frequency spectrum, a very broad, starting from DC (direct current) up to several hundred Hz (several hundred oscillations per second) picture can be observed. Action potentials (Aps) and synaptic transmissions are held responsible as the main sources of LFPs (Einevoll et al. 2013). It is a plausible assumption that synaptic transmissions are the source of low-frequency components, while APs are the source of high-frequency components (>500 Hz) (Buzsáki et al. 2012). Logothetis et al. (2007) showed that pure ohmic impedance (i.e., the resistance is independent from frequencies) is a sufficient assumption in the frequency range, EEG can be measured and analyzed (<1000 Hz) (Logothetis et al. 2007). If additionally electric dipole sources are assumed, the contribution of single sources to the LFP decays with the square of the distance (Nunez and Srinivasan 2006). A recent modeling of the LFP (Lindén et al. 2011) indicated that for uncorrelated activity a range of 200μm is a realistic assumption. For correlated activity this assessment is more difficult, but they concluded that "...the LFP recorded by an electrode is dominated by populations with substantial synaptic processes in the recording layer." (Lindén et al. 2011). Nearby sources therefore contribute most to the LFP, while the contributions of remote sources are subject to strong attenuation. From this it can be concluded that it is only possible to measure synchronous activity of networks consisting of a large number of neurons on the scalp (Fabiani et al. 2007).

EEG is by far the most common non-invasive method for measuring electrical brain activity. With the help of various types of electrodes, which get mounted at the scalp with EEG caps, it measures brain potentials. These measured potentials are modified versions of the LFPs (Buzsáki et al. 2012). The change has at least two causes. First, as described above, the electric field decays with the square of the distance from the source, and therefore, the LFP substantially attenuates until it reaches electrodes on the scalp. Second, volume conductance of the various head tissues (i.e., brain, cerebrospinal fluid, skull, and scalp) causes spatial smoothing over an area of about 10 cm^2 (Buzsáki et al. 2012).

Due to the attenuation and smoothing, only synchronous brain activity, i.e., brain activity that sums up over brain areas, can be captured with scalp electrodes. Rhythms that occur synchronously are typical for lower frequency ranges of the LFP and are mainly caused by correlated synaptic transmissions. They can be seen as neural dipoles in parallel pyramid cells (see Fig. 3.1) (Buzsáki et al. 2012; Einevoll et

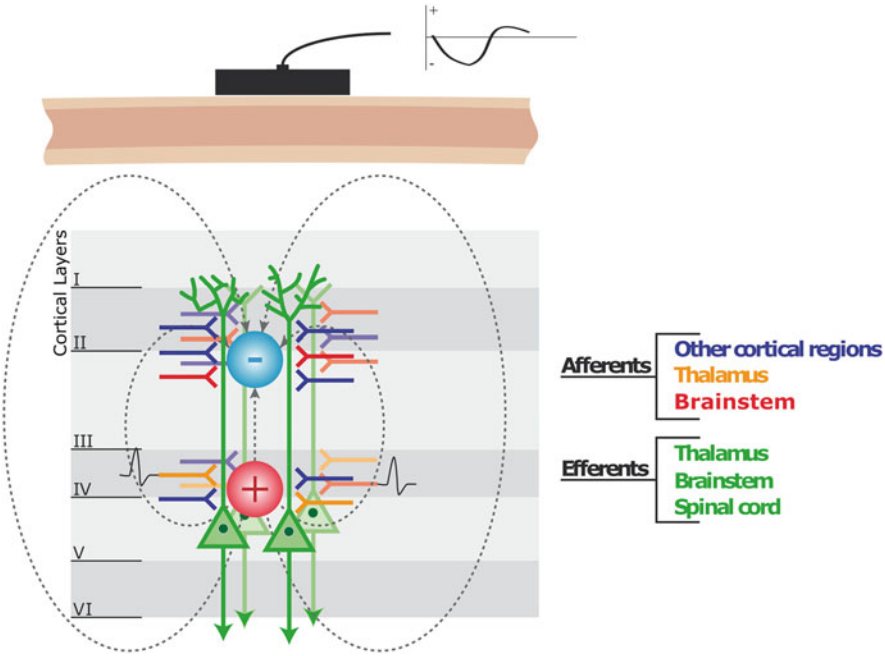

Fig. 3.1 Sketch of EEG signal sources. I–VI indicate the cortical layers. Pyramidal cells are displayed in green and their apical and basal synapses are colored according to their origin. The temporal and spatial dendritic integration of synaptic transmission leads to the formation of a dipole (indicated as red/blue ball indicating +/−). If millions of neurons receive synchronous basal or apical synaptic transmissions, the resulting electric field propagates even over long distances and can be detected on the scalp. There it is called EEG. Modified from (Steyrl et al. 2016)

al. 2013). Since only afferent APs lead to synaptic transmission, it can also be assumed that the main contribution to LFP at lower frequencies comes from this afferent activity of cortex layers 1 to 4 (see Fig. 3.1).

To summarize: (1) APs of afferent fibers in the cortex can cause synaptic transmissions. (2) Synaptic transmission, which correlate form parallel neural dipoles. (3) They contribute most to synchronous low-frequency components of the LFP and therefore also contribute to the scalp potentials and therefore to EEG.

The potential deflection depends on the number of synchronously active cells—the more cells are synchronized in a population, the higher the potential deflection, and therefore also the amplitude in the EEG. The sign of the deflection depends on the sign of the "neuronal dipole," i.e., in the following, on the place where the EPSPs currently appear (see Fig. 3.1). The main contribution to EEG comes mainly from cortical structures. This is in contrast to deep brain structures (e.g., amygdala). There, electric fields of neurons are typically oriented in various directions, which impedes the summation of potentials and therefore they distinguish each other (LORENTE de NO 1947). Dipoles generated in such brain structures are not large

enough (Harmon-Jones and Beer 2012) to be recorded as EEG oscillations at the scalp. To some extent, this holds also true for the orientation in sulci.

3.2.2 Brain Signals

In general, the EEG can be subdivided into two types of brain activity. Consequently, there are also two major types of EEG-based BCIs: (1) spontaneous or continuous EEG, which originates from internally induced processes and mental tasks that generate mainly changes in the ongoing EEG. (2) Event-related potentials are based on specific events or external stimuli and can be modulated through a cognitive contribution of the participant. The next section discusses these two different phenomena.

3.2.2.1 Spontaneous EEG

The continuous or spontaneous EEG is the ongoing brain activity and can be derived from individuals permanently. The signal amplitude in the healthy waking brain is typically below 75μV (Gevins and Smith 2006). Most of the signal power originates from rhythmic oscillations in a frequency bandwidth from below 1 Hz to approximately 40 Hz, even though higher frequencies are also measurable up to 100 Hz (Schomer and da Silva 2012). Historically, this frequency range got subdivided into smaller, functional frequency bands with associated names (Schomer and da Silva 2012), see Table 3.1.

When it comes to the analysis of ongoing EEG and specific rhythms, it is important to know that those can be time-locked to an event, but they are always non-phase locked. This means, when one compares to similar trials, the amplitude behavior may be similar; however, the oscillations do not have the same phase. There are several methods to analyze spontaneous EEG, but in contrast to analysis of event-related potentials (ERP), simple averaging over trials does not work (see Sect. 3.2.2.2). To get a first and solid impression of spontaneous EEG activity related to various conditions, one of the standard methods used in EEG but also BCI research is to compare power values of a specific frequency band with respect to a reference period. The method is named event-related (de)synchronization (ERD/ERS) and introduced by Pfurtscheller in the late 1970s (Pfurtscheller and Aranibar 1977). A detailed description can be found in (Pfurtscheller and Lopes da Silva 1999). This method compares band power values during an activity period with a reference band power of a defined reference (resting) period. This comparison results in relative band power changes given in %. A negative value indicates a desynchronization of activity, meaning lower amplitudes than in the reference period and indicating active, asynchronously working networks (Pfurtscheller et al. 2000a, b; Müller et al. 2003). Positive values, however, indicate a synchronization which can reflect (re) synchronization in mu rhythms, e.g., after a movement or even a post-movement

Table 3.1 EEG frequency bands, relevant functions, and references

Name	Frequency band	Description
α—alpha	8–13 Hz	Amplitudes are typically very large and can be ten times μV. Indicates states of relaxed wakefulness; resting periods with eyes closed and amplitudes are largest in the occipital areas; neural correlate of cognitive inactivity (cortical "idling"). Studies with evoked EEG activity (i.e., investigations of event-related potentials) showed that alpha rhythms may indicate different forms of information processing in which different alpha sub-bands (e.g., 8–10 Hz and 10–13 Hz) are dedicated to different functional processes.
	Berger (1929) Pfurtscheller et al. (1996) Niedermeyer (1997), Klimesch (1999)	
μ—mu	8–12 Hz	Alpha rhythms originating from sensorimotor areas can be further subdivided into lower (8–10 Hz) and higher (10–12 Hz) mu rhythms. Large amplitudes indicate resting sensorimotor areas.
	Pfurtscheller et al. (2000b)	
β—beta	13–30 Hz	Amplitudes are usually in the μVs. Related to several mental states: Active concentration, task engagement, excitement, anxiety, attention, or vigilance, but also indicates sensorimotor activity. Beta activity primarily constitutes an excitatory mechanism (Pfurtscheller and Lopes da Silva 1999).
	Pfurtscheller and Lopes da Silva (1999)	
γ—gamma	30–200 Hz	Amplitudes are usually between 1 and 2μV (Hughes 2008). Very high-frequency activity (30–200 Hz). Associated perceptual binding mechanisms (i.e., integration of various aspects of a stimulus into a coherent overall perception) and arousal.
	Hughes (2008)	
δ—delta	~0–4 Hz	Amplitude can be several tenth of μV. Very low-frequency activity; relates to deep and unconscious sleep. Associated with pathological neural states, such as the loss of consciousness or coma. Diminishes when age increases, which suggests that delta activity is primarily an inhibitory mechanism (Hobson and Pace-Schott 2002).
	Hobson and Pace-Schott (2002)	
ϑ—theta	4–8 Hz	Amplitudes are typically between 8 and 10μV (Cahn and Polich 2006). Theta waves are associated with specific sleep states, drowsiness, and meditation. Frontal midline theta is associated with mental effort, suggesting that attention is directed to existing stimuli.
	Cahn and Polich (2006)	

beta synchronization, a short burst with high amplitudes (Neuper and Pfurtscheller 1996; Pfurtscheller et al. 1998; Pfurtscheller and Solis-Escalante 2009). Similarly, other mental, attempted, or real tasks lead to different ERD/ERS time-frequency patterns (Obermaier et al. 2001; Friedrich et al. 2012, 2013a, b; Wriessnegger et al. 2018b). By the calculation of these values over a duration of a whole trial and for

several frequency bands, either overlapping or neighboring, ERD(S) maps representing time-frequency plots can be obtained (Graimann et al. 2002).

EEG oscillations recorded on the scalp only represent a subset of the electrical brain activity at a particular point in time. There is evidence that slow oscillations (e.g., theta) span larger neural populations, while faster oscillations (e.g., gamma) span smaller neural assemblies (Buzsáki and Draguhn 2004). Depending on the number and distribution of the electrodes, the position of the reference electrode several spatial filters needs to be applied. (More specific details about filtering in the section Preprocessing below).

3.2.2.2 Event-Related Potentials

Event-related potentials (ERPs) mainly originate from specific external stimuli or from tasks performed by the participant itself. When there are simple stimuli like visual, auditory, somatosensory, or even olfactory, then the potentials elicited get called evoked potentials (EPs). However, ERPs can also be elicited by actions which are generated by a person's internal volition to perform a task, e.g., when a person starts a movement or even when such a single movement is attempted or imagined (Shibasaki et al. 1980). This particular example of ERP illustrates the movement-related cortical potential (MRCP). The odd-ball paradigm leads to the establishment of another—in BCI research very important signal—the P300 component of an ERP (Donchin 1981; Polich 2007). By presenting many non-targets and rare target stimuli, the P300 elicited in the scalp midline electrode positions and can be used, inter alia, to establish BCIs for relatively fast communication (Farwell and Donchin 1988). Another example of an ERP is the error-related potential (ErrP). After a stimulus, which seems erroneous to a person due to a mismatch in his or hers expectation, the elicited ErrP can be recorded from the midline of the scalp (Falkenstein et al. 1991).

A specific definition is given by Regan (1989):

> An EP is a transient wave complex elicited by a certain stimulus or event that is, to be precise, repeated only once. The averaged transient EP reflects a true response if the relevant brain mechanisms were in their resting states before each stimulus, and return to their resting states before the next stimulus. It is consequently assumed that the EP response to a single event does not depend on a previous one.

ERP signals are typically not very strong, and, hence, it is difficult to distinguish them from the ongoing EEG in single-trial data. However, by repeated presentation of stimuli and averaging of the EEG responses, these ERPs can be made visible. Since spontaneous EEG is neither time-locked and nor phase-locked to the stimulus, averaging increases the signal-to-noise ratio (Fabiani et al. 2007; Regan 1989; Luck 2014) by the square root of the number of repetitions when comparing signals in μV. In BCI research, however, one goal is to achieve single-trial detection, in which case specific paradigm design, signal processing techniques, and machine learning

approaches are necessary. More details are given in Sect. 3.3 Brain–Computer Interfaces.

When a stimulus gets presented with a high repetition rate, usually higher than 6 per seconds, the so-called steady-state evoked potentials (SSEPs) are evoked (visual, tactile, or auditory). A specific definition is given by Regan (Regan 1989):

> SSEPs occur when sensory stimuli are repetitively delivered at high enough rates so that the relevant neuronal structures are prevented to return to their resting states. [. . .] Ideally, the discrete frequency components remain constant in amplitude and phase within an infinitely long time period. [. . .] In practice, SSEPs never completely fulfill this definition of an ideal SSEP.

3.2.3 Recording, Electrodes, Amplifiers, and Artifacts

3.2.3.1 Positioning of the Electrodes

For proper EEG recordings, especially when doing group studies, electrode locations need to be placed on (almost) the same position for every measurement. A standard positioning system, the 10–20 system was proposed by Jasper and colleagues in the late 1950s. It is one of the most recognized methods to describe the locations of the EEG electrodes. It ensures that the inter-electrode distances are equal ("The Ten Twenty Electrode System: International Federation of Societies for Electroencephalography and Clinical Neurophysiology" 1961). In that system, electrodes are placed at sites 10% and 20% from four anatomical landmarks: the nasion, inion, right, and left preauricular points. Achieving also higher spatial resolutions, extra electrodes can be added to the 10–20 system, leading to higher electrode densities such as the 10–10 or 10–5 systems. For that, intermediate positions between those of the original 10–20 system have been added (Oostenveld and Praamstra 2001). Figure 3.2 shows a 10–5 system with labels of the original 10–20 system only. For the naming of electrode position the following convention exist:

The position consists of two or three characters, where the first one refers to the cortical area (F = frontal, C = central, P = parietal, T = temporal, and O = occipital). Electrode positions between these areas are labeled using two characters (e.g., CP = central-parietal). The number following the character(s) indicates the site. Odd numbers indicate sites on the left hemisphere and even numbers indicate positions on the right hemisphere. Midline electrodes (which are in line with the nasion and the inion) have a "z" instead of a number as indicator. The midline electrode at the half-length from nasion to inion at the vertex is named Cz. This position is used very often as reference point when mounting the cap. Moreover, numbers increase as distance from the midline increases (see, for example, Fz, F3 F7 in Fig. 3.2).

However, for specific studies or applications, such as in the BCI field, researchers often choose individualized and/or end-user-specific electrode arrangements. The rules described above are usually applied in part (Hänselmann et al. 2015).

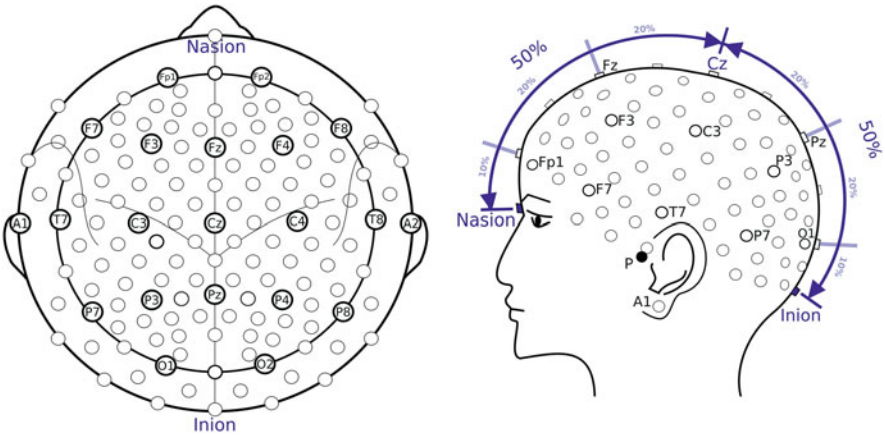

Fig. 3.2 Scheme of a 10–5 electrode system. Standard electrode positions according to the 10–20 system are labeled. A1 is the earlobe, P shows the preauricular point. It is on the line between nasion and inion above the tragus. Based on (Oostenveld and Praamstra 2001), taken from (Müller-Putz 2020)

3.2.3.2 EEG Electrode Principles and Amplifiers

When scientist started to record EEG in 1924, they inserted steel needles into the subcutaneous tissue of the scalp and used galvanometers to visualize and interpret the recorded signals (Berger 1929). With technological developments to amplify very small EEG signals, the quality and the interpretability of the signals improved drastically. At that time, in 1931, Berger introduced silver chloride (AgCl) covered electrodes, which is still a standard (Collura 1993).

For EEG measurement, a conductive connection must be made in the gap between the electrode and the skin surface. The electrode gel is standard. Currently, there are three main types of electrodes in use: gel-based electrodes, water-based electrodes, and dry electrodes. The latter, as the name suggests, do not require any additional conductive substance. Figure 3.3 shows different types of EEG electrodes.

Gel-based electrodes can be divided according to the use of abrasive gel or hydrogel. For passive electrodes mainly abrasive gel is used. In contrast, hydrogel is used for active electrodes. In such electrodes, a tiny preamplifier sits on the electrode and provides pre-amplification, thus increasing the robustness of the signals, which are then routed to the main amplifier. The main difference between the two types of gel is that abrasive gel removes dead cells and a small amount of fat from the top layer of skin in a time-consuming procedure to reduce the impedance. This can lead to skin irritation, and in rare cases to infection or inflammation. For both gel types, it is necessary for participants to wash their hair after the measurement. With water-based electrodes, felt or similar tissue is soaked in water or saline solution to connect the electrode to the skin. Using tap water to connect the two surfaces is a relatively new and practical method. This type of electrode should

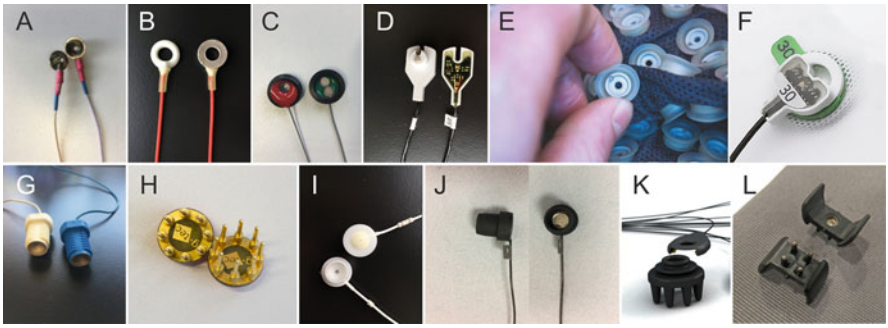

Fig. 3.3 Examples of electrodes. (**a**) cup electrode, (**b**) passive sintered AgCl electrode, (**c**) gel-based active Ag/AgCl electrode (g.LADYbird from g.tec), (**d**) gel-based active ActiCap electrodes (Brain Products GmbH), (**e**) gel-based wavegard electrodes (ANT Neuro), (**f**) gel-based active Ag/AgCl (actiCAP, BrainProducts), (**g**) passive gold electrodes for cap montage, (**h**) passive dry electrode with gold-coated pins (g.SAHARA electrode, g.tec), (**i**) (tap) water-based passive electrode (Mobita, TMSi), (**j**) (tap) water-based passive electrode (BitBrain Technologies), (**k**) hybrid electrode unicorn black (g.tec), (**l**) passive dry electrodes with pins (BitBrain Technologies)

provide a very good signal quality, the electrode assembly is less time-consuming, and no hair washing is required after the measurement (Volosyak et al. 2010).

Dry electrodes, in contrast, work without any additional conductive gel or other substance. Pins made of conductive rubber or metal alloy are pressed directly onto the skin, and rely on small amounts of existing perspiration to get a good contract, i. e., a low impedance with the skin. Several studies have highlighted the advantages of different dry electrode-based systems (Zander et al. 2011; Guger et al. 2012; Mota et al. 2013). However, experience shows that a main disadvantage of this type of electrodes is their sensitivity to movement and to capacitively coupled artifacts. Recently, so-called hybrid electrodes have also become available. These can be used dry on the one hand, but can also be additionally filled with gel and then used like gel electrodes to improve the signal quality.

Looking at the electrode technology from the perspective of the BCI end user, maximum comfort has to be achieved and additional inconveniences such as hair washing have to be eliminated. From a technical point of view, it is important to have a high signal-to-noise ratio so that BCI performance is not impaired by a poor impedance. The development of a system that is user-friendly and at the same time delivers the desired signal quality is a challenge. Recently, three different commercially available EEG amplifier systems were evaluated. They differed in the type of electrodes (gel, water, or dry electrodes), the amplifier technology, and the data transmission method. Each system was tested for three different aspects, namely (1) technical aspects, (2) BCI effectiveness and efficiency (P300 for communication and control), and (3) user satisfaction or comfort. The findings indicate that there is not one system, which is superior to the others. The water-based EEG system had the lowest short circuit noise level, the gel-based system had the highest P300 spelling

accuracy, and the dry electrode-based system caused the least inconveniences for the user (Pinegger et al. 2016).

Another recent study (Melnik et al. 2017) investigated the variance across four different EEG systems compared to the variance across subjects or sessions. The study comprised one mobile EEG system with dry electrodes, one consumer-grade system with a low number of channels, and two standard gel-based research-grade systems. They recorded EEG of four participants three times with each of the four EEG systems in six different standard EEG paradigms. As a result, no significantly different means from each other across all paradigms were derived with the two standard research EEG systems. However, EEG from the two other systems demonstrated different mean values from one or both of the two standard research-grade EEG systems in at least half of the paradigms.

It can be concluded that the decision which electrode technology should be used depend on the type of application and its requirements (Nijboer 2015). Furthermore, this is often strongly coupled with the choice of the amplifier, since many of those electrodes are company-specific.

EEG amplifiers are based on instrumentation amplifiers specifically designed to record very small voltage changes (in the range of μV) without putting a load on the signal source, i.e., the electrical sources of the brain. This means that the input impedance of the amplifier needs to be very high (>100 MOhm), so that there is minimal loading of the signal. Also, common signals (in phase and amplitude) recorded by the electrode and the reference will be dampened with a very high factor. This parameter of the amplifier is called common mode rejection ratio and is usually in the range of 150 dB (in ideal cases the output would be zero). Filter settings of low pass filters and high pass filters (in former days described with the time constant) can be adjusted via software or are preadjusted in a very broad way. Nowadays, all modern EEG amplifier systems have built-in analog-to-digital conversion and get connected to the computer via USB, local network connection, or are even wireless. To meet safety regulations and for the protection of the organism, isolation circuits are inbuilt.

Figure 3.4 gives an overview of typical EEG amplifiers used in BCI settings, except the old fashioned clinical EEG amplifier used in earlier days.

3.2.3.3 EEG Artifacts

Performing BCI research implies online single-trial classification. Therefore, it is very important to process clean or artifact-free EEG signals. However, there is always the danger of having contaminated data and therefore developers of BCI systems must carefully consider artifacts. Generally, technical and biological artifacts can be described.

Technical artifacts are mainly caused by external electrical and electromagnetic noises coming from power lines, electric machines, lights, or other fields. High impedances due to poor electrode contact can foster electromagnetic artifacts. Wrong electrode material can lead to high pass effects, which, in the consequence,

Fig. 3.4 Overview of Amplifiers: (**a**) old fashioned clinical ink-based EEG device (Neurofax, Nihon Khoden), (**b**) g.USBamp, 16 channel device, with USB connection to PC (g.tec medical engineering GmbH), (**c**) 32 channel Liveamp, wireless connection (Brain Products GmbH), (**d**) ANT Neuro eego amplifier, (**e**) TMSi water-based EEG, wireless connection, (**f**) BitBrain Technologies 16 channel brain-amp, wireless connection, (**g**) unicorn hybrid 8-channel, wireless connection (g.tec medical engineering GmbH)

can hide the requested signal—e.g., gold versus Ag/AgCl. Amplifier noise, i.e., the quality of the electronic components in general and quantization noise of the analog-to-digital conversion are covert artifacts. Aliasing effects due to wrong adjusted low pass filters can be problematic, but nowadays the amplifier supplier takes care of this.

Reducing technical artifacts, following countermeasures can be applied: shielding of the amplifier and recording system, high-quality amplifiers, and in-built filters (e.g., notch filters to remove power line noise). Impedances (electrode-skin impedance) should be low and checked before measurements. Modern systems provide an automatic impedance check. Finally, proper grounding of the participants to reach potential equalization between participant and measurement system is mandatory.

Main sources of biological artifacts are participants' muscle activities (EMG: electromyogram) mainly caused by contractions from neck and face muscles, eye blinks, eye movements, and saccades (EOG: electrooculogram). Baseline drifts, i.e., drifts of the zeroline of the signal due to sweating can also be problematic. While EOG covers a narrow low frequency range from DC up to 10 Hz, EMG occurs in a range between 20 and 1500 Hz. Artifacts from saccades are in higher frequencies. In standard EEG measurements and basic BCI studies, concurrent recordings of the EOG and EMG are performed usually so that artifacts can be detected or artifact removal algorithms can be applied. Importantly, in online systems where EEG data is processed and e.g., feedback to a user is generated, artifacts must be detected and somehow indicated. Independent from the type of data processing—offline or online—both, visual and automatic artifact detection (Oostenveld and Praamstra 2001; Scherer et al. 2007) or removal (Schlögl et al. 2007; Daly et al. 2015; Kobler et al. 2019) are important to record or process correct and artifact-free signals (i.e., non-artifactual features).

3.3 Brain–Computer Interfaces

A BCI translates brain activity such as measured by the non-invasive EEG into messages for communication and control. A more detailed definition describes a BCI as follows: "A BCI is a system that measures central nervous system (CNS) activity and converts it into artificial output that replaces, restores, enhances, supplements, or improves natural CNS output and thereby changes the ongoing interactions between the CNS and its external or internal environment" (Wolpaw 2012; Wolpaw and Wolpaw 2012). This definition also includes BCIs that do not require intentional control, which are sometimes referred to as passive BCIs (Zander et al. 2011). To generate detectable EEG patterns, BCI users must perform specific cognitive activities which result in different mental states. Feature extraction techniques are applied to the EEG signals for detection of these brain states. One way to generate distinct EEG patterns is to focus attention on external sensory stimuli like visual or tactile stimuli. After the presentation of a perceptually significant event, the P300 evoked potential (EP) can be detected which is a positive deflection occurring about 300 milliseconds after the stimulus. Alternatively, endogenously induced EEG patterns can be elicited by mentally engaging in a task. For example, imagination of limb movements results in a change of the amplitudes of different oscillatory EEG components (Pfurtscheller and Neuper 2001; Neuper et al. 2006; Friedrich et al. 2013a, b). These changes can then transformed into control signals by means of machine learning and pattern recognition algorithms (Lotte and Jeunet 2015; Lotte et al. 2018; Birbaumer et al. 1999).

BCIs can be used to interact and control applications. These include:

- communication devices (Birbaumer et al. 1999; Pokorny et al. 2013; Sellers et al. 2014; Faller et al. 2014; Halder et al. 2015; Pinegger et al. 2015)
- digital services (Leeb et al. 2007; Scherer et al. 2017; Si-Mohammed et al. 2020)
- neuroprostheses (Pfurtscheller et al. 2000a, b, 2003; Rohm et al. 2013)
- assistive devices (Müller-Putz et al. 2005a; Galán et al. 2008; Münßinger et al. 2010; Nijholt 2019)
- art (Galán et al. 2008; Münßinger et al. 2010).

Another type of BCIs monitors the ongoing brain activity with the aim of identifying specific mental states which are correlated to e.g., cognitive workload, attention, or fatigue (Roy et al. 2014; Sargent et al. 2018; Lamti et al. 2019; Zeng et al. 2019; Myrden and Chau 2017). A passive BCI is defined as a system that derives its outputs from arbitrary brain activity without the purpose of directly controlling an application, but rather for enriching human–machine interaction by providing implicit information on brain states (Zander and Kothe 2011). In recent times, such passive BCI systems have become increasingly interesting for the BCI research community. One reason might be the substantial improvements in the reliability and usability of BCI control (Edelman et al. 2019; Zhu et al. 2019; Abu-Rmileh et al. 2019; Guger et al. 2019), another reason could be the huge potential of these systems not only in end users with disabilities, but in particular in non-disabled people for

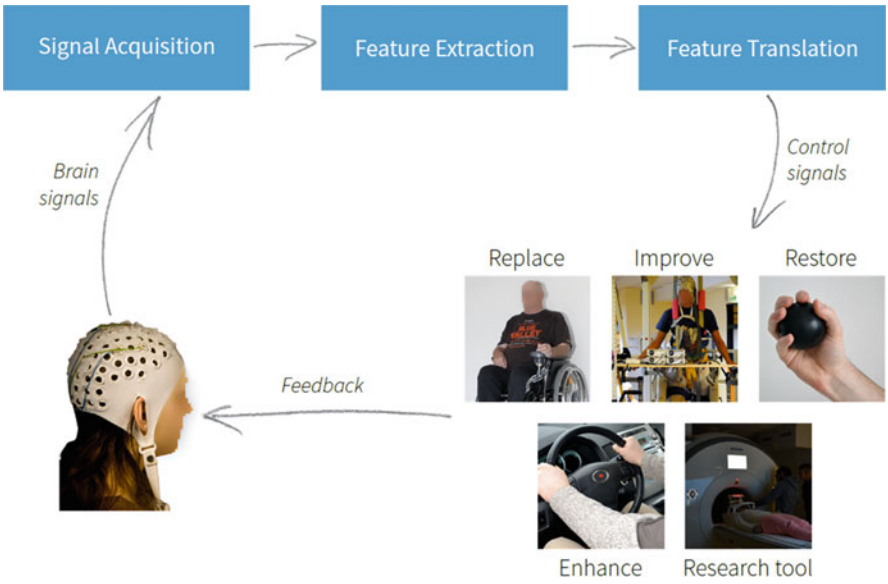

Fig. 3.5 Basic concept of a BCI. A BCI represents a closed-loop system with (1) signal acquisition, (2) feature extraction and translation (i.e., classification), (3) generation of control signals for various applications, and (4) feedback to the user

real time mental state evaluations. Having access to the user's ongoing brain activity enables applications spanning a wide variety of domains such as brain activity based gaming (Nijholt 2008; Bos et al. 2010), brain activity-based biometrics (Marcel and Millan 2007), or neuro-economics (Glannon 2016; Ayaz and Dehais 2018; Nam et al. 2018). BCI technology can also reveal valuable information about the user state in safety-critical applications, such as driving (Welke et al. 2009), industrial environments, or security surveillance (Fig. 3.5).

3.3.1 History of BCIs

Historically, BCI research began in 1973, when J. J. Vidal introduced the term "brain-computer interface" and its concept to the scientific community (Vidal 1973). But it took over a decade before BCIs have evolved to a serious research field with numerous high-quality publications in respected journals (for a review see: Lebedev et al. n.d.; Wolpaw et al. 2002; Lebedev and Nicolelis 2006; Nicolas-Alonso and Gomez-Gil 2012). Moreover, in the 1990s Farwell and Donchin introduced the, in the meantime, well-established so-called P300 speller (Farwell and Donchin 1988). This BCI enables the spelling of letters based on attention, more concretely on the detection of ERPs. ERPs are deflections in the EEG in response to a specific external stimulus. One type of ERP is the P300, a late positive deflection (around 300 ms after

stimulus presentation) in the EEG. In Europe, some years after the introduction of the P300-speller, other researchers, namely Gert Pfurtscheller and his team from the Technical University of Graz in Austria, developed another BCI system based on the analysis of sensorimotor rhythms (SMRs) (Pfurtscheller and Neuper 1993). SMRs are specific motor-related oscillatory activities, which can be recorded in the EEG over the sensorimotor cortex. Pfurtscheller and colleagues used machine learning methods to detect brain patterns elicited during the imagination of left or right hand movements and to translate them into commands for computer control. This type of BCI is commonly known as motor imagery-based (MI) BCI. Around the same time, another type of BCI, the so-called Thought Translation device (TTD), was developed by Birbaumer and colleagues (1999). This BCI is based on slow cortical potentials (SCP) which are low-frequency variations in brain signals. The rationale for using SCPs for a BCI is formed by the fact that SCP amplitudes can be voluntarily modulated by the user after neurofeedback training. This means that after successful training a user is able to select a group of commands for e.g., text entry on a virtual keyboard, by voluntarily increasing or decreasing the SCP amplitude.

This pioneering work has contributed significantly to the development of new BCI systems in over the past decades. Beside intensive research and development in the year 2000 and following, BCI researchers also organized themselves as an independent research community. In 1999, the first International BCI meeting was held in the USA with 50 participants from 24 research groups worldwide. This retreat-like BCI meeting evolved to the largest scientific exchange forum for BCI researchers worldwide. In 2000, the Graz BCI Group started its BCI Workshop and Training Course which further developed to the Graz Brain–Computer Interface Conference. In 2019, this international event took place for the eighth time. Ultimately, the BCI Society (https://bcisociety.org/) was founded in March 2015. It takes care of organizing the BCI Meeting every second year (in 2021 in Brussels) and puts effort in putting together the whole (invasive and non-invasive) BCI community.

While BCI research traditionally focused almost exclusively on replacing and restoring lost functions in people with disabilities (Müller-Putz et al. 2005a; Neuper et al. 2006; Silvoni et al. 2011; Lesenfants et al. 2014; Salisbury et al. 2016; Wolpaw et al. 2018), in the most recent years interest in additional fields of applications has increased substantially (Zander and Kothe 2011; Lotte et al. 2012; Brunner et al. 2015; Pinegger et al. 2015; Chun et al. 2016; Ayaz and Dehais 2018; Kerous et al. 2018; Putze 2019). The “BNCI Horizon 2020 Roadmap” (Zander and Kothe 2011; Lotte et al. 2012; Brunner et al. 2015; Pinegger et al. 2015; Chun et al. 2016; Ayaz and Dehais 2018; Kerous et al. 2018; Putze 2019) provides a comprehensive overview of all potential fields of BCI applications which are summarized later in this chapter.

3.3.2 *Definitions of BCIs*

From a user-centered approach, BCI systems can be categorized into three different types (Fig. 3.6): The *active* BCI systems derive their outputs from brain activity which is directly consciously controlled by the user. *Reactive* BCI systems derive their outputs from brain activity modulated by external stimuli. In contrast to the latter ones *passive* BCI systems derive their outputs from arbitrary brain activity without the purpose of voluntary control (Zander and Kothe 2011).

Active BCI

The term active BCI is commonly used for systems where users actively generate modulations of brain signals in order to control devices such as computers, wheelchairs, or neuroprostheses. A prominent example of an active BCI for device control is the MI-based Graz BCI system (Pfurtscheller et al. 2000a, b; Pfurtscheller and Neuper 2001; Neuper et al. 2006). The Graz-BCI is based on the analysis of oscillations in the mu and beta frequency bands of the EEG, which are reactive to both motor imagery and motor execution. Originally the system was designed to discriminate two classes of motor imagery, namely left versus right hand movements. The common feature of these two MI patterns is a contra-lateral event-related desynchronization (ERD), along with an ipsi-lateral event-related synchronization (ERS) (Pfurtscheller and Lopes da Silva 1999; Neuper et al. 2006). For example, when a user imagines a right hand movement, the activity in the mu frequency bands of the corresponding sensorimotor areas of the brain decreases in the left hemisphere and increases in the right hemisphere. The classification of such ERD/ERS patterns in single EEG trials during episodes of motor imagery forms the basis of this SMR

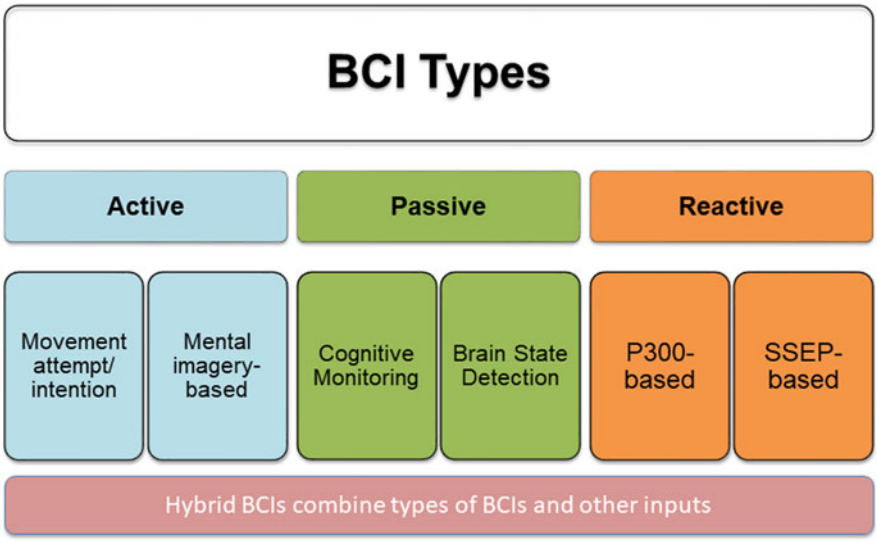

Fig. 3.6 Types of BCIs categorized into active, passive, and reactive BCIs

controlled BCI. Another example of active BCIs is hybrid BCIs which are composed of at least one BCI and another system providing additional control signals (e.g., another BCI, eye tracker, electrocardiogram, joystick, etc.). According to Pfurtscheller et al. (Pfurtscheller et al. 2010), a hybrid BCI system must meet the following criteria: (1) The system must rely on activity recorded directly from the brain, (2) the recorded brain signals, which can be intentionally modulated, must provide input to the BCI, (3) the signal processing must occur in real time, and (4) the user must obtain feedback about the success or failure of his/her efforts to communicate or control.

Reactive BCI

In reactive BCIs, the information about a user's intention is embedded in the brain signals related to external stimuli. By paying attention to target stimuli, a specific brain signal pattern is evoked every time the stimulus is presented. By detecting this specific pattern, a user's intent can be classified. For example, in a steady-state visual evoked potential (SSVEP)-based BCI, the user has to focus on different light sources each flickering with a specific constant frequency (Kelly et al. 2005; Müller-Putz et al. 2005b; Ortner et al. 2010; Faller et al. 2010; Lesenfants et al. 2014). In response to the visual stimulation, the flickering frequency of the light source in the focus of the user appears in the brain activity in the occipital area. Specifically, this means that the brain signal contains a prominent oscillation at 13 Hz, when the user attends to the light source flickering at 13 Hz. Besides visual, also somatosensory stimulation has been successfully implemented in reactive BCIs (Müller-Putz et al. 2006; Breitwieser et al. 2016; Pokorny et al. 2016). An established example of a reactive BCI is the P300 speller (Farwell and Donchin 1988), which has been already explained in the previous section.

Passive BCI

The primary goal in passive BCI is the continuous monitoring of a user's mental states (cognitive monitoring) without the purpose of controlling a device (Zander et al. 2011). In concrete terms, a passive BCI aims at quantifying the level of mental fatigue, workload, or attention to facilitate a human–computer interaction (brain state detection). Having access to the user's ongoing brain activity enables applications spanning a variety of domains such as brain activity based gaming (Nijholt 2008; Bos et al. 2010; Kerous et al. 2018), brain activity-based biometrics (Palaniappan 2006; Pfurtscheller and Neuper 2006; Pfurtscheller et al. 2006; Marcel and Millan 2007; Al-Hudhud et al. 2019), and neuromarketing (Brouwer et al. 2015; Wriessnegger et al. 2015; Kalaganis et al. 2018; van Erp et al. 2012). This BCI technology can also reveal valuable information about the user state in safety-critical applications, such as driving (Lin et al. 2010; van Erp et al. 2012; Zhang et al. 2017; Kalaganis et al. 2018), industrial environments, or security surveillance (Blankertz et al. 2010; Arico et al. 2017; Aricò et al. 2018) by using the implicit information of the user's actual mental states. With respect to driving assistance applications, recent studies have explored the use of BCI systems in a simulation environment for assessing driving performance and inattentiveness, as well as robustly detecting emergency brake intents before actual braking onset (Venthur et al. 2010). Other

studies show the successful use of passive BCIs for determination of cognitive workload levels workload types, or to compare user interfaces' cognitive utility (Antonenko et al. 2010; Iwata et al. 2010; Gerjets et al. 2014; Chin et al. 2018). It may also be possible to use passive BCIs for continuous evaluation of the user interfaces cognitive utility and redesign them in real time to dynamically adapt to users' states. This list of applications of passive BCIs is not exhaustive, but shows only a few examples of the wide range of its applications.

3.3.3 Components of a BCI

3.3.3.1 Recording Site

BCIs typically are based on the recording and analysis of the bioelectrical brain activity. Although BCI approaches exist where metabolic signals like BOLD (blood oxygenation level dependent) signal changes recorded by functional magnetic resonance imaging devices (fMRIs), oxygenation of hemoglobin (via functional near-infrared spectroscopy, fNIRS) or non-invasive recordings of the magnetoencephalogram (MEG) were investigated. Practical applications for communication and control are based on the non-invasive recording of the EEG or invasive recordings of the ECoG or even multi- or single cell activity (Fig. 3.7). While a single non-invasive EEG electrode records the summed electrical activity of a high number of neurons over a large cortical area, ECoG electrodes are typically placed subdurally providing a much higher spatial resolution. Intracortical microarrays with an electrode length of about 1 mm penetrate the cortex up to layer IV. There, single and multiple cell activities can be recorded with a very high spatial. More details on ECoG and direct cell recordings can be found in Chap. 9.

3.3.3.2 Experimental Strategies

BCIs do not only differ in respect to the recording sites, but also according to their underlying physiological principle. Although they are all based on the detection of brain signal patterns, active and reactive BCIs used for control are based on different operating principles, which means the way in which brain patterns are modulated by a user during specific tasks.

Operant Conditioning

Generally, operant conditioning (also called instrumental conditioning) is a learning process through which the strength of a behavior is modified by reinforcement or punishment. This type of learning was first introduced and investigated by two

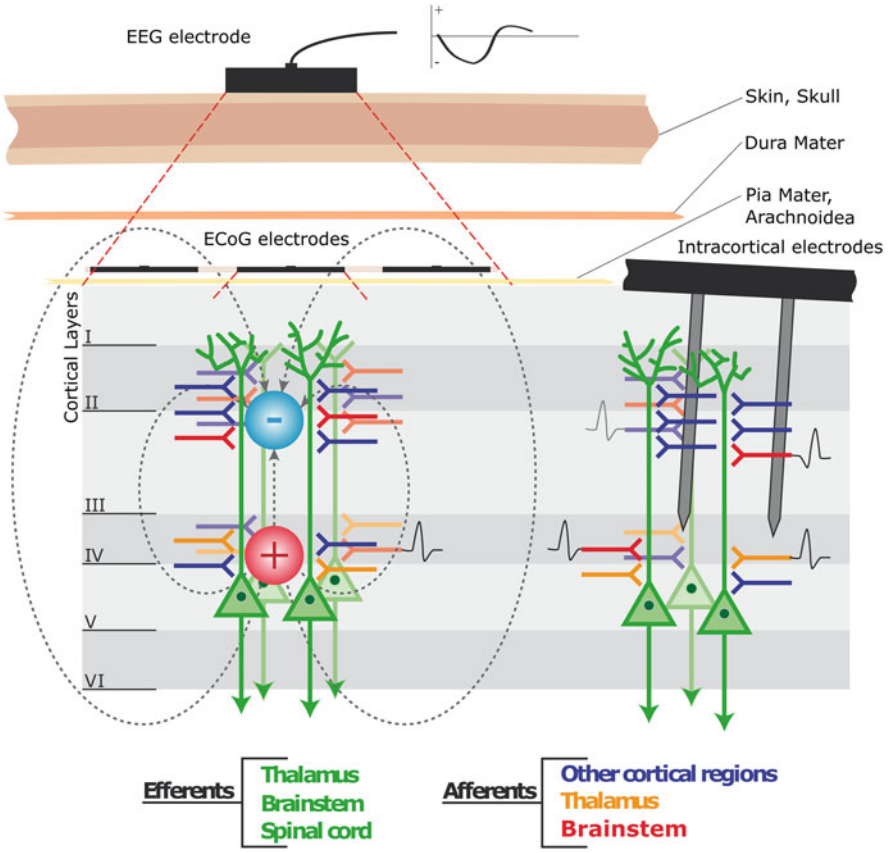

Fig. 3.7 Qualitative overview of the spatial resolution of non-invasive and invasive recording electrodes. Classical EEG electrodes on the intact scalp record activity of neurons (dipole is indicated as red/blue balls containing +/−) within several square centimeters (red dashed lines). Subdurally placed ECoG electrodes record from the surface of the brain and have a higher spatial resolution than the EEG electrodes (see red dashed lines). Intracortical microarray electrodes penetrate the cortex for about 1 mm and record the activity of a few cells in the vicinity of the electrode

famous psychologists, E. L. Thorndike (1874–1949) and B.F. Skinner (1904–1990) (Skinner 1971; Huitt and Hummel 1997). In animal and human studies, they observed that living creatures learn simple behaviors through operant conditioning. Behavioral reactions are maintained when they lead to a positive successful outcome and rejected when they produce negative or aversive effects. Using this principle in a BCI environment, a BCI operation must be seen as the interaction of two adaptive controllers, the BCI user on the one hand and the BCI system on the other (Wolpaw et al. 2002). Using operant conditioning, the user is expected to adapt her/his brain activity patterns and the analyzed signal features to the classification algorithm (Birbaumer et al. 2003), concretely by reinforcement learning. This means when

the user adapts the features appropriately, the BCI produces the output that the user intends. Based on this common principle, different experimental strategies for operation of a BCI are used based on attention or cognitive efforts such as motor imagery, attempt, or intention.

Focused Attention

In attention-based BCIs advanced computer algorithms are used to decode the brain signals which are associated with attention. External stimuli, e.g., different visually presented objects or lights, evoke specific neural responses which can be controlled by the users directing their attention to the stimuli of their choice. For example, Ray et al. (2008) found changes in high gamma band activity (30–80 Hz) when individuals concentrated on either a sequence of auditory or tactile stimuli. Other studies used attention-based BCIs analyzing EEG oscillations as a treatment of attention deficit hyperactivity disorder (ADHD). Another attention-based BCI based on ERPs is the P300-BCI with the P300-speller being the most established application. In P300-based BCIs, the participants have to look at a matrix of characters on a computer screen. While the matrix columns and rows flashed they have to focus on one letter of their choice and count silently how often this letter has been highlighted. Whenever the desired attended letter is flashed, the P300 occurs. This principle has been adopted in the past years and P300-based BCI systems are successfully used in people with severy paralysis due to e.g., amyotrophic lateral sclerosis (ALS). A very interesting application of an attention-based P300 BAI is the brain painting application, where patients paint instead of writing text, works properly (Hintermüller et al. 2015; Holz et al. 2015). More details on P300-based BCIs can be read in Chap. 8.

Mental Imagery

Mental imagery can be defined as pictures in the mind or a visual representation in the absence of environmental input. An abundance of evidence from brain scanning research shows that the same areas of the brain used for normal perception are also activated by mental imagery (Miyashita 1995). For example, "thinking about a telephone activates some of the same brain areas as seeing a telephone" (Posner 1993). But this is not only valid for cognitive activities, moreover the imagery of motor actions elicit neural responses similar to actual movements. According to Jeannerod (2001, 2006), MI, action observation (AO), and motor execution (ME) are assumed to be subserved by the same neural networks, with MI being the "covert stage" of ME.

Since it was found that not only motor tasks lead to decodable brain patterns (Obermaier et al. 2001), also other mental tasks (e.g., word association, mental singing, calculation, mental object rotation) have been studied (Friedrich et al.

2012, 2013a, b; Faller et al. 2014; Scherer et al. 2017) and applied in BCI applications (Statthaler et al. 2017).

Motor Imagery

MI is often used as a mental strategy of BCIs (Schlögl et al. 2005; Hwang et al. 2009; Pfurtscheller and Neuper 2001; Pfurtscheller and Neuper 2001; Neuper et al. 2006; Ahn and Jun 2015; Curran and Stokes 2003). MI can be divided into kinesthetic motor imagery (KMI) and visual motor imagery (VMI). During KMI, persons have the feeling that they actually perform the movement with all the associated sensory perceptions (first-person perspective). During VMI, the persons see themselves performing the movement as from a distance (third-person perspective) or they visualize the event. According to the used strategy, specific neural activation patterns were found (Lorey et al. 2009). For example, Lorey and colleagues found in their fMRI-study stronger activation in left motor-related structures, especially the inferior parietal lobe, for first-person imagery perspective compared with third-person. Others found that the inferior parietal lobule and the somatosensory cortex were more activated during the first-person than the third-person perspective. Furthermore increased activity was observed in the precuneus during the third-person imagery (Ruby and Decety 2003).The performance of a BCI can also be improved by optimizing the users' control strategies, e.g., using more vivid and engaging mental tasks for control (Lotte and Jeunet 2015; Jeunet et al. 2016; Wriessnegger et al. 2018a, b).

Movement Attempt

In recent years, it has been found that MI does not provide an intuitive control especially for motor neuroprostheses of the upper extremity. In several studies it has been shown that the execution of movements in non-disabled persons can be compared to attempting movements in people with motor impairments (Müller-Putz et al. 2016; Schwarz et al. 2018, 2019; Ofner et al. 2019; Hotz-Boendermaker et al. 2008). Thus, end users of a BCI-controlled neuroprosthesis do not need to imagine, but can directly attempt to perform a desired movement, e.g., opening of the hand, or doing a palmar grasp (Ofner et al. 2019), and therefore achieve an intuitive control of their hand function (see Chaps. 9 and 13 for more details).

3.3.3.3 Preprocessing

Preprocessing is the first step in the processing chain (sometimes called pipeline) from brain to control signals. In this preprocessing step, the amount of acquired raw data is first reduced, artifacts detected and whenever possible removed, and, most

importantly, the signal-to-noise ratio increased. Then features, which describe and characterize the brain activity pattern of interest will be calculated.

Typically, EEG signals are recorded with a high sample rate (> 200 Hz), which is of importance for increasing the data quality for later analysis and post processing. This sample frequency depends on the frequency band of interest and the quality of band pass filters in the EEG amplifier. Here, two steps can be performed: (1) artifact reduction/removal (Schlögl et al. 2007; Daly et al. 2015; Kobler et al. 2019) or (2) detection so that artifacts cannot influence the control signal. Very often, the sample rate is reduced at this stage or after feature calculation.

After the raw data has been filtered and artifacts removed, features are extracted as part of the preprocessing chain. Very often those features get derived from the time (e.g., P300 amplitudes or amplitudes of movement-related cortical potentials) domain or from the frequency domain (e.g., power densities of different frequency bands). Also, more complex features incorporating several recording channels in time and frequency (e.g., is common spatial patterns) are used for BCI applications.

3.3.3.4 Classifier/Machine Learning

Finally, for a BCI application distinct brain patterns need to be distinguished. This means that features associated with the brain patterns of interest. Associated to distinct mental tasks needs to be classified. A very simple way is to implement a threshold-based classification scheme, meaning that whenever the value of a feature exceeds the threshold, a control action is initiated. However, much easier to adjust are model-based approaches. In a first calibration session, brain signals get collected, where users need to perform specific mental tasks, or pay attention to specific stimuli. Then, after feature calculation, the model is trained with this data and the labels (meaning the different tasks). This is also known as supervised learning. In the online session, and this is the real application then, from new data the features get sent through this model and the model or classifier indicates the task with a specific probability. This is the so-called machine learning approach. How much calibration data is collected, how often the classifier model is updated, and more such specific questions is part of ongoing research and very critical for a stand-alone BCI-based application.

Directly connected with the classification of brain signals is the timing of the BCI application: During a spelling application, the user usually wants to communicate a high number of letters within a short amount of time, while in a control application (e.g., controlling a neuroprosthesis), the frequency of control actions is much lower. So far, synchronous (or computer driven) BCIs and asynchronous (user driven) BCIs have been established. While in a synchronous BCI the computer sets the pace and analyzes features only at distinct time points, e.g., directly after a visual stimulus has been provided, in an asynchronous BCI, the BCI continuously analyzes the brain patterns and needs to detect the time point, when a user wants to issue a control command. A typical example of a synchronous BCI is the P300-BCI, while an MI-

based BCI is a widespread asynchronous BCI. Asynchronous BCIs are much more challenging in respect to robustness and accuracy.

3.3.3.5 Feedback Types

Feedback is an essential part of all BCI systems, since the use of BCIs can be seen as a skill and therefore be learned (Wolpaw et al. 2002; Neuper and Pfurtscheller 2009). In a classical neurofeedback (NF) setting, a bar or cursor is used to give feedback on the user's brain state (Vernon 2005). If the desired brain state is detected, the bar, for example, will grow or the cursor will move towards a certain object. With many repetitions, the users should learn to modulate the size of the bar, and thus the amplitude of certain signal features in their own brain activity. Beside the improvement of machine learning algorithms, the further development and refinement of feedback (FB) protocols is one of the most important topics in BCI research. There are two types of NF commonly used in BCI systems, continuous and discrete.

Continuous Feedback

In continuous FB, the user receives, in many cases in a sub-second time-resolution, the result of the classification or decoding result. For example, in a classical mental imagery task, the classification result will be shown to the user by, e.g., increasing the bar in a visual modality. Many studies reported on the beneficial effects of continuous feedback, but also large differences between individuals and dependencies on tasks (Friedrich et al. 2013a, b; Neuper et al. 1999; Barbero and Grosse-Wentrup 2010). For example, Friedrich and colleagues (2013a, b) found differences in the evaluation of continuous FB between mental tasks as well as between individuals. These results are in line with McFarland et al. (2011) who found that in some users continuous feedback can be facilitatory to BCI skill acquisition, while in others they found it to be inhibitory (McFarland et al. 2011). Continuous FB seems to be more motivating and helpful in particular for MI BCIs or in continuous decoding of arm movement trajectories (Martinez-Cagigal et al. 2020).

Discrete Feedback

In discrete FB, the user only receives FB at the end of each mental task, also known as trial. Typically a delayed (discrete) FB provides information of a correct versus incorrect response, i.e., the success or failure, after the trial. It is a generally accepted fact that FB is necessary to support learning of BCI skills. However, there are controversial findings in the literature which type of the FB—continuous or discrete—is more beneficial. Recent studies reported on a combination of both types. For example, Kreilinger et al. (2012) implemented in a gaming environment so-called error potentials (ErrP). In their study, a BCI-driven car game based on MI was

used. Participants moved a car continuously left and right on a road while they tried to avoid obstacles and collect coins. When the car touched either an obstacle or a coin, discrete feedback on this event was displayed and therefore ErrPs were elicited (either correct or erroneous) on this single events. A decision was reached after a series of multiple events. They showed that the incorporation of error detection, based on discrete feedback is possible in continuous applications and that it can basically be included in any kind of feedback (Kreilinger et al. 2012, 2016).

Both FB types can be implemented with different modalities such as visual, auditory, or haptic. In a typical BCI, FB often consists of a bar displayed on a screen whose length and direction vary according to the EEG signal processing output (Neuper and Pfurtscheller 2009). This FB is mainly digital, i.e., it only indicates to users whether they have performed the mental tasks correctly or not. However, according to human learning principles the provision of explanatory feedback on which parts of the tasks were performed correctly or incorrectly is recommended for enhancement of learning (Shute 2008). Taking this into account, it seems very promising to design BCI systems including explanatory FB (Sollfrank et al. 2016). Recent research suggested that BCI FB should be multimodal (Merrill 2007) and adapted to the users' skills and traits (Kleih and Kubler 2015; Jeunet et al. 2016; Friedman 2015; Chavarriaga et al. 2017). Furthermore, training environments should be motivating and engaging. Some recent work showed the positive impact of video games and virtual reality on BCI training and performance (Putze 2019; Salisbury et al. 2016; Škola and Liarokapis 2018; Škola et al. 2019) since game-like feedback aims at keeping the motivation and engagement of the users at a higher level for a prolonged time (Kober et al. 2016, 2017; Faller et al. 2019; Chavarriaga et al. 2017).

Summarizing, the current literature suggests that multimodal FB and explanatory rather than purely corrective seem to be most effective in supporting users in efficiently acquiring BCI skills. However, these issues need to be more investigated in more details in future research.

3.3.4 Fields of Applications for BCIs

BCIs are an emerging technology, which can be used in different fields of applications:

1. BCIs are able to *improve* the natural response of the CNS. For example using a BCI in stroke rehabilitation it detects signals from a lesioned cortical area aiming to control an orthosis to improve arm movements. Another typical scenario using a BCI is to improve hand motor function in stroke patients additionally to existing state-of-the-art rehabilitation therapy (Silvoni et al. 2011; Biasiucci et al. 2018).
2. BCIs can *enhance* the natural response of the CNS. Examples include monitoring brain activity during prolonged demanding tasks such as driving a car. Here, a BCI detects lapses of attention and alerts the person aiming to restore attentional

deficits. Further applications assess covert aspects of the user's mental state and adapt to the environment accordingly. For example a BCI can be used in industrial workplaces to avoid dangerous situations (Kohlmorgen et al. 2007). Others can be used to improve human–computer interaction by measuring implicit information encoded in perceptual and cognitive processes (Martel et al. 2014). Such so-called passive BCIs could also be applied in the field of Neuro Information Systems (NeuroIS.org.). A study by Wriessnegger and colleagues investigated subconscious like/dislike decisions during the visual presentation of different car types (Wriessnegger et al. 2015).

3. BCIs are furthermore able to *replace* functions that are lost due to disease or injury. One example is the replacement of lost speech, caused by stroke (Sellers et al. 2014), or another degenerative disease (Vaughan et al. 2006; Halder et al. 2015; Kübler et al. 2015; McFarland and Vaughan 2016; Käthner et al. 2017; Lugo et al. 2019) such as amyotrophic lateral sclerosis (Vansteensel et al. 2016). To find solutions for people with such severe communication disorders intensive research is ongoing to decode brain signals from corresponding areas.
4. BCIs can also *restore* lost CNS functions by controlling prosthetic/robotic systems or functional electrical stimulation (FES). Such BCI-controlled neuroprostheses can provide persons with severe motor diseases (e.g., spinal cord injury (SCI)) an improved upper (see Chaps. 9 and 13) or lower limb functionality (see Chap. 6).
5. Finally, BCIs can also be used as a *research tool* to investigate CNS activation in healthy persons and patients. Such BCIs can deliver important results especially in research fields where single-trial analysis and immediate, i.e., online feedback are important. This is evident in all applications where neural responses need to be detected on a single-trial basis and consequently adapting to the environment. Moreover, brain responses are much more accurate and objective compared to behavioral responses. Additionally, BCIs are useful in investigating subliminal processes (Wriessnegger et al. 2015) or covert states of the user which are often not accessible with behavioral correlates or self-reports. In the last years several neuroscientists start to use BCI technology to decode different brain functions because they are able to decode brain activity and generate feedback in real time. In the future, BCIs for research can be connected to a variety of existing different types of neuroimaging systems (EEG, fNIRS, etc.) or MRI scanners which will open up new possibilities in neuroscientific studies.

3.4 Conclusion

This chapter focuses on non-invasive electrical measurement of brain signals, the EEG. Starting with its neurophysiological principles, EEG phenomena, signal recording methods, and signal patterns a second part discusses brain–computer interfaces, their history, main components and their field of applications.

Electroencephalography, though invented almost 100 years ago, is still one of the most popular neuroimaging tools for brain activity. In the last two decades, EEG amplifiers have undergone a transformation to small, lightweight, and highly sensitive devices, which are easy to apply in neuroscience as well as in BCI applications. An essential component all BCI devices is the electrode, which is directly in contact with the end user. Depending on the application intended, researchers and developers can choose between gel-based, water-based, or and even dry electrode systems. Portable or stationary, EEG recording, and EEG neuroimaging gained a new drive in neuroscientific research.

The BCI field is rather young but has shown a huge progress during the last 20 years. Today, P300-based BCIs are state of the art with many applications from classical communication to art (painting, music composing) to application control and internet and email serving. Mental imagery-based BCIs found their way into clinical settings (e.g., stroke rehabilitation) but also for competitions where end users compete against each other by playing computer games. Motor decoding made it from simple motor imagery to 2D trajectory control. Also, classification methods improved and more important labs work together and finally a BCI Society was founded.

Despite all the achievements, still there are problems to be solved:

First, it seems, not all people achieve a sufficient level of control with a BCI. This so-called BCI illiteracy has been subjected of many studies, however, there is still an ongoing discussion whether this can be attributed to the users individual physiology or if the training paradigms need to be adapted and elongated.

Second, the EEG is a highly non-stationary signal which changes over time. It is affected by many factors, such as fatigue, mood, day-time, and several more. The construction of a classifier system which handles all this factors and does not need repeated retraining (i.e., by complete new calibration) is matter of ongoing research. Adaptive classifiers, generic classifiers, to name a view, are part of the solution, but there is still more to be done.

Third, a high number of false positive detections represents a challenge in everyday BCI applications. Even one false positive per minute is disturbing for the end user and renders BCI control over a few hours impossible.

Fourth, the design of EEG caps is gaining importance. Since more and more end user studies are going on, feedback from end users is telling research to work also on the cosmetic appearance of EEG caps and integrated amplifiers. Although technologies such as headsets or earphones are apparent everywhere in the public, it might be annoying, if a person wears futuristic artifacts on the head.

More specific EEG-based BCI applications will be presented in Chaps. 9–13.

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Part II
Neuroprosthetics in Spinal Cord Injury

Chapter 4
History of Neuroprosthetics

Ute Eck and Rüdiger Rupp

Abstract The development of increasingly powerful and smaller electronics in the 1960s led to a push in development of portable devices for functional electrical stimulation (FES) for restoration of functions lost due to spinal cord injury (SCI). This chapter aims to provide a compact overview of the most common motor neuroprostheses, including devices for diaphragm pacing in people with very high SCI and for generation of upper and lower extremity movements. Introduced in the 1970s, diaphragm pacing by FES changed the life of people dependent on artificial ventilation completely resulting in less respiratory complications and increasing mobility. As early as 1960, the first neuroprosthesis ever for treatment of drop-foot was successfully tested mainly in stroke survivors and later commercialized. Many attempts have been undertaken for establishing neuroprostheses for standing and walking in end users with complete loss of leg movements. However, premature muscular fatigue due to the large FES-generated forces prevented until today a wider application of lower extremity neuroprostheses beyond training settings. In the 1970s, after problems with mechanical breakdowns of percutaneous electrodes became apparent, a fully implantable neuroprosthesis for restoration of two basic grasp patterns for people with preserved shoulder and elbow function, but lost finger movements was developed. Due to the positive experiences from many end users, this grasp neuroprosthesis was later transferred to the market. However, business stopped due to financial reasons. Here, systems based on surface electrodes represent a less expensive alternative. The lesson learnt from history tells us that—beside its clinical relevance—mainly the simplicity of the system design and easiness of use determine the market success of a neuroprosthesis. This insight might serve as a guideline for future developments of neuroprostheses.

Keywords Functional electrical stimulation · Neuroprosthesis · Diaphragm pacing · Upper extremity · Lower extremity · Drop foot

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4.1 Introduction

It has long been known that electrical stimulation (ES) of a nerve can elicit contractions of the muscles supplied by the nerve's fibers (Galvani 1791; von Humboldt 1797). Long before the basic mechanisms of neuromuscular electrical stimulation (NMES) have been systematically investigated, "natural electricity" present in some marine and freshwater fish was already in use therapeutically in classical times by Egyptians, Greeks, and later Romans (Kane and Taub 1975). However, it was the rapid progress in the 1960s in the fields of electronics and energy storage, new materials and an increased understanding of their biological interface properties that paved the way for portable electrical stimulation devices (McNeal and Reswick 1976). Miniaturization of electronics and increase in battery capacities allowed the therapeutic use of NMES for various purposes such as reduction of musculoskeletal pain or muscle training in particular in sports (Ward and Shkuratova 2002). Among the first applications of NMES was its use to reanimate paralyzed limbs and other impaired functions in people with injuries or diseases of the central nervous system (CNS) such as spinal cord injuries (SCIs) (Crochetiere et al. 1967). For this type of application of ES, called functional electrical stimulation (FES), portable devices ranging from one-channel, switch-controlled stimulators for simple single joint movements to multichannel, sensor-controlled stimulators for restoration of complex motor functions such as walking or grasping have been developed. In contrast to powered mechanical orthotic solutions, ES of muscles represented a promising way to use the body's own energy sources for generating movements. The energy needed to elicit physiological action potentials on peripheral nerves is relatively low, resulting in stimulation equipment with small size, low weight, and power consumption, which can be carried comfortably even by a person with motor impairments.

The term "neuroprosthesis" has been established as a generic term for technical systems interacting with the nervous system. A neuroprosthesis based on FES aims to substitute permanently lost motor, sensory, or vegetative functions of the body after severe CNS injuries such as complete SCI. Starting in the 1960s, engineers developed the first neuroprosthetic prototypes for the compensation of drop foot in stroke survivors (Liberson 1961) and a variety of other applications (for review see Creasey et al. (2004), Peckham and Knutson (2005), and Rupp and Abel (2005)). This chapter aims to give an overview of the history of the most common motor neuroprostheses developed and applied in end users with SCI.

4.2 Neuroprostheses for Respiratory Pacing

Injuries of the upper cervical spinal cord higher than C5 result in impairments up to a complete loss of diaphragm contractions and thus to an insufficient respiratory function. The diaphragm is a striated skeletal muscle that contracts at regular

intervals and is thus responsible for the expansion of the lungs with the associated inhalation. A complete paralysis of the diaphragm results in a full-day dependency on external artificial ventilation.

In 1783, Hufeland was the first who came up with the idea to activate the diaphragm in the absence of active breathing by electrical impulses applied to the phrenic nerve (Hufeland 1783). Fifteen years later, Caldanius was probably the first who showed the general feasibility of this approach for respiration support in animals (Caldanius 1786). It took further 150 years, when the first attempt to restore diaphragm function was made in a human being. In 1948, S.J. Sarnoff and colleagues at the Harvard School of Public Health showed that, in the absence of spontaneous respiratory activity, rhythmic phrenic nerve stimulation can be applied to achieve life-saving breathing. They successfully used ES as the only means of artificial respiration for 52 h in a 5-year-old boy with a cerebral aneurysm rupture (Sarnoff et al. 1948). At this time, the only way to achieve long-term survival of people with complete respiratory insufficiency was to put patients into an iron lung, a device that uses cycles of negative and positive pressure inside a tube to simulate breathing. These devices are large and do not allow users any kind of mobility nor participation in everyday activities.

Based on his pioneering research in cardiac pacemakers, Glenn and his colleagues at the Yale University School of Medicine set out to create the first practical application of phrenic nerve pacing in humans. Already in 1968, Judson and Glenn reported on transcutaneous radio-frequency transmission for external control of an implanted diaphragm pacemaker connected to cuff electrodes placed around the phrenic nerves (Judson and Glenn 1968). In 1972, Glenn achieved survival of a patient with complete diaphragm paralysis due to high SCI for over 11 months (Glenn et al. 1972). In collaboration with Roger E. Avery, Glenn's prototypes were brought into commercial distribution by Avery Laboratories, Inc. (Commack, NY, USA) in 1971. Since its market introduction, the Glenn system has not undergone substantial technical changes till today. It still uses monopolar or bipolar nerve cuff electrodes attached to a single-channel implant to stimulate the phrenic nerve on each side of the body leading to contractions of each hemidiaphragm (Glenn et al. 1986). The powering of the implanted stimulators via an inductive link has the advantage that skin penetrating wires are avoided. Thus the risks of infections and of cable failures are minimized, which makes daily care of end users much easier. Besides this, the biggest advantage of using a diaphragm pacemaker at that time has been the gain in wheelchair mobility of end users due to the small size of the respiratory neuroprosthesis compared to the positive pressure artificial ventilators.

Basic research in animals showed that the stimulation frequency has a substantial impact on the fiber type composition of a stimulated skeletal muscle such as the diaphragm (Buller et al. 1960; Salmons and Sreter 1976). While lower stimulation frequencies result in a transformation of the diaphragm into a more fatigue-resistant muscle, higher frequencies and supramaximal stimulation of the phrenic nerve lead to rapid fatigue and—as a consequence—the necessity for intermittent auxiliary ventilation. Therefore, the stimulation intensity and frequency need to be carefully adapted to the status of the end user and a proper conditioning of the fast fatiguing

diaphragm muscle is necessary before a full-day use is possible. Nevertheless, the positive long-term experiences with the Avery system in more than 2000 people show that chronic application over decades is possible without nerve damage (Elefteriades et al. 2002).

At the beginning of the 1970s, the group of Thoma (Vienna, Austria) introduced the so-called carousel stimulation for fatigue prevention. As the name "carousel stimulation" implies, in this approach different axons of the phrenic nerve are alternately electrically excited by four evenly spaced epineural electrodes placed around the nerve. This alternated excitation of only parts of the phrenic nerve causes in turn an alternating contraction of only parts of the diaphragm (Holle et al. 1974). By this principle, overall diaphragm muscular fatigue has been effectively reduced thus allowing an all-day, physiological breathing after a short conditioning period and the use of low threshold currents (Mayr et al. 1993). The first patients supplied with this fully implanted and inductively powered system have used it for more than 25 years and without the need for even temporary support by external ventilation. They achieved a significant improvement in their quality of life, in particular through the ability to speak loudly during expiration phases. Later, a Finnish group (Baer et al. 1990) has made a system commercially available (Atrotech OY, Tampere, Finland, founded 1984), which is based on a four-pole sequential stimulation principle similar to the one introduced by the Vienna group. Today, the Atrotech system represents the most widely used phrenic nerve stimulation system in Europe.

All phrenic nerve stimulation systems have in common that the surgical implantation has to be done by a cervical or—which is more preferable—by thoracic approaches. Although the cervical approach does not need a thoracotomy, the stimulation selectivity is worse compared to a thoracic electrode location and often accompanied by painful sensations (DiMarco 2009). The phrenic nerves in the thorax are usually accessed by incisions through the second or third intercostal spaces and the electrodes are secured behind or over the nerve. The stimulator is placed subcutaneously and connected to the electrodes by wires through a second incision, which is usually made in the lower anterolateral chest wall.

To overcome the drawbacks of the complex surgical procedures, since 2002 the company Synapse Biomedical Inc. (Oberlin, Ohio, USA) has developed in collaboration with the Case Western Reserve University in Cleveland (Ohio, USA) the diaphragm pacing system "NeuRx". This system is based on four percutaneous, intramuscular wire electrodes which are laparoscopically inserted near the motor points of the diaphragm (DiMarco et al. 2005; Onders et al. 2004). The minimally invasive implantation of the electrodes with a series of four incisions to the abdominal skin results in a generally less complex and time-consuming surgery. This results in a lower risk of causing harm to the phrenic nerve and a faster healing process. The ability to remove percutaneous leads very easily has led to the recent development of the TransAeris system for temporary support of the respiratory function for up to 30 days during weaning from the ventilator. Although there were initially concerns about the mechanical stability of the percutaneous wire electrodes for chronic use, long-term observations show that with proper care many years of complication-free device operation are possible (Onders et al. 2009).

Even in recent times, in which mobile positive airway pressure ventilators are available, respiratory neuroprostheses represent the preferred clinical therapy option due to their advantages with respect to restoration of physiological pressure conditions in the lung, to regain the ability to speak, to eventually abandon the tracheal cannula, and to their ease-of-use.

4.3 Neuroprostheses for Support of Complex Motor Functions

Compared to diaphragm pacing with a low number of degrees of freedom to control, the generation of limb and body movements by FES in cases of severe paralysis represents a much more complex task. To support people with motor impairments in successfully performing activities of daily living, a large number of muscle functions have to be activated by multiple stimulation channels in a coordinated manner. Over the last 40 years, many devices for restoration of grasping and walking have been developed by different research groups all over the world. However, only a few neuroprostheses have achieved a level of matureness to be applied to end users routinely. The neuroprosthetic success stories have in common that these systems are used for improvement of comparatively simple motor tasks such as the restoration of a basic grasp function or foot dorsal extension. Most of the more complex devices have not reached a level of usability for use outside a research setting.

4.3.1 Lower Extremity Neuroprostheses

The first application of electrical stimulation to support body movements introducing the term "Functional Electrotherapy" was published by W.T. Liberson (Liberson 1961). He was the first researcher comprehensively describing a simple feedforward-controlled stimulation system for foot drop correction in stroke survivors with hemiplegia (Liberson 1999). His pioneering invention was the starting point for a series of developments of more sophisticated non-invasive (Vodovnik et al. 1972, 1978) and implanted drop-foot neuroprostheses (Waters 1972; O'Halloran et al. 2003; Haugland et al. 2000; Weber et al. 2005). Several factors contributed to the success of this FES application: First, simple systems based on a few electrodes stimulating only the tibialis anterior and the peroneus muscles on one side of the body were sufficient to achieve a substantial improvement of a clinically relevant problem. The one degree of freedom of the drop-foot neuroprosthesis controlled by a foot switch in a binary manner allowed a quick setup by therapists and easy adjustment by end users. Although muscular fatigue and a relatively high error rate in step detection still represent major drawbacks, drop-foot neuroprostheses are among the most widespread neuroprosthetic systems so far. It has been successfully used in different gait pathologies such as stroke, multiple sclerosis, and incomplete SCI (Gil-Castillo et al. 2020).

4.3.1.1 Noninvasive Neuroprostheses for Standing and Walking

However, the situation is much more complex in people with severe paralysis of the lower extremities and trunk. The human body represents a mechanically instable system. To achieve standing and walking not only the paralyzed lower limbs need to reanimated, but also the trunk needs to be stabilized to make full use of the lower limb movements. In general, devices providing multiple independently controlled FES channels are necessary for restoration of complex functions.

While historically there has always been a strong focus on the development of devices, less efforts were undertaken to implement closed-loop systems for automatic control of a motor task (Crago et al. 1996). From a control engineering point of view, not only sufficient controllability but also observability are prerequisites for stable control (Kalman 1960; Vossius and Frech 1996). Therefore, for closed-loop control technical sensors are needed to record and analyze the reaction to the stimulation. Although the idea of using sensors for implementation of closed-loop control is appealing, not a single neuroprosthesis used in everyday life integrates sensors for closed-loop control of, for example, joint angle or grasp force. The reason for this is that, from an end users perspective, additional sensors result in an increased preparation time, the need for (re-)calibration, are prone to failure, and result in the perception of "not-being in control" of the system.

A systematic testing of the possibilities of FES to support standing and walking in individuals with paraplegia can be traced back to the 1960s, when several independent research groups started to use multichannel stimulation systems based on surface electrodes to activate lower extremity muscles in a coordinated manner. The first group introducing FES for walking and standing was formed by Vodovnik, Kralj, and Bajd in Ljubljana, Slovenia (Kralj and Vodovnik 1977a, b), who used a commercially available four-channel stimulator. Each swing phase was initiated by stimulation of the common peroneal nerve with sufficiently high intensity, which resulted in a foot lifting by triggering the withdrawal reflex. During the stance phase, the quadriceps muscle was activated by ES to extend the knee joint. The stimulator was connected to special crutches with button switches integrated into the handles. By pressing the buttons, an end user was able to select different stimulation patterns. With this system, walking and standing were possible, but no controlled standing up or sitting down. Due to the instability of the trunk and pelvis, a large part of the body weight had to be taken over by the shoulder and arm muscles of the user leaning on the crutches.

In 1986, Vossius and his research group in Karlsruhe, Germany extended this approach by introducing a processor-controlled eight-channel stimulator. In addition to the stimulation of knee extension and the withdrawal reflex, further stimulation channels were used to separately activate the antagonistic ischiocrural muscle group for stabilizing the knee joint and the gluteus maximus and medius muscles for extension and abduction of the hip joint (Fig. 4.1a). With the combined stimulation of agonistic and antagonistic knee joint muscles, Vossius was able to avoid hyperextension of the knee joint and to prevent mechanical stress due to overloading. The

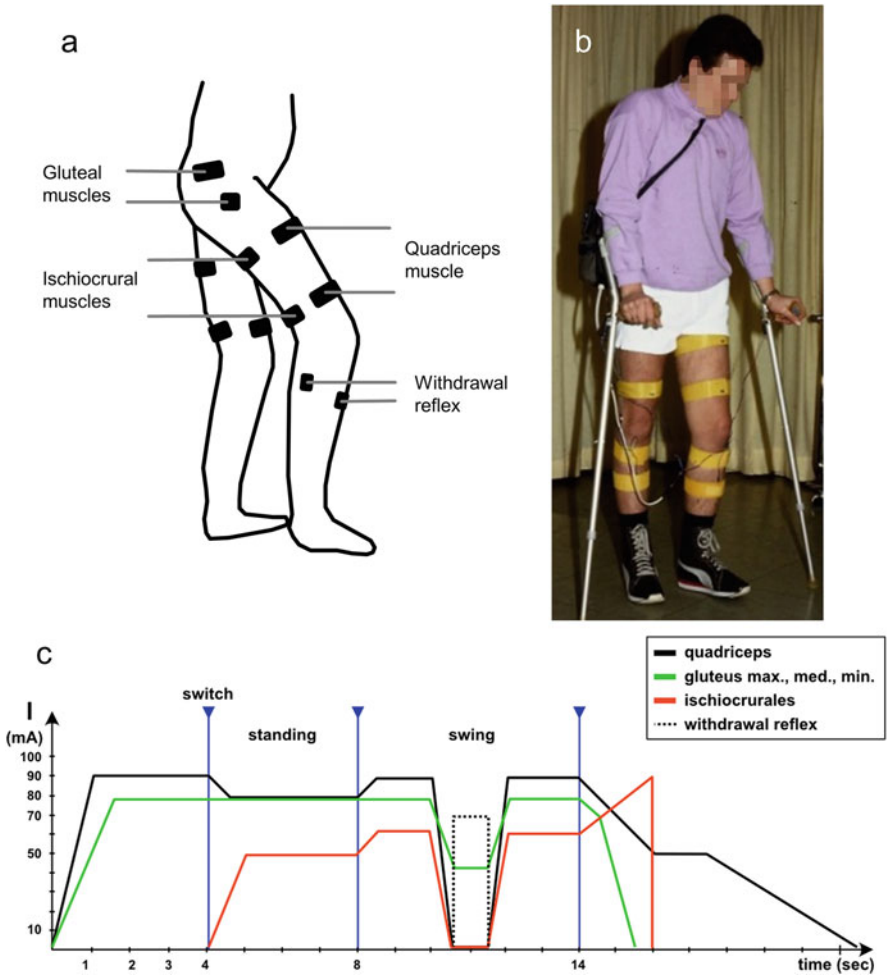

Fig. 4.1 Overview of the noninvasive eight-channel FES system by Vossius (Vossius 1990). (**a**) Electrode positions and activated muscle groups. (**b**) End user with complete paraplegia (level of injury T10) using the neuroprosthesis for standing and walking. (**c**) Electrode activation pattern. Steps are initiated by pressing switches integrated into the handles of the crutches

system allowed the user to initiate different pre-programmed movement sequences by pressing switch buttons in the crutches (Fig. 4.1b). These ranged from standing up, standing, to walking and sitting down (Fig. 4.1c).

With the additional stimulation of the hip joint muscles and the possibility to control its stiffness, a stable standing position together with a walking pattern much more physiological than with prevoius systems was achieved. Additionally, a "soft" controlled standing up and sitting down was possible.

In contrast to the 4-channel stimulation method of Kralj and Vodovnik, end users were effectively relieved from the need to stabilize their body position with the

crutches and to take over a substantial portion of the body weight with their arms and shoulders. In end users with high thoracic lesions, trunk stability was achieved by additionally stimulating back muscles (Vossius 1987). Although end users were very skilled in the independent use of these systems, none of them used them as everyday-life substitute for the wheelchair. Reasons for this include the long preparation times and the limited number of steps due to the rapid muscle fatigue because of the non-physiological activation of muscles by ES and the generally higher energy expenditure (see Chap. 2). However, people used the systems at their homes for cardiovascular training purposes, prevention of pressure injuries by maintaining muscle mass and avoiding joint motion restrictions.

In the following years, other noninvasive multichannel lower extremity neuroprostheses with similar functionality were developed. Of these, a six-channel FES system for standing and walking called "Parastep" operated by switches on a special rollator has been commercialized (Sigmetics Inc., Fairborn, OH, USA). Although it has been shown that the gains in autonomy by the Parastep system in everyday life (Klose et al. 1997) are limited, positive therapeutic effects including quality of life of end users have been demonstrated (Guest et al. 1997; Nash et al. 1997). The FDA-approved Parastep system represents an absolute exception and is—many years after market introduction—still commercially available today and reimbursement is possible in some countries.

4.3.1.2 Invasive Neuroprostheses for Standing and Walking

At the end of the 1970s, a research group in Cleveland, USA used percutaneous, thin helical electrodes directly inserted near the motor point of muscles to achieve microprocessor-controlled walking (Marsolais and Kobetic 1987, 1988). With up to 24 percutaneous electrodes per leg, individuals with complete paralysis achieved an amazingly fluid and fast gait almost like physiological walking. However, like in noninvasive neuroprostheses the maximum walking distance was very limited due to rapid fatigue of the stimulated muscles. In addition, the skin's immune system against infections was heavily stressed due to the high number and density of percutaneously inserted wire electrodes. The occurrence of inflammation due to the break of the fine wires with impending leg amputation in one study participant led to an abrupt termination of the test series. The concept has later never been taken up again due to the lack of perspective for a practical widespread use.

Since the 1970s, the development has focused on fully implantable stimulation systems. In the mid-1980s, the research group of Thoma in Vienna, Austria implanted a 4-channel system to achieve standing and walking (Thoma et al. 1987). Due to the low number of electrodes and the missing stabilization of the hip joints, pelvis and trunk, end users had to carry very high loads with their upper extremities. Over the years, this resulted in serious musculoskeletal problems of shoulder and arms in some of the study participants.

To overcome these problems, the group in Cleveland, USA used two eight-channel stimulators initially developed by Peckham for the use in the upper

extremity and implanted each of them into one body side (Kobetic et al. 1999). With this system, stable standing and transfer from and into the wheelchair as well as taking some steps for short distances were possible (Ho et al. 2014).

In 2002, a 24-channel FES system developed by Rabischong in Montpellier, France, was implanted in two patients as part of the European research project Stand Up And Walk (SUAW) (Von Wild et al. 2002). Users achieved a similar performance like with the above-mentioned Stand-and-Transfer system of the Cleveland group. However, after the research project ended, the system was not transferred into everyday use and it is not known whether a long-term support is provided to the study participants.

In a nutshell, even the most modern technology reaches its limits when it comes to restoring of standing and walking in people with complete paralysis of the lower extremities. On the one hand, the unstable upright body posture bears the inherent risk of falls, and on the other hand, end users are not free to use their hands because they need to stabilize their body by rollators or crutches. For taking over the complete body weight, high muscle forces need to be generated by ES permanently. Continuous co-contractions of agonistic and antagonistic muscles are needed to maintain an upright body position during standing. The resulting problems with muscle fatigue and constriction of the muscular blood supply have not been solved yet. Due to rapid muscle fatigue caused by the high muscle forces, end users of standing and walking neuroprostheses—be they surface or implantable systems—cannot walk more than a few dozens of steps despite intensive training. In addition, a number of incidents involving infections have occurred in implanted multichannel systems. In summary, currently available neuroprostheses for standing or walking do not represent an alternative to the wheelchair in everyday life, but may be used for short-term tasks such as transfers or for therapeutic purposes.

4.3.1.3 Hybrid-Neuroprostheses Combined with Lower Extremity Orthoses

Some researchers tried to counteract the fatigue problems by combining neuroprostheses with orthoses. Depending on the end user's condition, movements are generated by FES activation of paralyzed muscles and stabilizing a joint position during stance phase by an orthosis with motorized or passive joints. In 1984, the reciprocating gait orthosis "Parawalker" with fixed knee and ankle joints and limited degree of freedom of the hips was combined with FES of the quadriceps and later the gluteal muscles for standing, sitting, and walking (McClelland et al. 1987). In 1989, a research group in Belgrade, Serbia, reported on a "hybrid assistive system" combining FES of the gluteus medius muscle, the quadriceps femoris muscle, and the peroneal nerve with a self-fitting, modular orthosis. This orthosis included active knee joints and passive spring modules to achieve dorsiflexion of the foot (Popovic et al. 1989). It was tested in one individual with complete tetraplegia (motor level of C5/6; American Spinal Injury Association (ASIA) Impairment Scale A) without preserved motor and sensory functions below the waist.

The combination of FES and active orthoses represents a challenging system from the control point of view. Sophisticated control strategies are needed for hybrid systems that adequately manage the balance between these two actuation systems. In case of FES, the huge delay times and the non-linear behavior of muscles under stimulation add substantially to the control complexity.

To overcome this control problem, in 2009, the research group in Cleveland, USA, introduced and tested a self-stabilizing exoskeleton in one individual with a complete SCI (AIS A) at T7. This person had already 17 years of experience with his multichannel implanted standing and walking neuroprosthesis. In contrast to the "hybrid assistive system" presented above, this exoskeleton did not need to be synchronized with the FES because it was designed to self-stabilize against extrinsic/intrinsic disturbances during gait (Kobetic et al. 2009). FES of the extensor muscles of the knee and hip joints has been included in the active exoskeleton "Indego". Indego was developed in Vanderbilt, USA in 2010 and represents a powered exoskeleton with brushless DC motors at the hip and knee joints. It has been successfully clinically tested in three study participants with motor complete SCI with varying levels ranging from T6 to T10 (Ha et al. 2015). The FES inside the Indego exoskeleton is a pure feed-forward control. The step-phase related, predefined activation of different muscle groups is used rather for therapeutical than functional purposes.

While all these hybrid-FES solutions represent highly interesting technological developments, which have been experimentally tested with a few individuals with SCI, large-scale studies including routine home use are still pending. However, the combined use of active/passive orthoses and FES represents a promising approach to achieve a reliable closed-loop control because of the possibility for integration of joint angle sensors into the orthotic components.

4.3.2 Upper Extremity Neuroprostheses

Restoration of grasping and reaching has the highest priority in end users with high cervical SCI (see Chap. 1). When surgical methods in form of tendon, muscle, or nerve transfers are not applicable due to the lack of preserved functions, upper extremity neuroprostheses might represent an alternative to achieve some degree of independence. Since the early 1970s, upper extremity FES systems with different levels of complexity and degrees of invasiveness have been developed.

4.3.2.1 Noninvasive Grasp Neuroprostheses

At the beginning of the 1970s, researchers in Cleveland, USA, were the first to use FES for restoration of grasping. They did not believe in the practicability of noninvasive systems and started to develop an implantable neuroprosthesis for individuals with preserved shoulder function and elbow flexion, but lost finger

function (Mortimer and Peckham 1973; Peckham and Mortimer 1977; Peckham et al. 1980a). In parallel, researchers in Karlsruhe, Germany developed a noninvasive neuroprosthesis and successfully showed a restoration of the grasp function by using surface electrodes and patient-adapted human–machine interfaces such as head switches in end users with high SCI (Vossius et al. 1980). With both types of systems, it was possible to generate a few grasp patterns and allow end users with missing hand function to perform everyday tasks such as holding a pen for writing or typing on a keypad and grasping a fork, a cup, or a bottle for independent drinking and eating.

Later, more systems have been developed by other groups (for overview see (Popovic et al. 2002)): The "H200" (formerly Handmaster, NESS, Riddenderk, the Netherlands) represents a commercially available orthotic sleeve which is placed around the forearm and contains four to some extent individually placeable electrode pairs. These are used to stimulate the extensor and flexor muscles of the fingers and the thumb to enable a single gasp pattern (key grip) (Snoek et al. 2000). The user triggers different grasp phases in a sequential order by pressing an external switch. The clinical evaluation of the H200 showed a substantial functional improvement in users with tetraplegia below the level of C5 (Alon and McBride 2003). However, in the framework of these evaluations it became obvious that the additional functional benefit is associated with a high degree of effort during application, donning/doffing and stimulus parameter adaptation. Like in drop-foot neuroprostheses, the functional benefit has been mostly attributed to the training of residual functions (Hendricks et al. 2001). The applicability of the H200 in different end users is limited due to the lack of flexibility with regard to the number of stimulation channels and profiles, the connection of other sensors for control, and the adaptation to the anatomical constraints of different end users.

A similar concept is the "Bionic Glove," which was also commercially available for a short period of time (Prochazka et al. 1997). Similar problems with flexibility like with the H200 system together with the restriction that it can only be used by users with strong active dorsal wrist extension limit its use (Popovic et al. 1999).

A 4-channel system using surface electrodes with different control options (switch, slide control, EMG of shoulder muscles) was developed at the Paraplegic Centre of the Balgrist in Zurich, Switzerland, in cooperation with Compex Medical SA (Ecublens, Switzerland). The system provided a very versatile interface to sensors and flexible software control options. A disadvantage of this system is the placement of small stimulation electrodes on the palm of the hand. Due to the strong skin shifts together with the object to be grasped, the electrodes with their small adhesive surface are quickly detached. This questions the suitability of the system for everyday use in the domestic environment by end users themselves (Mangold et al. 2005).

In general, noninvasive upper extremity neuroprostheses have the advantage of a 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 (see Chap. 1). 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 (Creasey et al. 2000). However, noninvasive systems have the drawback that the achievable number and the quality of the grasp patterns are very limited. The reason for this is the poor selectivity in the stimulation of individual muscles by electrodes attached to the skin and problems in the daily reproducibility of grasping movements. A possible solution to overcome the problem of correct electrode placement is the use of multi-electrode arrays with the possibility of electronically (statically and dynamically) interconnecting individual electrodes to form a virtual large-area electrode (Popovic-Bijelic et al. 2005) (see Chap. 14). However, also these sophisticated surface electrodes will only partially solve the problem of selective activation of deeper muscles. In addition, often pain sensation limits the use of a surface system, especially in end users with hypersensitivity and hyperalgesia. The lack of autonomous handling of the systems independent from caregivers also results in low acceptance by end users (Popovic et al. 1999).

4.3.2.2 Implantable Grasp Neuroprostheses

In general, most difficulties of surface electrodes can be overcome by percutaneous, intramuscular electrodes. The first use of such electrodes for the improvement of grasping function was reported by Peckham, Marsolais, and Mortimer (Mortimer et al. 1980; Peckham et al. 1980b). In the mid-1970s, they developed a system for opening and closing the hand by eight fine-coiled metal strands inserted into forearm and hand muscles. In 1988, a Japanese group realized a similar system with a larger number of electrodes (up to 48). They used this system in several individuals with tetra- and hemiplegia to restore grasping and elbow function (Hoshimiya et al. 1989; Kameyama et al. 1999). Although the functional results were promising, these systems did not gain wide clinical acceptance due to the high risk of infection at the injection site and the frequent electrode breakdowns due to skin and muscle movements during contractions. To overcome these disadvantages, Peckham's research group in Cleveland, USA began developing a fully implantable neuroprosthesis consisting of epimysial electrodes, stretchable cables, and a connectable electrical stimulator at the beginning of the 1980s (Kilgore et al. 2003) (Fig. 4.2a). The first version of the stimulator with eight independently controllable channels (Peckham et al. 2002) was a pure receiver system (Fig. 4.2b). The second version offered the possibility of bidirectional data transmission from two bipolar analog recording channels to the external controller (Kirsch et al. 2005). The stimulator was completely controlled and powered from outside the body to avoid an exchange of the implant in case of an empty battery. Therefore, external components were needed including a battery powered control unit with connectors for an induction coil and for signal inputs from a 2-axis shoulder position sensor. The induction coil, placed on the chest on the skin above the antenna of the implanted stimulator, transmits energy as well as control commands (Fromm et al. 2001).

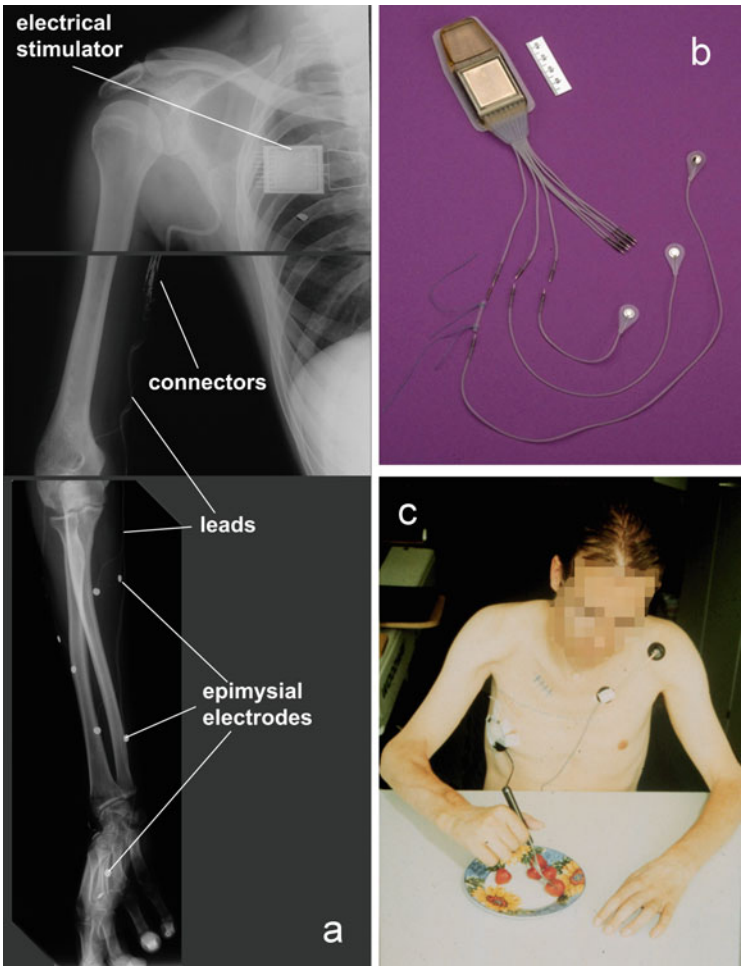

Fig. 4.2 Overview of the components of the Freehand neuroprosthesis. (**a**) X-ray of internal components of the Freehand neuroprosthesis in the right arm of an end user. (**b**) Implantable electrical stimulator with connectors, leads, and epimysial electrodes. (**c**) User eating with the Freehand 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 (with permission from (Rupp et al. 2018))

In 1987, the first implantation of this grasping neuroprosthesis was done in an end user with tetraplegia (motor level of C5) and completely missing hand and finger function on both sides of the body (Smith et al. 1987). With this neuroprosthesis, the restoration of two grasp patterns was possible, 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 (Fig. 4.2c), while the palmar grasp, in which the thumb is

positioned opposite to the index finger, permits larger objects to be handled. Later, this end user received a second implant on the other hand. Based on the positive experience with the grasping neuroprosthesis in a large population of end users (Peckham et al. 2001), the system was FDA approved in 1999 in the USA and 1 year later CE-marked in Europe and marketed under the name Freehand by Neurocontrol (Valley View, OH, USA). It has been implanted more than 200 times and has been the only implantable grasp neuroprosthesis to date. However, Neurocontrol got bankrupt and stopped business in 2002. This shows how difficult it is to survive in a niche market with a complex neuroprosthesis exclusively designed for people with SCI. Low sales numbers and limited sale prices, on the one hand, and the need for the presence of medical and technical experts and the high regulatory burdens, on the other hand, represent substantial barriers for a successful business.

4.4 Conclusion

Over the past 50 years, neuroprostheses with different levels of complexity, degree of invasiveness, and varying fields of applications have been developed. However, only a few of them were used beyond research studies in clinical routine. The question arises, why only a few were successfully transferred into everyday life of end users? Looking back to the history of neuroprosthetics, it may be concluded that the simpler the application and system design are, the higher is the change for market survival. Examples of neuroprosthetic success stories are the phrenic pacemaker and the drop-foot neuroprosthesis, which represent rather simple applications with only a very few or only one degrees of freedom to control. The neuroprosthetic systems for these applications are easy to use, work in a reliable way and can be successfully operated by end users themselves or by their caregivers.

Neuroprosthetic systems for complex motor functions such as standing and walking never made it through the translational valley to successful commercialization. The reasons are manifold, but the time-demanding preparation, the unreliable operation, and the short periods of use due to excessive muscle fatigue have prevented their wider dissemination so far. In contrast to lower extremity neuroprostheses, active exoskeletons represent a much more realistic assistive technology for use in everyday life of people with different degrees of walking impairments.

Upper extremity neuroprostheses represent an effective technology for restoration of basic everyday-life grasp patterns in people with completely lost hand function. Restoration of reaching function in very high lesioned individuals is still limited to the laboratory environment. Although implantable systems are easier and more reliable to use, neuroprostheses based on surface electrodes represent a noninvasive alternative for people in the early phase of rehabilitation or not willing to undergo surgery.

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Chapter 5
Upper Extremity Neuroprosthetics for Spinal Cord Injury

Kevin L. Kilgore

Abstract Neuroprostheses for upper extremity (UE) function in cervical spinal cord injury (SCI) are designed to provide increased independence by providing user-controlled grasp and release. All UE neuroprostheses are composed of a means of activating paralyzed muscles, a means of enabling the user to control the stimulation, and a computational component that translates the user's command to the stimulation output. An important distinction of UE neuroprostheses when compared to other electrical stimulation systems is that the user must have direct real-time control of the stimulation. The selection of the control method is important to the design. Often a single command signal is used to control the stimulation to a dozen or more muscles, reducing the burden on the user during functional activities. In addition to the elements of stimulation, control, and processing, some systems include feedback loops.

UE neuroprostheses are very successful in increasing the independence of the user. Commonly improved activities include eating with a fork and writing with a pen, but can also include general office tasks, using a cell phone, getting money out of a wallet, and embroidery. The functional results in the literature for individuals using UE neuroprostheses of any design are universally positive. There is more than a 20-year track record of daily use of UE neuroprostheses, clearly indicating that these systems have a significant utility in the lives of individual with SCI.

Keywords Neuroprosthesis · Upper extremity neuroprosthesis · Spinal cord injury · Grasp and reach function · Motor restoration

In this chapter we will focus on the basic principles of neuroprostheses when they are designed to provide increased independence for individuals with cervical spinal cord injury (SCI). Specifically, we will focus on neuroprostheses that produce hand grasp

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and reach for individuals with motor complete tetraplegia, typically with a motor level of C5 or C6 according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) and an American Spinal Injury Association Impairment Scale (AIS) grade A or B with no or functionally not relevant motor zone of partial preservation (ASIA and ISCoS International Standards Committee 2019). The information provided here is based on over three decades of experience with the design and implementation of UE neuroprosthetic systems for these individuals. Throughout the chapter, we will review the common components of these systems as well as address some common misconceptions that persist in the literature.

The general design of an upper extremity (UE) neuroprosthesis for SCI is shown in Fig. 5.1. All UE neuroprostheses are composed of a means of activating paralyzed muscles, a means of enabling the user to control the stimulation, and a computational component that translates the user's command into the stimulation output. Further, it is nearly always necessary to consider the interaction between the stimulated function and the user's residual function as an integral part of the UE neuroprosthesis. In addition to these elements, some systems include a machine-level feedback loop (closed-loop feedback) and/or a human-level feedback loop (sensory feedback). We will consider each of these features in some detail, reviewing the current status of the field.

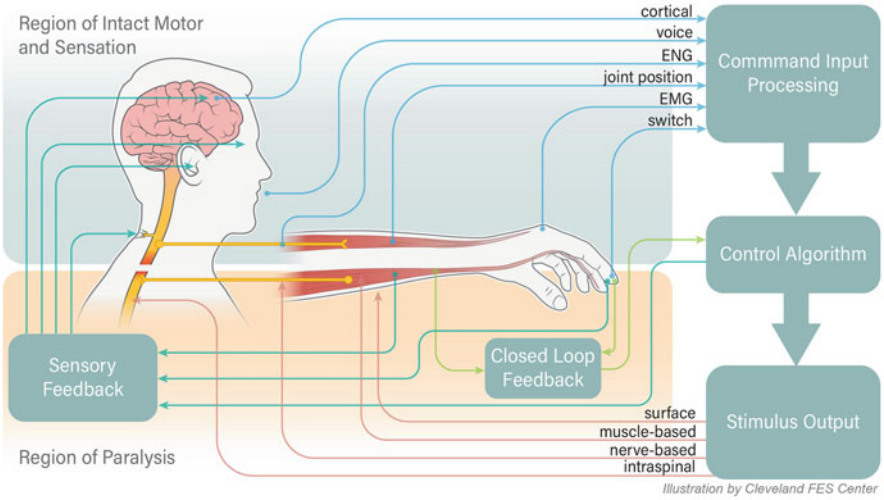
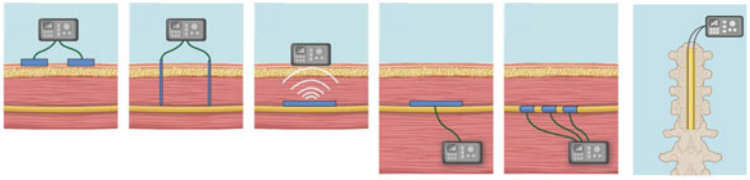


Fig. 5.1 Components of UE neuroprostheses. All systems include command input, control algorithm processing, and stimulus output. Some systems also include closed-loop feedback and sensory feedback. The impact of the user's intact motor control and intact sensation is important to consider

5.1 Stimulus Output

A UE neuroprosthesis is designed to produce grasping and reaching movements via activation of paralyzed musculature. To date, this is achieved through electrical activation of the paralyzed muscles, supplemented, as necessary, with splints and braces. Thus it is important to recognize that the most fundamental, and in many ways most important, component of any neuroprosthetic system is the electrode. The electrode is the interface between the technology and the biology. The electrode delivers the stimulus directly to the tissue surrounding it in order to generate the desired output or response. There are a variety of electrode designs that can be utilized, as outlined in Fig. 5.2. In general, electrodes in a neuroprosthetic system deliver electrical pulses to activate nerves. Neural activation, in turn, produces a desired muscle contraction or other organ response (sensory input, etc.). The desired characteristics of the stimulated response must be matched to the features of the electrode.

Peripheral nerve fibers are much more responsive to an electrical pulse than muscle fibers (see Chap. 2), particularly when the pulse width is shorter than a few hundred microseconds (Mortimer 1981). Thus, even electrodes that are inserted directly into the muscle will preferentially activate the small nerve fibers innervating the muscle rather than the muscle directly. Most stimulators do not deliver sufficient charge to activate muscle directly and, in general, the charge required to activate muscle is not safe for the tissue. Given this principle, it is necessary that the nerves are capable of conducting action potentials in order for neuroprosthetic applications to be effective. Diseases or trauma which cause peripheral nerve damage and degeneration, such as brachial plexus injury or amyotrophic lateral sclerosis, are



Feature	Surface	Percutaneous	Inductive	Implanted - Muscle Based	Implanted - Nerve Based	Intraspinal
Specificity	+	+++	+++	+++	++	++
Day-to-day Consistency	+	+++	+++	+++	+++	+++
Channel Density	+	++	++	++	+++	+++
Longevity	+	++	+++	+++	+++	+++
Non-invasive	+++	++	+	+	+	+
Minimal Infection Risk	+++	+	++	++	++	++

Fig. 5.2 Electrode styles used for UE neuroprosthetics and their relative trade-offs. +++ high quality for the feature identified; ++ medium quality; + low quality

not candidates for neuroprosthetic intervention. This is a particularly important principle in SCI, because SCI nearly always results in a mix of upper motor neuron and lower motor neuron (LMN) damage (see Chap. 1). LMN damage must be evaluated as part of the selection criteria for the use of neuroprosthetics in SCI (Peckham et al. 1976b; Bryden et al. 2016, 2018), and extensive LMN damage may require alternative procedures such as tendon transfers (Keith et al. 1996; Keith and Peljovich 2012).

The most common electrode design is a surface electrode, which involves placing a conductor on the skin surface, usually with an interposed electrolyte gel. Electrical stimulation is then delivered through the skin to the neural structures underneath. Surface stimulation therefore is primarily suited for neural targets near the skin surface. Also, because most areas of skin contain superficial sensory fibers, surface stimulation is almost always accompanied with a strong sensation, sometimes described as "stinging." Electrode location and stimulus waveform can be used to minimize these sensations. Individuals with cervical SCI usually have diminished sensation in their forearms, so skin sensation is less of an issue. Unfortunately, SCI can also cause hypersensitive zones in an area of partial preservation and, in our experience, these can be over key skin regions such as the proximal volar forearm where electrodes are commonly placed to stimulate finger flexors.

Although easy to apply, surface electrodes are not left on the skin for longer than a few hours (Rupp 2017). Therefore, the use of surface stimulation requires daily placement of the electrodes. Accurate placement from day-to-day is important if repeatable response is required (Nathan and Ohry 1990). To ease the daily placement of electrodes, splints and garments have been developed. However, these wearable devices require a mechanism for customizing the electrode placement, since the optimum placement varies between individuals (Rupp et al. 2015). One proposed alternative is to place an array of electrodes over the entire forearm (Bouton et al. 2016), although such an approach requires calibration each time the system is donned (see Chaps. 9 and 13).

Percutaneous electrodes are a slightly more invasive option than surface electrodes, but can be used to reach deeper nerves and are particularly useful for muscle activation without activation of skin sensation (Yu et al. 2001). Percutaneous electrodes are inserted into the muscle belly via a hypodermic needle. After the needle is removed, the electrode remains in place with a lead wire that exits the skin. The tissue heals around the electrode tip and therefore these electrodes provide a consistent response from day-to-day. Although percutaneous electrodes are often considered to be a temporary system, typically used only for a few months, it is possible for these electrodes to last for many years (Memberg et al. 1993; Smith et al. 1994; Knutson et al. 2002). However, the electrode exit site is susceptible to damage from external forces and can become irritated and, in some cases, infected. Therefore, percutaneous electrodes require ongoing maintenance by the user and by a treating clinician, reducing their desirability for chronic systems.

Implanted electrodes connect to an implanted stimulator and therefore do not have any lead crossing the skin. Thus, they can be used during showering or swimming. Many different stimulating electrode designs have been developed, but

they can generally be categorized as either "muscle-based" or "nerve-based." Note that, in either case, the nerve is the activation target. Muscle-based electrodes are designed to anchor on the muscle epimysium or inside the muscle belly (Memberg et al. 1994). The anchoring of the electrode ensures that it stays in place while the tissue heals around it. Tissue healing occurs within days to weeks of implantation. Full tissue encapsulation is complete within weeks, and by 3 months post-implant the stimulated response to these electrodes is very repeatable from day-to-day. Grasp patterns developed using implanted muscle-based electrodes are stable for many years, providing reliable day-to-day function without the need for any re-calibration (Kilgore et al. 2009). One persistent misconception is that implanted electrodes are a source of common failure of neuroprosthetic systems. For example, Shin et al. (2017) mention that, with respect to implanted electrodes, "the long-term stability of the implants still needs to be improved." In contrast, our results show that implanted electrodes are extremely stable in their stimulated response and extremely durable inside the body (Kilgore et al. 2003). Such electrodes have been used in excess of 20 years, and there is no indication that the response of the electrode degrades over time (Kilgore et al. 2009). Muscle-based electrodes are a proven option as the foundational component of successful UE neuroprosthetic system (Peckham et al. 2001; Kilgore et al. 2018).

Nerve-based electrodes are placed directly adjacent to a peripheral nerve. This includes nerve cuff electrodes that encircle the nerve (Naples et al. 1988). Because the electrode is adjacent to the nerve, nerve cuff electrodes require a much lower charge per phase than muscle-based electrodes—typically an order of magnitude less charge. Some nerve cuff electrodes have multiple electrode contacts that are distributed spatially around the nerve, allowing activation of specific regions (or fascicles) of the nerve near each contact (Grill and Mortimer 1996). If the nerve is spatially organized, it is possible to activate individual muscles or groups of muscles through a single contact. In addition, full activation of the nerve results in maximal contraction of the target muscle, something that can be difficult to achieve with muscle-based electrodes. Nerve cuff electrodes provide the possibility of activating multiple muscles from a single multi-contact electrode placed proximally on a major nerve branch. In practice, however, the nerve is less spatially organized in the larger proximal nerve branches, and it is difficult to fully activate individual muscles without activating other muscles (which may be antagonists to the desired function) (Polasek et al. 2007, 2009).

Intraspinal electrodes involve fine wire electrodes inserted into the spinal cord for activation of motor neuron pools to produce a specific function. To date, attempts to utilize this approach have been limited to neuroprostheses for standing and walking and not for the UE (Bamford and Mushahwar 2011).

If the electrode response is poor, or inconsistent, or fails, the rest of the neuroprosthetic system often becomes unusable. It is not possible for any other component of the system to overcome a poor electrode–tissue response. Given this, neuroprosthetic system design should begin with the electrode design and every other aspect of the system should be designed to accommodate the optimum electrode design and not vice versa.

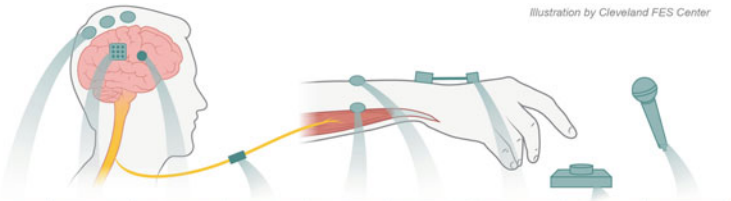
An example of the mismatch in the trade-offs with respect to electrode design and function is illustrated in a recent BCI-controlled UE neuroprosthesis (Bouton et al. 2016). In this case, an advanced intracortical array and signal processing system is utilized for control of electrically stimulated hand grasp. However, the electrode system chosen was an array of transcutaneous electrodes that circumferentially covered the middle two-thirds of the forearm. The type and arrangement of electrodes in this case represents a poor trade-off with respect to functional outcome. This design concept sacrifices the ability to activate key intrinsic hand muscles, particularly the thenar intrinsics, which are critical to functional grasp patterns (Kilgore et al. 1989; Lauer et al. 1999). However, in this particular case, the goal was the demonstration of the potential of the cortical control rather than the features of hand grasp.

Another common misconception in UE neuroprostheses is that muscle fatigue due to reverse recruitment is a major factor limiting function. It is not. For upper extremity systems, and especially for hand grasp, there is no evidence that fatigue is a major limiting factor in achieving function. In fact, well-exercised muscles are very fatigue-resistant (Peckham et al. 1976a). The effort expended towards creating electrical stimulation waveforms that can activate small fatigue-resistant motor fibers at lower threshold may have usefulness for activities such as standing and walking, but such waveforms would not provide any practical benefit for neuroprostheses providing grasp and release.

5.2 Command Input

Most of the widely used active implantable medical devices, such as pacemakers and spinal cord stimulators, are not required to be under the direct voluntary control of the individual with the device. UE neuroprostheses, by contrast, are intimately tied to volitional activities, such as reaching and grasping. The means by which the individual user exerts control over the neuroprosthesis is very important in system design. Ideally the control is as "natural" as possible, meaning that the user generates the same control signal to produce a neuroprosthetic movement that they would have used prior to their injury or disability. This feature is a major goal driving the development of brain–computer interfaces (BCI) described in this book. In addition to BCI, a wide variety of command control methods have been evaluated for UE neuroprosthetic systems, as outlined in Fig. 5.3. This includes extremely simple external control systems, such as voice or switch control, to more invasive control methods such as myoelectric control (MES) or intracortical recording arrays.

Command control options are sometimes divided into "logic" and "proportional" control options. Logic commands refer to signals that change the state or mode of the system, such as switching between grasp patterns or turning the stimulation on or off. Logic commands are discrete on/off commands and thus have the lowest demands on signal precision. Proportional commands refer to signals in which the amplitude of the signal is directly proportional to the device output over a specified



Feature	EEG	ECOG	ICMA	ENG	iEMG	sEMG	JA	Switch	Voice
Information Bandwidth (potential)	++	++	+++	++	++	++	+	+	+
Day-to-day Consistency	++	+++	++	+++	+++	++	++	+++	+++
Non-invasive	++	-	-	-	-	++	++	+++	+++
Cosmesis	+	+++	++	+++	+++	+	+	+++	++

Fig. 5.3 Command input signals used in UE neuroprostheses and their respective trade-offs. +++ high quality for the feature identified; ++ medium quality; + low quality; − negative with respect to the feature quality. *EEG* electroencephalogram, *ECOG* electrocorticography, *ICMA* intracortical multi-electrode array, *ENG* electroneurogram, *iEMG* implanted electromyogram, *sEMG* surface electromyogram, *JA* joint angle

amplitude range. The most common use for a proportional command is for controlling grasp opening and closing where it is desirable to have control over the degree of grasp closure.

The functional use of a neuroprosthesis involves entering and exiting a variety of system states, such as turning the stimulation on/off, switching between a variety of grasp patterns (typically four to six different patterns), locking/unlocking (grasp remains closed regardless of the proportional input) the hand, and opening and closing the hand. In our experience, an array of options for control of a UE neuroprosthesis is extremely desirable. Thus, we provide control of the system via switches as one option in addition to any other control methods. This allows users to determine the method of control that works best for them.

Myoelectrically controlled implanted neuroprostheses have been successfully implemented for individuals with complete cervical SCI (Hart et al. 1998; Kilgore et al. 2008, 2018). Subjects successfully use the processed myoelectric signal from a wrist extensor for proportional control of grasp opening and closing (Hart et al. 1998). Subjects have also demonstrated the ability to generate myoelectric signals from trapezius, platysma, deltoid, and biceps muscles. The use of myoelectric control in neuroprostheses allows considerable flexibility in the control algorithms, enabling them to be tailored to each individual person.

Neuroprostheses providing hand grasp function usually rely on one or more pre-programmed grasp patterns and the user selects the desired pattern prior to attempting a task. One of the methods utilized to evaluate brain–computer interfaces (BCI) is to measure the classification accuracy of the BCI with respect to select a particular grasp pattern. Unfortunately, this approach typically ignores any specific criteria that should be applied to the classification accuracy. Thus, although a

classification accuracy of 80 or 90% is reported as a successful classification, such success rates are unlikely to be acceptable for a system intended to provide daily, reliable function. The criteria for these accuracy rates should be established based on what is acceptable to the user for tasks of high importance. For example, if a grasp pattern is to be used for holding a glass for drinking, object slippage would be a huge disincentive for use of the system. Fundamentally, a high classification accuracy of 90% means that, on average, one in ten manipulation attempts results in the wrong classification and, likely, dropping the object. If an individual takes ten sips from the glass during a meal, then a spill accident is likely to occur during *every* meal. Such a task failure rate is certain to be unacceptable. In fact, spilling a glass once a month may be unacceptable to most users and that would translate, using the same assumptions, to a required classification rate of 99.89%. Further, if the task is acquiring a hot cup of coffee, the required accuracy is probably even more stringent. Performing the testing and surveys of users to understand these accuracy requirements is of high importance if neuroprostheses are to be successfully translated to regular use.

A common issue in neuroprosthetics, particularly with respect to the use of cortical control, is the over-specification of grasp pattern resolution required for functional tasks. In particular, the accurate, graded control of individual digits is often identified as primary test target. While such a goal is reasonable as an ultimate system and can serve to demonstrate scientifically relevant features of the control system, it is not a necessary target for functional outcomes. Most daily tasks can be performed with two grasp patterns: a lateral pinch and a palmar grasp (Peckham et al. 1983). Further, most objects encountered in everyday activities are rigid and essentially indestructible even at maximum grip forces (fork, pen, glass, book, etc.). Thus, the ability to achieve finely graded grip force or digit position is rarely required. Given this, a simple on-off grasp can be extremely functional and can allow a large number of tasks to be completed. Further refinements in providing multiple grasp patterns, finely graded control, and independent digit control will generally have diminishing returns with respect to functional benefit on a daily basis.

5.3 Control Algorithm

The control algorithm translates the processed command signal or signals into the stimulation patterns that will be delivered to each electrode (Kilgore et al. 1989). This is necessary because there is a significant mismatch between the number and quality of the command signals in relation to the stimulus output channels. Often a single command signal is used to control the stimulation to a dozen or more muscles. This reduces the burden on the user during functional tasks, as the user can focus on a concept such as “open grasp” or “close grasp” rather than on the individual stimulation patterns for each muscle involved in those motions. This processing must be performed in real time with minimal delays. Given that most muscles are stimulated at 10–20 Hz, the processing should be performed within the inter-pulse

interval so that the next pulse can be appropriately updated, and thus the processing should take place within 50 ms or less. In our experience, when processing delays approach one-third of a second, they become very noticeable to the user and performance is degraded to the point that functional capacity is lost.

Current UE neuroprostheses use a look-up table approach to create the relationship between a single command input and the stimulation output. The command input for grasp opening and closing is typically a proportional command relating a fully open grasp to 0% and a fully closed grasp to 100%, with a table resolution of 1% or better. In theory, this should allow users to select and maintain the grasp pattern at, for example, 88% fully closed. In practice, the ability of the user to maintain the control signal is not close to the resolution of the algorithm. In a study by Johnson and Peckham (1990), the maximum resolution for shoulder position control was 8 to 13 levels over full range or approximately 10%. In addition, the response of muscles to stimulation is variable from pulse to pulse over time. Thus, fine control of grasp force or grasp opening is not possible using any current neuroprosthesis. Fortunately, for most practical daily tasks, a high resolution of force or position is not required. Most objects acquired in daily life are rigid or highly durable (fork, pen, cup, etc.). Achieving a significant increase in the force and position resolution of neuroprosthetic function would require significant improvement in the resolution of both the user's ability to generate a control signal and in the consistency of the stimulated output. The need for increased resolution will become more apparent when the neuroprosthesis is used to perform active manipulations of objects within the hand. Increased resolution will probably need to be coupled with high resolution sensory feedback. Thus, significant improvement in all aspects of the system will be required to achieve activities that require high resolution position and force control, such as cutting paper shapes with scissors or manipulating a pencil between the fingers. The importance of achieving such tasks will need to be weighed against the complexity of the systems required to achieve them.

5.4 Feedback Loops

A UE neuroprosthesis has at least one, and as many as three, distinct feedback loops. First, and often overlooked, is the feedback loop consisting of the user's intact sensation and volitional control. Second, within the neuroprosthesis there can be closed-loop feedback in which one or more outputs of the system are used to directly influence the operation of the neuroprosthesis. This loop occurs without the user being consciously aware of it. Third, information about the system output can be fed back to the user through one or more sensory modalities, allowing the user to respond to that input and alter the system performance as needed. Each of these loops will be discussed in this section.

There are two main aspects of the user's own intact physiological feedback to consider. First, voluntary movement is coupled with the stimulated movement in order to achieve functional tasks. This is particularly important at the wrist for

individuals with SCI and a motor level of C6. Voluntary wrist extension directly affects the passive positioning of the fingers. The fingers are simultaneously under control by the neuroprosthesis, and the extrinsic finger flexors and extensors are strong wrist flexors and extensors as well. When a user attempts to passively flex their wrist to open their fingers (passive tenodesis effect), electrical stimulation of the finger extensors can cause the wrist to actively extend, pulling the hand away from the object to be grasped. It is important to take these interactions into account when the stimulation parameters are developed.

The second aspect of the user's physiological feedback is residual sensory feedback that influences how the user controls the grasp. All users have intact vision and have to perform tasks under visual guidance given the lack of normal sensation. Some users have some residual sensation in the hand (typically impaired) and users also have referred sensations from the muscle contractions. This feedback can be important in the success of functional tasks.

Closed-loop feedback at the machine level has only been implemented in a limited manner in existing systems, due to the lack of sensor information in most systems. Grill and Peckham (1998) demonstrated the use of an accelerometer on the upper arm to directly control triceps stimulation. When the upper arm was raised above horizontal, stimulation was automatically applied to the triceps.

At least some sensory feedback is incorporated into every system as it is necessary for the user to have knowledge of the state of the system in order to operate it successfully. At a minimum this feedback includes visual displays and audio feedback. More recent systems utilize connection to a smartphone app to display information about the status of the system.

Electrocutaneous feedback provides a rapid and very personal and discrete means of providing feedback. The Freehand System, an implanted UE neuroprosthesis, utilized a subcutaneous electrode placed in the shoulder (area of normal sensation) to provide feedback regarding the state of the system and the degree of opening and closing, encoded in the frequency of the electrocutaneous stimulation (Kilgore et al. 1997; Peckham et al. 2001). When multiple electrodes are used, information can be encoded as both position and frequency, allowing a rich array of directly accessible information for the user (Riso et al. 1991).

Significant effort has been expended in attempting to develop sensory feedback of grasp sensation such as grip pressure or object slip. Initially, the concept was to develop externally worn or implantable sensors (Crago et al. 1986). However, externally worn sensors were found to interfere with the user's acquisition of objects. Gloves worn for this purpose change the passive properties of the grasp and make flexion difficult. Reliable implanted sensors have proven to be difficult to develop. Further, the location of such sensor on the digits is difficult to determine. Initially, it was proposed to place the sensor on the thumb pad. However, the maximum pressure on an object varies widely over the surface of the thumb, fingers, and palm.

Inmann and Haugland (2012) studied the possibility of gaining sensory information related to grasp by recording the neural signal from a nerve cuff electrode implanted on the digital sensory nerve of the index finger. In a controlled setting, it was possible to use the amplitude of the electroneurogram (ENG) as a signal of

object slip. However, during uncontrolled functional activities, it was too difficult to separate increased ENG amplitude due to slip from signal increases due to other qualities of the device, such as object contact or compliance. More importantly, however, the appropriate change in stimulation to prevent object slippage depended on many factors. The initial hypothesis was that if an object was slipping the appropriate response was to increase the stimulation to the flexors until the object stopped slipping. However, in practice this hypothesis is rarely true. Frequently, in fact, increasing the stimulation to the flexors resulted in the object being squeezed out of the hand. Successful response to slipping would require knowledge of the manner in which an object is slipping, the shape of the object, the position of all of the digits, where each digit contacts the object, and the effect that changing stimulation will have on each digit. This is a difficult biomechanical problem that has yet to be solved.

5.5 Principles of Operation

In this section we describe the operation of a typical UE neuroprosthesis from the user's perspective. We are using, as an example, a two-channel myoelectrically controlled implanted neuroprosthesis providing grasp and reach. For this description, we are assuming that the user has a C6 motor complete (AIS A or B grade) SCI with no relevant motor functions preserved below the motor level. Coordinated stimulation of selected hand and forearm muscles is controlled via myoelectric activity from muscles that are still under voluntary control of the user. This makes maximal use of their remaining voluntary musculature to control multiple paralyzed muscles in a manner that allows the patient to perform activities that they could not perform without the stimulation.

The UE neuroprosthesis is implemented with myoelectric signal (MES) recordings from two muscles, typically a wrist extensor and a neck muscle (platysma being the most common). The wrist muscle provides a direct proportional control, which the user can vary from 0% to 100% by maintaining varying degrees of contraction of the muscle. The neck muscle is generally utilized as a "logic" signal. Some muscles are better-suited for use in generating logic signals because the user does not have to maintain contraction of these muscles for prolonged periods nor does the user have to learn to produce a graded contraction from these muscles. The functions controlled via MES include the grasp pattern selection, opening and closing of the hand in a proportional manner, turning the system on and off, turning elbow extension on and off, and the ability to lock and unlock the hand so that a grasp can be maintained in a fixed position without the need for continued control input.

During active functional use, the user will normally be in the hand open position, and their proportional control muscle, usually the wrist muscle, will be relaxed. If the user wants to acquire an object, the user will reach out using their voluntary musculature and position their open hand around the object. Once the hand is properly positioned around the object, they will then contract their proportional

control muscle. This will increase the proportional control signal, which will cause the grasp to close around the object. The user can adjust the force of the grasp by adjusting the level of contraction of their proportional control muscle. Once the user has acquired the object, they can maintain their grip on the object by maintaining a consistent intensity of muscle contraction in their proportional control muscle.

If the user intends to hold an object for a prolonged period of time, it is desirable to initiate a "lock" command, which maintains a constant level of stimulation irrespective of the proportional command signal. The lock command is routinely desirable for most tasks. Therefore, if the user maintains the command at 100% for a brief period (typically 2 s), the lock state is automatically initiated. Alternatively, the lock command can be executed by performing a quick jerk of the user's "logic" control muscles. Once the hand is locked, the user can fully or partially relax their proportional control muscle and the grasp will still remain closed around the object. The lock command reduces fatigue in the user's voluntary muscles, which are often weakened due to their SCI.

Once the user has completed the activity and they wish to open their hand and place the object back on the table or shelf, they can generate an "unlock" command. The unlock command can consist of two quick bursts of activity from the forearm (referred to as a "double-click") or a quick burst of activity from the logic muscle. Typically, the "double-click" is performed using a predetermined time pattern so that the second burst of activity must occur within 1 to 2 s after the first burst. When the unlock command is initiated, the grasp transitions back into the state where grasp opening and closing is controlled directly by the contraction level of the proportional control muscle. During the initial period immediately after unlocking, the proportional control slowly transitions to direct proportional control with a slow time constant. This prevents the grasp from suddenly opening when the subject unlocks and the proportional control happens to be at a low level. Once the user regains proportional control, relaxation of their proportional control muscle will decrease the proportional control signal, causing the grasp to open and releasing the object.

If the user is anticipating performing multiple tasks, they will typically leave the stimulation "on" with the grasp open and ready to perform the next task. If the user desires to use a different grasp pattern, they can switch grasp patterns by activating the logic muscle with a rapid twitch or series of twitches. The timing and magnitude of these twitches are established, through evaluation, to be a movement pattern that is very unlikely to occur unintentionally during normal activities. Each successive activation of the grasp mode logic command will toggle the grasp pattern among multiple types of grasp patterns. Once the user identifies that their hand is in their desired pattern, the grasp is open and the user immediately gains proportional control of their grasp. Grasp control proceeds as it does with any grasp; a strong contraction results in grasp closing and relaxation results in grasp opening.

The user can also independently activate other functions, such as elbow extension, forearm pronation, or shoulder stabilization, by producing a specific pattern of myoelectric activity in the logic control muscles. The system can be tailored to the needs and physiology of each user, within the configuration of utilizing myoelectric activity from one or more voluntary muscles to control the electrical stimulation of

one or more paralyzed muscles to produce functional movements. In general, reaching functions enhanced with electrical stimulation are either "on" or "off" and the user contracts their voluntary antagonists against the stimulated musculature to modulate position if necessary (Lemay et al. 1996; Grill and Peckham 1998; Bryden et al. 2000).

5.6 Outcomes

The functional impact of UE neuroprostheses is demonstrated by evaluating the user in performing activities of daily living (Stroh and Van Doren 1994; Davis et al. 1998; Bryden et al. 2008). Studies are designed to compare the user's function with the neuroprosthesis turned on and the user's function with the neuroprosthesis turned off (Peckham et al. 2001). This study design works well because there is essentially no "wash-out" period between the muscle's response when stimulation is on and when it is turned off. Functionally testing performed in this manner can be a powerful demonstration of the potential impact of these systems. For example, with the stimulation turned off, an individual may require full assistance in order to eat a meal, and then with the stimulation turned on, the individual is instantly able to hold a fork to stab and eat and hold a glass to drink. In fact, holding a fork to eat is the most common task performed using a UE neuroprosthesis.

An example of the typical results obtained by users of a myoelectrically controlled UE neuroprosthesis with 12 stimulation channels was reported by Kilgore et al. (2008, 2018) and is shown in Fig. 5.4. Twelve subjects were studied and every subject demonstrated improvement in at least two activities of daily living, and as many as eleven activities. Most commonly, improvement was demonstrated in eating with a fork and writing with a pen. Other tasks in which subjects showed improvement included: office tasks, using a cell phone, getting money out of a wallet, and embroidery (Kilgore et al. 2008). This study demonstrated the adaptability of MES control for implanted neuroprostheses and confirmed the significant impact of these systems on the lives of disabled individuals.

The functional results in the literature for individuals using UE neuroprostheses of any design are universally positive (Keith et al. 1989; Peckham et al. 1993, 2002; Perkins et al. 1994; Smith et al. 1996; Prochazka et al. 1997; Biering-Sorensen et al. 2000; Carroll et al. 2000; Fromm et al. 2001; Taylor et al. 2002; Popovic et al. 2002; Kilgore et al. 2008, 2018; Bouton et al. 2016; Ajiboye et al. 2017). In fact, most studies report a 100% success rate, even when the study cohort exceeds 50 (Peckham et al. 2001). Such an unusually high success rate is due to two key factors. First, the screening procedure is a strong predictor of system outcome. Specifically, screening of UE muscle response can be performed using surface stimulation, even if the neuroprosthesis will ultimately use percutaneous or fully implanted electrodes or even nerve cuffs. If muscle contraction can be achieved using surface stimulation, then it can be achieved at least as well using any other electrode design (barring total mechanical or electrical failure of the electrode design). Muscle contraction will

Fig. 5.4 Example of individuals with a motor level of C6 demonstrating function achieved using an implanted neuroprosthesis

result in joint movement, barring severe contractures, which can be screened out prior to neuroprosthetic intervention. Joint contraction can be coordinated into a rudimentary grasp pattern, which at a minimum can be finger and thumb flexion around an object. Given that the individuals targeted for UE neuroprostheses do not have grasp function without the stimulation, the ability of the individual to perform some tasks more independently with the stimulation compared to without the stimulation is assured.

The second factor that contributes to the high success rate is that individuals seeking increased independence are very resourceful in utilizing any new tool to improve performance in a given task. High importance activities such as holding a fork or holding a pen are easily accomplished through contraction of the digits, even if the quality of the control over the stimulation is poor. An individual with complete paralysis in the hand is likely to be able to figure out at least some activities that he or she can perform even with a weak and poorly coordinated grasp pattern.

Given the universally positive outcomes with respect to laboratory-based functional tasks, it is important to assess the impact in daily activities at home and in the community (Wuolle et al. 1999). Regular daily use of a neuroprosthesis for months and years clearly indicates that the system provides improvement in at least one task that is of high importance to the user. It can be demonstrated that the potential for reduced need of assistance can result in an overall reduction in the cost of disability for individuals receiving a UE neuroprosthesis (Creasey et al. 2000). Performance of functional tasks in the laboratory and for short periods at home can serve to

demonstrate the potential of the system, but it is difficult to determine if the functional improvement is truly life-changing.

Our ongoing experience with the Freehand system provides some insight into the impact of an implanted neuroprosthesis in the life of an individual with SCI. Over 200 individuals were implanted with the Freehand system between 1986 and 2001. Some of these individuals continue to utilize the system daily even today, despite the fact that the company that marketed the Freehand system stopped supporting the users in 2001. These individuals have more than a 20-year track record of daily use, clearly indicating that the system has a significant utility in their lives. However, as reported by Wuolle et al. (1999), some individuals receiving the Freehand became non-users of the neuroprosthesis within months. This drastic dichotomy of usage results requires further study and analysis to understand the factors involved. Our preliminary analysis of these individuals revealed that daily use was *not* related to the degree of success in laboratory tests (recognizing that 100% demonstrated at least some improvement). Some individuals who demonstrated improved independence in multiple activities of daily living became non-users of the neuroprosthesis. Other individuals who demonstrated marginal improvement in one or two tasks became daily users for years and decades. Clearly there are other, more personal factors that determine the true utility of a neuroprosthesis.

Perhaps it is instructive to hear the unsolicited comments of individuals who have been users of implanted UE neuroprostheses for many years up to two and a half decades. Some comments are as follows:

"I . . . have been ecstatic about how much [the system] has increased my independence and daily functioning" [User in the USA].

"I'm a daily user and rely on it to enable me to work full-time with no support hours required during work hours" [User in Australia].

"My hand doesn't function without it" [User in the USA].

Regarding the failure of the implanted stimulator after approximately 5 years of use, a user was very upset with the loss of the function he had gained by the neuroprosthesis and commented "I consider the [date of implant failure] to be a second spinal cord injury date" [User in Germany].

5.7 Conclusion

UE neuroprostheses can increase functional independence for individuals with cervical SCI. These systems are unique in that the user must maintain real-time control over the stimulated grasp patterns in order to perform desired tasks. As described in this book, control of grasp functions via BCI presents the possibility of simultaneous control of multiple degrees of freedom. Myoelectric control and switch control have also proven to be successful methods of enabling the individual to perform functional activities. UE neuroprostheses implemented in individuals with motor complete cervical SCI are nearly universally successful in demonstrating increased independence in the laboratory. Home and community use of UE

neuroprostheses has now been demonstrated by some daily users for more than two decades. Although significant improvement in grasp, control, and feedback aspects of UE neuroprostheses can still be achieved, the major hurdle facing the field is the development of a sustainable, widely available UE neuroprosthesis for individuals with SCI.

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Chapter 6
Neuro-Robotics: Rehabilitation and Restoration of Walking Using Exoskeletons via Non-invasive Brain–Machine Interfaces

Atilla Kilicarslan and Jose Luis Contreras-Vidal

Abstract Using wearable robotic systems that assist people in their daily activities or provide them with the needed therapeutic support is not new. Some systems are designed around microelectromechanical properties for monitoring or feedback purposes (such as smart systems that monitor heartbeat or muscle activity). Others are designed at the macroscale for various medical applications (such as prostheses and orthoses). In recent years there has been an increasing number of efforts from engineers and scientists on the uses of such systems for people with disabilities. Systems that are wearable and able to provide functionality to the lower (or upper) limb fall into the category of exoskeletons. In this chapter, we focus on the active (actuated) lower-body exoskeleton systems that are designed for compensatory and restorative purposes. Due to their repeatability, reliability, and precision, the exoskeleton systems found application areas for supporting the physical therapy practices by moving the limbs at an intensity chosen by the clinician. One major shortcoming of these systems is the lack of engagement of the users into the therapy session to promote cortical plasticity and therefore maximizing the opportunity for motor recovery, while providing them with an intuitive control interface. The field of non-invasive electroencephalography (EEG) based Brain–Computer Interfaces (BCIs) is a big leap towards this direction. Closed-loop BCI systems harness users brain activation patterns in real-time, allowing the end-users to control exoskeletons functions by their mental imagery. In this chapter, we define several key aspects of such neuro-robotic systems, and discuss major issues and suggest solutions.

Keywords Neuro-robotics · Brain–Computer Interface (BCI) · EEG · Artifacts · Exoskeletons · Robotic rehabilitation

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6.1 Introduction

Successful implementation of neuro-robotic systems employing the EEG-BCI technology requires careful consideration of multiple factors as summarized in Fig. 6.1. In this chapter, we focus on the real-time implementation and discuss the limitations of the neuro-technology. We also provide solutions provided by our group to some of the major problems that prevent wide-scale usage of such systems.

The selection of the compensatory/restorative robot depends on the intended use, the user's capabilities, and the needed functionality. Exoskeletons differ on their number of actuated joints, mobility and speed, and how they are controlled by the user and/or therapist. The *usability* of an exoskeleton, for instance, depends on the user's needs and capabilities and also refers to the different modes of movement, support, and movement intensity that the exoskeleton can provide. The selection of an appropriate physical interface between the robot and the user (i.e., harnesses, straps) is generally concerned with the *form factor* and should provide safe and effective implementation during the dynamic motion of the exoskeleton. These options are usually promoted by the exoskeleton manufacturer. However, the *response time* of the exoskeleton systems are often overlooked. Response time refers to the time elapsed between a given movement command and the actual observed execution. Most of the systems provide time delays that are within acceptable ranges for generic use. However, interfacing with a physiological control modality (i.e., BCI control, myoelectric control, or even motion control) the exoskeleton time delay can cause lagged response, therefore, providing altered feedback to the users.

Another consideration should be made on the measurement modality, such as EEG or any other physiological (e.g., electromyography or EMG) or mechanical (e.g., detection of body tilt using accelerometers) signal, for the detection of the initial movement intent and continuation of the movements. Each control modality has its

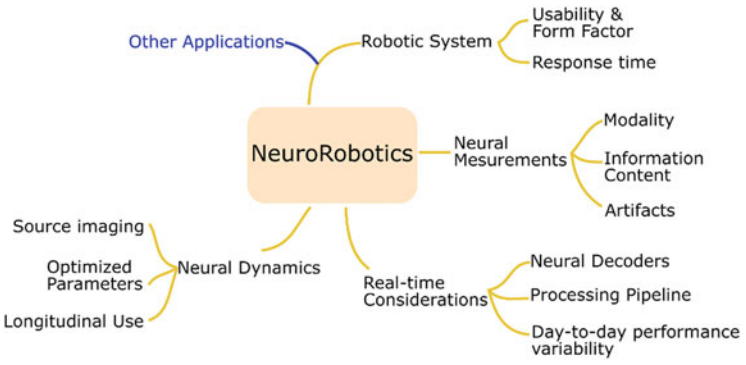

Fig. 6.1 Neuro-Robotics Framework: Many critical components have been defined for a successful Brain–Machine Interface (BMI) based neuro-robotics implementation. Although the application domain in this chapter is lower-body powered exoskeletons, these components also apply to other types of systems and application domains

own set of major challenges to overcome. In this chapter, we are concerned with the EEG measurements for BCI control of exoskeletons (Fig. 6.2) and the critical problems that are associated with them (for a recent review, see (He et al. 2018)). The cortical information that can be extracted from the EEG is proven to be adequate for motor movements (Bhagat et al. 2016; Venkatakrishnan et al. 2014; Bradberry et al. 2008, 2009; Contreras-Vidal et al. 2010; Kilicarslan et al. 2013). Our group demonstrated the decoding of movement intention for lower-body exoskeletons using slow cortical oscillations (delta band [0.1–4 Hz]) (Kilicarslan et al. 2013). EEG measurements, however, are considered having low signal-to-noise ratio (SNR), due to physiological and non-physiological *artifacts*. Any real-time implementation using EEG should consider the artifacts that have similar frequency contents compared to that of the EEG features used for control. The event-locked nature of many types of artifacts makes it exceedingly difficult to implement high-performance neural decoders. In EEG delta band, the ocular and motion artifacts, as well as impedance changes can be considered as dominant factors that adversely affect the EEG measurements on all scalp electrode locations. We will provide real-time compatible solutions to handle these two major EEG contaminants. Other considerations for a successful *real-time implementation*, such as the neural decoders, EEG processing pipeline, and day-to-day variability will also be discussed in this chapter.

Understanding the neural dynamics before and after the rehabilitation paradigms using BCIs is a major topic that can have a significant contribution to the implementation of such systems. Comparing the *neural source activations* and assessing neural plasticity during a *longitudinal use* can improve the overall success of the implementation. This allows for the *optimization of the decoder parameters* taking into account contextual information leading to changes in internal states of the user, day-to-day changes in neural variability, as well as optimizing the number of sensors. Most of the methods that are discussed in this chapter are also applicable to *other systems* that are intended for EEG-based BCI systems for rehabilitation robotics (i.e., upper limb, see Chaps. 2, 5 and 13), virtual reality, and software interfacing.

The generic framework of the implementations that are discussed in this chapter are summarized in Fig. 6.2. In this *closed-loop* implementation, the EEG data are measured, processed, and passed into a decoder that interprets the user's intention of movement. The decoder output is then applied to the exoskeleton as a control command. In our discussed application domain, unless an external device is configured to provide a specific type of feedback, the users experience visual, proprioceptive and kinesthetic feedback while wearing the exoskeleton. In a BCI setting, the completion of the task is usually felt by the motion of the exoskeleton or fed to the user as a computer graphic or audio cue. Following this closed-loop implementation, the clinician monitors the recovery and individually adjusts the intervention parameters according to the functional status of the user (i.e., range and speed of the movement, therapy times, and repetition rates of the given tasks).

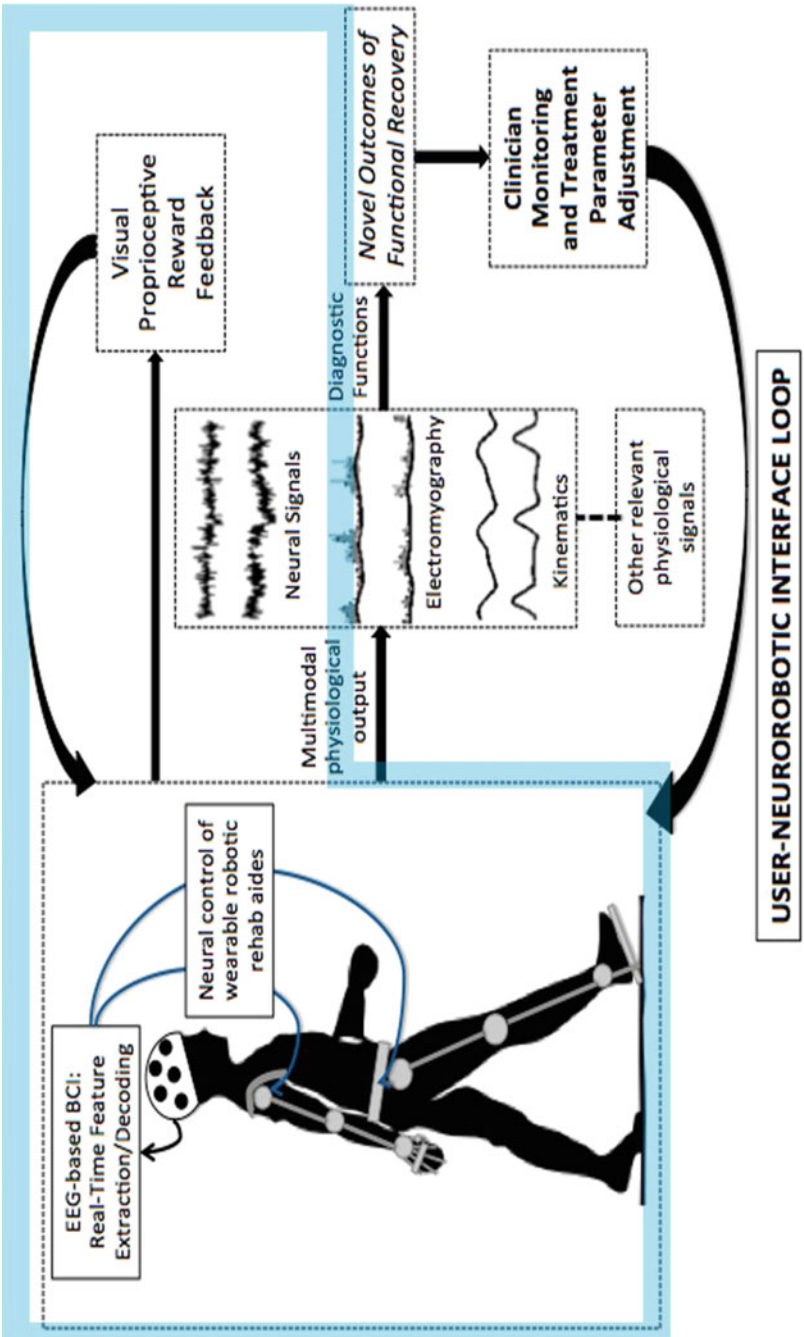

Fig. 6.2 General framework for a neuro-robotic application. Blue region indicates the type and closed-loop structure of the implementation discussed in this chapter. From Venkatakrishnan et al. (2014) with permission

6.2 Robotic Systems: Lower-Body Exoskeletons

Orthotic/prosthetic systems usually cover a single human joint and provide support or constrain the motion of the human limb. Both type of systems can be active or passive in design. An active system is one which provides actuated motion or assistance to a human joint or artificial limb via an external electromechanical system attached to it, such as electric motors, pneumatic or hydraulic actuators. A passive system does not have an energized external actuation mechanisms. Systems that have freely rotating joints fall into this category. A passive system can also be designed to apply resistance to the free motion via a dampening system or it can store energy and release it via a rotational or extension/compression springs. We define a lower-body exoskeleton as an electromechanical system that is attached to multiple human lower-limb joints to provide a coordinated activity, support or motion. These robotic devices can also be designed as active or passive systems. However, since the main purpose of an exoskeleton is to provide assist-as-needed support of coordinated movements of two or more joints, at least one is usually designed as active joint. It is also possible to implement a combination of active and passive joints in a single exoskeleton system.

Exoskeletons can be grouped by their control modalities as being assistive, resistive, corrective, or fully active. An assistive (or assist-as-needed) control of an exoskeleton is based on the measurement of the residual limb activation of the end-user (using sensors on the exoskeleton). For a given task, the measured voluntary effort of the end-user is compared against the effort that is required to complete the task. If any deviation is detected, the exoskeleton completes the action and helps the user to complete the given task. The degree of assistance that the exoskeleton applies can be adjusted by the physical therapists. A resistive exoskeleton utilizes like in assistive exoskeletons the residual limb activation of the person. In this case, the exoskeleton applies resistance to the motion, similar to an exercise equipment, to execute a strength training. A corrective exoskeleton is combining the basic characteristics of an assistive and a resistive control modalities. Given that a patient is able to complete the task, but not in an optimal way, the exoskeleton measures the limb activation and trajectory (i.e., the limb joint angles at any given time) and compares it with the optimal values that of an person without disabilities. It then corrects the deviations from the physiological task trajectories. This control modality mostly concerns with providing synchrony between individual joints. Finally, a fully supportive exoskeleton exerts the optimal path, force, and speed to the impaired limb of an end-user to accomplish the given task. This is usually the case for patients with motor complete spinal cord injury (SCI) with very little to no residual voluntary limb movement.

Lower-limb exoskeletons are considered as a promising tool in motor rehabilitation programs with the potential to improve motor and physiological functions such as bladder and bowel or cradiovacular functions, (Federici et al. 2015; Contreras-Vidal and Grossman 2013). In addition, these devices may also reduce the physical

burden on clinical staff, quantitatively assess the progress of rehabilitation, and benefit from the fidelity of repetitive training (Banala et al. 2008).

6.2.1 User Selection, Usability, Form Factor, and Response Time

There are several key factors on selecting the appropriate robot for lower-limb rehabilitation. The area of application of the exoskeleton is depending on the ability of the exoskeleton to provide the needed assist-as-needed, supportive, resistive or corrective control modalities. The selection of one or multiple control modes depends on the end-user's needs and capabilities. As an example, if the implementation is chosen for patients with complete SCI, the assist-as-needed control mode might not be feasible as the users will not be able to exert any voluntary residual movements. Whereas for end-users with incomplete SCI or after stroke, the assist-as-needed or corrective modes might be preferable. The control modality should be determined by the clinical expert as the implementation often needs to be individualized. This, in general, concerns the personalization of the exoskeletons for specific patients, closely followed by the patient's needs for personalized form factors.

The form factor can be defined as the patient's physical interaction with the exoskeleton which must be done in a safe and comfortable manner. For lower-body exoskeleton systems, the end-user's joint locations must be matched to those of the exoskeleton. Unless the exoskeleton is personalized for a specific patient, most systems are designed to be adjustable to the upper and lower-limb segmental lengths of the users. However, since the exoskeleton joint cannot precisely mimic the physiological trajectory of human joint center of rotation (i.e., knee), some level of mismatch is unavoidable. The exoskeleton can only be adjusted to the center of the human joint for a given fixed position for the knee, meaning that only the instantaneous center of rotation can be measured, albeit within a reasonable margin. Most exoskeletons are designed to carry almost 100% of the body weight of the users and thus are comprised of powerful actuation mechanisms. Therefore, a large mismatch between the anatomical and the technical joints can cause serious injuries, especially when the end user has a pathological bone density. Exoskeletons are dynamic systems, thus any unwanted forces that are caused by the joints' mismatch will be experienced by the end-user in a cyclic fashion during walking. The unphysiological loading pattern might cause musculoskeletal problems, depending on the end user's physical condition. Another rather unavoidable consequence of misalignments of technical and anatomical landmarks is the rubbing of padded harnesses on the skin (harnesses that hold the upper and lower leg, i.e., at shin level). It is advisable to check for skin conditions before, during, and after each exoskeleton session while the user is in a safe position (e.g., sitting with the exoskeleton). The intensity level of the training and duration of the session, therefore, should be

adjusted in a way to minimize the risk for such complications. Other usability and form factor considerations include the safe placement of the user's feet, not to limit any physiological movements (e.g., at the ankle level) and setting an adequate level of pressure that the harnesses provide to the user's legs as excessive pressure can negatively impact local perfusion and blood flow (He et al. 2017). One way towards optimal fit would be to 3D scan the user's legs and providing custom, individualized harnesses as we are currently pursuing for pediatric applications (Savage 2018). Overall, it is very important to clinically assess prospective users of exoskeletons and to mitigate any potential risks of using this technology (for a recent review, please see (He et al. 2017)).

Most exoskeleton systems provide negligible time lags (decent time response for a given command to be executed). Although this might not be an issue for generic use, excessive time lag becomes a major issue when fast response to other control modalities is required (such as BCIs). Late response to BCI generated commands affects the overall performance of the human-in-the-loop-control of exoskeletons as the users might receive altered proprioceptive and kinesthetic feedback even though the command generated by their mental imagery processes are correct. Even worse, the response times can be variable, depending on where in the overall gait cycle the exoskeleton is. In such cases, the compensation of the lagged response is left to the user's adaptation to the overall system dynamics, which is not preferable in any situation.

6.3 Neural Measurements and Brain–Machine Interfaces

6.3.1 Measurement Modalities and EEG

Engaging the patient to the rehabilitation session, thereby promoting cortical plasticity, is perhaps the most critical component in rehabilitation of patients with neurological gait disorders (Venkatakrishnan et al. 2014; Nudo 2003; Kortte et al. 2007; Blank et al. 2014). Providing the most intuitive and engaging control interface to robotic rehabilitation devices is an active research area. With their high repetition rates, sustained, precise joint activation trajectories and controllable intensities, robot-based rehabilitation at first represent a promising add-on to classical rehabilitation practices (where physical therapists manually assist with the movement of the neurologically impaired limbs). However, it was soon realized that the autonomous actuation of such devices removes the human-factor from rehabilitation and as a result the user engagement level drops significantly. In such devices, the end-users can practically be mentally and physically passive while the device moves the limbs. These factors can diminish the effectiveness of the rehabilitation as the mental component necessary for enhancement of reorganization within the central nervous system (CNS) and thus neurological and functional recovery is missing or dramtically reduced. One solution to this challenge is to harness the residual muscle activation measured by the residual EMG of the neurologically impaired limbs and assisting the patient to achieve a physiological movement accordingly (Hargrove et

al. 2013). Since the electromygraphic muscle activation is a measure for the user's voluntary intent, it could be used to estimate the end users level of mental effort. One challenge of such a control interface, however, is that the EMG activation required for a specific joint movement cannot always be accurately measured, and not all muscle activation pathways might be activated by the patient. In other words, patients might substitute physiological muscle groups' activation pattern with unphysiolgical ones that are better suited for control of the actuated joint. This can happen consciously or unconsciously, as the goal is to make the robotic device's activation most accurate. Avoiding this drawback is an unsolved problem, which can be minimized by very accurate placement of EMG electrodes to all subjects at all sessions and avoiding sensor shifts. It should also be mentioned that the residual muscle activation of the neurologically impaired limb is a result of the actual cortical motor intent, and thus, there is an unavoidable cortico-muscular delay between the onset of the actual intent and the muscle activation. A control interface seamlessly integrating in the body motor control sheme, therefore, require the measurement of the intent without time delays, even predicting the activation before it happens. Similar to the EMG control interfaces, some researchers measure the interaction forces between the robotic rehabilitation device and the user's limbs as the only parameter for gait initiation. Any residual movement at a specific joint would be originating from the user's intent, and the robot would use the detection of the voluntary generated forces to complete the full movement cycle. Although this is a good practice in terms of providing task completion for rehabilitation after the gait is initiated, the abovementioned time delay problem also applies to this type of interfaces for the actual initiation of the gait. Additionally, the residual electrical (EMG) or mechanical activation levels can be very low, and as a result, the residual movement can be increasingly hard to detect. Therefore, robust control is in some cases with very little preserved residual motor functions hard to achieve. The BCI control of such active devices, on the other hand, provides important advantages compared to the aforementioned control modalities (Venkatakrishnan et al. 2014; Wang et al. 2010; Bhagat et al. 2014). Since BCIs inherently harness one's own thought processes and movement intentions, it ensures full user engagement to the therapy session and as a result, promote CNS reorganization and ultimately functional recovery (Luu et al. 2017). EEG-based BCI systems detect the intent of movement non-invasively and provide an intuitive control interface for exoskeleton users. In this framework, the modulation of cortical signals during user's movement intents are detected by advanced algorithms to initiate exoskeleton movements. The individual joint angles tajectories are then executed by the exoskeleton's internal control loop, forming an overall shared control structure.

6.3.2 EEG Artifacts and Information Content

The rich information content of EEG for detection of motor intent has been proven by many research efforts (Bradberry et al. 2009; Kilicarslan et al. 2013; Lotte et al. 2007). However, these analyses are mostly done offline using previously collected

EEG (see Sect. 6.4.1 for a detailed discussion). The major problem with the EEG-based BCI systems is the recovery of underlying neural sources, in real time, when physiological and non-physiological artifacts are present. Here, we will review our solutions to minimaize the influence of some of the major EEG contaminants, namely ocular artifacts (eye blinks and eye movements), signal bias and drift (due to impedance changes), and motion artifacts (electrode movement). The suggested solutions for handling these physiological and non-physiological artifacts are fully real-time applicable.

Physiological artifacts can be defined as contamination of the neural source measurements by the non-neural source activations via volume conduction. As an example, eye blinking generates electrical signals due to dipoles that are located around the eyes. This activation contaminates the scalp EEG recordings where the largest contamination occurs at electrodes close to the eyes (i.e., forehead sensor locations), and propagates towards the posterior locations with changing amplitude, polarity, and phase characteristics. Non-physiological artifacts, on the other hand, can be defined as the changes in measured signal characteristics due to external causes. As an example, motion artifacts during walking are caused by the movement of the electrodes. These artifacts are manifested as oscillatory patterns with frequency harmonics, which are not present in any clean neural source activation pattern. Due to the measurement setup and subjects' movements, these artifacts do not belong to any distinguishable statistical distribution and are highly variable even among EEG sensors, even for the same session and subject. Electrode movements also cause sudden or gradual changes in the impedance values (see Fig. 6.4b (Kilicarslan et al. 2016)). The transient behavior of these impedance changes causes the measurement to have high-peak semi-oscillatory behavior. Continuous disruption of these transients (continuous movement) result in superimposed transients and manifest themselves as artifacts with very complex dynamics. Even without the electrode movements, sensor impedances can be affected by sweating and dryed gel at the electrode/skin interface. For a successful implementation of real-time BMI applications, these highly non-linear physiological and non-physiological artifacts should be removed from all EEG sensor signals simultaneously and in real time (more details on EEG artifacts can be found in Chap. 3).

Our group has developed a real-time denoising framework for high-performance artifact removal based on the robust adaptive H^{∞} filtering formulation (Kilicarslan et al. 2016). We have demonstrated the effectiveness of our technique for cleaning ocular artifacts (eye blinks, eye movements), signal bias, and signal drifts, for 60 EEG locations simultaneously, in real time. Comparisons with the very-well established offline cleaning tools clearly show the improved cleaning performance accomplished by our method. One important advantage of our method is that it depends on the real-time measurement of the noise source. This might seem like a disadvantage at first due to its requirement of additional sensors for measurement; however, compared to other existing methods that depend on the definition of clean EEG segments or statistical distributions, it allows us to be very selective on what exactly is removed from the EEG measurements. Figure 6.3(top) shows before and after cleaning of EEG data, in a pseudo-real-time setting (sample by sample processing) for two subjects and frontal (FP1) electrode. Frontal electrodes are

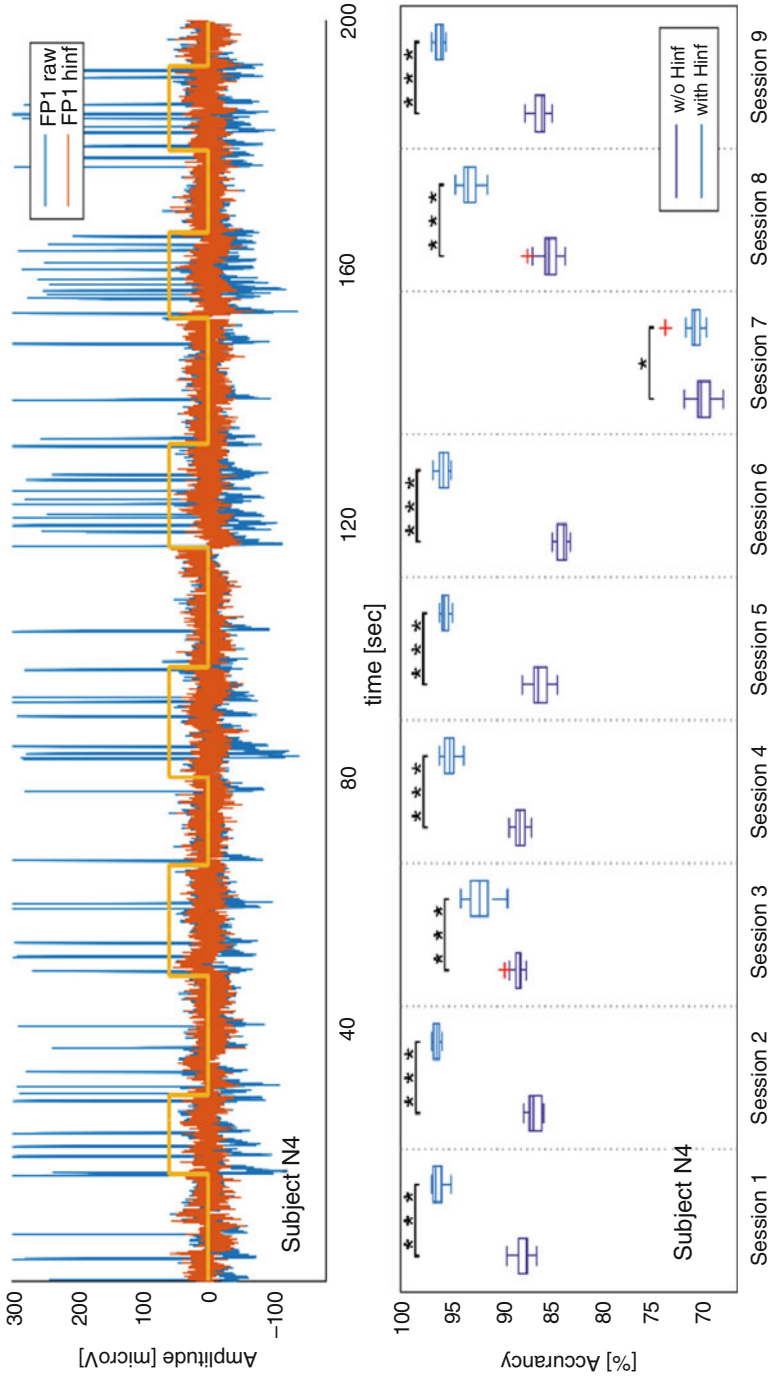

Fig. 6.3 Sample time trace of before and after ocular artifact cleaning of frontal electrode FP1 (top), and the overall decoding accuracy increase for the same subject, for multiple sessions (bottom). From (Nudo 2003), with permission

most affected by ocular artifact contamination. The yellow traces depict the stop (low) and walk (high) segments of the session while the subjects execute the tasks using a lower-body exoskeleton. The increase in longitudinal BCI decoder accuracies (for 9 sessions, spanning 3 weeks) before and after ocular artifact cleaning are shown in Fig. 6.3(bottom).

Artifact presence in a BCI framework has often been interpreted as a factor improving the decoding accuracies when the artifacts are also task dependent and are in the same frequency range. Both conditions are true for the ocular artifacts. However, the improved accuracies after cleaning ocular artifacts suggest that our decoder (Kilicarslan et al. 2013) is selective of the neural delta-band sources. Additionally, it suggest that the delta-band oscillations have an information-rich structure, allowing effective implementation in real time. The adaptive nature of our method allows for the real-time (sample by sample) identification of the volume conduction effects on scalp EEG measurements (Fig. 6.4). Figure 6.4c shows a snapshot of the raw EEG scalp distribution (left) and the identified artifacts (middle) when the artifacts are at their peak values. The similarities between the two indicate a high level of neural information loss due to ocular artifacts. The artifact-free scalp map (right), composed of recovered actual neural source data shows a very different amplitude distribution, demonstrating the effectiveness of our method in enhancing the information content per sample of EEG data (Kilicarslan et al. 2016).

Another worsening of the signal-to-noise (SNR) ratio occurs due to impedance change of the EEG electrodes. The impedances of 8 EEG sensors were measured at the beginning and end of a 10-min data collection. Gradual reduction in impedances during an experimental session affects the amplitude characteristics of the artifacts (blue and cyan traces in Fig. 6.4b). This is an example of one artifact (impedance change) affecting another artifact (ocular) in a continuous and gradual manner. Our adaptive method was able to identify the changes in skewness and sharpness of the artifacts themselves and clear them accordingly.

The robust sample adaptive formulation and the selective nature of the method make this framework a good candidate for complex tasks as motion artifact handling, in real time. We extended our linear ocular artifact mapping technique to a non-linear mapping for the motion artifact problem (Kilicarslan and Contreras-vidal 2019). We have discovered that the gravity compensated acceleration values of the head (i.e., measured via a forehead-mounted intertial measurement unit (IMU) sensor) allow for a non-linear projection to identify artifact components in each EEG sensor separately, and thus used as a reference signal for our implementation. We have used a second order Volterra Series representation and identified the kernel weights using our H^{∞} formulation. To target the harmonics of the motion artifact contamination, we have used a filter banked version of the reference signal.

Figure 6.5 shows the before and after gait locked events for a subject walking on a treadmill at speeds of 2.0 and 4.0 mph. Our algorithm handled the clear gait-locked structure of the artifacts (i.e., electrodes moving relative to the head due to walking causing cable pulling/tagging, etc.) and their harmonics. Both the signal power increase (lighter colors) and suppression (darker colors) caused by the artifacts were cleaned effectively. Figure 6.5 bottom plot shows two EEG spectra of different

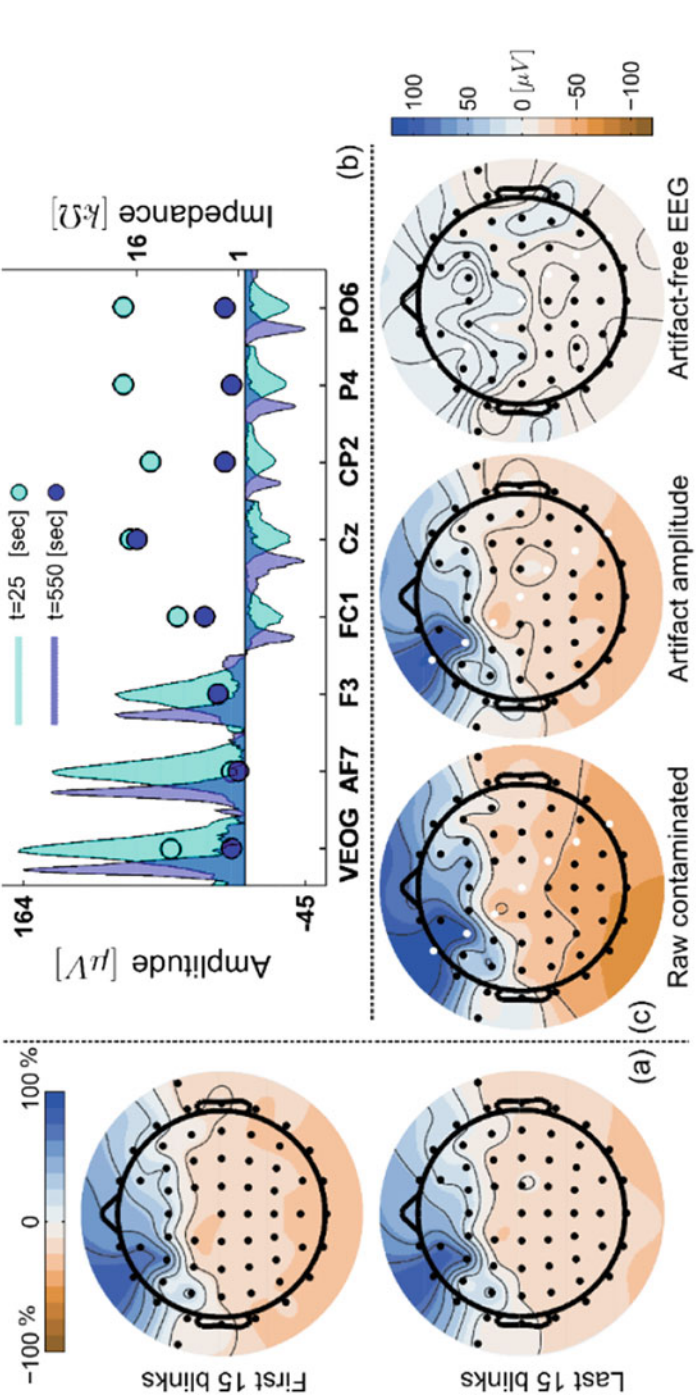

Fig. 6.4 (**a**) shows the percentage contamination of scalp areas to the characterized eye-blink (VEOG) component, where upper plot shows scalp distribution of the mean values of 15 eye blinks near the beginning of the session, and lower plot shows the mean of last 15 eye blinks for a 10 min data collection. Compared is the effect of electrode impedance changes on the scalp distribution of eye blink contamination. (**b**) shows the time traces of single blink components at the beginning (blue) and end (cyan) of the session for select electrodes that cover the scalp diagonally (marked white on **c**). Blue and cyan circles are impedance values recorded at the beginning and end of the experiment, respectively. (**c**) is a single sample amplitude distribution over all scalp areas when the

Fig. 6.4 (continued) contamination is in its peak value. The left topographical plot shows the raw EEG data amplitudes and the middle plot is only the identified contaminants' amplitudes. High similarity between two plots suggests a high level of contamination overall scalp areas in both amplitude and scalp distribution. Right topographical scalp map shows the EEG amplitude distribution after cleaned of ocular artifacts using the real-time H∞ filter. From (Nudo 2003), with permission

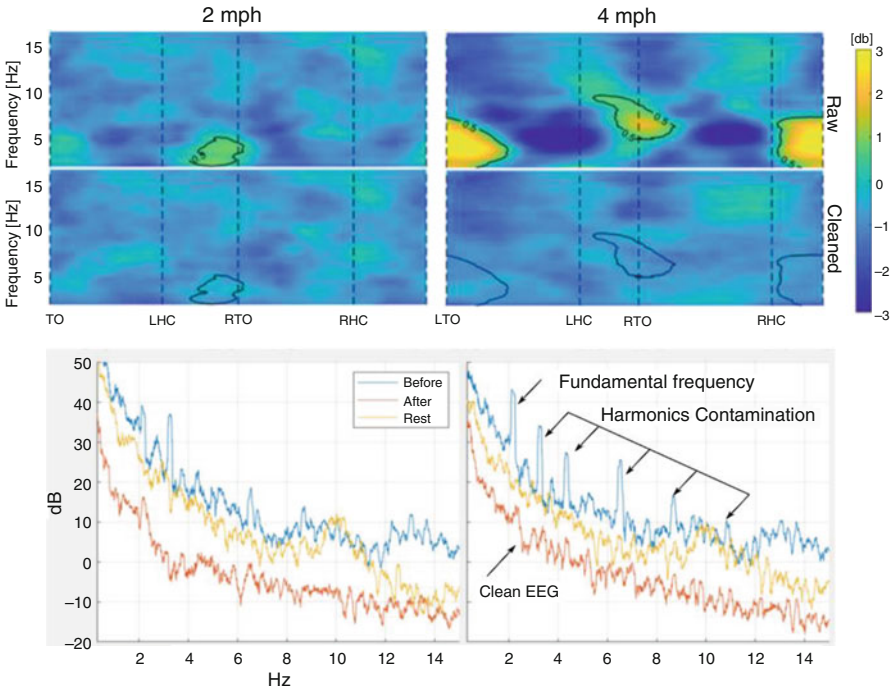

Fig. 6.5 (top) Event Related Spectral Perturbations (ERSPs) showing gait locked motion artifacts averaged for all gait cycles within the session, for two walking speeds of 2 and 4 [mph]. Gait phases are marked as LTO/RTO: Left/Right Toe Off, LHC/RHC: Left/Right Heel Contact. Raw and cleaned ERSPs were compared. Clean ERSPs show no sign of artifacts and their harmonics. (bottom) two sets of EEG spectra showing multiple levels of contamination. Raw EEG spectra (blue) can exhibit a few artifactual peaks (left) or severe harmonics (right). The rest EEG spectra (yellow) was also shown for comparison. After cleaning the motion artifacts, no sign of contamination was observed (red). From (Kortte et al. 2007), with permission

levels of artifact contamination. The power spectrum on the left is contaminated less compared to the spectra on the right for which the harmonics of the artifacts are dominant. Our method was able to adapt to both conditions without relying on any pre-statistical knowledge or pre-measurement of EEG data.

The real-time compatibility and generalizability of our adaptive filtering framework allows for the effective use of non-invasive BCI systems and dramatically expands the implementation type and application domains to other types of problems where signal denoising is desirable. Combined with our previous efforts of filtering ocular artifacts, the technique allows for a comprehensive adaptive filtering framework to increase the EEG SNR. We believe the implementation will benefit all neural measurement modalities, including studies discussing neural correlates of movement and other internal states, not necessarily of BCI focus.

6.4 Real-Time Implementation

6.4.1 Neural Decoders, Processing Pipeline, and Day-to-Day Performance Variability

Similar to the real-time compatibility of artifact processing methods, other EEG analyses and feature extraction tools need to be applicable for real-time implementations. Although the necessary calculation for a single processing step might be fast enough, the combined processing time, elapsed from the raw EEG measurements to the output of the decoder must be faster than the time between successive EEG samples. The violation of this rule would cause unpredictable behavior at best. If the feature extraction is based on windowed EEG data, e.g., features found on past 1 s of data, the minimum delay expected from the system response would also be 1 s. The overall calculation time of the neural decoder is therefore detemining the overall response time of the neuro-robotic system.

Many of the decoding accuracies reported in the literature are based on offline processing and evaluation of EEG data, which are modeled using advanced machine learning and classification tools. This step is also referred to as the training or calibration session, when followed by an online implementation. For the model training stage, many repetitions of the same task are executed by the user, and the corresponding EEG and exoskeleton data are collected. The idea behind having high number of repetitions is to collect statistically rich EEG data, and thus to be able to identify and later filter out task-independent neural activations. The EEG features that are calculated per task are then mapped to the robot states that are measured for the same task (i.e., robot's state as walking vs standing/stop). The successful mapping is called the *model* for that specific user. In real-time implementations, this model is then evaluated for the measured EEG data, and the output is considered to be the user's intended command to the exoskeleton. However, it should be noted that, as it stands, the real-time implementation of these offline generated models is not expected to work well, at least initially, for two main reasons; (1) the highly complex nature of the measured cortical signals; and (2) the user training. The first concerns with the dataset shifts (Quionero-Candela et al. 2009). Even when many trials have been executed by the user and the overall statistics is considered rich, the properties (e.g., distribution, mean, variance, etc.) of the extracted EEG features are usually different from the training data. This results in the wrong interpretation of the EEG data by the model, thus overall reduced decoding accuracies. As the sessions progress and significantly more data are collected, two major improvements can be observed; the statistics can get richer for the training algorithm to achieve a better generalization in decoding; and on the measurement level, EEG with better information content (stronger task-dependent data). The second is concerned with the user's learning and cortical plasticity. As a way of coping with the low initial decoding performance levels, often a new EEG decoder is trained for each session.

As an examplary application of this framework, Fig. 6.6 shows an offline processing pipeline (Kilicarslan et al. 2013) and real-time implementation of a neural

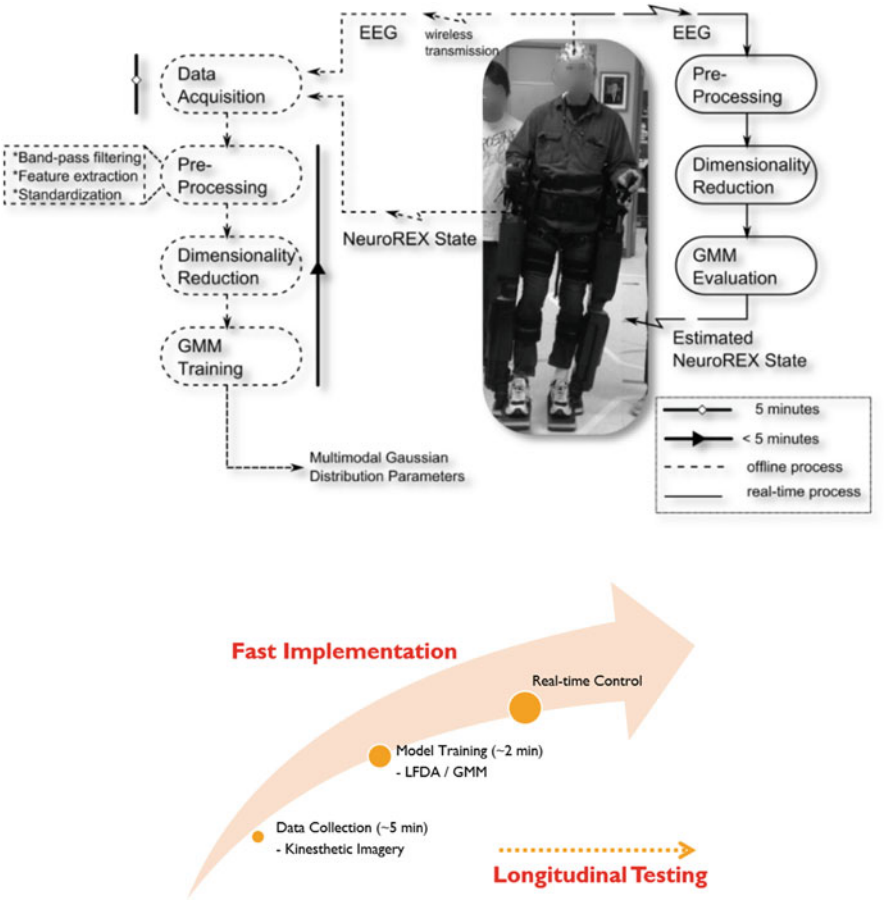

Fig. 6.6 An example of processing steps for a closed-loop BCI implementation (NeuroREX (Kilicarslan et al. 2013)). The implementation seeks for fast implementation of neural decoders and longitudinal testing to assess performance and statistical variability of the data

decoder applied to the REX lower-body exoskeleton system [REX®, Rex Bionics Inc], where the user imagines his/her leg moving as a mental task. This moving intent is then decoded in real time for BCI control or offline for further analysis and quantification of the changes in neural signals (assessment of user learning, brain plasticity, etc.). The dashed lines represent the offline data acquisition and model training phases, whereas the solid lines represent the real-time implementation. The only difference between the two is that instead of training the model (which requires heavy calculations and optimization), the real-time implementation only uses the model parameters generated during the training. Substituting the calculated parameters requires very little computational load. The idea behind the presented example is to collect the EEG data and identify a model for the user per session, within 7 min, and implement the real-time decoder by evaluating the model immediately after

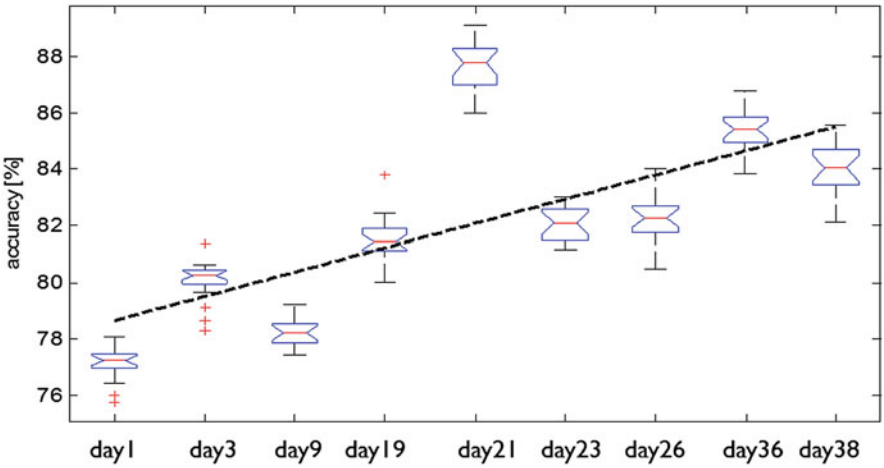

Fig. 6.7 Offline training accuracies per session for an SCI user executing stop vs walk tasks using the NeuroRex closed-loop BCI system. Unpublished data

training. For the results that will be discussed below, this process was repeated for nine sessions spanning 3–4 weeks (*longitudinal testing*).

The offline validated decoding accuracies for an end user with SCI are shown in Fig. 6.7. There is a clear increasing trend in decoding accuracies, which suggests the user's learning process, thus cortical plasticity. For each day in the plot, the accuracies were calculated with ten-fold cross-validation. All training settings were kept constant, and a new model was trained for each day. This indicates that the model was able to identify stronger correlations between the EEG features and the exoskeleton states (walk vs. stop) as sessions progress, and the task-relevant EEG data becomes stronger over time.

Figure 6.8 shows the accuracies for an non-disabled subject. In contrast to Fig. 6.7, this figure shows the real-time decoding accuracies. The purpose of this real-time implementation is to assess the subject's adaptation process to two cases; first, training a new model for each session (similar to the results reported in Fig. 6.7); and second, keeping the trained decoder fixed and implementing the last trained model for the last four sessions. In the first case, the data from all previous sessions were concatenated and used for training a new model. This model is then tested in real time for 12 trials. The completion time of each trial were used as the success metric (time-weighted task completion accuracy in Fig. 6.7). For the case 1, the decoding accuracies are low due to the previously mentioned dataset shifts and subject's adaptation. For the second case, the model was fixed at session 5 and evaluated for the remainder of the experiment. Gradually increasing decoding accuracies for this case suggests user's adaptation to the fixed model.

As previously mentioned, longitudinal BCI implementations are mostly based on a new model training for each session to cope with the changes in data statistics and signal shifts. This implies mathematical model's adaptation to the newly collected

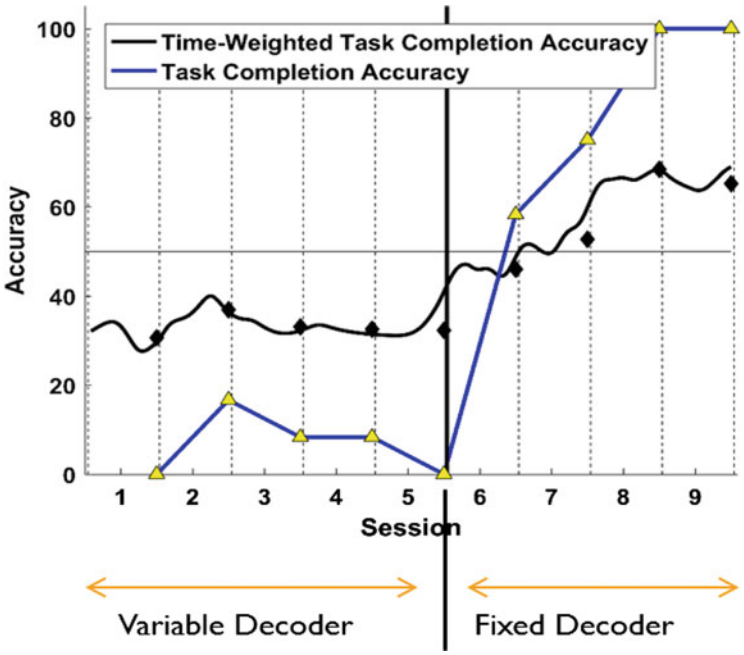

Fig. 6.8 Real-time decoding accuracies per session for a non-disabled user executing stop vs. walk tasks using the NeuroRex closed-loop BCI system. Unpublished data

EEG data. However, it also requires the user's adaptation to the new model dynamics, creating a complex loop of adaptations to changing dynamics. The adaptation reported after session 5 (Fig. 6.8) brings the question of whether or not this practice is suitable for all subjects. This is an active area of research and the presented results are not conclusive and not all subjects have the same level of adaptation and overall control. However, there is clear evidence that the EEG information content and users' adaptation to the BMI implementation to exoskeletons can increase over time, suggesting cortical plasticity. It should also be noted that the exoskeleton REX (Rex Bionics, Auckland, New Zealand) used in the reported sessions exhibit large and variable time delays, especially in stopping from a walk task. The delayed exoskeleton response, even when the correct command was sent, brings additional difficulties for the users to associate their thought patterns to the exoskeleton states, thus makes the adaptation to the overall system exceedingly difficult.

6.5 Assessing Neural Dynamics and Optimization of Parameters

The previous section underlined some of the difficulties associated with the real-time implementation of BCI systems. The subject and/or model's adaptation to the rehabilitation session is one of the key difficulties discussed. In all BCI implementations, the most important goal is to increase the information content in the EEG and developing models using advanced tools (i.e., machine learning frameworks, classifiers, etc.) that can capture the task-dependent information. EEG artifact cleaning, longitudinal use, and statistically rich data (i.e., using many trial and session data for training) were also discussed. An additional step towards data with reliable and rich information content relates to pinpointing the spatial locations of relevant neural dynamics on EEG sensor level, as well as the cortical source level. Namely, instead of using the EEG from all scalp locations and identifying relevant data in the model building stage, a prior analysis can be done investigating which sensor locations contain rich data and what relevant features are in the data per given task. Figure 6.9 summarizes the EEG sensor space analysis to pinpoint relevant electrode sites (Zhang et al. 2017). This multiple Kernel importance weight (a form of machine learning algorithm employed to find relevant information in highly complex multi-dimensional EEG data) study investigates which electrode locations contribute most to the decoding accuracies. Panel (a) shows the analysis for a study participant with SCI executing walk vs stop tasks with the REX exoskeleton for nine sessions. The analysis is complementary to the offline analysis summarized in Fig. 6.7. The electrode information at region of interest (ROI) 4 and ROI 5 are found to be most relevant for the successful decoding. The topographical plot of the important regions for the last session (when the subject has the most experience with the exoskeleton) is shown in the left plot of panel (b). The right plot on panel (b) shows the same analysis for a non-disabled study participant.

An additional analysis can be done on the source level, either by utilizing functional magnetic resonance imaging (fMRI) or source analysis using the projections from the EEG electrode data. Figure 6.10 shows the fMRI identified sources for a subject (complementary to Fig. 6.8). These scans were taken after the ninth and last session of the exoskeleton usage, while the subject executed the same mental task but this time in the scanner, watching first-person view of their exoskeleton usage. The hotter color scale points to increase activity while imagining the walk compared to stop, and the colder color scale refer to the increased activity of the lack of walking imagery compared to the existence of it. The green colored regions point to the active areas that are common to both conditions.

The increased activations in motor and somatosensory cortices during walking imagery are visible. The increased activation in visual cortex can be explained by the subject's fixation to a visual cue (cross) in the video which indicates the start of the stopping task. The key conclusion that can be drawn from these analyses would be projecting the source activation patterns to the EEG sensor domain and pinpointing the locations of the information-rich EEG electrodes. Combined with the results

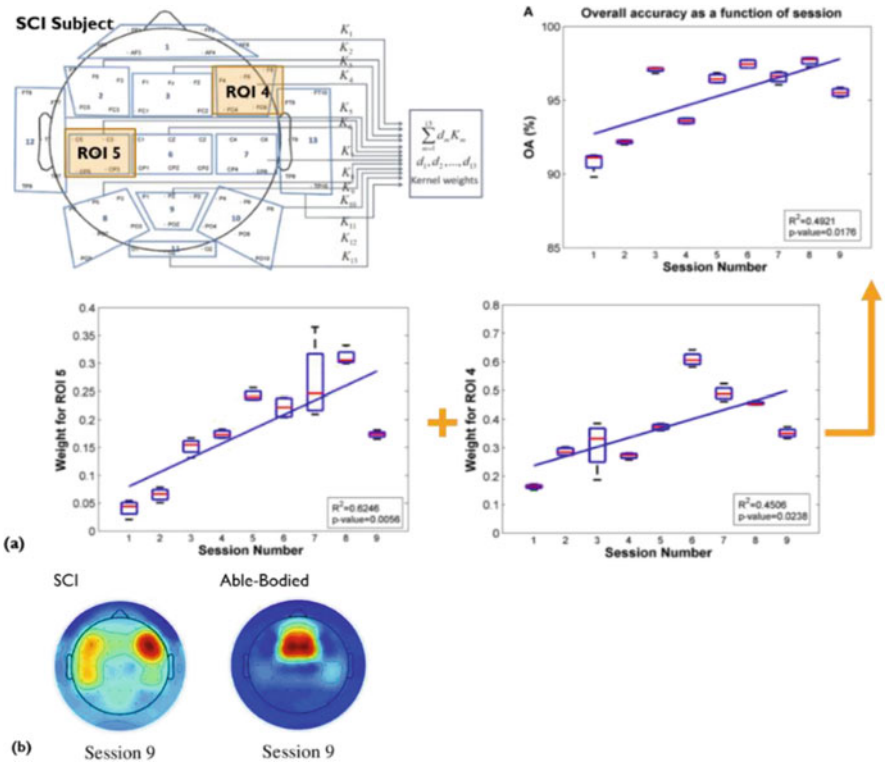

Fig. 6.9 Framework for determining the information-rich EEG sensor locations. Adapted, with permission, from (Hargrove et al. 2013). (**a**) summarizes the results for a study participant with SCI. The increasing decoding accuracies per session suggest increase in information content in the EEG, due to neural plasticity. (**b**) shows the topographical plots of the importance levels for each EEG sensor for session-9, for both the SCI and a non-disabled subject

from the sensor domain analysis, we hope to be able to provide information-rich data to the classifier. This, in turn, would result in a better generalization capability of the decoder for real-time implementations and would reduce the subject's adaptation time to the closed-loop decoder.

6.6 Conclusion

Despite recent advancements in robotic technologies and neural control modalities for rehabilitation, there are still many unknowns for their effective integration in clinical rehabilitation programs and high-performance usage. This multi-disciplinary integration requires careful considerations from hardware and software engineers, clinicians, and machine learning/signal processing experts. We have provided

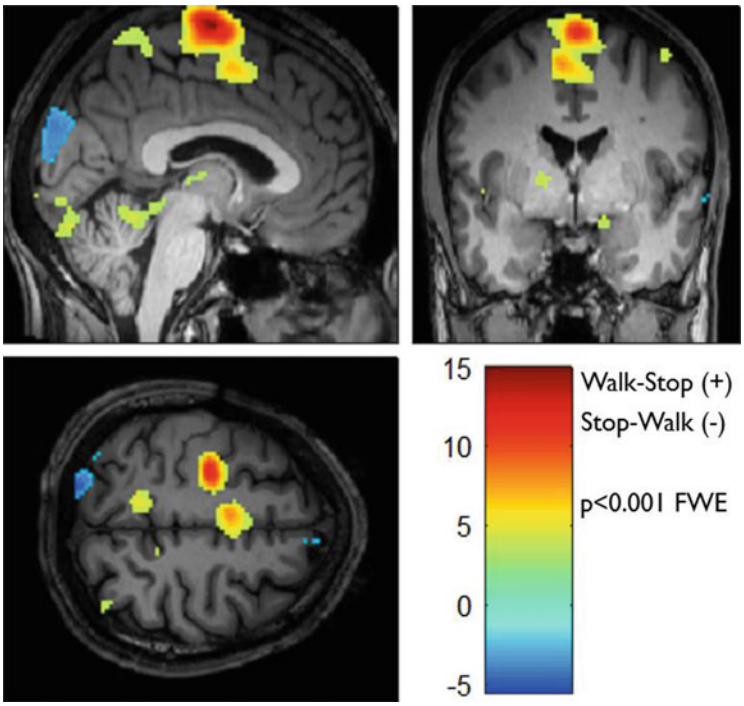

Fig. 6.10 fMRI contrast analysis of a non-disabled subject executing the same mental imagery of stop vs walk as in the NeuroREX sessions. The scans were taken after the ninth session of the subject's NeuroREX usage. Unpublished data

solutions and suggestions to some major difficulties that applies to many types of neuro-robotic systems. Wide-scale applications and deployment of neuro-robotics technology could benefit from further investigation of multiple aspect from all disciplines, which include:

From the engineer's perspective

- adapting the neural decoders per session (to account for shifts in internal states of the user and external environmental factors), and its potential adverse effects,
- improving the robot dynamics, balance control, and time lags,
- providing a generic interfacing data protocol and synchronization capabilities to third party systems (for multi-modal recordings),
- identifying and adopting engineering metrics to facilitate comparison across systems.

From the clinician's perspective

- Inclusion/exclusion criteria for the patients
  - determining risk profiles of potential users,
  - history of health complications,

  - identifying and adopting metrics that assess clinical improvements compared to classic rehabilitation routines.

  Both the clinician's and the end-user's perspective

- Feedback about the feasibility and therapeutic effects and side effects
  - Usability,
  - Independence,
  - Training time,
  - Bladder and bowel function,
  - Spasm intensity,
  - Circulatory function improvements,
  - Skin conditions,
  - Overall well-being.

As discussed before, the combined effort from multiple disciplines can provide the designers and end-users a comprehensive overview of the possibilities and limitation of the current technology.

We have also discussed the user adaptation time to any neuro-technology and the fact that the information content of the neural data can dramatically increase with new data registered. Additionally, the improvements in the user's learning and adaptation process were described. Another effective practice for neuro-robotic implementation is to provide the users prior access to the robotic system in question, before it is controlled via the neural interfaces. This process not only helps the clinicians to assess the feasibility and safety of the exoskeleton in a specific user, but also allows the user to gauge the dynamics and operating conditions of the exoskeleton. The effective use of a BCI based neuro-robotic system requires some level of focus while the user executes mental imagery of their limb movement. Early access to the robotic technology will help in this regard, as the users would become confindent in the use of the mechanical system and therefore be able to direct their focus on the mental and functional task dueing the training session.

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Chapter 7
Epidural and Transcutaneous Spinal Cord Stimulation Strategies for Motor Recovery After Spinal Cord Injury

Karen Minassian, Ivan Perret, and Ursula S. Hofstoetter

Abstract Recent studies combining spinal cord stimulation (SCS) with intense neurorehabilitation training have demonstrated unprecedented improvements of motor function in individuals with chronic, severe spinal cord injury (SCI). Invasive and non-invasive methods for SCS have emerged, all with the goal to augment functional activity of spared spinal circuits distal to the lesion. Here we provide background information on the development and function of these SCS techniques and give a detailed and critical view on contemporary studies that have shaped a new era of neurorehabilitation in SCI. Epidural lumbar SCS using conventional technology has enabled intentional movement of paralyzed legs, standing, and overground stepping with training when SCS was applied and participants actively contributed. A novel strategy of spatiotemporal epidural SCS interfaced with leg-kinematic feedback has induced unparalleled recovery of motor function lasting even without stimulation. Skin-surface electrode based methods for non-invasive lumbar SCS, with conventional or Russian currents, have produced qualitatively similar improvements like those seen with epidural stimulation. Early studies of cervical SCS in tetraplegic patients found augmented upper extremity motor function and increased grip strength. Together, these neuromodulation therapies provide various perspectives for recovery of motor function in chronic patients in whom limited improvement is expected with standard-of-care rehabilitative options.

Keywords Cervical spinal cord · Enabling stimulation · Epidural spinal cord stimulation · Locomotor training · Lumbar spinal cord · Motor function · Spatiotemporal epidural electrical stimulation · Spinal cord injury · Tonic stimulation · Transcutaneous spinal cord stimulation

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7.1 Epidural Lumbar Spinal Cord Stimulation for Lower Extremity Motor Function

7.1.1 History and Background of Epidural Spinal Cord Stimulation

Epidural SCS involves the placement of a set of implantable electrodes into the spinal canal, outside the dura mater, within a distance of a few millimeters to the posterior aspect of the spinal cord (Fig. 7.1a). There are two designs of these stimulating interfaces: percutaneous leads with linearly arranged electrodes and surgical leads with electrodes arranged in columns and rows on a paddle-like array (Fig. 7.1b). Linear electrode designs are percutaneously inserted into the epidural space, while paddle array electrodes require a surgery to expose the dura through flavectomy and partial laminectomy. To form a closed system, the electrode lead is connected to an implantable pulse generator that is programmed and switched on/off through a compact external programmer via induction telemetry.

SCS was originally developed for the treatment of diffuse intractable pain, with the rationale to "gate" inputs from pain fibers through the stimulation of larger-diameter sensory fibers (Melzack and Wall 1965; Shealy et al. 1967). The spinal cord dorsal columns present an optimal target to inhibit pain transmission associated with wide body areas, since they contain the longitudinal ascending continuations of large-diameter nerve fibers originating from many spinal cord segments. By moving the site of the electrodes from subdural to epidural, and with fully implantable commercial systems becoming available (Gildenberg 2009), SCS was applied in an increasing number of patients, got FDA approval for chronic intractable pain in 1989, and accounts today for about 70% of all neuromodulation treatments (Krames et al. 2009). The fully implantable SCS systems for pain relief have reached an

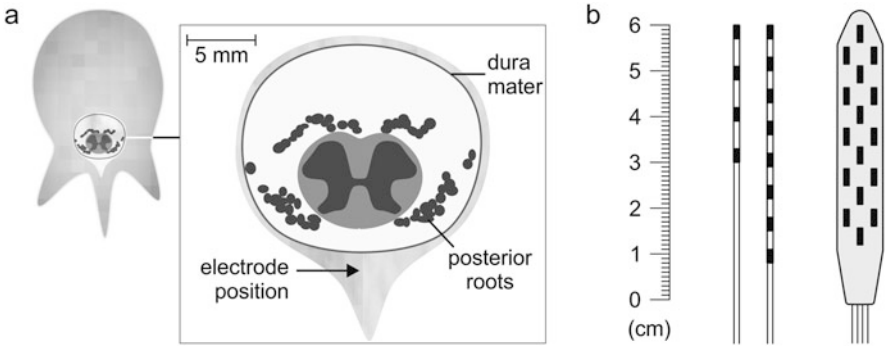

Fig. 7.1 Epidural electrode implantation site and lead designs. (**a**) Spinal canal and dural sac, containing spinal cord and anterior and posterior roots, with epidural electrode site indicated; based on transverse magnetic resonance imaging view at T12-vertebral level. (**b**) Cylindrical percutaneous (catheter-type) electrodes, quadripolar and octopolar examples, and paddle (plate-type) electrodes, example of a three-column 5-6-5 design

advanced, mature design and current developments focus on improving stimulation patterns for enhanced efficacy (De Ridder et al. 2010; Kapural et al. 2015).

The potential of SCS to improve function in motor disorders was recognized unexpectedly. A patient with partial paralysis due to multiple sclerosis, when treated for intractable pain, regained volitional control of near normal strength in her legs with stimulation—an acute improvement that had never been seen before (Cook and Weinstein 1973). SCS was then tested in many patients with various motor disorders (Siegfried et al. 1981). Striking effects were reported in individual cases, mainly in multiple sclerosis, including the regain of voluntary control in upper and lower extremities, facilitation of sitting, standing, and ambulation (Cook and Weinstein 1973), and the enabling of unaided walking in previously wheelchair bound patients (Illis et al. 1976; Davis et al. 1981). In SCI, the major interest was the alleviation of spasticity, although secondary effects on the autonomic system were observed as well (Richardson and McLone 1978; Richardson et al. 1979a, b; Barolat-Romana et al. 1985; Barolat et al. 1988). Improved movement in SCI during stimulation was often ascribed to reduced spasticity that had masked residual voluntary control (Barolat et al. 1988). Yet, at least one case study clearly documented a motor-enabling effect, as the patient regained intentional activity in paralyzed muscles under stimulation, independently of changes in spasticity, including complete knee extension against gravity (Barolat et al. 1986). Voluntary control was present only when SCS was on and stopped immediately when it was turned off. The motor-enabling effect of SCS was explained by an increase of background-afferent activity and neurotransmitter release into a weakened neuronal system, depolarizing spinal neurons so that naturally generated residual inputs would be augmented in their ability to discharge them (Illis et al. 1976, 1980; Davis et al. 1981).

In spite of these unprecedented effects, the interest in SCS for motor disorders declined in the 1990s (Nagel et al. 2017), probably due to inconsistent outcomes when tested in larger populations (Siegfried et al. 1981; Davis et al. 1981; Waltz 1997; Tator et al. 2012). This inconsistency likely resulted from a lack of physiological criteria to predict responders to SCS in patient populations with a wide variety of lesion profiles and neurological symptoms (Siegfried et al. 1981; Illis et al. 1980, 1983), as well as a lack of agreement on electrode implantation sites that ranged from high-cervical (C2) to low-thoracic (T10) vertebral levels (Minassian et al. 2012). These positions were influenced by the assumption that treatment effects would result from antidromic activity into spinal cord segments caudal to the stimulation site.

A key contribution to the modern applications of epidural stimulation in individuals with SCI came from Dimitrijevic and colleagues, when they found that the optimal position for electrodes to control leg spasticity was over the posterior aspect of the spinal cord and below the lesion level (Dimitrijevic et al. 1986). Further, when placing the electrodes directly over the lumbar spinal cord, at T11-L1 vertebral levels, Dimitrijevic and colleagues reported in six individuals with chronic, complete SCI that "tonic" epidural stimulation (i.e., a long-duration train of stimuli with invariant intensity and frequency) could generate rhythmic muscle activity in paralyzed legs in the supine position (Dimitrijevic et al. 1998). Some of these activities

resulted in involuntary smooth and coordinated flexion–extension movements, resembling stepping. This finding was interpreted as the most direct evidence of that time for the existence of a central pattern generator for locomotion in humans (Dimitrijevic et al. 1998; Guertin 2013; Minassian et al. 2017). Remarkably, all contemporary scientific investigations with the aim to improve lower extremity function use the same rostro-caudal level for epidural electrode placement, i.e., below the injury and over the posterior aspect of the lumbar and upper sacral spinal cord regardless of the SCI level, to take advantage of the spared sensorimotor circuits (Angeli et al. 2014; Gill et al. 2018; Wagner et al. 2018).

No clinical neurorehabilitation studies immediately followed the observation of Dimitrijevic and colleagues, but initial investigations rather focused on the neurophysiological mechanisms underlying the motor effects resulting from SCS. Computational modeling (Rattay et al. 2000; Ladenbauer et al. 2010) and electromyography based studies (Murg et al. 2000; Minassian et al. 2004, 2007a) in individuals with SCI suggested that the stimulation predominantly recruits large-to-medium diameter proprioceptive and cutaneous afferents within the lumbar and upper sacral posterior rootlets/roots. Today, the prevailing view is that the stimulation-generated afferent input to the spinal cord transsynaptically recruits mono- and polysynaptic spinal reflex circuits (Minassian et al. 2007a, 2016a; Sayenko et al. 2014), circuits involved in the regulation of proprioceptive input and of motoneuronal excitability (Pinter et al. 2000; Hofstoetter et al. 2015a), as well as spinal neural networks controlling lower extremity synergies and components of locomotor movements (Minassian et al. 2017; Danner et al. 2015). In vivo physiological and pharmacological animal experiments came to the same conclusion, i.e., epidural lumbar SCS interacts with spinal feedback circuits through the electrical stimulation of afferent root fibers to modulate muscle activity and locomotion (Gerasimenko et al. 2006; Capogrosso et al. 2013; Moraud et al. 2016).

7.1.2 Tonic Lumbar Spinal Cord Stimulation

7.1.2.1 SCS Enables Voluntary Control Over Paralyzed Muscles

The next key concept that clearly signaled a new era for SCS in SCI came from Harkema and colleagues, who used SCS specifically for neurorehabilitation purposes (Harkema et al. 2011). In an initial case study, an individual with motor-complete, sensory-incomplete SCI (AIS-B) was implanted with an epidural stimulation system, originally to facilitate an intense stand and treadmill training (Harkema et al. 2011). Stimulation applied at 15 Hz (*cf.* Jilge et al. 2004) evoked sustained co-activation patterns in lower extremity muscles, induced bilateral extension, and allowed independent (self-assisted) full weight-bearing standing with training. SCS applied at 30 Hz (*cf.* Minassian et al. 2004) enhanced rhythmic EMG activity produced during treadmill stepping with body-weight support and physiotherapist assistance at the legs. However, the major outcome was the

re-discovery of the enabling effect of epidural SCS that came about essentially by accident. Seven months after implantation, the subject reported that the stimulation had enabled him to intentionally activate some muscles that were otherwise paralyzed, and he was eventually able to initiate toe extension, ankle dorsiflexion, and leg flexion when in supine position with epidural stimulation continuously provided. This ability was lost when SCS was turned off. The investigators focused on this motor-enabling effect in their following study and added an intense training of voluntary leg movements in a supine position under tonic SCS (Angeli et al. 2014). The participant of the original study (Harkema et al. 2011) and three additional subjects with chronic, motor-complete SCI (two AIS-A, one AIS-B) were included. The three additional participants could induce movement while supine already in the first experimental session when tonic SCS at either 25 or 30 Hz was applied. With training, enabled movements included hip and knee flexion, ankle dorsiflexion, and toe extension and could be timed to visual or auditory cues. Three patients were able to generate graded levels of force in at least one leg. Two could augment electromyographic (EMG) activity in their lower extremities produced by assisted treadmill stepping and epidural stimulation, when consciously thinking about moving the legs, though independent treadmill stepping was not achieved. After the completion of this study, one of the participants (AIS-B) was enrolled to receive additional activity-based training with SCS in the laboratory and at home (Rejc et al. 2017). The participant's voluntary leg motor control progressively improved throughout the overall duration of 3.7 years of training. EMG recordings collected without stimulation over different time points documented increased EMG amplitude of prime movers with decreased co-activation of antagonists and distant muscles. The subject finally attained the ability to perform unilateral hip flexion and knee extension when in the supine position even without using SCS. Additionally, independent standing (self-assisted only) was achieved, bearing full body weight without stimulation. With the goal to reproduce these findings, an independent research team initiated a study, in which an individual with chronic, complete SCI (AIS-A) underwent 2 weeks of volitional control training with lumbar SCS, with only eight sessions overall (Grahn et al. 2017). Stimulation was applied at 25 and 40 Hz for volitional control and stepping movements and at 15 Hz for standing. When in a side-lying position, stimulation enabled volitional knee flexion movements. With the top limb suspended with slings, the participant could initiate and terminate rhythmic movements at hip and knee under stimulation. He achieved full weight-bearing standing, only using his arms to maintain balance, and could voluntarily generate step-like movements while stationary in an upright position with body-weight support. Without SCS, the patient was unable to perform any of these tasks.

The mechanisms underlying the enabling effect of epidural stimulation on consciously controlled movement are not yet clear. Positive findings within the first experimental session (Angeli et al. 2014) must have occurred without structural changes such as axonal regeneration. One theory is the modulation of the excitability state of spinal interneurons and motoneurons, driving them closer to their activation threshold (Angeli et al. 2014; Harkema et al. 2011) and thus enabling intentional

movement through a residual but otherwise silent descending translesional neural system (Grahn et al. 2017; Dimitrijevic et al. 1984; Kakulas 1988). This assumption is identical with earlier theories (Illis et al. 1976, 1980; Davis et al. 1981), yet it might appear paradoxical, as the enrolled SCI individuals likely presented spasticity (Maynard et al. 1990), i.e., a chronic state of already increased spinal excitability (Nielsen et al. 2018). Another theory is the involvement of inherent spinal locomotor circuits or modules of this system that control movement synergies (Minassian et al. 2017; Danner et al. 2015), see also Supplementary Appendix in Angeli et al. (2018). However, patterned multi-muscle activation through the locomotor circuitry requires higher stimulation amplitudes (Dimitrijevic et al. 1998; Danner et al. 2015) than those typically used for enabling movements (Barolat et al. 1986; Harkema et al. 2011; Grahn et al. 2017). The case of regained voluntary control (Rejc et al. 2017) without stimulation-support indicates strengthening of residual supraspinal influence upon lumbar spinal circuits or plasticity in translesional descending systems.

7.1.2.2 SCS Enables Independent Overground Stepping

In 2018, two independent studies demonstrated for the first time that individuals with chronic motor-complete SCI could achieve overground walking under tonic SCS. Harkema and colleagues enrolled four additional patients with chronic motor-complete SCI (two AIS-A, two AIS-B) who followed a standing training, step training on a treadmill with body-weight support and manual assistance, and overground walking sessions (if possible), always under ongoing SCS optimized for standing or stepping (Angeli et al. 2018). The two AIS-B participants achieved the ability to walk overground, which occurred only when tonic SCS was continuously applied (20–40 Hz) and the participants consciously engaged in the motor task. For the first participant the transition to overground walking using horizontal poles for balance occurred after 278 training sessions over a period of 85 weeks. The second participant achieved overground walking after 81 training sessions over 15 weeks and was able to walk independently with a walker after 147 sessions. All four participants achieved standing and had improved trunk stability with stimulation. In the second study, an individual with chronic complete SCI (AIS-A) who had previously trained to perform stepping-like movements in a side-lying position (Grahn et al. 2017) received additional training of multiple motor tasks with SCS to test whether weight-bearing stepping could be achieved (Gill et al. 2018). After 43 weeks, the subject could perform standing, treadmill stepping without body-weight support (self-assistance only), as well as overground walking with a walker and physiotherapist assistance to maintain balance in the presence of continuous SCS.

Understanding the control strategies used by individuals with clinically classified motor-complete SCI during highly dynamic motor tasks is not trivial. During tonic stimulation with constant parameters from a fixed site, the initiation and control of a movement, i.e., phasic feedforward and feedback information, completely depend on a very limited supraspinal capacity to modulate segmental activity and on the

exploitation of proprioceptive feedback below the injury level that is naturally generated during movement (Moraud et al. 2016; Minassian and Hofstoetter 2016; Courtine and Sofroniew 2019). However, continuous stimulation partially cancels this movement-related information through antidromic collisions in proprioceptive fibers, limiting the usability range of applicable stimulation intensities and frequencies of tonic SCS strategies (Formento et al. 2018).

The use of tonic SCS in all clinical investigations in motor disorders between 1973 and 2018 resulted from the available SCS technology, developed for chronic pain to continuously cover affected pain areas 24/7. For motor control applications, it is practically impossible to program a given set of tonic stimulation parameters for simultaneously facilitating flexor and extensor function during left-right alternating movements such as those involved in walking (Gill et al. 2018; Jilge et al. 2004).

7.1.3 Spatiotemporal Epidural Electrical Stimulation

In view of the technological limitations of tonic SCS, Courtine and colleagues developed a new strategy of spatiotemporal epidural electrical stimulation (EES) of the spinal cord in preclinical studies (Courtine and Sofroniew 2019; Capogrosso et al. 2016; Wenger et al. 2016). The concept of spatiotemporal EES lies in the reproduction of natural, task-specific motoneuron pool activation through the timed recruitment of the respective proprioceptive spinal circuits (Capogrosso et al. 2018). Closed-loop controlled spatiotemporal EES was first validated in rat models of SCI (Wenger et al. 2016). These experiments recorded hindlimb EMG activities in intact rats and discovered that spinal locomotor output was characterized by the sequential activation of motoneuron pools in spatially restricted spinal segments, termed hot spots, which were associated with extensor or flexor muscle synergies. Four electrodes of an epidural array were sufficient in this model to recruit select posterior roots with afferents projecting to these extensor and flexor hot spots bilaterally. The stimulator was triggered by gait events identified through real-time processing of hindlimb kinematics to deliver short trains of stimulation via the appropriate epidural array sites. Thus, none of the electrodes was tonically active, but each had specific on and off phases timed to mimic the natural activation of their respective target motoneuron pools. This closed-loop real-time stimulation strategy generated hindlimb EMG activity in the SCI rats that closely resembled that of intact rats. Compared to tonic stimulation, spatiotemporal EES improved weight-bearing capacity and endurance during treadmill stepping. Exploiting a linear relation between EES frequency and induced step height (Wenger et al. 2014) allowed for the real-time adjustment of hindlimb endpoint trajectories. This study together with the validation of an implantable pulse generator for human use with real-time triggering capability in non-human primates (Capogrosso et al. 2016) laid the foundation for the first-in-man study STIMO (STImulation Movement Overground).

STIMO combined two novel technologies, spatiotemporal EES and a cable-based robotic body-weight-support system, to allow for a swift transition to overground

locomotor training in individuals with severe SCI. Spatiotemporal EES is realized by a 16-electrode epidural array connected to an implantable pulse generator with real-time triggering capabilities (Capogrosso et al. 2016). The first report of the ongoing study presented the results of three participants, all with a cervical SCI, which had bound them to a wheelchair for 4 years and more (Wagner et al. 2018). Participant P1 had a completely paralyzed left leg (AIS-C), P2 had nonfunctional flexor muscles (AIS-D), and P3 had bilaterally paralyzed legs (classified as AIS-C based on present voluntary anal contraction). EMG recordings in individuals with intact nervous system while walking had identified a spatiotemporal map of motoneuron pool activity that included the succession of three hot spots underlying weight acceptance, propulsion, and swing. In analogy to the preclinical study (Wenger et al. 2016) EES protocols in the SCI participants were individually configured to separately target posterior roots projecting to these hot spots. In closed-loop mode, the spatiotemporal stimulation was triggered by a controller analyzing foot trajectory in real-time and wirelessly (Fig. 7.2). The spatiotemporal stimulation sequences could be also applied in an open-loop mode, which repeatedly delivered a programmed sequence of stimulation for a complete gait cycle with a preset gait cycle frequency. In the open-loop mode, the participants synchronized their voluntary intent with the predetermined stimulation sequences to execute the intended locomotor activity. With the identified spatiotemporal EES protocols, the patients went on to participate in an intense locomotor therapy over a period of 5 months. Spatiotemporal EES immediately (without training) restored EMG activity underlying locomotion in otherwise quiescent or poorly active lower extremity muscles and enabled the participants to train walking overground with assistive devices and the robotic support system. Participants could walk with different speeds and exaggerate step elevations during locomotion and could cover distances of up to 1.2 km without deterioration of kinematics or muscle activity. Throughout the rehabilitation phase, all three participants improved their overground walking capacities, both with and without EES. Participants P1 and P2 regained the ability to transit from sitting to standing and walking independently with crutches, without EES or body-weight support. P1 could even walk for several steps between parallel bars without other assistive devices. The perhaps most significant outcome was the neurological recovery that restored voluntary control over paralyzed or weakened muscles—even without stimulation. Participant P1 gained a total of 16 points in his lower extremity motor scores (14 to 30; max 50), improving from AIS-C to AIS-D, and P2 gained a total of 11 points (25 to 36). Some degree of neurological recovery was also induced in participant P3 (0 to 4); however, these improvements were not sufficient to allow him to perform voluntary movements against gravity. Yet, dynamometry demonstrated an improved ability to produce maximum isometric torques under EES.

The spatiotemporal stimulation technology is highly suitable to be interfaced with motor intentions, decoded not only from movement feedback information but also from cortical recordings by means of brain–computer interfaces (Courtine and Sofroniew 2019). Feedback-controlled spatiotemporal EES depends on residual leg movements to decode the participant's motor intention and trigger the appropriate stimulation protocols. Recording leg motor cortex activity and translating the

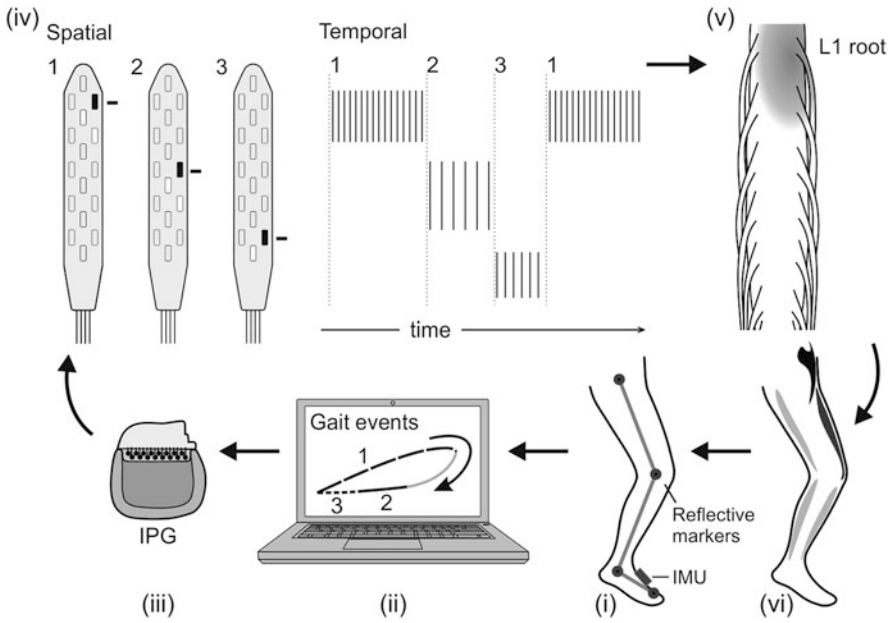

Fig. 7.2 Closed-loop controlled spatiotemporal epidural electrical stimulation. (i) Gait kinematics are recorded by a motion capture system or inertial measurement units (IMUs) and transmitted wirelessly to a control computer. (ii) The kinematic information is processed in real-time and specific gait events corresponding to the phases of a gait cycle are identified: swing (1), weight acceptance (2), and propulsion (3). (iii) Stimulation commands are sent wirelessly to an implanted pulse generator (IPG) to trigger specific programmed stimulation protocols. (iv) The pulse generator is connected to an epidural electrode array overlying the L1 to S2 posterior roots. Each stimulation protocol consists of a set of active electrodes, together with a specific frequency and amplitude. Their sequential activation follows the detection of events by the computer. (v) Each stimulation protocol is defined to target select posterior roots projecting to hot spots corresponding to the gait phases, here exemplified for swing. (vi) The stimulation enhances activity in muscles underlying the required movement for each gait phase. The closed loop ensures that the stimulation coincides with the movement intent

neural activity into predictive executive commands for a spatiotemporal EES system would have obvious advantages in severely paralyzed individuals and allow more flexible adaptations in daily living situations. The feasibility to technologically bridge a SCI by the use of a brain-to-EES interface was demonstrated in a non-human primate model (Capogrosso et al. 2016). Rhesus monkeys with one hindlimb paralyzed were implanted with a microelectrode array into the leg area of the motor cortex, with an implantable pulse generator for human use with real-time triggering capability, and an epidural electrode array targeting the lumbar posterior roots. Neural recordings were transmitted wirelessly to a control computer, where a decoder identified motor intentions (gait initiation) and states (stance and swing phases) that triggered the pulse generator to deliver EES protocols for the intended movement. This technology immediately enabled weight-bearing quadrupedal

stepping on a treadmill and overground. In humans, first approaches will likely rely on less invasive technologies to record neuronal activity, such as subdural electrode paddles for recordings of electrocorticogram signals, a technology that is already available, compatible with clinical use, and can be operated fully implantable and wirelessly (Vansteensel et al. 2016; McCrimmon et al. 2018).

7.2 Transcutaneous Lumbar Spinal Cord Stimulation for Lower Extremity Motor Function

7.2.1 Development and Background of Transcutaneous Lumbar Spinal Cord Stimulation

Transcutaneous lumbar SCS involves the placement of skin-surface electrodes in specific configurations to generate a current flow that partially crosses the thecal sac containing the lumbar spinal cord and roots (Ladenbauer et al. 2010; Minassian et al. 2007b). Such currents are permitted by the transversal conductivity of the spine which is considerably reduced by the ligaments and vertebral discs. The stimulation of deeply located afferent structures associated with distant dermatomes and myotomes is reflected by the generation of tingling sensations (given preserved sensory function) and muscle activity in the lower extremities (Minassian et al. 2007b, 2011; Courtine et al. 2007; Hofstoetter et al. 2014). The common electrode configuration is a dorsoventral montage, with an active electrode over the spine at the thoracolumbar junction, overlying the lumbosacral spinal cord, and much larger indifferent electrodes placed over the lower abdomen or the iliac crests (Fig. 7.3a) (Minassian et al. 2007b; Courtine et al. 2007).

The development of transcutaneous SCS (Minassian et al. 2007b) was inspired by high-voltage percutaneous electrical stimulation, an earlier method designed to assess efferent conduction along an entire peripheral nerve by supramaximal stimulation of the anterior roots (Maertens de Noordhout et al. 1988; Troni et al. 1996). This technique used stimulators intended for transcranial electrical stimulation of the motor cortex, generating high-intensity spike-like pulses to penetrate the cranium (Hofstoetter et al. 2015b). While high-voltage stimulation delivered through small skin-surface electrodes at cauda equina levels generated direct M-wave like responses in most of the studied lower extremity muscles, mixed M-wave and H-reflex responses in soleus indicated that large-diameter proprioceptive afferent fibers within the posterior roots could be recruited as well (Maertens de Noordhout et al. 1988; Zhu et al. 1998). Two methodological adaptations were made for transcutaneous SCS. First, computational modeling of epidural simulation had earlier predicted low-threshold sites along proprioceptive fibers at the posterior rootlet-spinal cord interface, created by changes in spatial fiber orientation and the crossing of the electrical conductivity boundary between the cerebrospinal fluid and the spinal cord (Rattay et al. 2000). Since these low-threshold sites resulted from

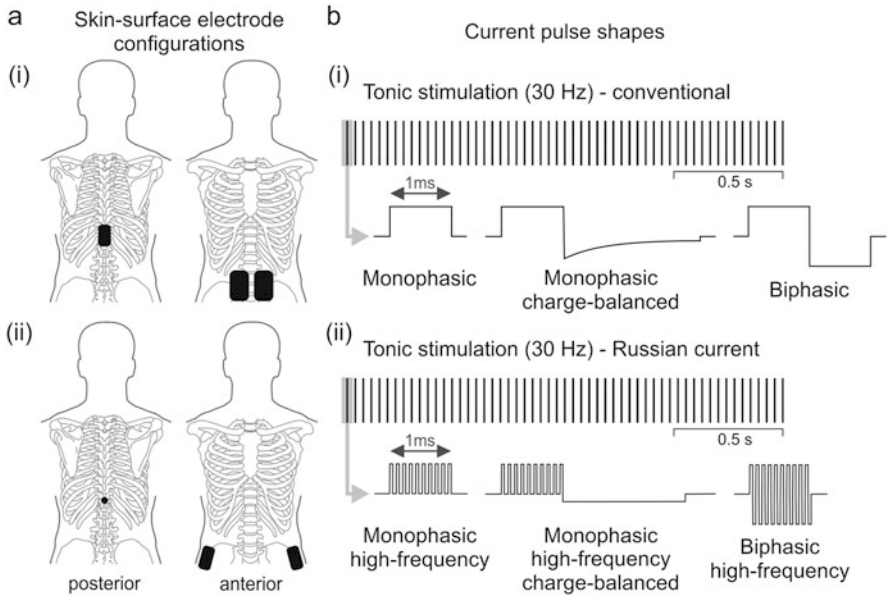

Fig. 7.3 Transcutaneous lumbar spinal cord stimulation methods. (**a**) Different set-ups of skin-surface electrodes used to generate tissue currents that partially flow through the spinal canal and stimulate posterior structures of the lumbar and upper sacral spinal cord. An active electrode is placed over the spine at low thoracic or upper lumbar vertebral levels and indifferent electrodes either (i) para-umbilically over the lower abdomen (ii) or bilaterally over the anterior superior iliac spine. (**b**) Current pulses generated by (i) conventional and (ii) Russian stimulators for transcutaneous spinal cord stimulation. Russian currents are constituted of 1-ms bursts of 10-kHz pulses. Monophasic high-frequency pulses can be followed by a longer conventional pulse of opposite polarity for charge-balance

anatomical conditions, recruitment of posterior root afferents does not require focal stimulation, and skin-surface stimulation electrodes with large active areas can be used to reduce maximum current densities and discomfort when applying repetitive stimulation. Second, the method capitalized on the difference in the strength-duration properties of sensory and motor axons (Burke 2016) by utilizing stimulators that generated long pulse widths (1 ms).

Transcutaneous SCS can consistently stimulate proprioceptive afferent fibers within multiple lumbar and upper sacral posterior roots and reflexively evoke activity in practically all lower extremity muscles with conventional stimulators used for functional electrical stimulation (FES) or transcutaneous electrical nerve stimulation (TENS) applications (Minassian et al. 2007b; Hofstoetter et al. 2008; Dy et al. 2010; Roy et al. 2012). Computational studies found that epidural and transcutaneous lumbar SCS indeed share same low-threshold sites along posterior root afferent fibers (Ladenbauer et al. 2010; Danner et al. 2011) and a study in individuals with SCI demonstrated electromyographically near-identical reflex

responses evoked by both techniques, further supporting that common neural structures are activated (Hofstoetter et al. 2018).

This analogy motivated the use of transcutaneous SCS as a neuromodulation method in SCI (Minassian et al. 2010, 2011, 2016b; Hofstoetter et al. 2014, 2015c). Like other surface-electrode based techniques, transcutaneous SCS results in cutaneous and neuromuscular stimulation beneath the skin-surface electrodes in addition to the stimulation of the intrathecal neural target structures, which is perceived as uncomfortable in persons with intact nervous system when stimulation is continuously applied. Most SCI individuals have absent or reduced sensation at the stimulation site, and no issues due to discomfort have been reported in any interventional study.

To reduce potential discomfort, while still allowing to administer high-current electrical stimulation (Gerasimenko et al. 2015a), an alternative method of transcutaneous SCS was introduced using "Russian currents". In the Russian current stimulation waveforms, each conventional rectangular pulse within a stimulus train is replaced by a burst of same duration consisting of 10-kHz pulses (Fig. 7.3b). Such stimulation is considered to be less uncomfortable beneath the stimulating electrodes; however, it is unclear how the recruitment capability of neural targets located deeper in the body would be maintained, while the recruitment of neural structures at the body surface is reduced. Early results of an ongoing study (Al'joboori et al. 2018) suggest that thresholds for monophasic high-frequency waveforms to elicit lower extremity muscle responses are three times higher than for conventional monophasic stimulation, and that responses could not be evoked with intensities <200 mA when the biphasic form of the high-frequency stimulation was used (Fig. 7.3b(ii), right; the waveform most consistent with the original definition of Russian currents as sinusoidal alternating currents). When tonic stimulation was delivered with conventional monophasic pulses and monophasic high-frequency waveforms at their respective thresholds, the participants graded similar levels of discomfort—hence the advantage of the "painless stimulation" was lost at its higher necessary intensities. When both methods were applied at the lower threshold of conventional stimulation, trains of monophasic pulses but not the Russian current facilitated motor evoked potentials (MEPs) produced by transcranial magnetic stimulation. In line with these observations, a study testing transcutaneous lumbar SCS with Russian currents in individuals with SCI reported that using 1-ms duration biphasic 10-kHz pulses did not induce responses in the lower extremity muscles and used this mode of stimulation as an ineffective sham (Sayenko et al. 2019). Further investigations will need to identify the best applications of the different non-invasive stimulation strategies.

Finally, it should be noted that most studies applying transcutaneous lumbar SCS in individuals with SCI consider the presence of metal implants within the expected volume of generated current flow as an exclusion criterion, see also section on cervical spinal cord stimulation below.

7.2.2 *Transcutaneous Lumbar Spinal Cord Stimulation: Conventional Stimulators*

In small case series, non-invasive tonic lumbar SCS augmented stepping function on a treadmill in individuals with chronic, motor incomplete SCI (AIS-D) (Minassian et al. 2010; Hofstoetter et al. 2013, 2015c). Participants were capable of active treadmill stepping for short durations without stimulation when holding onto the handrails, requiring only intermittent unilateral physiotherapist assistance. Applying stimulation during short sessions of treadmill stepping had immediate effects on lower extremity EMG activities and gait kinematics, and participants required no physiotherapist assistance anymore. Stimulation was applied at 30 Hz with an intensity that generated tingling sensations in the lower extremity dermatomes, yet no EMG activities without the subjects' voluntary attempt to step. In spite of the continuous and invariant stimulation, EMG activities were augmented in a step-phase appropriate manner. The most consistent modification of the gait kinematics was an increased hip range of motion due to exaggerated flexion resulting in elevated foot clearance. Turning the stimulation off caused an immediate degradation of the EMG activities and kinematics to control conditions (Fig. 7.4a). Potential spinal mechanisms underlying the neuromodulative effects of transcutaneous lumbar SCS were addressed in a dedicated study in four individuals with chronic, clinically complete SCI (AIS-A) (Minassian et al. 2016b). A robotic-driven gait orthosis guided reproducible stepping motions on a treadmill with different speeds and hip kinematic conditions, and induced muscle activities were electromyographically recorded without and with concomitant 30-Hz transcutaneous SCS. Cases of

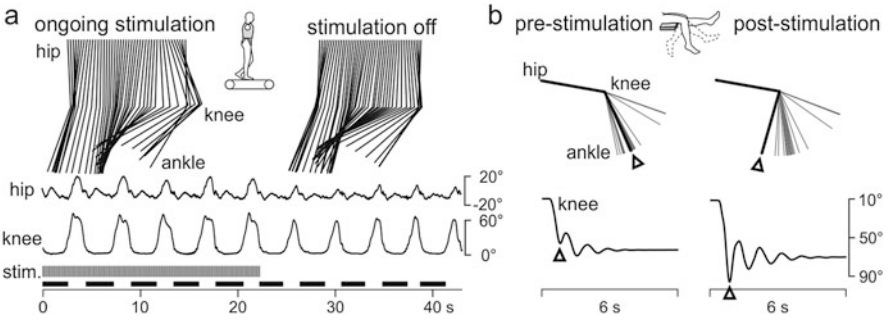

Fig. 7.4 Motor effects of transcutaneous spinal cord stimulation. (**a**) Tonic 30-Hz stimulation acutely enhances stepping function on a treadmill in an individual with sensory and motor incomplete SCI (AIS-D). Stick-figures derived from hip and knee goniometric data (Hofstoetter et al. 2015c) display a smooth and coordinated exaggeration of the swing phase, which is lost after stimulation (stim.) is turned off. (**b**) A 30-min session of 50-Hz stimulation induces carry-over effects on lower extremity spasticity. Pendulum test assessing spastic hypertonia of muscle groups spanning the knee before and after the intervention. Stick-figures derived from knee goniometric data and maximum flexion angles at the end of the first swing (arrowheads) document quadriceps-stretch induced spastic reflex contraction before and free swinging movement after stimulation. Exemplary data of an AIS-D individual (Hofstoetter et al. 2020)

augmented EMG activity in muscles during their respective eccentric phases (stretch imposed by the robot) suggested that transcutaneous SCS interacted with the flow of step-induced proprioceptive feedback to modulate muscle activity during locomotion through muscle spindle feedback circuits (Formento et al. 2018). Occasionally, robust rhythmic EMG activities were generated with a rhythm-frequency that did not adapt to the externally imposed step-cycle frequency and remained unchanged in the absence of step-induced rhythmic proprioceptive feedback (supported standing). These examples of independent rhythmicity suggested that the stimulation could engage autonomous spinal rhythm-generating networks (Minassian et al. 2017; Danner et al. 2015) in addition to "simpler" proprioceptive feedback circuits (Capogrosso et al. 2013; Moraud et al. 2016; Hofstoetter et al. 2017).

Another application of transcutaneous SCS to modify altered motor control after SCI is in spinal spasticity (Minassian et al. 2011). While epidural SCS for spinal spasticity (Pinter et al. 2000) can be applied 24/7, the transcutaneous method is not a chronic solution and a potential clinical value would depend on anti-spasticity effects temporarily persisting after stimulation has been discontinued. Therefore, carry-over effects on lower extremity spasticity were the focus of the first pilot studies, examined by assessments before and after a single 30-min session of transcutaneous SCS. All current studies applied 50-Hz stimulation below the intensity that generated reflex responses in lower extremity muscles, continuously eliciting tingling sensations in lower extremity dermatomes in participants with residual sensory function—in line with previous epidural SCS applications (Barolat et al. 1988; Pinter et al. 2000). A preliminary study in three individuals with chronic, motor-incomplete SCI (AIS-D) suggested that transcutaneous stimulation could modify some measures of spasticity immediately after a single 30-min intervention (Hofstoetter et al. 2014). The most obvious effect was a reduction of EMG activity associated with tonic stretch reflexes and a considerable increase in walking speed measured by the timed 10-m walk test in two of the participants by 59% and 69%, respectively. A later study with a statistically sound sample size (12 individuals with chronic SCI, AIS-A, C, D) demonstrated reduced muscle hypertonia (Fig. 7.4b), clonus, and cutaneous-input-evoked spasms for 2 h after a single 30-min session of stimulation (Hofstoetter et al. 2020). In the same study, stimulation administered for 30 times over a period of 6 weeks in one participant prolonged the carry-over effects, which lasted for 7 days after the final application. An independent study showed improved stretch-induced quadriceps spasticity in ten individuals with chronic SCI (AIS-B, C, D) at an assessment time point of 45 min after a single session of 30-min 50-Hz transcutaneous SCS when compared to a sham-control intervention (Estes et al. 2017). The anti-spasticity effect of transcutaneous SCS with relatively low stimulation amplitude and high stimulation frequency is thought to be based on the continuous generation of multi-segmental afferent synaptic inputs to the lumbar spinal cord circuitry, which enhances intrinsic inhibitory function to a level that outweighs the excitatory action upon the motoneuron pools (Pinter et al. 2000; Hofstoetter et al. 2020).

7.2.3 *Transcutaneous Lumbar Spinal Cord Stimulation: Russian Currents*

Transcutaneous lumbar SCS using a proprietary custom-built Russian stimulator has been tested by one group of researchers for enabling voluntary control over paralyzed lower extremity muscles, facilitating stepping-like movement and inducing standing, motivated by earlier success with epidural stimulation (Angeli et al. 2014; Harkema et al. 2011). In five individuals with chronic motor-complete, sensory-incomplete SCI (AIS-B), a training strategy was tested that involved voluntary engagement during induced movements with transcutaneous SCS, combined with the orally active serotonergic agonist buspirone (Gerasimenko et al. 2015b). Participants were assessed and trained while lying on one side, with their legs strapped to a pendulum-like support system that facilitated hip and knee movements in a near-horizontal plane. Eighteen weekly training-testing sessions were performed without and with the attempt of voluntary contribution to move the leg in a stepping-like motion under transcutaneous SCS applied at the T11/T12 interspinous level (30 Hz) and/or over the coccyx (5 Hz). The stimulator generated 1-ms bursts of 10-kHz monophasic rectangular pulses (Fig. 7.3b(ii)). Buspirone was additionally administered for the last 4 weeks (7.5 mg twice daily). Transcutaneous SCS could immediately generate stepping-like movements in the support system, and subjects were able to voluntary augment these movements. This voluntary control improved with training, and the participants gained the ability to perform movements even without stimulation. The evolution of the improvements suggested that the drug treatment contributed to the enhancement of voluntary control. At the final assessment, voluntary control over otherwise paralyzed muscles in the presence of the neuromodulatory interventions (without washout period) was equivalent to the abilities of AIS-C patients. The effects on motor function of a combination of transcutaneous SCS and buspirone administered during overground step training using an exoskeleton were further tested in an individual with chronic, motor, and sensory complete SCI (AIS-A) (Gad et al. 2017). The training consisted of 4 weeks of robot-assisted overground training alone, followed by subsequently adding stimulation, drug, and the combination of stimulation and drug for 1 week each. The exoskeleton allowed the subject to actively contribute in generating overground stepping. Transcutaneous SCS was applied as described previously (Gerasimenko et al. 2015b), and buspirone was administered 10 mg twice daily. SCS alone or in combination with the drug, but not drug administration alone, resulted in lowest dependence on robotic assistance. EMG activity in various thigh and lower leg muscles was differently modified by the neuromodulation treatments. During the week trained with transcutaneous SCS alone, but not under the other neuromodulatory conditions, the participant could perform voluntary knee flexion when in the supine position. These studies suggested that transcutaneous SCS with or without an orally active serotoninergic agonist can modulate lumbar spinal cord circuitries to a state which is sufficient to enable an otherwise nonfunctional translesional descending system to engage them.

In a later study, transcutaneous SCS to acutely induce standing was tested in 15 individuals with chronic SCI (AIS-A, B, C) (Sayenko et al. 2019). The stimulation waveform consisted of 1-ms bursts of 10-kHz monophasic rectangular pulses, applied at frequencies of 5, 15, or 25 Hz over the T11–T12 or L1–L2 vertebrae. Without stimulation, none of the participants was able to stand. Applying transcutaneous SCS and gradually increasing the stimulation amplitude generated muscle activity in the lower extremities, until participants could stand with one or both legs fully extended and with self-assistance using handrails of a standing frame and hips unsupported or minimally supported. Six of the participants could stand without therapist assistance within the first experimental session. Best results were achieved with stimulation over the L1–L2 vertebrae and a frequency of 15 Hz (Jilge et al. 2004), while biphasic Russian current (Fig. 7.3b(ii)) used as sham intervention was ineffective to induce standing. Six of the participants followed 12 sessions of stand training, which further reduced their dependence on external assistance and improved upright balance control. In summary, the results of this study were qualitatively similar to those seen in previous investigations with epidural stimulation (Harkema et al. 2011; Rejc et al. 2015). Notably, post-training clinical evaluations revealed increased muscle tone in all participants.

7.3 Cervical Spinal Cord Stimulation for Upper Extremity Motor Function

Paralysis of upper extremity muscles is a condition for which no satisfactory method of treatment exists, while even moderate improvements in volitional reaching and grasping function would considerably enhance quality of life (Anderson 2004). A few studies have started to explore whether SCS strategies can be translated to the cervical spinal circuits that are integrated into the control of upper extremity function in individuals with tetraplegia.

An initial study in two individual with chronic, cervical SCI (AIS-B), with total upper extremity motor scores of 9 and 17, respectively (max. 50), and epidural electrodes implanted at C5-T1 vertebral levels found that tonic stimulation delivered caudal to site of injury immediately improved maximal hand strength and control within the first session (Lu et al. 2016). With repeated stimulation sessions, grip force increased gradually even when tested without SCS. Hand opening and closing tasks and maintenance of grip force improved with training when SCS was delivered. Upper extremity motor scores improved when evaluated during stimulation at the conclusion of the study. It was suggested that neuromodulation of cervical pre-motorneuronal network activity had enabled the participants to volitionally induce and control movement, although activity in all upper extremity muscles studied was also dominated by stimulus-triggered EMG responses, suggesting recruitment of motoneuron pools via proprioceptive afferents fibers. Thus, the conceptual framework of spatiotemporal EES could be principally transferred to

cervical EES protocols. Targeting subsets of posterior roots to engage specific arm and hand muscles for reaching and grasping function is currently being tested in non-human primates and by computer modeling (Barra et al. 2018; Greiner and Capogrosso 2019). Due to the sophisticated neural control of upper extremity motor function, spatiotemporal cervical EES would likely rely on brain–computer interfaces for neuronal recordings of motor cortex activity to trigger appropriate stimulation protocols (Courtine and Sofroniew 2019).

The same group that had applied transcutaneous lumbar SCS with Russian current waveforms to improve lower extremity motor function tested whether a similar neuromodulatory strategy could also be used for cervical stimulation. Six individuals with chronic cervical SCI (2 AIS-B, 4 AIS-C; all with residual grip strength) underwent eight training sessions over 4 weeks, performing voluntary handgrip tasks while tonic cervical stimulation was applied (Gad et al. 2018). A proprietary prototype device, generating biphasic or monophasic pulse-bursts (Fig. 7.3b(ii)) was used, delivering tonic 30-Hz stimulation via surface-skin electrodes, two small midline electrodes over the cervical spine (C3-C4 and C6-C7, respectively), and two larger ones over the iliac crests. Already during the first session, stimulation enabled all participants to generate greater grip forces, and with repeated intervention sessions grip force progressively improved, both with and without stimulation. All subjects reported improvements in finger and hand dexterity in daily life activities, and some reported enhanced lower extremity and autonomic function. Clinical assessment demonstrated improved sensory and motor scores in most of the participants. A following study tested the training effects of transcutaneous cervical SCS with and without buspirone on upper extremity function in six individuals with tetraplegia (AIS-B; average total upper extremity motor score: 17.5) (Freyvert et al. 2018). Stimulation was delivered via skin-surface electrodes overlying the C5 vertebra and over the iliac crests at frequencies of 5–30 Hz. The participants received 6 weeks of training with cervical stimulation, combined with a placebo (weeks 1–2 and 5–6) or buspirone (weeks 3–4; 7.5 mg twice daily). Maximum hand grip force increased in four participants after each successive treatment phase and clinical scores including the upper extremity motor scores improved. A case study explored the long-term therapeutic potential of transcutaneous cervical SCS on upper extremity function in an individual with chronic, incomplete cervical SCI (AIS-D; total upper extremity motor score 23) (Inanici et al. 2018). The intervention consisted of a three-phase, alternating program: 4 weeks of transcutaneous SCS combined with activity-based exercise therapy, 4 weeks of therapy alone, and a final week with the combined therapy. Stimulation was applied as in Gad et al. (2018). Hand function measured by the standardized Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) test improved throughout the alternating intervention program. Lateral pinch force increased during stimulation combined with physiotherapy, while therapy alone maintained the gains but resulted in no further improvement. The total upper extremity motor score increased by 14 points, and sensation improved in several dermatomes. All functional gains were maintained over a period of 3 months

despite no further stimulation or therapy. Changes were also seen in daily life activities, including an improved ability of self-feeding.

While these first studies in cervical SCS are highly promising, significant challenges yet remain to be faced. Wrist and hand contracture are a common complication in chronic cervical SCI. The resulting restricted range of motion and deformity of the joints not only impair function in daily life activities, but also impede rehabilitation efforts. Other than in case of lumbar transcutaneous SCS, the cervical method uses electrodes directly overlying the spinal cord injury level as well as the fractured vertebrae. Permanent segmental gray matter damage and root lesions associated with cervical spine fractures can destroy relevant circuitry and motoneurons associated with upper extremity function, i.e., those neural structures otherwise conveying SCS effects. The effectors of the system—the upper extremity muscles—become partially denervated. Further, cervically placed stimulating skin-surface electrodes directly overly osteosynthesis or spinal fusion material, titanium screws, rods, and plates for the surgical fixation of bones. While compared to some other metals (copper, silver), titanium is a rather poor conductor of electricity, its specific conductivity is still orders of magnitude (10^6–10^8) higher than that of anatomical tissues, which can have at least two consequences. First, the electrical field is distorted in an indefinite way, depending on the individual implants, which could augment stimulation of the targeted neural structures but also channel electrical currents to distant structures. Second, with repetitive stimulation over longer periods of time, tissue damage may potentially occur at metal–tissue interfaces at sites of high-current densities (metal edges, screw tips) that are difficult to estimate, as such effects have not yet been addressed by dedicated animal experiments or computer simulations. Finally, the current flow through the trunk (between the neck and hip electrodes) and related side effects have not yet been studied. Alternative electrode configurations are being evaluated (Milosevic et al. 2019).

7.4 Conclusions

SCS technologies applied in intense neurorehabilitation programs have fundamentally changed our view on the adaptive capacities of the spinal motor system in the chronic stage of SCI. These strategies have enabled the active and repeated generation of task-specific motor outputs to weakened or paralyzed muscles and the voluntary engagement in producing movements over prolonged training periods, which have led to unprecedented functional improvements. The neuromodulation approaches are perhaps the first practical exploitation of the “discompleteness” of a severe SCI. The discomplete SCI was defined after recognizing that many patients with chronic, clinically classified complete injury had retained some ability to augment or suppress spinal segmental activity below the lesion, likely through a subclinical, translesional neural system (Dimitrijevic et al. 1984; Kakulas 1988; Calvert et al. 2019). The cumulative actions of a weak excitatory activity via residual descending systems and epidural stimulation-induced increase of

background-afferent activity may not only achieve a level of excitation that is sufficient to produce movement, but the converging inputs on common lumbar spinal targets may also provide for the necessary conditions to induce persisting enhancement of residual functions. Various invasive and non-invasive methods for SCS are currently being examined, all with the common goal to facilitate movement through neuromodulation of central spinal activity, which in turn enables activity-based therapies in a patient population with limited or no other effective rehabilitation options. Approaching the recurrent question of how these different strategies compare to each other is challenging because each is tested largely by different, sometimes competing groups of investigators, and is further impeded by the involvement of proprietary technologies. Tonic epidural SCS uses available technology validated for decades in pain patients, yet success with this technology in SCI is based on neurorehabilitation therapies with intensities and durations exceeding by far those of the current standard of practice. Spatiotemporal ESS may prove to have advantages in inducing lasting neurological recovery, based on the temporal coincidence of stimulation-induced neural drive with consciously generated descending inputs, and the causal relation of motor outputs with these activities, yet it is a technology-intensive strategy. This technology will however be pivotal in future attempts to interface spinal neuromodulation with direct recordings of motor cortex activity by means of brain–computer interfaces for technologically bridging a SCI. Non-invasive SCS methods may be established for applications that do not depend on spatial resolution of stimulation effects, such as in regaining the ability to stand, or in the control of diffuse types of spinal spasticity. Applicability can also be foreseen in patients who may already benefit from stimulation applied for limited periods. Future efforts should not constrain themselves to the demonstration of clinical superiority of one single technology, but rather strive to establish various solutions to bring the best long-term benefit to those still waiting for treatments to improve their quality of life.

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Part III
Clinical Brain–Computer Interfaces

Chapter 8
P300 BCI for Persons with Spinal Cord Injury: A BCI in Search of an Application?

Andrea Kübler, Rüdiger Rupp, and Sonja Kleih

Abstract By now, in the year 2020, the P300 BCI looks back on a history of more than 30 years. A plethora of studies have been conducted with visual stimulation mostly for control of communication devices. The major target population were people with severe motor impairment including those in the locked-in state in which no communication is possible and different applications controlled by the P300 BCI have been suggested. For people after spinal cord injury, restoring motor functions such as grasping or walking is of utmost importance. In this chapter we review studies which used the P300 BCI as control of assistive devices and included people with spinal cord injury. We dwell on the pre-requisites for quality of life in spinal cord injury and how a P300 BCI may potentially support maintenance thereof. We outline how the P300 BCI might be used as a tool for training to prevent cognitive decline often seen as a consequence of spinal cord injury. We outline necessary steps for further research and end by concluding that the potential of P300 BCIs for people with spinal cord injury is limited, albeit its value for immediate communication in patients with ventilatory support during intensive care, for cognitive training and wheelchair control remains to be investigated.

Keywords Brain–Computer Interface · P300 BCI · Spinal cord injury · Well-being in SCI · Cognitive impairment

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8.1 Introduction

P300 BCIs can now look back on more than 30 years of research. In the late 80s of the last century the first paper was published by Farwell and Donchin that demonstrated the feasibility of a P300-based spelling system (Farwell and Donchin 1988). Letters and numbers were presented in a 6 × 6 matrix and rows and columns were flashed randomly. By directing one's attention to the cell containing the desired letter, this specific cell becomes a rare event as it flashes less often as, taken together, all the other cells do. The rare stimulus elicits a typical positive event-related potential (ERP) around 300 ms after stimulus onset—the P300. The P300 ERP can typically be seen when a person is presented with a stream of standard visual, auditory, or tactile stimuli interspersed with deviant or "oddball" stimuli that attract his or her attention. Such stimulation paradigms are accordingly called "oddball paradigms". In a 6 × 6 matrix only 2 of 12 flashes are relevant for any specific letter or other cell content resulting in an oddball paradigm. The by now famous approach to BCI control was not readily taken up by the community. It was not until the mid-90s that the research effort started to increase and did then so almost exponentially. The history and current state-of-the art of the P300 BCI have just recently been summarized (Allison et al. 2020). Figure 8.1 provides a coarse overview of the

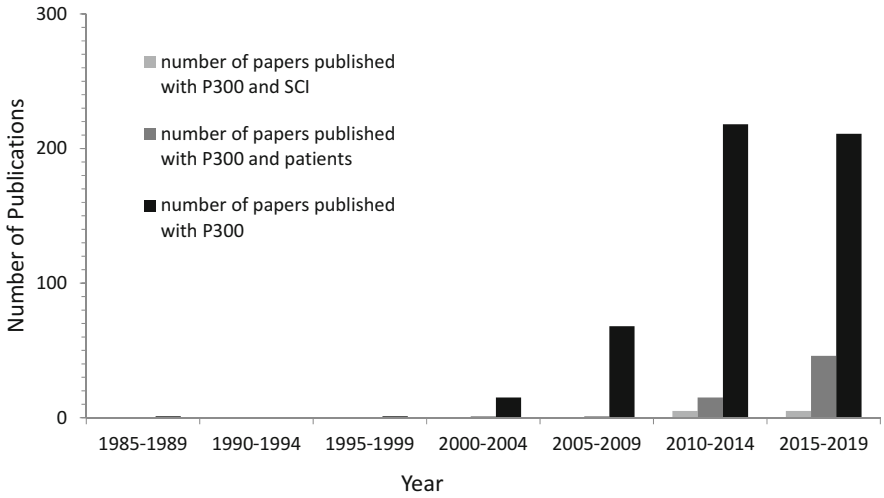

Fig. 8.1 P300 BCI related publications in PubMed. The very coarse search algorithm was "Brain" AND "computer" AND "interface" AND "P300" (black bars) and, for studies with end users with disease, AND "patient*" (grey bars) was added. For assessing publications with P300 BCI related to people with spinal cord injury AND "SCI" respective "spinal cord injury" was added. Note that neither of the hits was checked for actual content. As many papers mention "patients" as target population but do not include patients as participants of the study, the number of studies "with patients" is very likely to be overestimated. All hits with "BCI AND P300 AND SCI/spinal cord injury" were checked for the samples included, and those with at least one participant diagnosed with SCI were included in the review

number of studies including the P300 BCI and patients with SCI since the eighties of the last century.

P300 based BCIs used mainly the visual modality for presentation of stimuli and selection results. Most applications were aiming at communication and interaction for patients in the locked-in state (Allison et al. 2020). Many different stimulation paradigms were implemented and improved accuracy and information transfer rate. Specifically, the so-called face paradigm in which light flashes are replaced by a flashing image of a face led to a more than incremental improvement of performance (Cheng et al. 2017; Jin et al. 2014; Kaufmann et al. 2011), specifically in patients with neurodegenerative disease (Kaufmann et al. 2013). The face paradigm has been implemented in the so-called Brain Painting application which allows for creative expression. The BCI controlled Brain Painting was installed at the home of two artists in the locked-in state due to ALS, was used for many years independently of researchers being present, and improved QoL (Holz et al. 2015).

However, patients in the locked-in state due to brain-stem stroke, neurodegenerative disease, and other conditions often cannot use visual BCIs. For this reason P300 BCI paradigms have been suggested that realize stimulation in the somatosensory or auditory modality. Specifically the somatosensory modality has been suggested as viable for wheelchair control in virtual environments (Herweg et al. 2016), and proof-of-principle studies in a real world environment were also conducted (Halder et al. 2017). Those studies were, however, conducted with healthy volunteers.

8.2 P300 BCI and SCI

To get an overview of studies conducted with people diagnosed with spinal cord injury (SCI), the following search terms were entered in PubMed connected by AND: brain, computer, interface, spinal, cord, injury, P300 and yielded 11 hits when searched in "all fields". Replacing "spinal, cord, injury" by "SCI" yielded 19 hits including four duplicates to the previous search. The results of 26 hits were checked for whether they actually included people with SCI and a P300 BCI. Of these 26 hits ten included people with SCI and nine a P300 BCI, three additional papers were found through a review paper (Lazarou et al. 2018). Table 8.1 provides an overview of these studies. Altogether 43 people with SCI were included in those studies that were conducted between 2006 and 2018. Applications implemented were spelling and robotic devices, wheelchair control and gaming. All but three studies (Corralejo et al. 2014; Jeon and Shin 2015; Ortner et al. 2011) also included healthy subjects; only one included only patients with SCI (Jeon and Shin 2015). The aim of this study was to implement a P300 BCI with a "cheap bioamplifier and open source software" (Jeon and Shin 2015) (p. 120). The application tested with the system was the traditional spelling matrix. Two studies included control of a robotic arm and wheelchair control (He et al. 2017; Tang et al. 2018). Tang and colleagues realized a "smart wheelchair system" that required selection and confirmation of a command

Table 8.1 Overview of P300 BCI studies that include patients with SCI

Authors	Year	Subjects H/SCI/ other	Level of injury	Application	Online performance			Location	Number of electrodes	Number of sessions (days)
					Subjects	% Corr (range)	Bit/ min			
Piccione et al.	2006	7/**1**/4	C4	4-Choice paradigm	Healthy	76.2	7.6	Lab; Italy	4	1
Hoffmann et al.	2008	4/**1**/4	C4	Application scenarios presented on the screen without real function	Healthy	100[a]	29.3	Lab; Switzer-land	32	4/2 Days
					SCI + others	100	15.9			
Ikegami et al.	2011	10/**10**/–	C2–C6	2 Different coloured 8 × 10 Hiragana matrices	Healthy	77.3/ 86.0	–	Lab; Japan	8	1
					SCI	88.0/ 90.7	–			
Krausz et al.	2011	Same data set as in Ortner et al. (2011)								
Ortner et al.	2011	–/**8**/7	C2–C6	10 × 5 An 6 × 6 letter matrix	All	70.7	–	Lab; Austria	8/16 Active	1
					SCI	77.5	–			
					MS	80	–			
Pires et al.	2012	10/**1**/13	C3/ C4	6 × 6 Matrix; single characters presented laterally	Healthy	89.3/ 91.7	18.9/ 22.2	Lab, Hospital, Facilities Cerebral Palsy Asso-ciation of Coimbra; Portugal	12	1
					ALS	91.7/ 91.3	17.8/ 20.0			
					SCI + others	85.4/ 81.6	13.0/ 11.6			
Corralejo et al.	2014	–/**1**/14	Not specified	Navigation/10 menus/ 113 control commands/ 8 electronic	SCI + others	>77% $n = 10$ >95% $n = 8$	20.1	Rehab Centre; Spain	8 Active	1
Jeon and Shin	2015	–/**10**/–	C3–C67	6 × 6 Matrix	SCI	59.4	2.26	Lab; Korea	Not stated	10

Halder et al.	2017	6/**1**/–	C3/C4	Auditory BCI for spelling, Hiragana selection	Healthy	37–41	1.8–3.3	Lab, Japan	16 Active	3
					SCI	12–56	0.2–2			
He et al.	2017	8/**5**/–	C4–C5	Wheelchair control (start/stop)	Healthy Static/motion	94.4–98.8	–	(Moving around in the) Lab; China	8	2 (SCI)/3 (Healthy)
					SCI Static/motion	92.6–96.4	–			
Tidoni et al.	2017	18/**3**/–	C4–C6	Cooperative game in a virtual environment; control of a robot—via 3 × 3 matrix; proprioceptive feedback	Healthy VR/Robot	95/93.8	11.9/11.6	Lab; Italy	8 active	1
					SCI VR/Robot	75, 91.6, 66.6/3, –, 100	5.1, 10.4, 4.8/0.6, –, 14.2			
Tang et al.	2018	4/**1**/2	Paraplegic	Robotic arm and wheelchair control, 6 stimuli	All	100[b]	–	Lab; China	8	1
					Others	68.6	7.8			
					SCI	75.7	7.7			

SCI spinal cord injury, *MS* multiple sclerosis, *VR* virtual environment, *H* healthy/non-impaired

[a]"Close to 100" (p. 121)

[b]"Rate of successfully completed tests" (p. 15)

and then the wheelchair would autonomously drive along a pre-defined path; the same approach was used for control of the robotic arm. The tasks to be performed were placed in a hospital, i.e., in a real world environment. Tasks included drinking water, leaving the room, driving along a gallery, talking to a person. Of the seven to-be-performed commands four were automated, and three had to be issued via the BCI; commands and visual stimulation were presented on a monitor in breast height in front of the person. The study included one end user with SCI who issued around 75% of the commands correctly. He and colleagues implemented an "intelligent wheelchair" (p. 718) and BCI control included a start and stop command and choosing a destination, the wheelchair then moved autonomously along the pre-defined path (He et al. 2017). The system was validated with SCI patients. Performance measured in percent correct, information transfer rate, or number of completed tasks was not generally lower in patients as compared to healthy subjects (Table 8.1).

8.3 The Significance of P300 BCI for SCI

When thinking about BCIs for individuals with SCI it is important to know what such people consider most important for their quality of life (QoL). In a survey including 681 people after SCI, 48.7% of those with tetraplegia stated arm and hand function as most important for their QoL. Those with paraplegia stated sexual function as most important (26.7%), which was ranked as second by patients with tetraplegia (13%). In both groups trunk stability was third on the list (11.5% tetraplegic, 16.5% paraplegic). For patients with paraplegia bladder and bowel function control was second most important (18%) (Anderson 2004). Most of these functions have never been targeted in the realm of a P300 BCI. However, "walking movement" has been also mentioned, more so by those with paraplegia than those with tetraplegia, and thus, BCI based wheelchair control may be considered relevant for this population. Also, grasping function via a robotic arm has been demonstrated (Pathirage et al. 2013). Bowel function has recently been targeted with biofeedback (Mazor et al. 2016). The seemingly limited scope of BCIs for people with SCI may well be the reason why only few studies with the P300 BCI in SCI exist (Table 8.1). However, BCIs have been shown to be well adopted (Kübler et al. 2014) and contribute to quality of life if they provide something meaningful in a patient's life (Holz et al. 2015). Before we speculate how BCIs might contribute to QoL in SCI and suggest respective research directions, we introduce the results of a small study on the correlates of QoL in SCI, apart from body-related functions such as captured by Anderson (2004). More precisely, we were interested in how different coping and emotion regulation styles influence QoL, anxiety, and depression and in turn, how the latter two influence QoL in people with SCI. We also investigated how disease related factors affected coping and emotion regulation. Finally, we tested whether QoL affects the perception of the illness, conceptualized as illness-related words. We summarize the study in the next paragraph.

8.4 Well-Being in SCI (QoL, Depression, Anxiety, Coping, and Emotion Regulation)

When talking about QoL it is important to define exactly what is meant and how it is assessed, because many definitions of QoL exist and the respective instruments measure only the respective QoL, but not another. Furthermore, SCI is a high risk factor for psychological disorders, which in turn influence QoL (Tate et al. 2015). We will thus dwell on depression and anxiety as the main psychological disorders in SCI and on concepts of QoL and research on QoL in SCI. Furthermore, we explore coping and emotion regulation strategies as they affect QoL.

8.4.1 Psychological Comorbidities of SCI: Depression and Anxiety

SCI is "associated with reduced mobility and functional independence, impairment of social and vocational activities, as well as negative influences on the persons' health and wellbeing" (Craig et al. 2009, p. 1). Having lost the ability to walk independently excludes individuals with SCI from many social and vocational activities (Whiteneck et al. 2004). A lack of accessibility and participation can lead to social isolation which is experienced as very incriminating by many individuals with SCI (Newman et al. 2016). If individuals after an SCI need support to manage household and bodily hygiene, it is often experienced as a loss of control and predictability (Craig et al. 2015). However, the degree of participation after an SCI greatly depends on their perceived self-efficacy and self-esteem (Geyh et al. 2012). Given this multitude of stressors, people with SCI face an increased risk of psychological morbidities, however, individual perception and coping tremendously influence this risk and can also have a protective effect.

Across the literature, the life-time prevalence of a major depressive episode is reported to be about 22% among persons with SCI (Williams and Murray 2015), which substantially differs from the life-time depression rate (16%) in the general population (Kessler et al. 2003). In the first 6 months after the injury when patients mostly remain in a trauma hospital, in a rehabilitation centre, or both, the rates for depression or respectively depressive mood range from 20% (Judd et al. 1989) to 43% (Frank et al. 1985), with a mean of approximately 30% (Craig et al. 2009). However, it is important to note that these depression rates are comparable to the ones that occur in samples of in-patients with other conditions (Walker et al. 2018).

Approximately one-third of the individuals with SCI report elevated levels of anxiety, excessive worry, and fear or panic (Mitchell et al. 2008). This may be triggered by the traumatic origin of the SCI, wariness of secondary, life threatening consequences, and experienced helplessness due to the lack of mobility in many situations (Le and Dorstyn 2016). These factors contribute to a heightened risk of experiencing disorders such as Generalized Anxiety Disorder (GAD) or

Posttraumatic Stress Disorder (PTSD) (Craig et al. 2015). In fact, 10–40% of the individuals with SCI show symptoms of PTSD (Kennedy and Duff 2001). Furthermore, pain syndromes such as chronic neuropathic pain that occur in as much as about 80% of the SCI population (Rekand et al. 2012) may contribute to the expression of a clinical disorder since pain is correlated with high levels of anxiety and depression (Norrbrink Budh et al. 2005).

8.4.2 *Longitudinal Trajectories of Psychological Comorbidities in SCI*

Clear inter-individual differences can be observed with respect to the psychological outcomes following this event. Bonanno and colleagues identified unique trajectories of mental health during the first 2 years after the injury: In a longitudinal analysis, they revealed that about 50% of individuals with SCI show a stable, low level of depression and 24% recover from an initially high level of depressive symptoms over the course of 2 years (Bonanno et al. 2012). Another distinct group of individuals (13%) showed a delayed onset of depression starting from low depression which ultimately resulted in elevated levels of depressive symptoms. The last group (13%) was characterized by chronically elevated levels of depression that remained constant during the first 2 years following the injury. In a regression analysis, the different trajectories could not be sufficiently explained by weeks since injury and degree of bodily impairment alone. However, it is crucial to identify individuals that are at risk of an unfavourable trajectory as early as possible to grant them specific psychological support. Various coping and appraisal strategies are known to predict psychological health in chronic disease (Lazarus and Folkman 1984). This supports the relevance of psychological variables in relation to both a patient's susceptibility to psychological comorbidities and his or her maintenance of high QoL after having experienced an SCI. The link between depression and QoL has been demonstrated in many studies with large samples. For example, Hartoonian and colleagues found in a sample of $N = 4.976$ (survey data) patients after SCI, that QoL was negatively associated with nonsomatic symptoms of depression (Hartoonian et al. 2014).

8.4.3 *QoL in SCI*

With introduction of the comprehensive care concept by Sir Ludwig Guttmann after the second World War, the numbers of individuals surviving the acute phase of an SCI has been steadily increasing in western countries. In the 1980s, a high QoL after SCI became a central focus and ultimate goal of rehabilitation (Hammell 2004). Rehabilitation should empower individuals with SCI to regain a satisfactory level of

well-being and to stay a contributing member of the society. In a meta-synthesis of qualitative findings, ten main concepts were reported by people with SCI: bodily problems, loss, relationships, responsibility for and control of one's life, occupation and ability to contribute, environmental context, new values/perspective transformation, good and bad days, self-worth, and lastly self-continuity (Whalley-Hammell 2007). Coping and emotion regulation strategies also contribute to QoL in SCI. A considerable body of research suggests that different handling of stressful situations has predictive value on the adjustment and the resulting QoL after an SCI (Chevalier et al. 2009). According to Lazarus and Folkman (1984), a situation is perceived as stressful if it is appraised by the individual as personally significant and as having demands that exceed the person's resources for coping. Coping refers to the efforts people undertake to manage the internal and external demands of a stressful event (Folkman 2013; Lazarus and Folkman 1984). Lazarus and Folkman (1984) distinguished task-oriented coping strategies, characterized by actively focusing on the task at hand, and emotion-oriented coping strategies, thus modulating the way one feels about a situation. Later, avoidance-oriented coping strategies were also identified, such as social diversion or distraction (Endler and Parker 1990). Coping strategies have proven to be reliable predictors for future depression and QoL of people with paraplegia (Kennedy et al. 2000; van Leeuwen et al. 2012).

According to Gross (2002), another predictor of perceived QoL may be emotion regulation, namely how we "[. . .] influence what emotions we experience, when we do so, and how we experience and express them" (Gross 2002, p. 282). Research about emotion regulation mainly focusses on two prominent strategies, namely cognitive reappraisal and expressive suppression (Gross and John 2003; Webb et al. 2012). While the latter refers to actively avoiding the surfacing of an emotional response, cognitive reappraisal aims to change the primary evaluation of the situation at hand. Cognitive reappraisal is considered to be more adaptive than expressive suppression (Gross and John 2003). Only Znoj and Lude (2002) examined "adaptive", e.g., positive reinterpretation and the ability to clearly express emotions, and "maladaptive", e.g., impulsive action or suppression to avoid unpleasant emotions, emotion regulation strategies in a sample of 264 people with SCI (Znoj and Lude 2002). In this sample, maladaptive forms of emotional regulation contributed significantly to depression and non-depressed people distinguished themselves by more adaptive and less maladaptive regulation strategies. Emotion regulation strategies did account for 8% of the variance in the depression score. Longitudinally, the ability of individuals with SCI to regulate emotion and mood moderates pain intensity and therefore indirectly affects the quality of life (Lam 2014).

8.4.4 Measuring QoL

Quality of Life can be assessed objectively and subjectively. Objective measures evaluate characteristics that can be impartially judged by an external evaluator. These instruments try to infer subjective well-being from measuring a person's

achievements. Such instruments are usually of a quantitative nature. However, they implicitly assume that individuals share the same domains which are important to them and that life satisfaction is directly proportional to the individual fulfilment of those categories (Hill et al. 2010). Most frequently, those instruments are assessing health-related QoL (Dijkers 2003), but they tend to overestimate the impact of health-related domains to the individual life satisfaction (Moons et al. 2006). Tulsky and colleagues introduced an instrument, which takes also into account emotional health and social participation (Tulsky et al. 2015). Subjective instruments which consider an individual's emotions and evaluation in the context of their expectations and achievements are needed to acquire a full image of a person's QoL (Dijkers 2005). Research tools developed for this purpose either request quantitative answers to predetermined categories or try to qualitatively summarize free answers or domains named by the participants. It can be argued that quantitative tools may mislead participants to only choose among the domains predetermined by the researchers (Dijkers 1999). Qualitative measures distinguish themselves by high internal validity, but are less representative and comparable. Mixed tools that collect answers in a qualitative way, but make them comparable by applying measurable scales to those answer categories, may present a solution compensating for the disadvantages of both qualitative and quantitative designs. Such an instrument is the Schedule for the Evaluation of Individual Quality of Life-direct weighting (SEIQoL-DW) (O'Boyle et al. 1993). It first asks the individual to define five domains that are most important for their QoL. Then satisfaction with each domain has to be indicated on a scale from 0% to 100%. Finally, each domain has to be weighted. High satisfaction with domains that are then highly weighted, results in high a QoL.

We investigated with questionnaires individual QoL, anxiety, depression, coping styles, and emotion regulation strategies in a sample of $N = 19$ patients with SCI. Additionally, participants were presented with disease related and disease unrelated, positive, neutral, and negative words (Table 8.2) and had to rate their valence and arousal. We correlated those ratings to depression and anxiety. The sample is described in Table 8.3 and a summary of our results is provided in the next section.

8.4.5 Summary of Results from the Study

Results of all questionnaires are summarized in Table 8.4. Individual quality of life scores and individually defined domains are summarized in Table 8.5.

In our sample, only emotion-oriented coping styles were marginally correlated with a higher degree of psychological symptomatology. None of the coping styles or emotion regulation strategies were related to QoL, neither were the amount of physical symptoms. Furthermore, in a multiple regression analysis, none of the coping or emotion regulation variables did uniquely explain a significant part of the variance in the SEIQoL-DW score or in the Hospital Anxiety and Depression Scale (HADS) score, an instrument that quantifies symptoms of depression and

Table 8.2 Words used for valence and arousal ratings; words were in German (English translation in parentheses)

Illness-relevant			Illness-irrelevant		
Positive	Neutral	Negative	Positive	Neutral	Negative
• Kraft (power) • Starkbleiben (stay strong) • Wille (will) • Pflege (care) • Durchhaltevermögen (stamina)	• Veränderung (change) • Hilfe (help) • Gespür (grasp) • Duschen (taking a shower) • Ebenerdig (at ground-level)	• Barriere (barrier) • Krankheit (illness) • Behinderung (disability) • Trauma (trauma) • Blasenentzündung (bladder infection)	• Lachen (laugh) • Freude (joy) • Humour (humour) • Liebe (love) • Partnerschaft (partnership)	• Toilette (toilet) • Zukunft (future) • Rente (pension) • Waschen (wash) • Sport (sports)	• Feind (enemy) • Langeweile (boredom) • Panik (panic) • Waffen (weapons) • Krieg (war)

The words were collected and rated for illness-relevance in a pre-study with different sample of participants

Table 8.3 Socio-demographic and medical data of the sample of individuals with SCI (SD = standard deviation)

Age (Mean; SD): 50.97 (14.32)	
Months post injury	
(Mean; SD): 166.42 (198.91)	Number (*n*)
Sex	
Male:	13
Female:	6
Injury	
Traumatic:	14
Non-traumatic:	5
Neurological level of lesion	
C1	1
C3	1
C5	1
C6	1
Th4	1
Th5	2
Th6	1
Th7	2
Th9	3
Th10	2
Th11	1
Th12	2
L5	1
SCIM-III	0–100;
(range 0–100; Mean;	53.47;
SD)	18.19
Marital Status	
Single	10
With Partner	1
Married	6
Separated/divorced	1
Widowed	1
Living situation	
Alone	6
With children	1
With partner	5
With partner and children	2
With parents	3
In flat share	2
Education	
University degree	4
Finished apprenticeship	12
Finished main school	3

(continued)

Table 8.3 (continued)

Age (Mean; SD): 50.97 (14.32)	
Months post injury	
(Mean; SD): 166.42 (198.91)	Number (*n*)
Occupation	
Full-time	6
Part-time	1
Job seeking	5
Pensioner	7
AIS	
A	10
B	2
C	4
D	3
E	0

SCIM spinal cord independence measure III
AIS American spinal injury association (ASIA) impairment scale

Table 8.4 Summary of applied instruments to measure the respective variables (coping, emotion regulation, anxiety, and depression) and results of the sample (mean and standard deviation)

	Mean (SD)
Coping inventory for stressful situations (CISS)	
(1 = very untypical; 5 = very typical)	Range: 1–5
Task-oriented coping	3.84 (0.57)
Emotion-oriented coping	2.80 (0.90)
Avoidance-oriented coping	3.20 (0.78)
Distraction	2.72 (0.95)
Social diversion	3.68 (1.05)
Emotion regulation questionnaire (ERQ)	
(1 = strongly disagree; 5 = very typical)	Range: 1–7
Cognitive reappraisal	3.32 (1.26)
Excessive suppression	3.38 (0.82)
Hospital anxiety and depression scale (HADS)	
(Max score = 42; max subscale = 21)	Range: 0–21
Anxiety score	4.90 (3.35)
Depression score	4.42 (3.29)
Overall symptom score	Range: 0–42
	10.00 (6.53)

anxiety (Zigmond and Snaith 1983). The second goal of our study was to examine whether the perception of negative and illness-relevant words would be indicative of a low QoL and/or a high degree of psychological symptoms. It is well known that depressed or chronically disabled individuals experience a cognitive bias toward illness-related and negative stimuli (Traxler et al. 2019; Wingenfeld et al. 2013). We

Table 8.5 Results of the SEIQol-DW

Schedule for the Evaluation of Individual Quality of Life			
	Range: 0–100		
(Index Range 0–100)	Mean (SD): 64.42 (17.78)		
Reported categories	*N*	Low QoL	High QoL
Family	16	7	9
Living situation	14	6	8
Health	12	6	5
Friends	11	4	6
Leisure	9	4	5
Work	9	4	4
Independence	8	5	2
Access/Mobility	7	5	2
Sport	5	3	2
Self-fulfilment	4	1	2

could confirm such a cognitive bias because valence and arousal ratings of illness-relevant, negative words—but not for illness-irrelevant, negative words—were significantly correlated with the participants' HADS score (Fig. 8.2). In a post-hoc analysis, a marginally significant interaction showed that negative, illness-relevant words were perceived as more arousing than negative but illness-irrelevant words, and more so by patients with a high degree of psychological symptoms. Such relations were not found for neutral or positive words. This strengthens the hypothesis that individuals with SCI with higher psychological burden process negative contents more intensively.

8.4.6 Brief Interpretation of the Results and Link to BCI

Real and colleagues recently provided an explanation of the involvement of subjective well-being in the perception of illness-related stimuli: to reduce the difference between hopes and expectations of the individual and that individual's present experiences, coping efforts are undertaken by the individual (Real et al. 2014). If these efforts fail to reduce the difference, this individual evaluates her/his subjective well-being to be low. Thus, the evaluation of QoL can be seen as a feedback loop, or a test-operate-test-exit (TOTE) model (Miller et al. 1960). The individual constantly checks the difference between expectations and present experiences until this gap is minimized. Therefore, individuals with SCI that evaluate their QoL to be low may repeatedly process illness-related information without being able to exit the loop with a satisfying result.

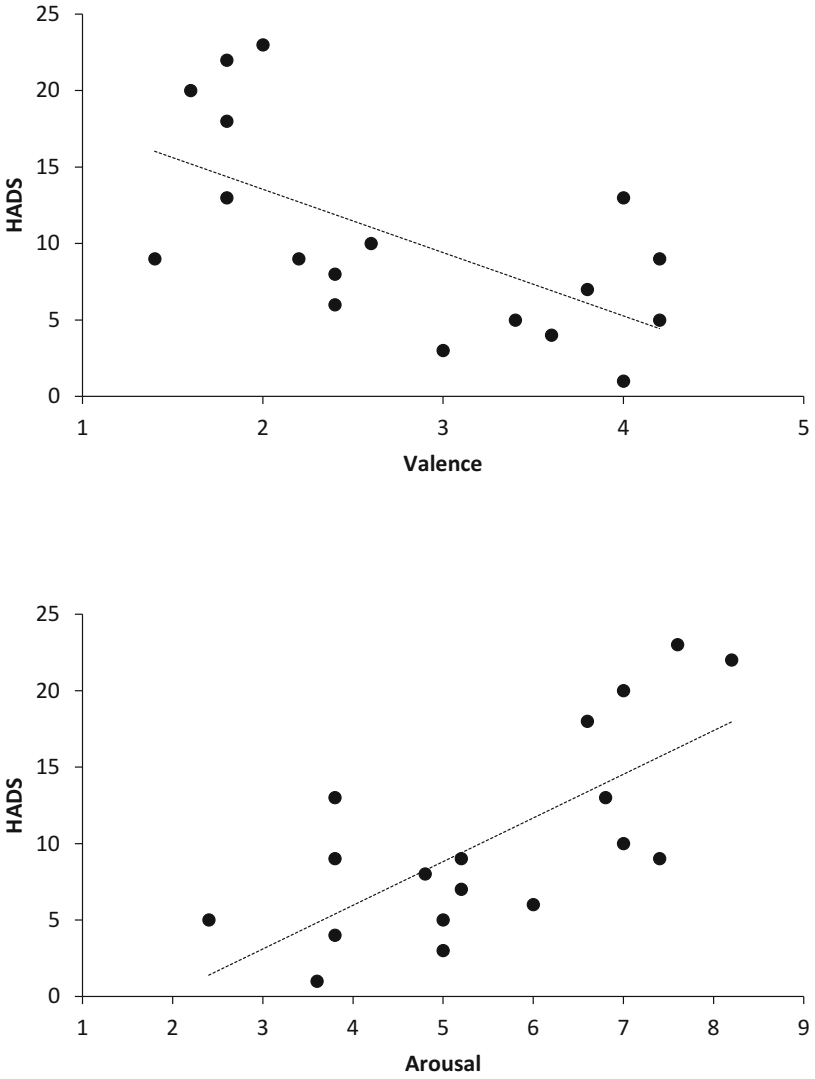

Fig. 8.2 Correlations between the HADS score (anxiety and depression measure) and valence (top, $r = 0.63$) and arousal (bottom, $r = 0.70$) ratings of illness relevant, negative words. Both were significant ($p < 0.005$). Lines show linear trends

The life domains stated as important for QoL were mostly family and living situation. Table 8.5 distinguishes between individuals with high and low quality of life. It can be seen that in the group of low QoL independence and access/mobility were more often stated as important than in the group of high QoL. Improving these factors may, thus, improve QoL. Both aspects may be addressed by a BCI.

8.5 P300 as Marker for Cognitive Impairment in SCI

Depression is not only negatively linked to QoL. Craig and colleagues could show that negative mood states, which may in the long-term lead to an affective disorder such as major depression, were specifically prevalent in patients who experienced impaired cognitive performance after the SCI. With a prevalence rate of 60% cognitive impairment is highly prevalent in patients with SCI. Reported deficits were found, for example, in attention and memory function (Craig et al. 2017). A recent review listed concomitant brain injury, psychological or somatic comorbidities, decentralized cardiovascular control, and sleep apnea as potential co-contributors (Sachdeva et al. 2018). Like in the non-motor-impaired population, cognitive functioning in SCI is negatively correlated with age. Although no clear dependency has been found between the incidence of cognitive impairment and the level of injury, different patterns of cognitive dysfunction are reported for individuals with tetra- and paraplegia (Chiaravalloti et al. 2019). Results from mice suggest that a common underlying mechanism may be neuroinflammatory neuronal loss and cellular dysfunction in areas associated with cognitive decline and depression (Craig et al. 2017). Another proposed typical SCI-associated complication contributing to cognitive impairment is cardiovascular dysfunctions in particular orthostatic hypotension (Nightingale et al. 2020). When living in the community, depression and anxiety increased in those patients who experienced cognitive impairment. Lazzaro and colleagues also found more variable response time and higher false positive rate in a "two-tone button press oddball discrimination paradigm" (p. 59) in patients with SCI as compared to a non-impaired control group, which was interpreted as inhibitory dysfunction, which is also a facet of cognitive functioning (Lazzaro et al. 2013). In this study early evoked and later event-related potentials were recorded (N100, P200, N200, P300) in a group of $N = 37$ participants with SCI. Specifically the P300 ERP was affected presenting with a lower amplitude and a prolonged latency as compared to a non-disabled age-matched control group. The P300, of course, is specifically relevant in the context of this chapter. A lower P300 amplitude was also found in a standard oddball task with tactile stimulation, and the amplitude was even more attenuated in patients with tetraplegia (Cohen et al. 1996). This has to be considered when probing the somatosensory modality for wheelchair control as described in the next section.

8.6 The Potential of P300 BCI for SCI

It is well established that the P300 is related to and a marker of attention. Arvaneh and colleagues implemented an automated procedure that reduced the number of flashes automatically depending on the individual performance, and thus, rendered the task more difficult. This resulted in an increased P300 amplitude elicited with the classic 6×6 spelling matrix within one session that lasted less than 2 h (Arvaneh et

al. 2018). The effect on attention was probed with a continuous version of the random dot motion task in which a left or right button has to be pressed as soon as the randomly moving dots start moving coherently to the left or right. The performance in this task improved from pre- to post-training and more so in the experimental than in the control group, albeit these effects were only marginally significant. In a study with stroke patients diagnosed also with Broca aphasia, Kleih and colleagues also demonstrated that the P300 amplitude increased with training which led in turn to increased speech efficiency (Kleih et al. 2016). Thus, it seems well feasible that cognitive and specifically attentional performance may be enhanced after training with the P300 speller or similarly challenging applications.

Apart from communication in severe paralysis, P300 controlled BCIs have been suggested for other applications. The P300 BCI controlled spelling program and Brain Painting application have been used extensively by patients in the locked-in state at home for many years and positively affected QoL (Botrel et al. 2015; Holz et al. 2015; Sellers et al. 2010). This demonstrates that a BCI can be used at a patients' home if it provides something valuable for the person which is otherwise not accessible. It can be used on a daily basis if appropriate support is provided by significant others. Individuals after SCI with paraplegia could even set-up the BCI for themselves. Handling of a media player and web browser has also been shown in feasibility studies including patients with motor impairment albeit not with end users with SCI (Halder et al. 2015; Martinez-Cagigal et al. 2016; Mugler et al. 2010; Zickler et al. 2011; Yu et al. 2012). In combination with current state-of-the-art mobile EEG devices, a BCI could be a valuable approach to Assistive Technology, diagnostics, and even cognitive training (Bleichner and Debener 2017; Bleichner et al. 2015; Debener et al. 2015; De Vos et al. 2014). A cognitive test battery has been implemented into a P300 BCI (Poletti et al. 2016). On this basis a cognitive training battery on the basis of existing cognitive training tools used in rehabilitation clinics could be developed that may be entertaining and challenging. It has been demonstrated that training with a P300 BCI that implemented adaptation of the classifier depending on the current strength of the P300 event-related potential could improve subsequent performance in a random dot motion task, which is an indicator for spatial attention (Arvaneh et al. 2018).

Mobility is of course much more difficult to achieve. In exemplary experiments lower limb exoskeletons which support walking in individuals with SCI have been tested in selected end users (Donati et al. 2016; Lebedev and Nicolelis 2011), however, those were not based on the P300 as input channel. More realistically, mobility can be achieved by means of a smart wheelchair system, which has been controlled by a P300 BCI in proof-of-principle studies (He et al. 2017; Tang et al. 2018) (Table 8.1). These approaches, however, use the visual modality for feature selection and subsequent wheelchair movement. In a real world setting this may constitute an access barrier, because vision is the most used sensory modality for social interaction and orientation in the environment. For this reason, the somatosensory modality has been explored for wheelchair control in virtual (Herweg et al. 2016; Kaufmann et al. 2014; Eidel and Kübler 2020) and real environments (Halder et al. 2017). Tactile stimulators were placed at different bodily locations to move a

wheelchair forward, left, and right and to stop. As most P300 BCI studies were feasibility studies, translational effort has to be made to judge the practical value of these approaches.

8.7 Research Directions

Exploiting the relation of the P300 to attentional processing it would be very valuable to investigate whether the P300 amplitude constituted a marker of cognitive functioning over time. The course of the P300 amplitude over time should be investigated, such that the potential value as early marker of cognitive decline could be estimated. Furthermore, it would be interesting to see whether a training with a P300 BCI would counteract the potential decline of cognitive functioning. Furthermore, there seems to be a relation between cognitive functioning and quality of life (Abrahamson et al. 2012; Hill et al. 2017). In a sample of Parkinson patients Lawson and colleagues found attention measured at baseline to explain 11% of the variance in QoL assessed 36 months later (Lawson et al. 2016). It may be worth investigating whether such relation between attention and QoL also exists in people with SCI. If yes, a P300 based attention training could not only contribute to cognitive improvement but also prevent decline of QoL.

With respect to wheelchair control it would be valuable to investigate whether navigation first in a virtual, and as decisive translational step, in a real world environment can automatize such that it can be executed while other tasks are conducted such as having a conversation. Such studies require a repeated measures approach, and many training sessions will most probably be required. However, the minimum number of sessions necessary to achieve reliable control has to be determined in future studies. In a study with a locked-in patient diagnosed with amyotrophic lateral sclerosis we experienced that even many training sessions do not necessarily lead to high fidelity performance as we observe constant accuracy on a significant but not high level (unpublished data). Due to the impairment of sensation, the bodily positions where to place the tactile stimulators are restricted in persons with high cervical spinal cord injury. It remains an open question whether such an approach would be at all feasible in this population.

8.8 Conclusion

The potential for P300 BCIs in people with high SCI is clearly limited. This is reflected in the low number of studies conducted with this target population. From the twelve studies reviewed, only two investigated wheelchair control and one control of a robotic arm. These functions are indeed relevant for people with SCI. Translational studies with the target population are urgently needed to judge whether such a control function would be valuable in daily life situations. Such studies must

also implement long-term measurements to evaluate the effects of practice and the potential of automatization. The potential of a P300 BCI as a tool for cognitive training is appealing and should be further investigated, also with respect for subsequent improvement of quality of life.

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Chapter 9
Invasive BCI Approaches for Restoration of Upper Extremity Movements

Gernot Müller-Putz

Abstract With neuroscientific investigations of analyzing neuronal activity of motor areas directly in the cortex in the 1980s, the foundation of invasive brain–computer interfaces (BCIs) or brain–machine interfaces (BMIs) was laid. Since then, researchers were studying motor cortex activity with multielectrode arrays, first in primates and later in humans, and applying decoders that allow multidimensional control of robotic limbs. Less invasive, but still with high signal-to-noise ratio, electrocorticography (ECoG) signals have been used for the investigation of motor cortex activity since the 2000s. After many basic investigations and decoding examples, this type of brain signal also seems to be promising for motor restoration.

Keywords Electrocorticography (ECoG) · Multielectrode array · Multiunit activity · Single-unit activity · Reach and grasp restoration · Motor control

9.1 Introduction

In this chapter, we provide a brief overview of invasive recording techniques and the designated brain signals that can be obtained. Invasive recording of brain signals usually requires a surgical intervention and a close follow-up monitoring. There are different degrees of invasiveness, starting with low-invasive electrodes placed on the surface of the brain to highly invasive electrodes in the cortex. In this chapter, we describe the different invasive techniques for recording brain signals and give state-of-the-art examples on how they can be applied for real-time movement decoding and artificial limb control.

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9.2 Electrocorticography (ECoG)

The electrocorticography (ECoG) describes an invasive recording technique where brain signals are directly recorded from the surface of the brain.

The first pioneering work on ECoG recordings in humans was conducted around 1940 by Penfield and colleagues at the Montreal Neurological Institute (Geddes and Hodge 1996). At the same time, the possibility of epilepsy treatment by surgically removing abnormally active neurons was introduced. In this context, there was an increasing need to precisely identify the localization of epileptic foci on the exposed brain. This was fulfilled by the recording of the electrical activity on the brain during surgery. All this has led to the development and use of ECoG as a widely used invasive technique for neurosurgery interventions (O'Leary 1970). Through a craniotomy, a large section of cranial bone is removed, and an electrode array can be placed on the exposed brain, either subdurally or epidurally, acquiring brain activity from a wide area of the cortex (Schalk and Leuthardt 2011; see Fig. 9.1). Between 4 and 256 electrodes in the form of an electrode matrix or electrode strips (see Fig. 9.2) are used for the purpose (Schomer and da Silva 2012).

For processing of the multiple ECoG signals, various signal analysis techniques are used to enhance the signal-to-noise ratio and to identify characteristic brain signals (Hill et al. 2012). Nowadays, ECoG recordings are performed for advanced diagnosis of epilepsy and are considered the "gold standard" for defining epileptogenic zones (Pistohl et al. 2012; Hill et al. 2012). In the past two decades, ECoG has been recognized as a formidable tool for neuroscience and also as a method for acquiring data to implement brain–computer interfaces (BCIs; Graimann et al. 2003; Schalk and Leuthardt 2011).

Brain signals acquired invasively through ECoG electrodes have similar characteristics to non-invasively recorded signals of the electroencephalogram (EEG; see Chap. 3). However, ECoG signals have a higher signal-to-noise ratio and a broader spectrum available for analysis of up to 200 Hz (Pistohl et al. 2008). This offers a more local brain activity.

9.2.1 Intracortical Recording of Single- and Multiple-Cell Activity

Extracellular activity from single neurons can be recorded by inserting microelectrodes directly into the brain's neuronal tissue. Nowadays, those microelectrodes are arranged in a grid-like geometry based on a thin layer that contains wires for further signal transmission. The most advanced example is the Utah-array, which typically contains 96 electrodes on a 4×4 mm base. Those electrodes are 1.1 mm long (for details see Fig. 9.2) and record electrical activity only at the tip.

Neuronal activity needs to be recorded with a sample frequency much higher than, for example, EEG signals, that is, in the range of 10 kHz. After high-pass

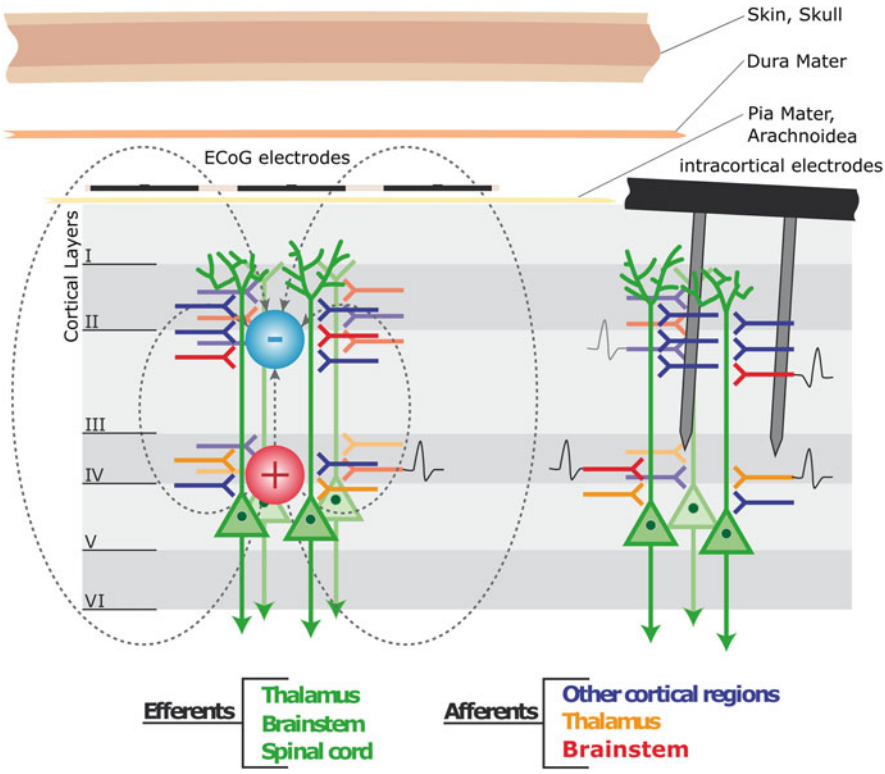

Fig. 9.1 Spatial relation of implanted brain electrodes with different degrees of invasiveness to neural cortical structures. (Left) ECoG electrodes can be implanted either subdurally or epidurally to record summed potential changes from the cortex similar to electroencephalogram (EEG), but with larger amplitudes and higher spatial resolution. (Right) Implanted multielectrode array. Electrodes penetrate the cortex up to layer IV and record neuronal activity of only a few cells

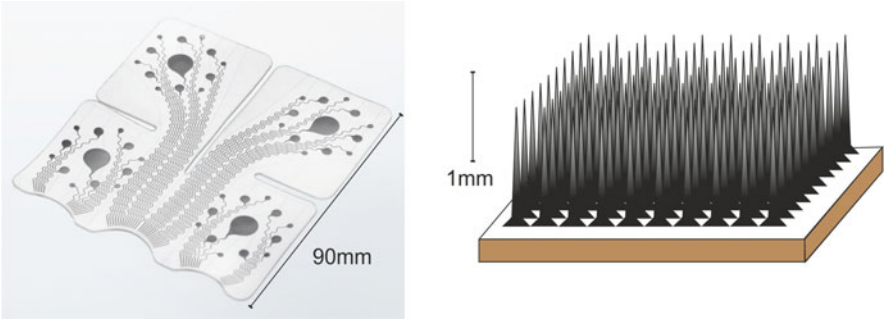

Fig. 9.2 Types of electrode arrays with different degrees of invasiveness. (Left) Innovative ECoG electrode Grid (CorTec GmbH). (Right) Sketch of an implantable microelectrode array (4 × 4 mm) based on the Utah-array

filtering around 300 Hz (this means that all components below 300 Hz are greatly attenuated), it is possible to separate action potentials, also called neuronal spikes. Those spikes have an amplitude of about 100 mV and last for about 1 ms. Since volume conduction happens here also (see Chap. 3), it leads to a distribution of the potentials; and since one electrode records summation potentials of spikes from many neurons, so there is an array of electrode-acquired activity from multiple neurons, but it is not clear which electrode records which neural activity. This mix of signals is called multiunit activity (MUA; Stark and Abeles 2007). State-of-the-art spike sorting algorithms allow to separate neuronal spikes (Brown et al. 2004; Caro-Martín et al. 2018) from MUA. Individual spike activity is referred to as single-unit activity (SUA). From the extracellular signals recorded with grid electrodes, local field potentials (LFPs) can also be derived. The LFP, the low-frequency (<500 Hz) content of the raw recording, is believed to be generated by membrane currents of the neurons in the local neighborhood of each recording electrode, while the MUA, the high-frequency (>1000 Hz) portion of the recording, represents the spiking of local neurons. This means that for LFP analysis, it is first necessary to apply a low-pass filtering.

9.2.2 Deriving Directional Information from Single- and Multi-Unit Activity in Animals

In the early 1980s of the last century, Georgopoulos and colleagues (1982, 1983; Georgopoulos 1988) measured the SUA in the motor cortex in rhesus monkeys during center-out reaching tasks. From the summation of SUA, depending on movement direction, they could calculate a vector, which pointed into the same direction as the arm movement. They named it population vector. Ten years later, Caminiti et al. (1990) extended the findings of Georgopoulos and was able to show in non-human primates that the population vector still points in the direction of the movement when performing discrete movements in similar directions but using different sets of muscles. In 2000, a first attempt to use directional information directly decoded from motor cortex neurons (recorded by microelectrode arrays, NBLabs, Dennison, USA) to derive a control signal was performed by Wessberg and colleagues at Duke University. While an owl monkey performed arm movements, they found that a summation of the electrical activity could predict the arm movement already milliseconds in advance (Wessberg et al. 2000). From this prediction, a control signal was calculated to drive a robotic arm in three-dimensional (3D) space. It was shown that around 70% of the arm movements of the monkey could be successfully decoded by analysis of brain signals. Furthermore, it was proved that the invasive recordings remained stable over a long time period (24 months). In a next experiment, Nicolelis and Chapin (2002) were able to increase the decoding accuracy to 95%, however, only in a 1D plane. Follow-up experiments investigated 3D control (Taylor 2002) or reaching and grasping (Velliste et al. 2008; Carmena et

al. 2003). In a more complex scenario, Velliste et al. (2008) showed that monkeys were able to feed themselves with a robotic arm.

9.2.3 State of Invasive BCIs for Restoration of Movement in Humans

Many research groups' pursuit to decode directional information from the human brain signals using invasive recording techniques has been presented in the presthis section. In the following, we refer to selected experiments in this field that are of particular interest for the restoration of movements in people with severe motor impairments.

9.2.4 ECoG-Based Movement Control

ECoG is widely used in the field of BCI, but still mainly is recorded in persons who undergo surgical epilepsy treatment. In only a few cases, ECoG arrays were implanted in the context of a BCI application to improve the quality of life of end users with motor disabilities. Recently, Vansteensel et al. published their work about a BCI for communication. A woman with ECoG stripes implanted attempted hand movements to control a communication device in spelling mode (cf. Vansteensel et al. 2016). This device is permanently implanted and sends commands to a spelling system outside the body that is attached, for example, to the wheelchair.

ECoG-based BCIs for the purpose of controlling a (neuro)prosthetic limb has not been reported so far; however, this topic is a matter of research.

In 2004, Leuthardt and colleagues realized a 1D cursor control. Here, study participants (four patients with epilepsy) imagined a hand movement or imagined saying a word to move a cursor on a screen up or down. Leuthardt and colleagues analyzed frequency bands in the range from alpha (8–12 Hz) to high gamma (up to 100 Hz). They could show that during the mental imagery, power in alpha and beta bands decreased (also known as desynchronization; compare Chap. 3) while power in gamma frequencies increased. Single-trial decoding accuracies between mental states in this control task were between 70% and 100% (Leuthardt et al. 2004). After these first results, several other groups started to investigate movement decoding using ECoG recordings.

Schalk and colleagues further investigated two approaches to 2D control. In a first study, they involved five subjects with intractable epilepsy in whom ECoG grids (48–64 electrodes, 4 mm diameter, and 1 cm inter-electrode distance) for localization of seizures were applied (Schalk et al. 2007). They performed a pursuit-tracking task, in which study participants had to operate a joystick by hand to follow a target cursor that circled counterclockwise on a screen. For the decoding, they analyzed the

positions and velocities of the joystick input. ECoG was analyzed in the frequency band of 0.15–200 Hz. The correlation results between joystick positions and velocities with the ECoG-based signal were between 0.2 and 0.7.

In the second study, a similar group of participants was included. Here, spectral features from either executed or imagined movements of hand open/close, tongue, jaw, shoulder, legs, and individual fingers were derived and two pairs of movement for 2D cursor control were selected. Decoding accuracies ranged from 53% to 73% (Schalk et al. 2008).

A different approach to 2D control was performed by Pistohl et al. (2008). Six participants (individuals with epilepsy and implanted ECoG grids [4 mm diameter and 1 cm inter-electrode distance] for seizure detection) were moving their hands in the horizontal plane navigating a screen-cursor from one target to another. For decoding, they used the 2D hand position and its velocity. For prediction, they applied a state-space model and analyzed only the low-frequency (in the range of the movement) components of the ECoG signals. Decoding performances ranged in correlations between 0.3 and 0.6.

Milekovic et al. (2012) also used low-frequency components of ECoG signals. After training and model calibration, participants (similar group as described above) were able to control a cursor on a computer screen either to the left or to the right, with a decoding accuracy above chance level of 69–86% in four out of five patients.

In the following years, further investigations toward decoding of not only arm, but also finger movements during slow grasping actions (Acharya et al. 2010) and of natural grasp types (Pistohl et al. 2012, 2013) from ECoG recordings were performed. Recently, the decoding of complex hand gestures has also been investigated (Bleichner et al. 2016; Branco et al. 2017; Wu et al. 2017).

In 2019, a first-in-human study on chronic use of an implantable ECoG-based BCI system was described by Benabid et al. (2019). A fully implantable ECoG recording system (WIMAGINE—Wireless Implantable Multichannel Acquisition system for Generic Interface with Neurons [Mestais et al. 2015]) was implanted bilaterally in a 28-year-old male study participant with high tetraplegia and no preserved finger and leg movements (Neurological Level of Injury [NLI], C4; ASIA Impairment Scale [AIS], grade A: American Spinal Injury Association [Kirshblum et al. 2014]). In the right side, only the biceps and muscles above C5 were under voluntary control. In the left side, he had voluntary biceps and wrist flexors. The sensory map is similar on both sides (C4).

Each system consisted of 64 epidural electrodes and was implanted over upper limb sensorimotor areas reaching into the central leg movement area. ECoG recordings were processed directly in the device using an adaptive decoding algorithm and commands were sent wirelessly to external effectors. These effectors were either a virtual reality (VR) based training system or a real wearable exoskeleton with 4 limbs and 14 degrees of freedom (DoF). Gradually, the study participant achieved voluntary control, starting from 1D (unidirectional movement), 2D movements, 3D upper limb movements on both sides, 4D limb movements (including arm rotation) of both arms, and finally reaching full exoskeleton control, which involved also a 1D

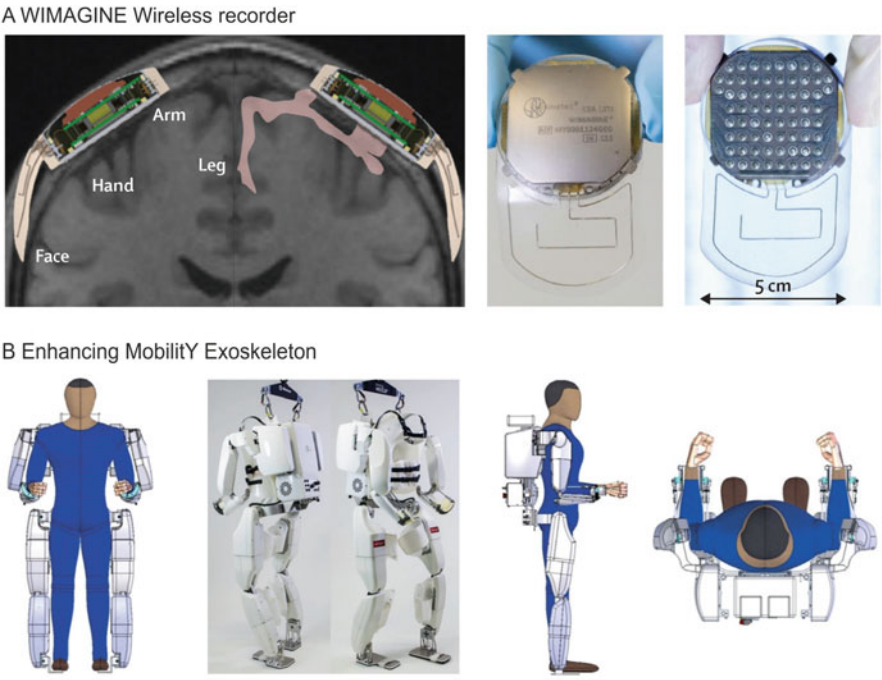

Fig. 9.3 (**a**) The biocompatible wireless WIMAGINE recorder was designed for chronic implantation. (**b**) The exoskeleton was designed as a wearable humanoid universal neuroprosthesis mimicking the human body shape and its mobility. The exoskeleton is self-supporting, wireless, and can be autonomously used for 2.5 h. Equilibrated walking in a natural environment is not yet possible, but has been achieved with software that produces a humanoid walk and a ceiling suspension system under laboratory conditions (Vector Elite model [Bioness, Valencia, CA, USA]). Modified with permission from (Benabid et al. 2019)

control of lower limbs movements. Simultaneously, the participant was able to control 8 degrees of freedom in bimanual tasks with an accuracy of 70.9% (Fig. 9.3).

9.3 Movement Control Based on Intracortical Recordings

In 2006, the first-in-human implant of an intracortical sensor array (Utah-array) was done in a man with complete spinal cord injury (SCI [NLI, C4; AIS, A]). He was not only able to control a 2D cursor on a monitor by selecting several commands, but also to open and close a prosthetic hand only using his brain activity (Hochberg et al. 2006). A further study has been reported by Kim et al. (2011): Two males, one with a brain-stem stroke and the other with amyotrophic lateral sclerosis (ALS), demonstrated BCI control of a 2D cursor task, including continuous and discrete commands.

9.3.1 Anthropomorphic Prosthetic Limb Control

In 2013, a first breakthrough using intracortical implant technology was demonstrated. Collinger and colleagues implanted two 96-channel intracortical microelectrode arrays in the motor cortex of a person (female, 52 years) with spinocerebellar degeneration and the associated tetraplegia that occurred 13 years before. She presented a quite unusual neurological status with a complete motor paralysis, however with generally intact sensation and some hypersensitivity (Stone and Landau 2013). The goal of this study was to control an anthropomorphic prosthetic limb (modular prosthetic limb, MPL) with seven degrees of freedom (3D translation, 3D orientation, 1D grasping). Doing so, the BCI training was performed stepwise: (a) 3D endpoint translation control, (b) 4D translation control and grasping, and then (c) 7D full arm control (Collinger et al. 2013).

For decoder setup, the participant went through an observation phase, where the robot arm made movements in all seven degrees of freedom and neural activity was recorded. After 60 trials, a decoding algorithm was set up and two online tests were performed: (a) target-based control test, and (b) functional control test. In target-based control tests, the participant was given random targets (in space) involving all seven degrees of freedom and was instructed to execute them using the BCI. During these tasks, the arm was stabilized, and a decoder signal was idealized to some degree (i.e., wrong decoder outputs were reshaped toward the correct target), so that the person in control could adjust to the task. After 66 days of training, the participant was able to move the robot arm in all seven degrees of freedom without any assistance. During functional control tests, parts of the action research arm test (ARAT [Lyle 1981]) were performed by the participant. Although not all tests were performed, the total score across 7 test days was between 15 and 17 out of 27. Movement time was between 9.5 and 23.5 s. Since the test result without the system was 0, she reached a clinically significant improvement.

In a follow-up study performed by Wodlinger et al. (2015), four new commands replacing the 1D grasping channel were introduced. Since the MPL's hand allows movements in up to ten degrees of freedom, they were projected into a 4D hand-shape space: pinch, scoop, finger abduction, and thumb opposition. These additional four degrees combined with the six degrees of endpoint velocity led to a total of ten simultaneously controllable dimensions. Calibration was similar to the earlier study (Collinger et al. 2013). Tests in this study were either performed in a VR environment or with the real MPL setup. Performance was again assessed with the ARAT and achieved similar results as in the work by Collinger and colleagues. However, it could be shown that also hand shape can be included into this type of control. Lessons learned from this study: it was beneficial to present real objects during calibration as well as during BCI control; contest helped to get the hand shape controlled.

9.3.2 *Restoration of Reaching and Grasping Through Functional Electrical Stimulation*

Another possibility of restoring movement is by directly activating the muscles of the paralyzed limb via functional electrical stimulation (FES; see Chap. 2). In 2008, one of the first works on applying a decoder on intracortical recordings for the control of FES was done in animals. Moritz et al. (2008) blocked the peripheral nerves (of the right wrist muscles) of monkeys and inserted arrays of 2 × 6 electrodes into the left hand and wrist area. Eventually, the monkeys learned to directly control the stimulation of muscles using their neural activity recorded from motor cortex. An interesting side-effect was that neurons could control functional stimulation equally well regardless of any previous association to movement.

The first human study to control the paralyzed arm with control signals derived from intracortical recordings was presented in 2016 by the group of Bouton (Bouton et al. 2016). The male participant had a cervical SCI after a diving accident 4 years before his study participation. He had full elbow flexion on both arms (grade 5/5), active wrist extension (grade 2/5), but no voluntary motor function in the hands or fingers. His NLI was C5 and had preserved sensory function in the right thumb. He had an AIS grade of A (complete).

A Utah-array (Blackrock Microsystems, Salt Lake City, Utah, USA) was implanted into the left primary motor cortex of the hand area. The area was identified prior to surgery with functional magnetic resonance imaging (fMRI) while the participant attempted to mirror videos of hand movements (Fig. 9.4).

For FES stimulation, Bouton and colleagues used two multiarray electrodes (40 electrodes each, 12 mm diameter, center-to-center distance was 22 mm, monophasic stimulation pulses with a duration of 500 μs, stimulation amplitudes were adjusted between 0 and 20 mA every 100 ms and applied with a frequency of 50 Hz) and placed them on the paralyzed forearm to form six different wrist and hand movements (wrist extension/flexion, hand extension, thumb extension/flexion, middle finger flexion).

The decoder training included the stimulation on the forearm in each but the initial setup session. For training, graphical representations of the hand were shown on a monitor and the participant attempted the movement. The intensity of the stimulation was set according to the output of the decoder (see Fig. 9.5). The participant attended 3 weekly sessions for 15 months. For the evaluation of the system performance, test blocks with five trials for each of the six movements were performed in a random order. The participant received visual cues by a virtual hand on the monitor. The overall accuracy was 70% (one versus rest). For the assessment of the upper limb "recovery," the Graded Redefined Assessment of Strength, Sensibility, and Prehension (GRASSP) test (Kalsi-Ryan et al. 2012) was performed. Here, specific decoders for each action on the GRASSP test were trained. Finally, a functional test was carried out: the participant's task was to grasp a bottle, pour water into a jar, set the bottle back, grip a stirring stick and stir the contents of the jar with at

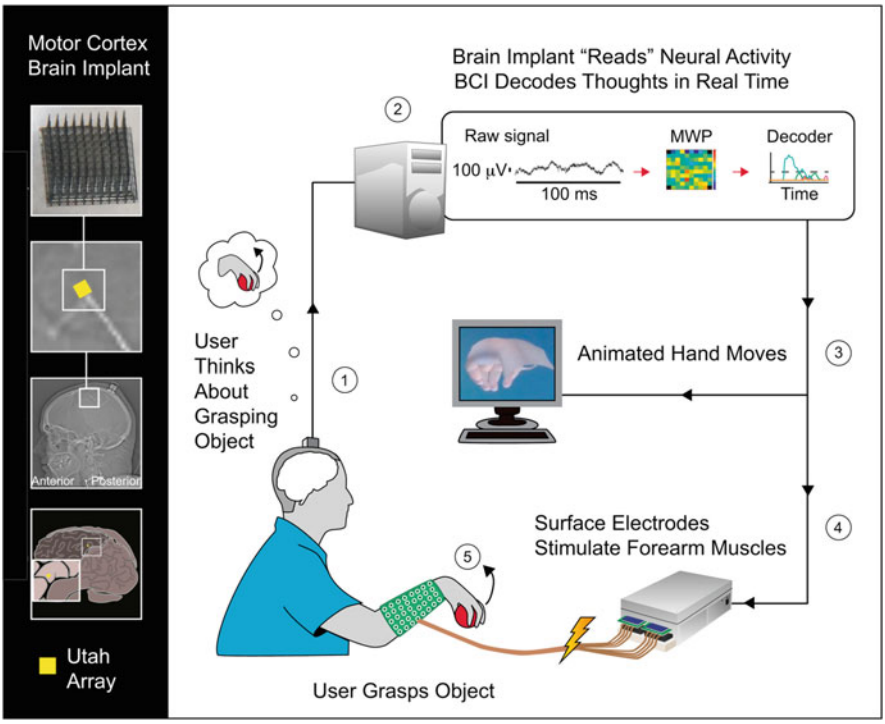

Fig. 9.4 Cortical implant for controlling a non-invasive grasp neuroprosthesis. (Left) Position of an implanted multielectrode array (Utah array, 96 channels) on the left motor cortex. (Right) BCI-FES operation: (1) Motor cortex neurons get active when user thinks about grasping. (2) Neural activity is sampled at 30 kHz with a Neuroport system and classified with a non-linear support vector machine classifier trained iteratively over five blocks (three to four trials/block). (3) Continuous decoder outputs, updated every 100 ms, animate a computer-generated hand and (4) stimulate transcutaneous, forearm, cathode, and anode electrode sites calibrated to finger and wrist flexors and extensors. (5) FES-evoked movements allow the user to manipulate objects. Note. Figures and photographs by M. Bockbrader and N. Austin. Modified with permission from (Bockbrader et al. 2019)

least two circles, and leave the stick in the jar. He was able to perform this task three out of five times in 10 min with a mean completion time of 42 ± 10 s.

The next step toward restoring the arm function with a BCI-controlled FES was done by Ajiboe et al. (2017). At the time of the study, the male study participant was 53-years old and with chronic (8 years since trauma) tetraplegia with an NLI of C4 and an AIS grade A (complete lesion). He was still able to perform limited but non-functional voluntary shoulder girdle motion, though without functional shoulder or elbow movements, and missing hand function.

He was implanted with two 96-channel microelectrode arrays (Blackrock Microsystems, Salt Lake City, Utah, USA) into the corresponding hand area of the motor cortex.

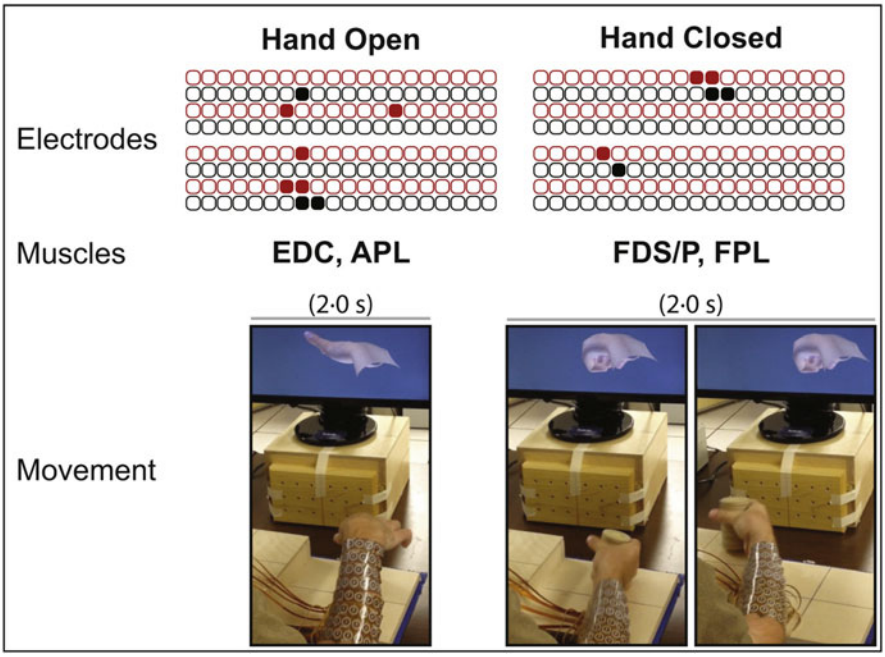

Fig. 9.5 BCI-FES activation for grasp-release test (GRT; Stroh-Wuolle et al. 1993) and grasp sequences. The inset depicts electrode stimulation patterns, target muscle groups, and FES-evoked movements during "hand open" (left) and "hand closed" (right) states. Cathodes are shown in black and anodes are shown in red. Note. Figures by M. Bockbrader and N. Austin; photographs by M. Bockbrader and S. Colachis. Abbreviations: *APL* abductor pollicis longus, *EDC* extensor digitorum communis, *FDS/FDP* flexor digitorum superficialis/profundus, *FPL* flexor pollicis longus. Modified with permission from (Bockbrader et al. 2019)

The FES system applied consisted of 36 percutaneous electrodes located in his right upper and lower arm to restore finger and thumb, wrist, elbow, and shoulder movements. He exercised 18 out of 45 weeks, on average 8 h/week (on 2–3 days), to improve strength, range of motion, and fatigue resistance. Stimulation was applied as biphasic pulses with a fixed amplitude (20 mA) but adjustable pulse widths ranging from 0 to 200 μs. Stimulation frequency was set to 12.5 Hz (pulses per second). Additionally, a mobile arm support (also controlled with the BCI) was used, since the patient was not able to regain shoulder function with FES due to the high forces needed and the problems with precise control of movements (see Chap. 2).

The neural decoder was retrained every day at the beginning of each experimental session. Finally, the participant underwent several assessments: (a) simple single-/multi-joint movements in virtual reality and FES in order to compare them, and (b) functionally meaningful hand/arm movements.

For quantifying single-/multi-joint movements, the decoder was set up by observing a virtual arm making goal-directed arm movements. Afterward, the participant used this decoder to control the virtual arm in single- and multi-joint movements.

During FES control, the participant performed single- and multi-joint movements with his own, reactivated arm. All accuracies were between 80% and 100% during single-joint movements to specific target positions. On average, he reached fewer targets during controlling his own arm as compared to VR but was far more successful than chance. During multi-joint control, the success rate was rather low.

During functional reach-to-grasp tasks (b), the participant was more successful. In 11 out of 12 attempts lasting between 20 and 40 s, he was able to perform a drinking task (extend elbow, open hand, grasp cup, flex elbow, take a drink, extend elbow, and release cup). Furthermore, he was able to feed himself navigating his hand to his mouth to take several bites of food.

9.4 Limitations and Clinical Outlook

9.4.1 Biocompatibility and Stability

After making the transition from research with non-human primates to humans, one of the main questions is whether biostability of the invasive systems for chronic recording of brain signals can be achieved. In the study by Simeral et al. (2011), it has been demonstrated that accurate neural control of a cursor is still possible even after 1000 days of implantation. Another study on macaque monkey showed that neural recordings are even possible after 7 years (Krüger et al. 2010). However, it is not clear how many of the single electrodes are still active after such a time period and how good decoding accuracy will be then. Anyway, chronic use, that is, as compared to pacemaker implant of 8–10 years, is still not reached and also not shown in human.

On the other hand, findings by Flint and colleagues indicate that while decoder retraining is necessary for using SUA, it is not necessary when working with LFP and MUA. This was demonstrated in monkeys for a 12-month period (Flint et al. 2013). So far, it is still unclear if the removal and replacement of microelectrode arrays is feasible.

Also not clear is, what happens if such a microelectrode array needs to be removed. What happens, or whether it is possible to insert a new array and receive neuronal activity again, is completely open. In a recent study with ECoG array electrodes implanted epidurally for more than 24 months, the authors did not report on any degradation of the signals and confirmed that their (pattern recognition) model for controlling an 8-DoF exoskeleton was reusable for up to 7 weeks without recalibration (Benabid et al. 2019). This seems to represent superior results to the intracortical microelectrode recordings.

9.4.2 User Perspective

Besides the technical characteristics of implantable electrodes, the most important determinant for a successful translation of the research results is: the users' perspectives. In a survey by Anderson (2004), a representative cohort of individuals with chronic SCI had to rank seven functions in order of importance to their quality of life. A total of 681 responses were received and evaluated. Regaining arm and hand function was most important to people with tetraplegia, while the highest priority for people with paraplegia was regaining sexual function. Improving bladder and bowel function was of shared importance to both groups.

In a survey from (2015), Blabe and colleagues directly assessed BCI technology in respect to several characteristics, including degree of invasiveness (EEG, ECoG, intracortical micro-arrays), and wired and wireless recordings in comparison to a commercial eye tracker. The respondents rated their likelihood to adopt these technologies for 13 potential control capabilities, ranging from low-speed to high-speed typing; controlling a cursor, a wheelchair, a robotic arm; and restoring arm movement and grasping. One major outcome was that wireless technology is much more appreciated than wired BCIs. Survey participants were most likely to adopt BCI technology to restore some of their natural upper extremity functions, including restoration of hand grasp and/or some degree of natural arm movement. High-speed typing and control of a fast robot arm were also of interest to this population. Wireless non-invasive BCIs received the highest interest as technology. Also, maintenance and cosmetic appearance were important factors.

The recent work from Benabid and colleagues (2019) presented a wireless implanted ECoG-based system that allowed multidimensional upper limb and binary lower limb exoskeleton control. The system has only been tested in a laboratory environment and is questionable whether it can be used by severely paralyzed end users in a domestic environment (Shakespeare and Watson 2019).

9.5 Conclusions

So far, the main focus of invasive BCIs is the compensation of lost motor functions in people with severe paralysis. Studies with BCIs based on intracortical recordings have successfully demonstrated that transformation of brain activity into multidimensional control signals is feasible. Because of the high spatial and temporal resolution of intracortical BCIs, it was shown in end users with massive motor impairments to simultaneously control up to seven DoF of robotic arms. This by far outperforms the performance of non-invasive BCIs. However, many challenges remain to achieve this exceptional control performance: Still, the biostability of the electrode arrays and the decoder stability are limiting the long-term everyday application. Today, the decoders must be retrained almost on a daily basis. Currently, those BCI systems are not wireless and use transcutaneous cables, which

result in a high need for medical care (risk of infections). The complex BCI hardware is not mobile and end users are bound to the room where it is installed. Finally, invasive BCIs inherently are associated with the general risk of surgeries such as infections or wound-healing problems. Many of the studies on invasive BCIs use a robotic arm as end effector, which comes with the advantage of easier controllability than movement restoration of a whole arm with FES. This might also serve as a role model for non-invasive BCIs.

Concluding, on the one hand intracortical BCIs offer the highest available performance control of multiple degrees of freedom, but, on the other hand, this comes with the risks of surgery, still bulky hardware, and need for recalibration of the movement decoder. A game changer could be the broad availability of wireless electrode grids for epicortical recordings, which are less invasive and more robust in respect to the stability of movement decoding. First evidence on the feasibility of such systems in the area of communications and also recently for simultaneous control of a motor task is available.

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Chapter 10
Toward Non-invasive BCI-Based Movement Decoding

Gernot Müller-Putz

Abstract Although motor imagery was used for the first BCI-controlled neuroprosthetic applications, it has turned out that it is a limited experimental strategy when it comes to control of more than two degrees of freedom. More natural ways for controlling the hand and ultimately the whole arm function have been identified in using attempted movement and even the attempt to move the whole arm. First evidence on the feasibility of these new BCI principles for neuroprosthesis control is discussed in this chapter.

Keywords Motor imagery · Attempted movement · Movement decoding · Error-related potential · Electroencephalogram · Reach-and-grasp restoration · Non-invasive BCI

10.1 Introduction

While the main research focus of brain–computer interfaces (BCIs) was on developing a means of communication (Birbaumer et al. 1999; Kaufmann et al. 2013; Halder et al. 2015; Holz et al. 2015; Shahriari et al. 2019), from the early 2000 on, the application of BCIs for control of devices has gained importance.

First, non-invasive BCI-controlled functional electrical stimulation (FES) systems were developed and applied in people with spinal cord injury (SCI) to restore their hand function (Pfurtscheller et al. 2003; Müller-Putz et al. 2005; Kreilinger et al. 2013; Rohm et al. 2013; Rupp et al. 2013). All the systems presented so far have in common that they are based on the imagination of repetitive limb movement to be detected from the electroencephalogram (EEG). Since those studies were relevant to prove the concept of applying non-invasive BCIs for the control of hand movements, the control itself can be described as not-natural and artificial.

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In recent years, however, the concept of attempted hand movements was researched and it was found that, in principle, this provides a more natural control strategy (Müller-Putz et al. 2016). When a person, however, is affected by an SCI higher than cervical level C5, also elbow function and shoulder functions are restricted. While in invasive studies, full arm control concepts are investigated since many years (see Chap. 9), recently, we were able to provide first evidence of natural commands for hand function (Müller-Putz et al. 2019; Ofner et al. 2019) and continuous arm movement decoding approaches for the non-invasive control of a robotic limb.

This chapter gives a brief overview of the state of the art, and highlights some new aspects in non-invasive full arm control.

10.2 Motor Imagery Based BCI for the Control of Hand Function

10.2.1 Motor Imagery

As described in detail in Chap. 3, motor imagery (MI) is one of the most prominent experimental strategies for the design of a BCI. Through the imagination of a movement, sensorimotor rhythms (SMRs) get modulated similarly as through an executed movement (Pfurtscheller and Neuper 1997; Pfurtscheller et al. 1997; Neuper et al. 2006).

We used MI as a mental strategy early on to design a BCI (Kalcher et al. 1996; Guger et al. 2001) where MI leads to the desynchronization or synchronization of SMRs over central areas (Pfurtscheller and Lopes da Silva 1999; Neuper and Pfurtscheller 2001). These band-power changes, mainly in mu and beta bands (i.e., between 8 and 30 Hz), were used to differentiate between left hand, right hand, and feet MI (Pfurtscheller and Neuper 2001). In all these studies, typical kinesthetic MI tasks (Neuper et al. 2005) were the imagination of repetitive user-specific movements of either a hand or both feet.

10.2.2 Control of Hand Function

First attempts to use the brain–computer interface as an alternative controller for neuroprosthetic devices was presented in the early 2000. In a pioneering work of the Graz BCI group, a male with tetraplegia (American Spinal Injury Association [ASIA] Impairment Scale [AIS], A; Neurological Level of Injury [NLI], C4) was trained in imagining left hand (open and close) and feet movements (dorsiflexion and plantarflexion), respectively. When he was able to control the open and close function of a reciprocal finger orthosis (Pfurtscheller et al. 2000), he started FES

training thereafter. After having trained his muscle strength over a period of 9 months, for the first time, the coupling of an FES device and a non-invasive BCI was demonstrated in 2003 (Pfurtscheller et al. 2003). This work demonstrated that it is possible to switch through distinct grasp phases of the hand generated by the non-invasive grasp neuroprosthesis with commands originating from a non-invasive BCI. It is important to note that the frequency of the EEG signals of interest and the stimulation frequency were in the same range. By carefully selecting the frequency bands for the BCI classifier, the artifacts elicited by the stimulation did not interfere with the BCI operation. Encouraged by this result, our research group investigated also a non-invasive BCI setup with a paralyzed male end user (AIS, A; NLI, C5) with an implanted neuroprosthesis (Kilgore et al. 1997; Peckham et al. 2001). In Müller-Putz et al. (2005), we showed that it is also possible to couple at BCI with the implanted Freehand grasp neuroprosthesis. Although, from a technical point of view, the combination of the systems worked well, one of the clear limitations of these works was that the speed of the control was very low—and therefore other means of control are clearly favorable (e.g., a shoulder position sensor as described in Kilgore et al. [1997]). Another drawback was that the participants had to concentrate on the task, e.g., the repeated dorsiflexion and plantarflexion of the feet. The fact that those tasks were not directly linked to the movement generated by the neuroprosthesis contributed to this higher mental workload. A more natural task would be desirable for a future and realistic application. A first attempt to reach a naturalistic control of the hand function is briefly described in the next section.

10.3 Attempted Movement Based BCI for the Control of Hand Function

In the MoreGrasp project (www.moregrasp.eu, see Chap. 13), it was found that it is beneficial to use attempted movements instead of imagined movements for providing more natural control when speaking of hand function control. It has been shown that attempted movement provides a neural correlate, the movement-related cortical potential (MRCP), which differs not only in terms of type of grasp (Schwarz et al. 2018) and type of joint involved (Ofner et al. 2017, 2019), but also other characteristics (Gu et al. 2009; Jochumsen et al. 2013). During that project, we could show that even asynchronous detection in people with SCI can be realized (Ofner et al. 2019). However, to get a realistic use of this type of brain pattern, still several investigations have to be done. More details can be found in Chap. 13.

10.4 Non-invasive Decoding of Continuous Arm Movement

Early on, it was always the goal to provide full control for the arm and hand function. This means that not only the finger movements, as there are opening and closing, but also the positioning of the hand in three-dimensional (3D) space is desirable.

First studies toward this direction included hand and elbow control; however, the function was very limited to elbow flexion and extension from endpoint to endpoint (Horki et al. 2010; Müller-Putz et al. 2010). Although such systems were tested also in end users with severe paralysis (Kreilinger et al. 2013; Rohm et al. 2013; Rupp et al. 2013), an application in an everyday day-life setting is far from realistic.

A completely new approach toward three-dimensional arm control was proved by some authors working in the electrocorticography (ECoG) domain. They have shown that in very low frequencies, below 5 Hz, kinematic information is evident (Schalk et al. 2007; Ball et al. 2009; Pistohl et al. 2012). Bradberry et al. (2010) were the first who decoded 3D arm movements from EEG. This was a starting point for the invasive community. While Bradberry et al. demonstrated their results in a center-out task (COT), it was our group (Ofner and Müller-Putz 2012) that showed the reconstruction of 3D trajectories with a duration of about 60 s per trial.

However, how can such an approach be transferred to end users who cannot move, and therefore the training of a decoder model in the way described above is not possible? We demonstrated a first attempt by applying the imagination of movement in a given way (Ofner and Müller-Putz 2015). Participants had to imagine either horizontal or vertical arm movements in a certain rhythm following a sinusoidal trajectory for each dimension. Although those movements could be classified and decoded, the approach is not transferable to complex movements with higher dimensions.

On the scope of the "Feel Your Reach" project funded by the European Research Council (ERC), we are aiming at developing an EEG-based controller that is able to recognize the start of a goal-directed movement intention, decoding then trajectories to provide information to inform the kinematics of a robotic limb. Parallel to that we are introducing an error-recognition system that is able to detect limb movements that deviate from the intended trajectory allowing the user to keep on track. And finally, we develop a feedback system that informs the user of the current limb movement or limb position providing kinesthetic feedback to the user's body parts with preserved sensation (e.g., upper shoulder; see Fig. 10.1).

10.4.1 Goal-Directed Correlates

Goal-directed movements are of utmost importance for BCI control, since target interactions are very common in daily-life activities. Particularly, we study several aspects of movement planning in movement execution and imagination tasks

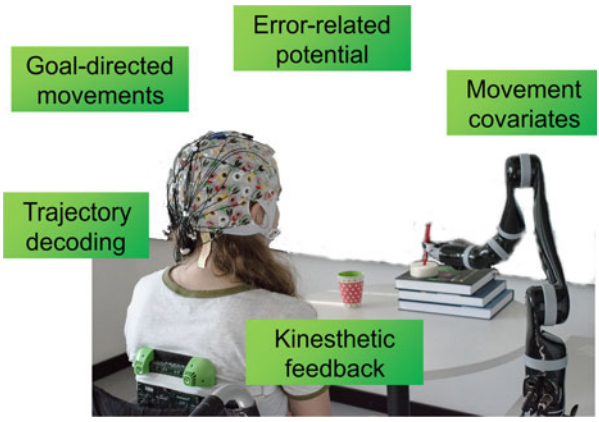

Fig. 10.1 Framework of an EEG-based full robotic arm control system as suggested in ERC project "Feel Your Reach"

directed to specific targets in participants without motor disabilities, as first steps toward intuitive BCIs for people with upper-limb motor impairments.

In a first study with movement execution ($n = 10$), we investigated whether the presence of a motor goal could influence the movement detection performance during a reach-and-touch task (Pereira et al. 2017). For that, we asked the participants to perform reaching movements directed toward several targets in specific spatial locations (goal condition), or to non-specific targets (no-goal). We could show that the underlying neural correlates, the MRCPs that reflect movement planning, are different between these two conditions. This difference was exploited by the movement detector (i.e., classifier of movement vs. rest), and positively affected its performance, which was higher for the goal-directed condition, and above chance level even before the actual movement onset for all participants. By analyzing the patterns exploited by the classifier, we could show that the differences were mainly attributed to premotor and primary motor areas, as well as to the posterior parietal cortex.

On a second study ($n = 15$), we then focused on more specific stages of goal-directed planning on a movement imagination task of a reach-and-grasp (Pereira et al. 2018). Concretely, we investigated whether it is possible to decode from the EEG differences between movements that have different target selection processes. We found out that the late event-related cortical potentials reflect differences between the perceptual and cognitive processes prior to the movement imagination: the late event-related potentials (ERPs) with frontal and parietal brain sources differ depending on whether the target of the movement was externally cued by the paradigm itself, or the target of the MI was actually selected by the participant. Additionally, our protocol allowed us to estimate a reliable onset of the movement imagination, which enabled us to train for the first time a movement detector directly on a self-paced imagination task, also exploiting low-frequency time-domain EEG features like in Pereira et al. (2017). This could be particularly interesting when transferred to people with severe motor disabilities, since—like with movement imagination—it is often not possible to determine a movement onset by means of

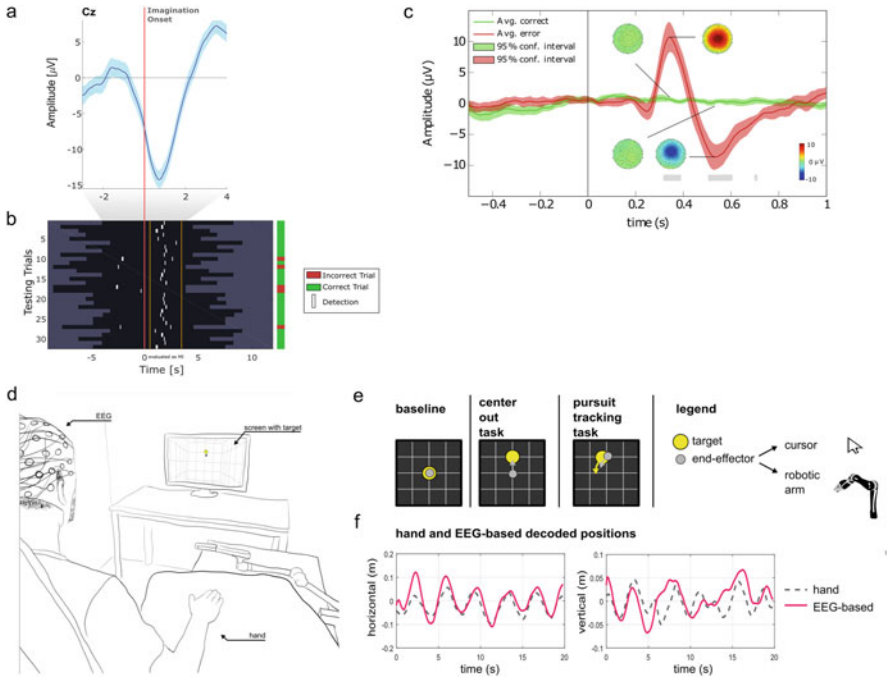

Fig. 10.2 (**a**) Movement-related cortical potentials time-locked to the imagination onset. (**b**) Performance of the movement detector on the testing trials for a non-disabled subject with a good performance (75% correct trials). The orange lines delimit the positive window (i.e., actual movement period). Detections outside this period are considered false positives. A trial without false positives and with detections within the positive window is considered a correct trial. Adapted from Pereira et al. (2018). (**c**) Grand-average correct and error signals across the 15 participants at channel FCz as well as the activity across all sensors at the peak time-points. (**d**) Participants were seated in front of a screen, with their right arm supported. Their hand movement was recorded, simultaneously with the EEG. The screen presented a target stimulus, moving differently according to the experimental paradigm. (**e**) Schematic representation of the experimental paradigm for the center-out task (COT) and pursuit-tracking task (PTT). The yellow ball represents the target, while the gray dot represents the end effector. Depending on the experiment, the end effector was either a cursor or a robotic arm. (**f**) Decoding example for the pursuit-tracking task. The traces depict the real hand and EEG-based decoded 2D positions

electromyography (EMG) or other sensors. The onset was estimated by asking the participants to memorize the number that was shown on a scroller presented on the computer screen, at the time-point they felt the urge to initiate the movement imagination. Figure 10.2a, b shows the performance achieved by the movement detector for a non-disabled participant with a performance above average, and respective MRCPs around the imagination onset on electrode Cz. The average performance of correctly classified trials was at 52.5 $\pm$ 16.8%, with all participants performing above chance level (20%).

10.4.2 Non-invasive Movement Decoding

In the past years, movement decoding in the context of non-invasive BCIs has mainly been studied offline in non-disabled people on the basis of executed movements. The reported findings indicate that upper-limb kinematics can be decoded (Robinson and Vinod 2016). However, a detailed analysis of the various factors (e.g., proprioception, vision, motor commands, state estimation) that potentially contribute to the control of human upper-limb movements and consequently to the decoding of kinematics is required. We have focused on investigating movement decoding offline and online under various conditions.

In a first study, we investigated the influence of vision in executed upper-limb movements during center-out tasks (COT) and pursuit-tracking tasks (PTT). In these visuomotor tasks, subjects would intuitively track the (moving) target with their eyes. We decided to not impose the additional task of inhibiting these eye movements. As a consequence, electrooculogram (EOG) artifacts arise. We evaluated several eye artifact correction algorithms (Kobler et al. 2018, 2020b). One algorithm, based on artifact subspace subtraction, achieved the best trade-off between attenuating eye artifacts and maintaining resting brain activity and event-related potentials.

The experimental paradigm of the first study involved two visual stimuli (target and cursor) and continuous visual feedback (Kobler et al. 2018). Each trial started with a center-out task (COT) followed by a pursuit-tracking task (PTT). We studied the COT and PTT in two experimental conditions. In one condition (execution), subjects controlled the cursor by moving their right arm (Fig. 10.2d–f). In the second condition (observation), subjects observed a computer-controlled cursor.

We used the PTT to investigate the tuning characteristics of low-frequency EEG (in the frequency range of the upper-limb movements) to positions and velocities (Kobler et al. 2018). As expected from the findings of previous studies, we found that the low-frequency EEG amplitude signals carried significant information about positions and velocities in both conditions (Bradberry et al. 2009; Kobler et al. 2018; Ofner and Müller-Putz 2012). For example, the grand-average velocity decoder correlations were 0.4 (execution) and 0.35 (observation) for a 300 ms long sliding window. By analyzing the patterns associated to the position and velocity decoders, we found that premotor and primary sensorimotor areas carried significant information about cursor velocity if the arm was used, whereas parieto-occipital areas carried significant directional information in either condition.

We used the COT to investigate discrete reaching movements. We were specifically interested in seeing whether MRCPs carried information about upper-limb movement direction. MRCPs are typically related to the initiation of limb movement, but have also been shown to carry information about movement speed and force. We observed significant classification accuracies for the factors' condition (execution vs. observation; 78.2% classification accuracy, chance level at 50%) and direction (left, up, right, and down; 44.0% classification accuracy, chance level at 25%). The two classifiers relied on different cortical networks. Contralateral pre- and

primary motor areas predicted the condition, while parieto-occipital areas predicted the direction in both conditions (Kobler et al. 2020a).

In a second EEG study (ten healthy participants), we investigated how the results of the PTT translate to an online control scenario (Mondini et al. 2020). The participants had to follow a pseudo-randomly moving target on the screen with a robotic arm. Initially, the robotic arm was fully controlled by the participant's arm movement. After an EEG decoding model was fitted to predict the arm movements, the robotic arm control was gradually switched from arm to EEG-based decoded movements, up to a final condition of 100% EEG-based control. Grand-average correlations between real and decoded movements were approximately 0.3. Although the correlations were significantly higher than chance level (approximately 0.13), we found an amplitude mismatch between the real and decoded trajectories. The amplitude ratio was approximately 0.4, meaning that the real movements were 2.5 times larger than the decoded ones.

Fortunately, the encoding of amplitude information (e.g., speed) in the low-frequency activity of motor areas has been reported by several studies (Gu et al. 2009; Hammer et al. 2016). To further investigate this, we conducted a magnetoencephalography (MEG) study (20 non-disabled participants), where we implemented a similar PTT as before. In this study, the participants controlled a cursor with their right index finger (Kobler et al. 2019). We found that the magnetoencephalographic signals in primary sensorimotor areas carried significant information not only about velocity, but also simultaneously about speed.

In an offline analysis, we investigated decoding models that could incorporate speed information into the estimates of positions and velocities (Kobler et al. 2020b). A non-linear Unscented Kalman Filter (UKF) approach was successful in combining the information and thereby improving the decoding performance. In a follow-up study (five non-disabled participants), we tested how the results of the UKF approach would translate to an online scenario (Martínez-Cagigal et al. 2020). We obtained grand-average correlations between the real and decoded movements of approximately 0.3. Moreover, the UKF approach was successful in adjusting the amplitude mismatch; the amplitude ratio was 1.07.

On a parallel line of research, we investigated the expression of movement direction in the absence of visual input during rhythmic, circular, arm movements (Kobler et al. 2020a). We found that low-frequency time-domain and beta band-power modulations predicted direction; the correlations between the real and decoded direction were 0.68 and 0.27 for the low-frequency and beta domains, respectively. This information originated in premotor, primary sensorimotor, and posterior parietal areas.

10.4.3 Grasp Representation

During the project we also investigated the similarity in human grasping movements between EEG representations and their associated movement covariates (in terms of

muscle and kinematic representations) in three stages of the movement: hand pre-shaping, reach of the final grasping posture, and holding (Sburlea and Müller-Putz 2018, 2019). Movement covariates, such as electromyographic or kinematic activity, have been proposed as candidates for the neural representation of hand control (Kawato 1999; Todorov and Jordan 2002; Sburlea and Müller-Putz 2018; Leo et al. 2016; Ejaz et al. 2015). However, it is not clear how these different aspects are represented in the brain, and which of these can be read out from EEG.

It is difficult to relate directly different perspectives: that is, it is difficult to say how dedicated muscle activation patterns relate to certain brain activations. But what is comparatively easy, is to look at second-order isomorphism, that is, if a certain aspect of movement is represented in the brain, then two movements that are similar in that aspects will also be similarly represented in the brain. This brings us to the three questions: (1) Can differences between multiple types of grasps determined by EEG signals? (2) Which grasping covariate best explains how grasps are represented at the EEG level? (3) To what extent do grasping representations based on movement covariates and on EEG patterns resemble each other?

We recorded a rich dataset containing simultaneous electroencephalographic, electromyographic, and kinematic activities, while 31 human subjects performed 33 different types of grasping movements. For a better description of the grasping movements, we also built three categorical models based on the type of grasp, position of the thumb relative to the palm, and shape of the grasped object. To explore the relations among the neural, behavioral, and categorical patterns of different grasping movements, we chose to conduct a representational similarity analysis (RSA; Kriegeskorte 2008). Because it is a multivariate pattern analysis method, the use of RSA allowed us to study both the representational geometries and informational content of the grasp conditions in a multidimensional space spanned by EEG sensors, different frequency bands, and time-points (Kriegeskorte and Kievit 2013). As with classifier decoding, RSA is a technique that is sensitive to information encoded in patterns of activity. However, rather than attempting to determine what information can be (linearly) read from the patterns of activity, the use of RSA allowed us to characterize the representational geometry of a rich set of conditions and compare it to various representations or models. Our findings indicate that EEG patterns from motor-related areas and frequency bands reflect different movement covariates during different stages of grasping. Specifically, during the hand pre-shaping stage, the shape and size of the grasped object are reflected in the lower-beta frequency in the centro-parietal regions. During the grasping finalization and holding stages, the EMG-based representation is reflected in the mu frequency band in the contralateral parietal regions.

When upper-limb motor function is lost (e.g., due to a high cervical SCI), muscle activations and kinematics become unreliable, but the person can still imagine/plan/attempt or observe grasping or upper extremity movements (Pfurtscheller et al. 2003; Hochberg et al. 2012; Collinger et al. 2013; Ofner et al. 2019; Ajiboye et al. 2017; Onose et al. 2012). Therefore, we asked which of the EEG patterns during movement observation are related to muscle activation and kinematics during movement execution? During the observation phase, EEG activity reflected the object's shape

and size. Furthermore, we found strong similarities between the EEG during observation and the EMG during holding, which indicates that when visually processing hand-object grasping interaction, we focus on the final grasping posture.

While these findings contribute to a better understanding of the dynamical organization of cortical patterns during grasping stages, they have the potential to influence the design of BCIs and the process of features selection to the extent that can facilitate a more intuitive control of a neuroprosthesis and endow individuals with SCI with the independence of movement.

10.4.4 Error-Related Potentials During Continuous Feedback

The performance of state-of-the-art BCIs is not optimal and sometimes the user's intentions are misinterpreted and unintended actions are performed. In a decoding scenario, we do not expect 100% control, so a robotic limb might do an unintended movement following inaccurate decoding. When this happens, the mismatch between the expected action and the received feedback triggers a brain pattern in the BCI user associated with error processing, named error-related potential (ErrP). Such brain patterns have been studied using different imaging techniques such as EEG, functional magnetic resonance imaging (fMRI), and MEG. Using traditional EEG measurements, this pattern can be detected in single trial with some degree of reliability. The single-trial real-time detection of ErrPs can help improving a BCI performance: by detecting and potentially correcting the unintended action and/or recalibrating the classifier.

In the past, BCIs worked in a discrete way: allowing participants to control an external device in discrete steps. The use of error-related potentials to improve the performance of such BCIs is well established (Chavarriaga et al. 2014).

Currently, several groups (as we do) attempt to offer BCI users continuous control of the BCI (see above). In such a situation, the users can perceive at any moment that an unintended action occurred. This requires continuous decoding of ErrPs. The feasibility of continuously decoding ErrPs started by being investigated in offline conditions, in which data are recorded and only after an experiment (Omedes et al. 2015a, b; Lopes Dias et al. 2018). Recently, the continuous decoding of ErrPs has also been investigated in an online situation, in which data are recorded and analyzed in real time. This allows participants to receive real-time feedback of their own brain activity. In this experiment (Lopes-Dias et al. 2019), we analyzed the EEG data of 15 non-disabled participants while they controlled a robotic arm toward a target using the movement of their right hand. In 30% of trials, the control of the robot was artificially halted in order to trigger an ErrP in the participants. In this experiment, there were eight offline runs that were used to collect personal EEG data to train a classifier for detection of ErrPs. In the following four runs, the continuous online classifier was used and the participants were given feedback of the true

positive trials. This means that when the robot made a mistake in a trial (by stopping), the participants had the possibility of regaining control of the robot and finish the task, if the online classifier detected an ErrP in the participant's brain, after the "mistake" of the robot. In this study the online continuous detection of error-related potential worked in a relatively reliable manner for most non-disabled participants. Figure 10.2c shows the grand-average correct and error signals across the 15 participants at channel FCz as well as the activity across all sensors at the peak time-points. Whether the same results can be obtained in people with SCI needs to be shown in future work. First offline experiments involving people with SCI showed the same morphology of the ErrPs, but a reduced amplitude (Keyl et al. 2019).

10.4.5 Kinesthetic Feedback

Intact motor control operates on the basis of a fine-tuned control loop, wherein any movement is continuously regulated and adapted according to a variety of sensory inputs, e.g., proprioceptive information provided by receptors in joints and muscle spindles, haptic sensations, visual impressions, and/or auditory cues. When afferent somatosensory pathways are damaged, proprioceptive and haptic information falls out of the equation, so a person controlling an artificial end effector to substitute arm movement function would have to rely on other sensory modalities, most prominently the visual sense. The visual system is capable of handling a multitude of information, but relying solely on visual feedback restricts the use of the visual sense for other tasks. Moreover, artificial somatosensory feedback plays an integral part in perceptually incorporating a prosthesis into one's own body image by closing the sensorimotor control loop in an intuitive way (Johansson and Westling 1984; Galán et al. 2015; Biddiss and Chau 2007; Saunders and Vijayakumar 2011).

We are working on developing methods to deliver kinesthetic feedback utilizing non-invasive vibrotactile stimulation. We exploit interpolation effects arising due to the inaccuracy of tactile perception, specifically on the back, where the receptor density is relatively low. When two tactile stimuli are simultaneously active in locations of relative proximity, they are perceived as a single stimulus at a location in between the physical stimulation points (Alles 1970; Israr and Poupyrev 2011; Luzhnica et al. 2017). The perceived location of the stimulus is determined by the relative amplitudes of the two physical stimuli (e.g., if both stimuli are equally strong, the perceived stimulus will be in the middle). By systematic modulation of intensities, smooth patterns of moving sensations may be evoked with a sparse grid of actuators. Thus far, we have realized patterns that operate along any axis spanned by two actuators (Hehenberger et al. 2019).

When introducing artificial somatosensory feedback in a context where control signals are extracted from EEG recordings, we have to be aware that external stimuli elicit responses in the brain, which may have an influence on the EEG (Hommelsen et al. 2017). On the one hand, the captured brain activity generally includes a superposition of both sensory and actuatory information. In addition, sensory input

influences control processes in the brain, possibly altering properties of control features derived from EEG signals.

We have conducted a study to examine the potential impact of vibrotactile feedback on movement-related parameters, comparing four conditions: hand movement with kinesthetic vibrotactile feedback, hand movement with static vibration, hand movement with no vibrotactile input, and no movement with vibrotactile sham feedback (Hehenberger et al. 2020). In order to provide real-time feedback, the hand position in space was tracked via a Leap Motion controller. In the kinesthetic feedback condition, a moving sensation mimicking the one during hand movement was evoked on the person's back. In the sham feedback condition, a movement sensation according to a movement trajectory of a previous movement trial was triggered. In the experiment, participants were seated, with their right hand placed on a table in front of them, and performed unidirectional center-out hand movements. The vibrotactile feedback was provided via a sparse grid of vibrotactile actuators integrated into an elastic shirt (Hehenberger et al. 2020).

We found subtle differences in the shape and peak amplitude of MRCPs for the three movement conditions, indicating a potential weak positive effect by the kinesthetic feedback. Classification time-locked to the movement onset of movement trials against rest yielded comparable discriminability between conditions (Hehenberger et al. 2020). To be able to make more affirmative claims, more thorough investigations are needed.

10.4.6 Discussion and Future Work

In summary, we have demonstrated that non-invasive BCIs can be used to detect the onset of goal-directed hand movements and that we are able to decode kinematics, that is, position, velocity, distance, and speed, with moderate accuracy. The offline simulation results transfer to an online control scenario. Furthermore, we present novel results about the multimodal representation of human grasping movements. These findings contribute to a better understanding of the dynamical organization of non-invasive cortical patterns during grasping stages. Also, we showed that online continuous ErrP detection in a robot control scenario is feasible. Finally, we started to work on provision of kinesthetic feedback that in the future will provide the user additional feedback about the movement and the generated or measured forces of the end effector, that is, the robotic arm.

All studies so far have been carried out with non-disabled participants and therefore all of these principles and methodology need to be transferred to end users with motor impairments. Currently, the study with ErrPs described above was carried out with a group of people with SCI and first evidence was shown that even a generic classifier (based on the data of non-disabled) worked in a way that without calibration end users could control the robot with an online ErrP detector running so that they were able to finalize the task, even in system-generated errors (Catarina Lopes-Dias et al. 2020a).

Besides putting together all the methodologies described above, which is more an engineering challenge, however, one should not forget about the calibration of many classifier systems. Since this is usually a time-consuming and exhausting procedure, we work also on generic classifiers (e.g., Catarina Lopes-Dias et al. 2020b). Besides the decoder setup also artifact removal and detection algorithms need to run simultaneously and need to be calibrated beforehand.

10.5 Conclusion

This chapter presents a first review of work done toward natural control of hand movement and non-invasive trajectory decoding. We gave a brief overview on hand movement control based on movement-related cortical potentials, which indeed could be a promising neural correlate. However, there is still work to be done to translate this into real-life settings (see more in Chap. 13). The main part of this chapter, however, gives an overview on the state of the art of decoding full arm movement as it is in the scope of an ERC funded project ("Feel Your Reach").

We believe that with the EEG, enough information can be retrieved to successfully decode hand and arm movements to finally create control signals for artificial arms providing the same degrees of freedom as a human arm. We have provided first evidence that in general this can work; however, still the reliability, which comes with a higher signal-to-noise ratio, needs to be improved. We did not show 3D-movement decoding yet, and need to get more experience and evidence from online studies.

The next step is to target end users who would be the real beneficiaries of a naturally controllable BCI. Such an end user would be people with tetraplegia due to a spinal cord injury at the cervical level above C4 with a total loss of arm and hand functions. If the EEG-based system works to some extent in such an end user, we believe, this would be the first evidence that such complex BCI systems really can make a difference for severely disabled people.

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Part IV
Clinical Use Cases and Practice

Chapter 11
Therapeutic Applications of Electrical Stimulation in Spinal Cord Injury

Ines Bersch

Abstract This chapter is meant to provide practitioners and people affected by spinal cord injury (SCI) with basic guidelines and examples on how to use electrical stimulation (ES) for therapeutic purposes. There is substantial evidence that ES can be effectively used for motor learning as well as for treatment of secondary complications as a consequence of SCI such as muscle weakness, shoulder subluxation, or skin injuries. This chapter is intended to serve as a practitioner guideline and summarizes the essence of the available literature on the therapeutic use of ES in respect to stimulation parameters and electrode positions. It encourages therapists to implement ES into their daily work to support a better treatment outcome. A distinction is made in the chapter between the use of functional electrical stimulation (FES) to improve or support activities and participation of people with SCI and to improve body structures and function such as weakness, muscular atrophy, and pain. Treatment protocols as well as the rationale and the stimulation parameters based on the available scientific evidence and the clinical experience are given.

Keywords Spinal cord injury · Electrical stimulation · Therapy · Stimulation parameters

11.1 Introduction

In literature, there is no consistent use of nomenclature related to electrical stimulation (ES). Functional electrical stimulation (FES) is often used as a synonym for neuromuscular electrical stimulation (NMES), which is not fully correct. NMES is a rather general term which only implies that the mode of action is via stimulation of an efferent nerve that leads to muscle contractions. These contractions do not

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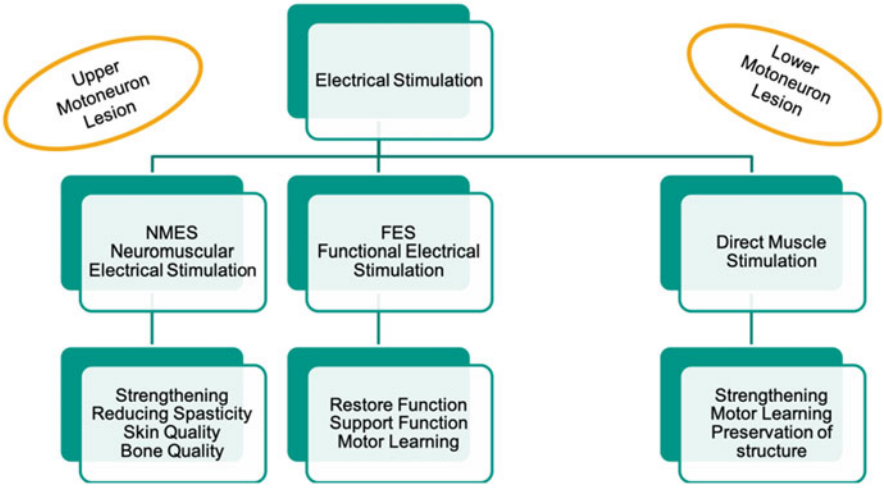

Fig. 11.1 Definition of terms and therapeutic aims of different categories of electrical stimulation (Ines Bersch: "Upper and Lower Motorneuron Lesions in Tetraplegia—Diagnostic and Therapeutic Implications of Electrical Stimulation," Dissertation, Sahlgrenska Academy, printed by Brand Factory, Gothenburg, ISBN 978-9-7833-7)

necessarily need to result in a functional activity, which is the aim of FES. FES initiates or supports functional activities such as walking, eating, grasping, or coughing.

Furthermore, it is crucial to understand the different mechanisms and therapeutic goals between ES applications in cases of upper motor neuron (UMN) lesions compared to lower motor neuron (LMN) lesions (for anatomical background see Chap. 1 and for physiological background see Chap. 2). Using the term FES for direct stimulation of muscles in cases of LMN damage implies that a restoration of functions such as standing or walking is possible. This bears the risk of raising wrong expectations among patients and therapists. Therefore, a precise definition of terms related to ES is helpful to avoid misunderstandings, ineffective or even wrong applications of ES and overestimated therapy goals (Fig. 11.1).

A distinction between LMN and UMN lesions is highly important for defining individual therapy goals and for selection of the appropriate stimulator (Fig. 11.2). As a general rule, the pulse energy needed to elicit contractions of denervated muscles is much higher (approximately 500–1000× higher) than those needed to stimulate innervated muscles.

Given the variety of available stimulators, it is important to know the devices' exact technical specifications in order to decide whether they match to the innervation status of an individual with SCI. Besides the pulse waveform, other parameters of the stimulator such as the number of independent channels, the pulse frequency and the channels' sequence of on/off-times should match to the individual therapeutic aims. Stimulators for clinical use in different patients need to cover a broad spectrum of stimulation parameters. Stimulators typically prescribed for home often

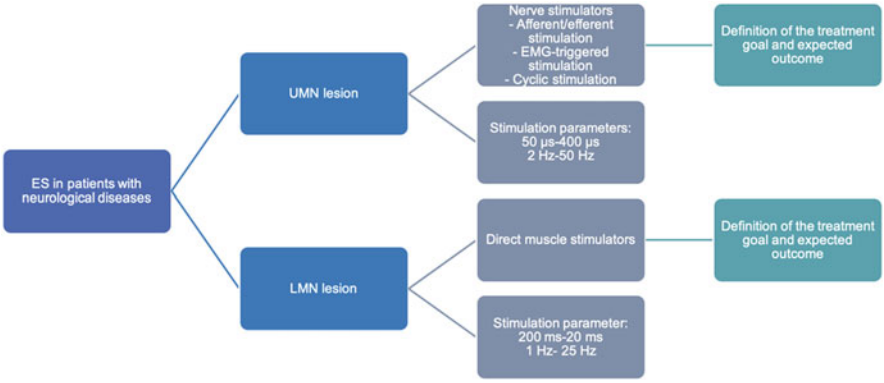

Fig. 11.2 Therapy goals and stimulation parameter in LMN and UMN lesions

lack this adaptability and provide only 1 or 2 stimulation channels with a limited set of predefined programs. However, individual therapeutic goals might change or have to be modified over time (see Chap. 1) and the limited adaptability of simple stimulators do not allow the full use the potential of ES. But even in stimulators providing maximum flexibility, therapists need a profound knowledge of the physiological mechanisms of ES and training to learn how to program stimulators and to modify preprogramed stimulation sequences according to the needs of the patients. Unfortunately, the level of complexity and intuitiveness for programming stimulation devices or modifying predefined programs varies to a large degree between stimulators. Manufacturers of stimulation devices are advised to collect feedback from patients and therapists already at the beginning of the development process.

11.2 ES in Neurorehabilitation

Over the last two decades, the knowledge about neurobiology and motor control caused a shift toward task-specific therapies based on the principles of motor learning. With such task-specific therapies actively involving patients in the execution of motor tasks neuroplastic changes in the central nervous system (CNS) are initiated, thereby leading to a better functional recovery (Adkins et al. 2006). In clinical practice, ES is often used as an additional and separate therapy beside of regular physio- and occupational therapies. However, best task-specific therapeutic therapies are combined with FES to support motor learning to optimize the functional outcomes. Integration of FES into the regular treatment has at least two advantages. The combined use increases the overall treatment outcome of task-specific therapies, while using the limited resources in terms of personnel and therapy time in an optimal way (Harvey et al. 2010; Popovic et al. 2011; Kapadia et al. 2014).

11.2.1 Challenges of Applying ES as Part of Task-Specific Therapies

While FES represents a promising component of task-specific therapies in respect to a better outcome in particular of upper extremity function, its application confronts therapies with some challenges. The highest barrier for use of ES in clinical routine is the additional time it takes therapists to include ES into the treatment sessions. Defining electrical stimulation therapy protocols needs a thorough examination of the patient including the assessment of the passive and active joints' range of motion, a reflex test, a manual muscle test, and a test of muscle tone/spasticity. It is mandatory to assess these domains also in a dynamic condition, because the status may change when moving from a supine to an upright position or by performing an integrated task and not only isolated joint movements. For example, for implementation of FES into gait training, therapists have to identify the major cause of the nonphysiological gait pattern and the muscle functions to train. This requires a profound knowledge about the biomechanics of gait. After determining the muscles to be stimulated and the stimulation parameters, the equipment has to be set up. This includes fixing the electrodes on the desired anatomical positions, eventually installing switches or other sensors and programming the stimulator to allow for activation of muscles in a physiological sequence. Even an experienced therapist needs 15 min before the treatment can start. To be effective, a task-specific therapy based on the principles of motor learning should at least last 30 min. This is necessary to achieve enough task repetitions for internalization of the learned tasks (Kleim 2011). A typical time frame for physical therapy sessions is 30 min. Taking these time constraints and the preparation time of FES into account, its integration into therapeutical treatment routine is challenging. In stressful situation, the risk to rehearse insufficient or even wrong movements in respect to the theory of motor learning is very high. All these issues contribute to the fact, that FES is often applied in a noneffective way just before or after the session for some minutes.

11.2.2 ES as Therapeutic Tool

Not in every patient, primary treatment goals are improvements of activities. In some people with SCI, the major rehabilitative aims are to improve body structures and functions such as strengthening of weak muscles, prevention of skin injuries, and reduction of spasticity. In these cases, ES can be used as an effective therapeutic tool apart from regular activity-based treatment sessions. An example is the treatment with ES to avoid skin injuries. To overcome the problem of the additional time demands of the application of ES, multiple patients can be treated in a group where ES is applied and supervised by a single therapist. In addition, patients with sufficient residual functions can perform their ES or FES training on their own. In these cases, the responsible therapist programs the stimulator and instructs the

patient on proper use. Regular supervision is necessary to check if the patient is able to adequately follow the instructions. The independent application of the ES treatment with regular supervisions enables therapists and patients to evaluate the feasibility for future ES/FES usage in the domestic setting. Varying time demands and levels of support by therapists or caregivers for different therapeutic aims need to be taken into account to judge the feasibility of at home-use (Table 11.1).

Patients, therapists, and most important healthcare payers need to understand that the time needed for an ES session is substantially longer than the exclusive ES application time due to preparation times. In particular, for some ES applications such as prevention of skin injuries by stimulation of the gluteal muscles, for placement of electrodes people need to transfer or be transferred from the wheelchair to a treatment table. For other ES applications, therapists need to help patients to verticalize on a tilt table or to position on a cycling system, etc. All of these issues result in a rather low willingness and motivation to include complex FES application into the regular treatments.

Improvements of the technology might help to reduce the preparation times. Stimulators or stimulation systems should operate without fault and should allow for quick setup of the stimulation procedure. Handling needs to be quick and easy, at best by wireless systems. If individual programs are needed, experts should be able to set these up in a fast and intuitive way. Real time synchronization with common robotic devices and/or virtual reality systems should be built in from the manufacturer. Additional features, such as reliable automated intensity adjustments or robust indicators of fatigue of the stimulated muscles are desired by therapists.

11.3 Examples of Therapeutic ES applications

In the following sections, key aspects are illustrated how ES and FES could be applied and integrated into an individual treatment and rehabilitation process.

11.3.1 ES to Support Motor Learning

Motor learning involves learning or relearning of movements, the activation of silent motor units that can be voluntarily recruited because of learned compensatory strategies and the reactivation of areas on the motor cortex which were affected by "learned disuse" of a function. The latter might also be successful in the chronic stage of SCI (Popovic et al. 2006; Kapadia et al. 2011).

In line with the theory of motor learning, therapies need to be repetitive, specific, and task-related (Fitts and Posner 1979). Task-specific treatments in combination with ES should be performed daily and at best twice a day. The stimulation does not need to be of high intensity to achieve a strong contraction, as lower amplitudes can be efficiently used for activation of afferent nerves as well.

Table 11.1 This table provides an overview of application times recommended to achieve different therapeutic aims and support needed by therapists

Goal		Motor learning		Strengthening		Support function		Preventing (skin injury)		Reducing spasticity	
Time expenditure		5 times a week 2–3x daily 20–30 min		3x a week 30 min		Daily 30 min		3x a week 30 min		3x a week 30 min	
Paraplegia	PT/OT Caregiver	**40 min**	No	**40 min**	No	**40 min**	No	**40 min**	Yes/No	**50–60 min**	No
Tetraplegia	PT/OT Caregiver	**50 min**	Yes/No	**50–60 min**	Yes/No	**50–60 min**	Yes/No	**50 min**	Yes	**60–90 min**	Yes

In the first row, a realistic estimate of the time expenditure for FES applications is given. Rows three and four list the effective time per session that is needed for a treatment including the preparation time before and clean-up time after the session. Abbreviations: *PT* physiotherapist, *OT* occupational therapist

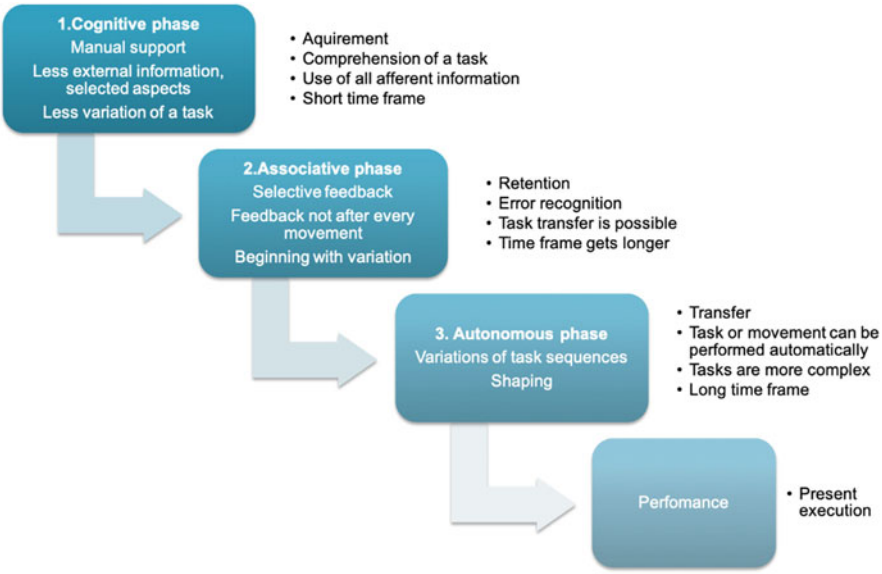

Fig. 11.3 The different stages of motor learning (Fitts and Posner 1979)

An EMG-triggered ES might be considered to support residual functions. With the recording of the electromyogram (EMG) is possible to measure the weak voluntary muscular activity without signs of movement and use this information to trigger an ES to amplify these residual activities.

The following example may illustrate how the theory of motor learning could be transferred into therapy programs in different phases (Fig. 11.3).

11.3.1.1 Cognitive Phase

In this stage, the cognitive comprehension of the task is essential. For the patient, as a first step of motor rehabilitation it is more important to know "what to do" rather than "how to do it." Hence, the motor tasks in the cognitive phase have less variations and less external focus of attention. Only selected feedback and instructions are verbally and manually given to the patient.

11.3.1.2 Associative Phase

The quality of the movement ("How to do it") becomes increasingly important in this stage of motor learning. Concurrent feedback about the quality of the refined movement or exercise execution is given by the therapist to allow for correction of errors. A random order of several tasks within a training session leads to a prolonged

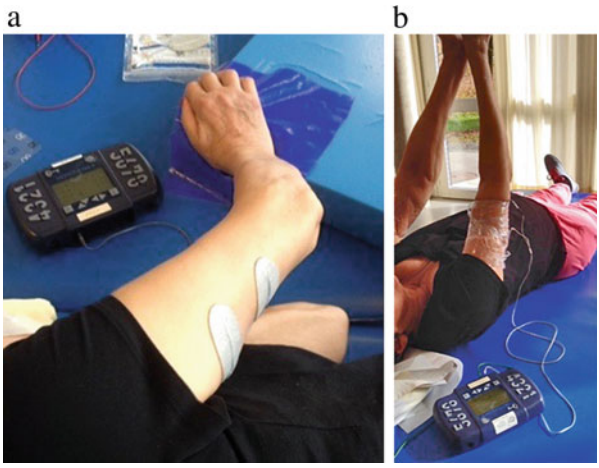

Fig. 11.4 Stimulation of elbow extension in (**a**) the cognitive phase of motor learning with elimination of gravity and in (**b**) in the associate phase of motor learning with gravity

training effect (better retention) of each of the tasks than practicing a single task at a time, even if the performance is better in the single-task training session.

As an example, imagine a patient with a weak elbow extension. In the cognitive phase, cyclical stimulation of the triceps brachii muscle is performed without the influence of gravity. The task is to extend the elbow when the stimulation arises (Fig. 11.4a). In the associate phase, the task is to extend both arms completely against gravity during stimulation and to flex them during the stimulation off times (Fig. 11.4b).

11.3.1.3 Autonomous Phase

In the autonomous phase, more complex tasks or movements can be performed ("Do it!") automatically. Principles of shaping can be included by, for example, varying the velocity of the movement without decreasing the quality of execution. More specifically expressed, a complex behavior is gradually formed by rewarding individual partial steps planned by the therapist. A gradual approach toward the desired behavior is to be made through small steps with each successful partial step being reinforced. A division into many small building blocks can be meaningful, because the learning of a complex behavior may consist in an excessive demand for the person in question or the behavior itself may be unusually complex. Having a high variability of movement is good in this phase and may contribute to generalization of skill to different contexts.

Finally, the movement is integrated into daily activities.

In respect to the example above of the patient with weak elbow extension, the stimulation supports elbow extension, for example, in transfers or the verticalization of the trunk in case the postural control is insufficient (Fig. 11.5). It can be exercised during standing in frame or during bench wheelchair transfers.

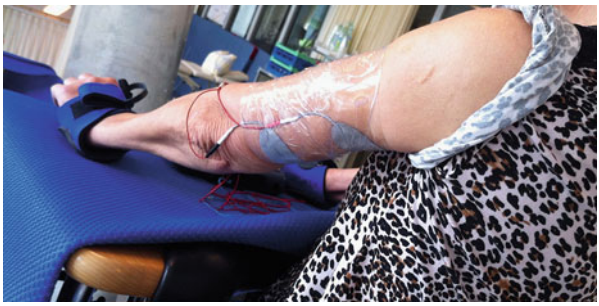

Fig. 11.5 Example of stimulation for elbow extension in the autonomous phase of motor learning

11.3.1.4 Stimulation Parameters for Motor Learning

The stimulation parameters to generate a duty-cycle may vary to a certain degree, but the following parameters might serve as a first reference to start. In any case, factors as muscle size, fatigability, sensation (hypo- or hypersensation), and the time after lesion should be considered.

Pulse duration:	250–400 μs
Frequency:	20–50 Hz
Current amplitude:	Depending on muscle size and if a contraction is intended or not
Stimulation devices:	– FES supported arm cranking for the upper extremities
	– FES cycling or FES rowing for the lower extremities
	– EMG-triggered stimulators
	– Foot drop stimulators with heel switches
	– Stimulators with switches to initiate the stimulation manually
	– Cyclical stimulation, where the duty cycle is programmed individually

11.3.2 ES for Support or Substitution of Impaired Motor Functions

The concepts of using ES for supporting motor functions and for motor learning are somehow related concepts. Supporting the weakest muscles needed for the execution of a certain motor task such as walking or reaching and grasping helps an individual to participate in a task-oriented training program, thereby enhancing motor learning. An improvement of the activity level in turn enhances muscle strength and endurance, showing that the two concepts are highly interlinked. The difference between both therapeutic approaches is the time after injury when they are applied. While therapies focusing on motor learning are most effective in the subacute phase after the injury, when the biggest amount of neurological recovery occurs, ES for substitution of permanently impaired or lost motor functions is mostly applied in the

chronic phase (see Chap. 1). ES can support motor functions on different levels: On the one hand, ES might act on a structural level such as strengthening of a single muscle or muscle group or reduce muscular tone or spasticity to demask voluntary motor functions still present. On the other hand, ES might be used during complex motor tasks like walking to generate an increased muscle power or to provide the user with feedback about the actual gait phase or joint positions thereby compensating the impairment of proprioception.

A very common example for the support of missing motor functions is the drop-foot neuroprosthesis. This system is applied in patients with restricted lifting of the foot. If the tibialis anterior muscle is innervated (typically the case in above T12 lesions), a dorsiflexion of the foot can be achieved with a drop-foot stimulation system instead of using a passive ankle foot orthosis (AFO) or knee ankle foot orthosis (KAFO). For this purpose, several commercially available systems are available (e.g., L300, Bioness, Valecia, USA; MyGait, Otto Bock, Duderstadt, Germany). Most of them operate with a help switch, which is mounted inside the show or the sock on the impaired foot. The stimulation of the dorsiflexion of the foot is triggered with weight relief on this leg by the use of a heel switch and/or intertial sensors. It should be taken into account that the accuracy of the step detection of the best systems using inertial sensors together with heel switches is 99.9%. However, although this seems to be a very high absolute accuracy, it means that 1 out of 1000 steps is not detected correctly. This might result in dangerous scenarios, where an end user depends on the stimulation and might not be able to compensate a potential failure of the device. This is one of the reasons why some end users are not very satisfied with a drop-foot stimulator and prefer the old-fashioned AFOs. The accurate evaluation of each patient by experts is crucial for the treatments' success and the patients' satisfaction.

Similar to other FES application, the activation profiles and timing of the stimulation is largely impacting the performance of an end user. People with spasticity in the plantar flexor muscles need longer ramp-up/-down times of the stimulation to achieve a sufficient degree of dorsiflexion without triggering involuntary contractions of antagonists. However, longer ramp-up times lead to delays in onset of the movements limiting the gait velocity.

In addition, neuroprosthetic devices like foot drop stimulators cannot be regularly applied without ES muscle training, especially in case of chronic SCI where muscle atrophy and fatigue limit the stimulation time and force. An iterative training and assessment algorithm is needed until an end user can successfully apply a neuroprosthesis such as a foot drop stimulator (Fig. 11.6).

In case of additional muscular weakness of the gluteus muscle group, FES can be combined with a drop-foot stimulator or an AFO (Fig. 11.7). For this, electrodes are placed on both gluteal muscles. The electrodes can be worn throughout an entire day. The setup of the stimulation of the gluteal muscles with large electrodes is quite easy and takes below 10 min. The stimulation should be programmed in a way that the stimulation of the gluteal muscle is activated during the stance phase of the respective leg. Alternatively, the patient may also use a knee–ankle–foot orthosis (KAFO). However, the stimulation of the gluteal muscles has the advantage of muscle training

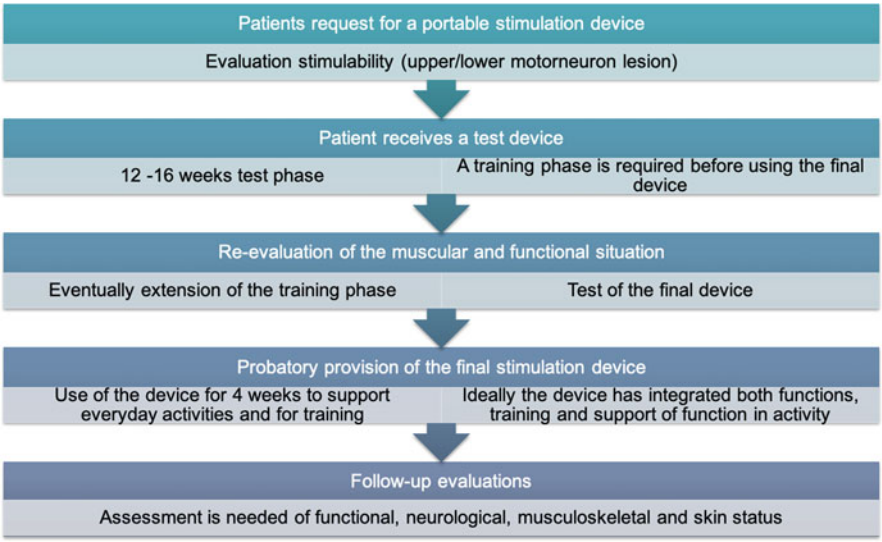

Fig. 11.6 Flow chart with a clinical algorithm for provision of a FES device for long-term support of motor functions

Fig. 11.7 AFO with integrated foot switch to trigger stimulation during stance phase. Abbreviation: *AFO* ankle foot orthosis

and patients, who are not ambulatory for the whole day and temporarily use their wheelchair, might feel discomfort when wearing the KAFO during wheelchair use.

11.3.3 ES for Improvement of Trunk Control and Posture

In all patients with cervical and thoracic SCI, stability of the trunk is an important issue to consider. In motor complete SCI, often a scoliosis occurs as a consequence of the imbalance of the activation of the trunk muscles. This might be caused by markedly increased spasticity or flaccid paralysis of those muscles on one side or by a collapsing spine in children. In incomplete SCI, an inhomogeneous voluntary muscle innervation pattern in combination with spasticity often leads to asymmetries or poor stability in the trunk.

It needs to be emphasized that ES of the trunk muscles alone will not lead to an improved outcome. Improving posture requires physiotherapeutic exercises in combination with FES, adaption of the sitting position in the wheelchair and, if necessary, adaptations of the domestic and professional environment.

Scoliotic deformities occur either in a C-shaped or S-shaped curve (Fig. 11.8) and are often combined with a rotation of the spine. ES might normalize the static deviation of the vertebrae in the frontal plane; however, it is hard to treat the nonphysiological rotation of the vertebral bodies.

For treatment of a scoliosis, the ES electrodes are positioned dorsally and ventrally on the convex side of the trunk. The selection of the stimulated muscles is depending on the clinical findings. On the convex side, the stimulation intensity should be set at a fairly high level to increase the muscle tone and the elasticity of the stimulated muscles. In addition, the concave side of the trunk should be stimulated as well but with low intensity to not neutralize the corrective effect on the convex side, but high enough to increase the number of sarcomeres in the shortened muscles. An adequate number of sarcomeres in a muscle is associated with a better stretching capacity. In paralyzed trunk muscles, the number of sarcomeres decreases. Furthermore, on the concave side the muscles are shortened and become less stretchable. FES in paralyzed muscles is able to increase the number of sarcomeres and thus the stretching capacity (Goldspink 1999).

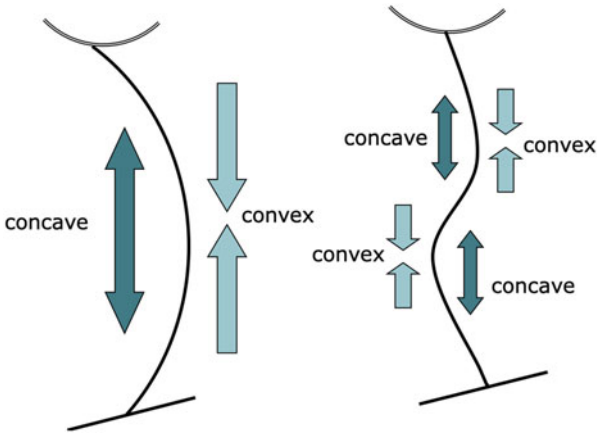

Fig. 11.8 Sketch of the two main forms of a scoliotic deformity: C-shaped (left) and S-shaped (right) deviation

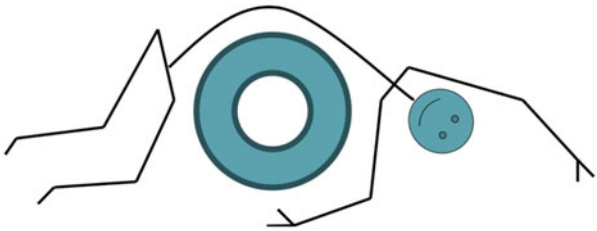

Fig. 11.9 Sketch illustrating the body position ES-treatment of a scoliotic deformity using a roll

It is recommended to combine FES with physical exercises. One possibility might be to position a patient over a roll or half-roll with the convex side lying on the roll. The concave side is pointing upward and thus stretched (Fig. 11.9). The electrodes on the convex side are located on the abdominal muscles including the quadratus lumborum and on the erector spinae muscles. On the concave side, the electrodes are positioned on the transversus, the erector spinae, and quadratus lumborum muscles.

Stimulation parameters for treatment of scoliotic deformities:	
Pulse duration:	300–400 μs
Frequency:	20–50 Hz
Current amplitude:	30–100 mA (depending on patients' preserved sensation and clinical intention)
Duration of ES:	5 times a week 30 min

There are numerous possibilities to combine ES with standard physiotherapy treatments. To activate muscles and muscle groups, the utilization of gravity is beneficial. Therefore, sitting on a therapy bench (Fig. 11.10), prone position with forearm support or upright standing/walking positions are recommended body positions for application of ES.

It often makes sense also to include the abdominal muscles (rectus and oblique muscles) in the stimulation sequence (Fig. 11.11). The task is to straighten up the spine against gravity during the stimulation. The stimulation time is set up with 10 s of stimulation (2 s ramp up, 5 s plateau, 3 s ramp down) followed by 10 s rest.

Trunk stability is in particular important for walking. Therefore, stimulation of the abdominal muscles during walking and in particular during the swing phase on a given side is essential. This gait-phase-related stimulation sequence is implemented by using a switch placed under the heel in or under the shoe (Fig. 11.12b). By lifting the foot, the stimulation starts until the foot touches the ground again (Fig. 11.12a). The stimulation intensity of the rectus abdominis muscle might be set differently on each side for better balancing the lateral movements of the trunk.

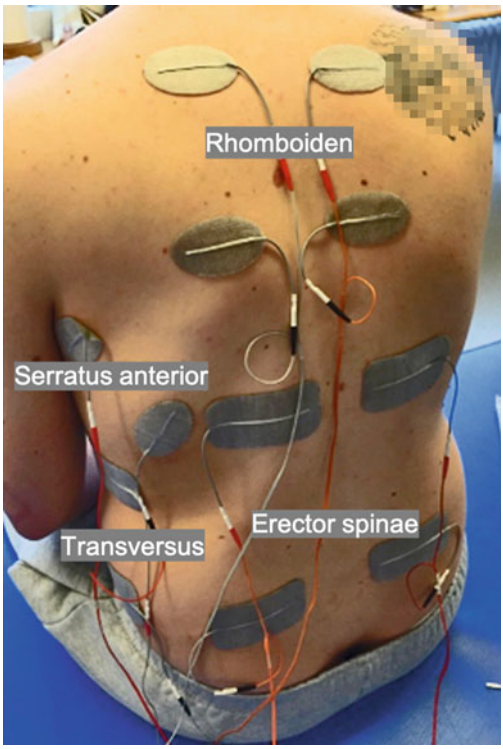

Fig. 11.10 Electrode setup for trunk stabilization

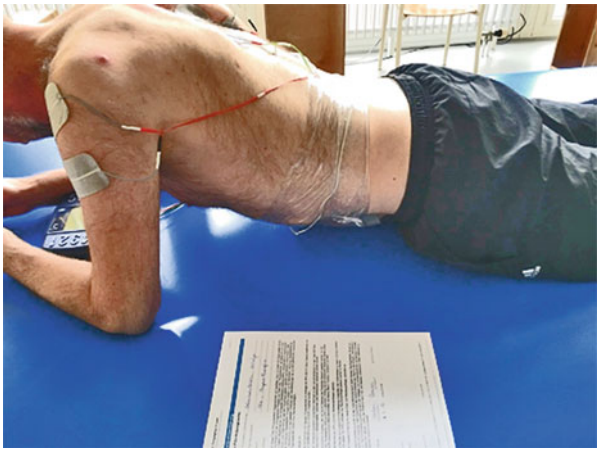

Fig. 11.11 Synchronous, antigravity stimulation of the abdominal together with the back muscles in a prone position with forearm supported. In addition, the rhomboid and the deltoid muscles are stimulated to support an active support function in the shoulder

11.3.4 ES to Support Coughing

In lesions of the CNS such as high cervical SCI, the voluntary or reflex activation of the muscles of the respiratory system is impaired up to a complete loss.

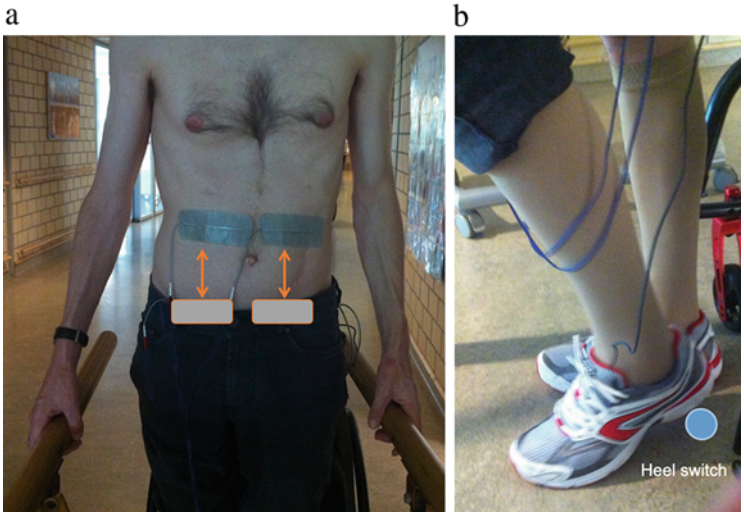

Fig. 11.12 Trunk stabilization during walking: (**a**) electrode setup for stimulation of the abdominal muscles; (**b**) heel switch to activate the abdominal stimulation during swing phase

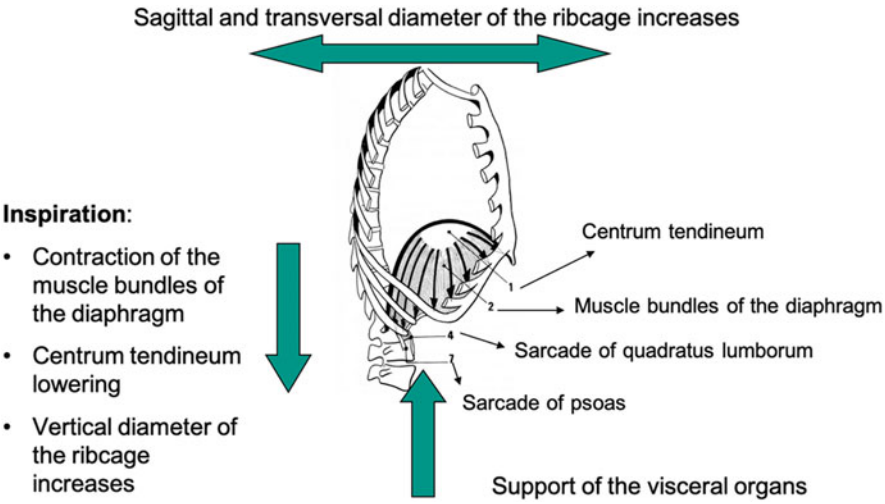

Fig. 11.13 Sagittal view of the diaphragm function

This results in functional restrictions of breathing, speaking, coughing, and sneezing. In many cases, the diaphragm is still under voluntary control, but it contributes exclusively to inspiration (Fig. 11.13). For ventilator functions, the voluntary support of the abdominal muscles that are innervated by the spinal segments Th6–Th12 is limited. Therefore, forced expiration and coughing are not efficient and there are problems with speaking due to the lack of controlled

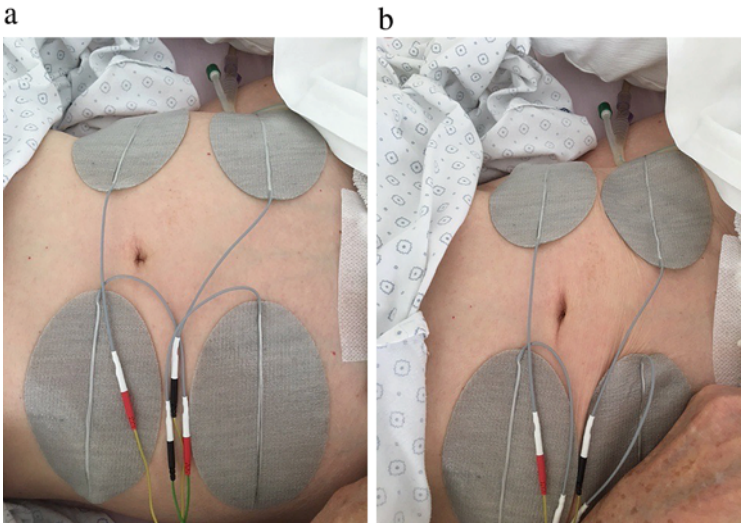

Fig. 11.14 Electrode setup to assist coughing: (**a**) Large electrodes are placed ventrally on the relaxed abdominal wall; (**b**) abdominal muscles activated by ES

expiration. Furthermore, generating an abdominal pressure is not possible. Trunk muscles contribute to stabilization during controlled expiration. Tetraplegic and high thoracic (Th2–Th5) paraplegic patients do often not show sufficient voluntary activity of abdominal muscles. The abdominal muscles are the major expiratory muscles required to cough.

In clinical routine, clearance of secretion and coughing is supported by manual support, usually performed by therapists, nurses, or trained caregivers. In some cases, manually supporting coughing is not possible, due to pain induced by a thoracic trauma, costal fractures, or stiffness of the ribcage caused, for example, by Bechterew's disease. Due to these limitations, manual compression is difficult, painful, or contraindicated. Hence, FES of abdominal expiratory muscles can help to enhance coughing. Effective coughing depends on strong contractions of the expiratory muscles (Fig. 11.14), which develop high pleural pressures to produce dynamic compression of the intrathoracic airways, which results in turbulent expiratory airflow.

As mentioned, abdominal muscles are expiratory muscles and their activation by ES can effectively support forced expiration and coughing.

Stimulation parameters for expiration support and coughing:	
Pulse duration:	300 μs
Frequency:	20/35/50 Hz
Current amplitude:	80–120 mA (depending on patients' preserved sensation)
Stimulation dose:	As often as needed, daily for airway management

The stimulation of the abdominal muscles should be applied simultaneously with voluntary coughing attempts. A manual switch is used by therapist or caregivers to apply the stimulation when necessary.

11.3.5 Muscle Strengthening by ES

A very prominent application of ES is for strengthening of single muscles or muscle groups. The reason for the widespread use of ES for increasing muscle strength is the high evidence level for this kind of application (Thrasher et al. 2013; Deley et al. 2015, 2017; Dreibati et al. 2010; Harvey et al. 2010; Coupaud et al. 2008; Duffell et al. 2008; Fornusek et al. 2013). ES supported muscle strengthening can be performed under static or dynamic conditions (Table 11.2). While a static condition includes the application of ES during active or passive standing, dynamic conditions are walking, cycling, or leg press activities.

The disuse of the paralyzed muscles and the altered neuronal activation caused by SCI trigger a structural change of the muscles together with a reduction of sarcomeres. ES under the above described static or dynamic conditions can accumulate the number of sarcomeres. A muscle that contains a more physiological number of sarcomeres can be stretched and strengthened more effectively (Goldspink 1999). Some application principles should be fulfilled for an effective FES strengthening therapy: The training should be performed at least 3 times a week for 30 min (Petrofsky et al. 2000). The stimulation intensity (current amplitude multiplied with pulse duration) has to be sufficiently high to cause powerful tetanic contractions which in turn have a positive effect on muscle mass and endurance (Scremin et al. 1999). It has to be taken into account that force of a muscle could be increased by the recruitment of additional motor units within this muscle. The recruitment is mainly influenced by the current amplitude. This is consistent with and comparable to training protocols designed for strength training in nondisabled persons (Filipovic et al. 2011). Furthermore, the combination of a resistance training with ES seems to be more effective than either resistance or FES training alone (Harvey et al. 2010).

Table 11.2 Overview about stimulation parameters given in the literature for FES cycling

Author	Pulse duration (μs)	Frequency (Hz)	Intensity (mA)
Gerrits et al. (2000)	450	30	Max. 140
Fornusek and Davis (2004)	250	35	70–120
Crameri et al. (2003)	250	35	112 ± 5
Hjetness et al. (1997)	350	30	Max. 130
Twist et al. (1992)	350	60	Max. 132
Russel Berry et al. (2008)	300–400	20/80	80 und 150
Kakebeeke et al. (2008)	300	50	Max. 140
Baldi et al. (1998)	500	35	100
Tawashy et al. (2008)	500	60	Max. 140

List of devices that can be used for strengthening muscles and muscle groups in people with SCI and UMN lesions:

- Upper and lower extremity ergometer.
- Robotic devices (such as the Erigo (Hocoma, Volketswil, Switzerland), Gait Trainer GT II (RehaS-tim Medtec AG, Schlieren, Switzerland), Motionmaker (Swortec AG, Monthey, Switzerland) controlling ES synchronized to the device-generated movements.
- Leg cycling or arm cranking and rowing combined with ES.

11.3.6 ES for Reduction of Spasticity and Spasms

Spasticity (increased muscular tone) and spasms (involuntary strong muscle contractions such as myoclonus) are often a burden for people with SCI. The risk for falls during transfer activities, pain in the body parts affected by spasticity and spasms, and the risk of skin injuries by sitting or transferring are often present and could have a major negative influence on the quality of life of the people affected.

ES represents a promising option to reduce spasticity and spasms in people with SCI (Sköld et al. 2002; Krause et al. 2008; Szecsi and Schiller 2009; Ping Ho Chung and Kam Kwan Cheng 2010; Rayegani et al. 2011). These positive results can be reproduced in clinical practice by applying FES with the parameters that have been shown to be effective in the literature. This includes the definition of the type of FES exercise, the stimulation parameters in particular pulse frequency, and the duration of stimulation per session and per week. An effective form of ES training to reduce spasticity and spasms could include either FES cycling, rowing, or arm cranking. To increase the users' motivation, FES devices integrated into virtual reality tools are recommended. In addition, cycle systems that can be used indoors as well as outdoors increase the motivation of users and herewith the frequency of use which is known to have positive effects on the therapy outcomes. These include not only positive effects on muscular tone, but also other health benefits from cardiorespiratory and vascular health, general fitness to an improvement of bone quality (Rayegani et al. 2011; Peterson 2004; Kamradt et al. 2013; Albertin et al. 2018).

Stimulation parameters of FES cycling, etc., for spasticity reduction:	
Pulse duration:	300 μs pulse duration
Frequency:	20/35/50 Hz
Current amplitude:	100–140 mA (depending on patients' preserved sensation)
Stimulation dose:	30–45 min per session for 3–5 session per week

It has to be clearly communicated to a patient that ES therapy might in the best case reduce the level of spasticity or spams for hours to days but does not achieve its complete suppression. Additionally, from a clinicians' and a patients' point of view, there are some issues to clarify before ES is considered as therapy option.

The following checklist may serve as a starting point for evaluation of the regular use of ES for spasticity reduction.

1. In the clinical setting, do the therapists have enough time resources to apply the stimulation and integrate it into the rehabilitation process?
2. Are devices for effective antispastic ES stimulation such as FES cycling, arm cranking, or rowing available in the clinical setting?
3. If the ES treatment has been proven to be effective in a patient in the clinical setting, can it be continued in an outpatient or domestic setting?
4. Are patients, caregivers, and—if necessary—therapists willing to spend the time of minimum 60–90 min for a session 3 times a week for a regular training? Is it realistic to integrate such a time-demanding physical therapy into the daily life of a person with SCI?

The main drawback of ES for treatment for reduction of spasticity is the large time requirements and the high costs of the devices. A user who is not able or willing to spend 3 times a week at least 1 h for the treatment (Table 11.1) might think about other methods such as medications to reduce spasticity.

For cost reasons, it makes sense to offer FES cycling, rowing, and arm cranking in fitness centers. People with SCI complaining about spasticity or spasms should have the possibility to train and use the required equipment based on a season ticket.

11.3.7 ES for Therapy and Prevention of SCI-Related Complications

11.3.7.1 Therapy and Prevention of Shoulder Subluxation

In persons with tetraplegia often shoulder pain due to paralysis of the shoulder joint stabilizing muscles occurs. The shoulder joint is not a mechanically self-stabilization joint such as the hip joint, but is stabilized by its surrounding muscles allowing for a large range of motion in many directions. A cervical SCI results in a total or partial paralysis of the shoulder muscles leading to a subluxation of the shoulder. In the literature, this subluxation has many synonyms, including the terms malalignment, medial displacement of the humerus, anterior displacement, or inferior and anterior subluxation. Glenohumeral subluxation is defined as an incomplete dislocation, where the humeral head slips out of the glenoid cavity due to rotator cuff muscles weakness or—in the non-SCI population—a blow to the shoulder area. A subluxation can occur anterior (forward), posterior (backward), and inferior (downward) (Bogie et al. 2006; Smit et al. 2012).

Until now, the information reporting positive effects of ES on shoulder subluxation in patients with high SCI is sparse (Peterson 2004). However, there is substantial evidence from randomized, controlled clinical trials with stroke patients proving its effectiveness. Although study protocols and time since stroke of study participants vary substantially, it can be concluded that a 6–12 weeks ES application

Table 11.3 Overview of shoulder muscles, segmental innervation, and function

Muscle	Innervation	Shoulder function
Deltoid muscle	C4–C6 axillar nerve	Abduction
Supraspinatus muscle	C4–C6 subscapular nerve	Abduction and stabilization of humerus
Infraspinatus muscle	C4–C6 subscapular nerve	External rotation
Teres minor muscle	C4–C6 axillar nerve	External rotation
Subscapularis muscle	C5–C8 subscapularis nerve	Internal rotation
Teres major muscle	C6–C7 thoracodorsal nerve	Internal rotation, adduction and stabilizes the humeral head in the glenoid cavity
Coracobrachialis muscle	C6–C7 musculocutaneous nerve	Flexion
Pectorales min. and maj. Muscles	C6–TH1 pectorales nerves	Adduction Internal rotation
Rhomboidei muscles	C4–C5 dorsal scapulae nerve	Retracts scapula and rotates it to depress the glenoid cavity, fixes the scapula to the thoracic wall
Levator scapulae muscle	C4–C5 dorsal scapulae nerve	Elevates scapula and tilts its glenoid cavity inferiorly by rotating scapula
Serratus anterior muscle	C5–C6 thoracic longus nerve	Protracts and stabilizes scapula, assists in upward rotation
Trapezius muscle	C2–C4 accessorius nerve	Rotation, retraction, elevation, and depression of scapula

in the acute phase after stroke helps to prevent or improves shoulder subluxation and pain (Kim et al. 2010; Smit et al. 2013). In chronic stroke survivors, the literature is quite inconclusive with some studies reporting additional positive effects of ES compared to a control intervention and no other detecting a difference (Vanoncini et al. 2010; Gyawali et al. 2011).

From the review of the literature about the effects of ES on shoulder subluxation in stroke survivors with hemiplegia, it may be concluded that the results can be transferred to the condition of patients with tetraplegia and innervated shoulder muscles (UMN lesion). However, since the rotator cuff muscles are mainly innervated from the spinal segments C4–C6 (Table 11.3), it is important to check for the presence and the extent of LMN damage of these muscles. Although, a direct muscle stimulation (Fig. 11.2) is possible and muscular atrophy of the denervated muscles can be delayed, prevented, or in the first year after the injury even reversed, it is questionable if a shoulder subluxation can be prevented in the long term in cases with severe LMN damage.

Although the scientific evidence for using ES in patients with high-level tetraplegia to treat and prevent shoulder subluxation is low, it represents an

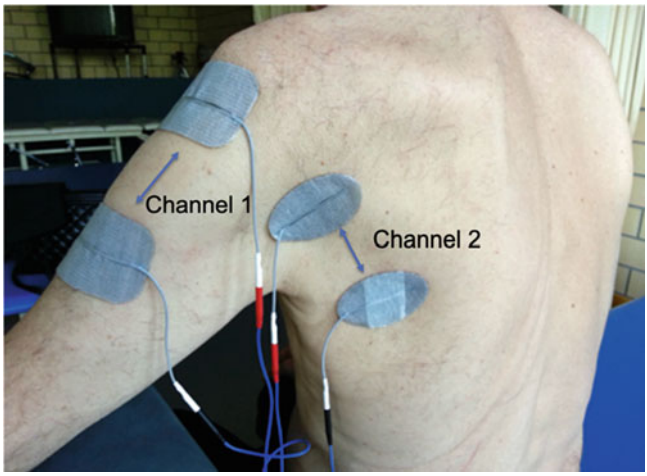

Fig. 11.15 Stimulation of the deltoid muscle and external rotators in a sitting position

inexpensive method. Additionally, it can be easily applied as an add-on therapy to regular treatment session or even in a home-based setting. From clinical experience, it has been observed that shoulder pain due to subluxation occurs less frequently and is reduced by ES in the acute and chronic phase after SCI. In particular in the acute phase, it seems that with regular ES the full passive range of motion can be maintained in a better way. In addition, the shoulder joints seem to tolerate higher loads during transfers and be more robust against failures in handling.

In general, the therapeutic goals of ES in patients with high tetraplegia are the reduction and prevention of muscular disuse atrophy, reduction of pain due to subluxation, and strengthening of the shoulder girdle muscles. In denervated muscles caused by LMN damage at the lesion site, the main goal is to avoid muscle atrophy and later muscle degeneration.

The ES treatment can be performed in sitting or standing position (Figs. 11.15 and 11.16). It can be combined with passive, assistive, or active movements of the upper limbs. Regarding optimization of strengthening, training against resistance can be used.

Stimulation parameters for prevention and therapy of shoulder subluxation:	
Pulse duration:	300–400 μs
Frequency:	20/35/50 Hz
Current amplitude:	30–80 mA (depending on patients' preserved sensation)
Dose of application:	30 min, 5 sessions per week

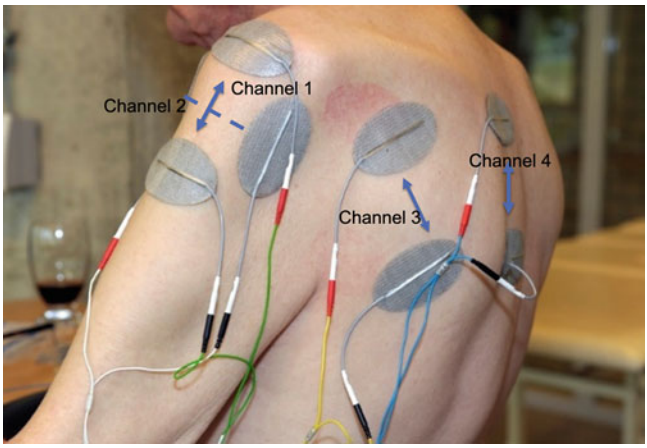

Fig. 11.16 Stimulation of the anterior, lateral, and posterior deltoid muscles together with the muscles stabilizing the scapula

11.3.7.2 Prevention of Skin Injuries

The treatment with ES for skin quality can be categorized into the treatment of pressure and skin injuries and the prevention to maintain skin integrity. Skin quality is associated with the integrity of the skin, including perfusion of the deep tissue and sufficient blood flow in the vascular system. The following paragraph concentrates on supporting a good skin quality by ES. Most pressure injuries occur in the buttock area in patients with SCI. In this area, the ischial tuberosities as well as the coccyx are exposed. For prevention and to reduce the risk of skin injuries, ES of gluteal muscles is used to build up muscle mass to support the natural cushioning effect. Anatomically, the bony structures in the buttock area are not covered by muscles. However, an increased mass of the gluteal muscles helps to better distribute the pressure during seating and lying and thereby to avoid pressure peaks at the bony prominences known to lead to pressure injuries (Boncompagni et al. 2007; Gargiulo et al. 2011).

The main aims of using ES for prevention of pressure injuries are to avoid and reduce muscular atrophy caused by disuse or denervation as well as to improve muscle trophic and tissue perfusion. For successful gain of muscle muss by ES, the distinction between UMN and LMN lesion is of utmost importance in particular in chronic patients many years after the injury. LMN damage usually occurs in conus and cauda equina injuries caudal to the neurological level of Th12 (see Chap. 1); however, it may also be a consequence of a peripheral nerve compression in patients with long-term complete injuries (Kamradt et al. 2013). It is known from clinical experience that patients with severely denervated and therefore atrophied gluteal muscles and reduced perfusion are at high risk for developing pressure injuries. Prevention of pressure injuries in this patient group is particularly important due to the prolonged wound healing times and wound healing problems in general.

Table 11.4 Different stimulation parameter and regimes in UMN and LMN lesions

Stimulationparameter	UMN	LMN
Frequency	20–50 Hz	2–20 Hz
Pulse duration	300 μs	20–200 ms
Current amplitude	80–140 mA	60–120 mA
Schedule	– 3–5 sessions per week – 30–45 min per session	– 5 sessions per week
Position	– Prone position – Sitting position – Standing in a frame or on a tilt table	– Prone position – Standing in a frame or on a tilt table
Type of electrode	Typically, self-adhesive gel electrodes	Special, large rubber electrodes and salt free gel or wet sponges

Abbreviations: *UMN* upper motoneuron, *LMN* lower motoneuron

While in other applications of ES the literature is quite inconclusive, this is different for ES to build up muscle mass for prevention of pressure injuries, where the conclusion of studies is quite consistent (Albertin et al. 2018; Bogie et al. 2006; Smit et al. 2012; van Londen et al. 2008). In particular, ES represents an effective treatment in patients with an UMN lesion as well as those with a LMN lesion. ES of the gluteal muscles is feasibly applied in the clinical as well as domestic settings. A lower incidence of pressure injuries goes along with a reduced number of rehospitalizations, with a faster would healing and therefore reduced hospitalization time, and with generally lower health care costs (Smit et al. 2013). For home-based applications of direct muscle stimulation in LMN lesions, the availability of appropriate stimulators for home use needs to be checked. Additionally, people with tetraplegia or other upper extremity restrictions need help in the placement of electrodes. Like in any other ES applications, the training and stimulation parameter needs to individually adapted and the progress needs to be reevaluated in regular intervals. In the clinical environment, the selection of adequate electrodes (wound electrodes or surface electrodes) is important.

Despite the similarities, the stimulation regime and parameters differ substantially for UMN and LMN lesions (Table 11.4).

The major differences concern frequency and current amplitudes. In UMN lesions, pulse durations for nerve stimulation of 250–400μs and frequencies in the range of 35–50 Hz with current amplitudes between 80 and 140 mA are used (Boncompagni et al. 2007; Kim et al. 2010; Smit et al. 2013; Vanoncini et al. 2010). The stimulation schedule is two to three sessions per week for 30–45 min each session. It is recommended to perform the stimulation against resistance and at best dynamically (Smit et al. 2012; Gyawali et al. 2011). In contrast to this, in LMN lesion pulse durations of 20–200 ms (=20,000–200,000 μs), frequencies in the range of in 2–20 Hz and current amplitudes between 60 and 130 mA are used. It is recommended to stimulate for 30–60 min daily (Boncompagni et al. 2007; Gargiulo et al. 2011).

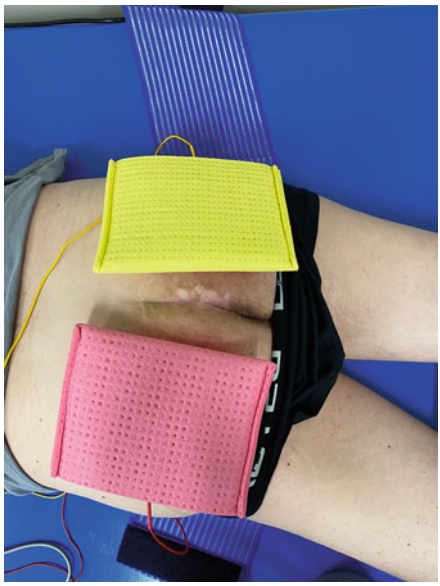

Fig. 11.17 Electrode positions (sponge size: 15 × 17.5 cm, electrode size: 12 × 15.5 cm) for stimulation of the gluteal muscles in case of a LMN lesion

For direct muscle stimulation, large rubber electrodes with sponge pockets or safety electrodes with salt-free gel are used. Direct muscle stimulation requires strict attention, because of the risk of skin burning due to high charge densities and coagulation.

As described in UMN lesions and LMN lesions, different electrodes and stimulation parameters are used. In case of a LMN lesion, sponges with rubber electrodes are used to avoid skin irritation or burn (Fig. 11.17). In contrast, in cases with UMN lesions self-adhesive electrodes can be applied (Fig. 11.18).

11.4 Conclusion

During all phases of rehabilitation, electrical stimulation represents a valuable and efficient adjunct or standalone therapy for treatment of different problems of people with spinal cord injury. In the early phase after an injury, the focus of the therapy is on restoration of motor functions by task-specific therapies. This is particularly true in motor incomplete lesions with preserved motor functions below the injury level in respect to training of lower extremity functions, but also in patients with complete tetraplegia, in whom a substantial gain in motor functions of the upper extremities can be expected. ES does most effectively support the functional recovery when integrated into regular task-specific physio- and occupational therapy sessions. Additionally, FES can be used to support weak or to substitute lost motor functions in the sense of a neuroprosthesis including walking, grasping, and reaching or coughing potentially resulting in a better recovery of voluntary functions. Besides

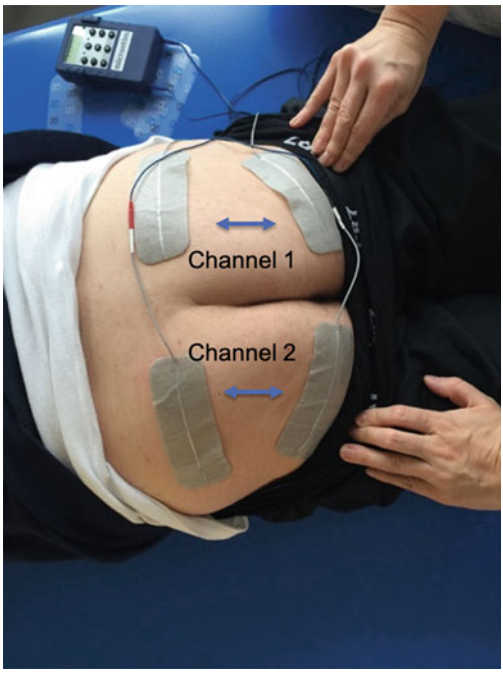

Fig. 11.18 Electrode positions (electrode size 5 × 9 cm) for stimulation of the gluteal muscles in case of an UMN lesion

these functional aspects, ES may be used as a therapeutic tool for treatment of different SCI-associated complications. This includes ES for muscle strengthening, for reduction of spasticity, and for prevention of skin injuries and joint misalignments such as shoulder subluxation. For an effective clinical use of ES by therapists, a deep understanding of the human musculoskeletal anatomy and biomechanics, neurology, and neurophysiology of the central and peripheral nervous system is of utmost importance. In particular, the presence and the degree of lower motor neuron damage clinically apparent in patients with tetraplegia as well as in conus cauda lesions need to be precisely assessed to select the appropriate stimulation parameters. If patients and caregivers have been carefully instructed in the correct setup and use of the ES, it can form an important component of a home-based therapy program after inpatient discharge.

Beside all advantages of ES, it adds a substantial time burden to the patients, therapists, and caregivers. This is in particular a barrier for its regular use in a clinical setting where personnel and timely resources are limited. Therefore, a high level of compliance and motivation is needed from all stakeholders for successful implementation of ES therapies into clinical routine. Device manufacturers should be aware of this fact when developing new technology. A strong focus should be put on ease of use, quick setup, and error-free operation while still providing enough flexibility and programmability to allow for adaption to the individual needs and priorities of end users. It is highly recommended to involve patients, their caregivers, and therapists in the development of stimulation devices from the beginning.

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Chapter 12
Brain–Computer Interface Controlled Functional Electrical Stimulation for Rehabilitation of Hand Function in People with Spinal Cord Injury

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Abstract Brain–computer interface (BCI) controlled functional electrical stimulation (FES) is a novel technique for volitional control of FES using a signal derived from the brain. The intuitive nature of BCI-FES has promoted its use to control FES-based assistive device to augment an imagined movement. Researchers are now exploring extensively the use of the BCI-FES as a neurorehabilitation system based on the fact that it necessitates active participation and establishes temporal association between efferent information, from cortical activation due to attempted movement and afferent information due to peripheral stimulation. The research literature mainly focuses on people with stroke for BCI-FES rehabilitation whilst people with spinal cord injury (SCI) have been considered good candidates for BCI-FES as an assistive device. This chapter discusses application of BCI-FES as neurorehabilitative system for the hand function in people with SCI, and highlights

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issues related to altered sensorimotor cortical activity as a result of the injury. Based on experimental results this chapter also introduces a concept of researcher-therapist-caregiver knowledge transfer and introduces a concept of caregiver and patient self-managed BCI-FES for home-based rehabilitation.

Keywords Brain–computer interface · Rehabilitation · Hand · EEG · Functional electrical stimulation · Spinal cord injury · Self-managed therapy

12.1 Introduction

Normal function of the human arm and hand is essential for activities of daily living (ADL), acting as a working tool and as a link to the outer world through the sense of touch and body language. Injuries affecting the upper limbs make a person dependent on their caregivers for fundamental ADLs such as drinking and feeding (Snoek et al. 2004).

Spinal cord injury (SCI) occurring at the cervical levels of the spinal cord can lead to the loss of function in all limbs known as tetraplegia. The incidence of SCI is between 250,000 and 50,000 per year worldwide (ISCoS, WHO 2013), about half with tetraplegia. About 60% of patients with tetraplegia due to traumatic SCI have an incomplete injury and can partially recover (see Chap. 1 of this book). Motor and functional recovery greatly depends on the early onset of therapies (Scivoletto et al. 2005). A survey performed among people with SCI found that regaining hand function was the highest priority in people with tetraplegia (Anderson 2004).

Because of this, the main focus of the rehabilitation of people with cervical spinal cord injury (SCI) and other injuries to the central nervous system (CNS) are the improvement of arm and hand function. However, in conventional therapy, patients who cannot perform functional movements are passive recipients of the therapy. During passive therapy, patient's brain is only inherently involved in control of movement through vision and partially preserved sensory feedback from the muscles (Duff et al. 1995).

Evidence from the literature confirms that faster and more complete recovery of motor function is achieved through the active engagement of patients (Popovic et al. 2006). Due to the bilateral nature of SCI active patient engagement can be challenging, making brain–computer interface (BCI) technology an ideal tool for rehabilitation based on patient active participation. BCI does not only enable non-muscular communication but can also provide quantitative information on user engagement. Allowing voluntary modulation and motor priming are considered core to neurorehabilitation (Grosse-Wentrup et al. 2011; Daly and Sitaran 2012). A BCI controlled by attempted movement has been used to control robots or to activate surface electrical stimulators applied to the hand (Cervera et al. 2018). In this way, efferent and afferent pathways are simultaneously activated closing the sensorimotor loop. Whilst this concept has been widely used in the research community to

promote rehabilitation of people affected by stroke, there is only a handful of similar studies on the SCI population.

Before explaining the therapeutic effect of BCI-FES, we provide an overview of the existing literature; then we will look at the underlying principles of motor attempt (MA) and MA-BCI and FES as methods for promoting sensory and motor neurorehabilitation and provide some experimental results by our group.

12.2 Neurorehabilitation Through Mental Simulations of Motor Actions

Corticospinal motor pathways can be activated either by overt or by covert movements. Physically executed movements present an overt motor action. Covert actions are defined as 'the mental execution of a movement without any covert movement and without any peripheral (muscle) activity' (Mulder 2007). Jeannerod (2001) suggested that imagined, observed and attempted actions all share the same basic mechanism of neural simulation, referring to them as 'the covert' action. The overt actions activate the same area of the brain (cortex, cerebellum, basal ganglia) as movement execution (ME), including the primary motor cortex, though this activation is weaker than during ME. Imagined and attempted movements retain some basic rules of ME such as biomechanical constraints and temporal characteristics described by Fitts' law (Fitts 1954).

Whilst there is one core network of activation for all overt actions, the extent of activation varies from one type of covert action to another and is also different for different modalities of the same covert action. For example, kinesthetic MI activates more similar cortical structures as ME, compared to visual MI (Neuper et al. 2005). Overt actions are therefore regarded by the motor system as real actions, which explain why training and learning processes occur during overt actions (Pascual-Leone et al. 1995).

Combined movement imagination and observation produce stronger motor evoked potentials (MEPs) and might be more effective than MI alone in improving sport performance and neurorehabilitation (Wright et al. 2014). Whilst there is multiple evidence of the beneficial effect of MI on the recovery after stoke (Page et al. 2007; Page and Peters 2014), evidence on SCI is scarce. Cramer et al. (2007) showed that a week of practice of MI in people with complete SCI improves motor performance and alters brain function despite lack of voluntary motor control and peripheral feedback. A single case study on a tetraplegic person who underwent a tendon transfer surgery, indicate that motor imagination combined with real exercise training improves movement trajectory (Grangeon et al. 2010). More recently, Mateo et al. (2015) showed that MI practice improved the range of movement of tenodesis grasp in six people with chronic tetraplegia. This evidence is quite modest, but all participants had a chronic SCI and they practiced MI rather than motor attempt.

For rehabilitation of movement in people with SCI, it is important to mention that MI influences not only cortical but also corticospinal excitability. The excitability pattern during MI dynamically mimics that occurring during ME (Fadiga et al. 1999; Grosprêtre et al. 2016) including modulation of the H reflex (Bonnet et al. 1997; Oishi et al. 1994; Jarjees and Vučković 2016). Activity dependent plasticity also takes place in the spinal cord (Wolpaw and Tennissen 2001) and is further shaped by a sensory input, including proprioceptive, visual, tactile, vestibular and auditory inputs.

There are several theories why MI does not result in the activation of movements in people without disabilities. The first possibility is that the cortical activation during MI is too weak to produce muscle activation (Lebon et al. 2008) whilst the second suggests the existence of a subcortical inhibitory mechanism that blocks the commands initiated by the motor cortex (Guillot et al. 2012). The latter favours MA over MI for therapeutic purpose, because people who cannot physically execute movements do not try to suppress MA.

12.3 Functional Electrical Stimulation

The primary purpose of functional electrical stimulation (FES) is to artificially generate action potentials in sensory and motor nerves to facilitate movement by inducing muscle contraction.

Large nerves in the upper limbs contain both sensory and motor fibres and FES activates them both. Whilst activation of efferent pathways results in muscle contraction, activation of afferent pathways results in activation of the sensory cortex and indirectly the motor cortex (Popovic 2014). This indirect activation of motor cortex presents a basis for neurorehabilitation with FES. Electrically generated muscles contraction, however, differs from naturally generated muscle contraction.

Muscle contractions caused by either natural or FES activation are initiated trough firing of motor neurons that activate muscles within the corresponding motor units. During natural contraction, smaller, slow propagating nerve fibres innervate smaller motor units whilst large fast propagating nerve fibres innervate large motor units (Grill 2002) thus gradually building force (Henneman et al. 1965) in order to minimise fatigue. In contrast to naturally induced contraction, FES results in nearly synchronous activation of nerve fibres of the same size (Popovic 2014). In addition, large, fast propagating nerve fibres which innervate large motor units have lower excitation threshold and are therefore activated with lower stimulation current than smaller nerve fibres (Grill 2002). All this results in rather unnatural activation of motor units, and as a consequence, fatigue develops much faster than during naturally driven muscle contraction. People with SCI may rapidly loose muscle mass within weeks post injury (Shields and Dudley-Javoroski 2009), which additionally increases their muscle fatigability.

Surface electrical stimulation of upper extremities is used in people with SCI to build muscles, and reduce spasticity (Hoffan and Field Fote 2009). Object oriented

FES which includes practicing activities of daily living, called functional electrical therapy, has been successfully used for rehabilitation of upper extremities in people with tetraplegia (Popovic et al. 2006; Kapadia et al. 2014). This requires multiple stimulation sites or custom-made multi-contact electrodes (Popović and Popović 2009), which are typically much more complex than FES reported in BCI studies.

12.4 Closing the Sensorimotor Loop Through BCI-FES

Closing a sensorimotor loop is achieved by providing a sensory feedback and muscle activation through FES, in response to activation of motor areas detected by BCI. Although this is a widely adopted paradigm for rehabilitation of stroke patients, one might argue that this concept is even more relevant for rehabilitation after SCI, because SCI affects sensory pathways to a much larger extent than stroke.

Injury to the spinal cord affects both the brain and the spinal cord (Wolpaw and Tennissen 2001; Pikov 2002; Jurkiewicz et al. 2007; Kokotilo et al. 2009; Nardone et al. 2013). In addition, SCI also causes secondary damage to the peripheral nervous system, such that, for example, a cervical injury affects lower limb axons (Petersen et al. 2017). Natural recovery of the nervous system following SCI may result in maladaptive plasticity resulting in secondary complications such as spasticity and neuropathic pain (Pikov 2002). In people receiving rehabilitation, therapy guides plasticity of the CNS towards activation pattern in people without disabilities (Hoffan and Field Fote 2009). Recovery of the neuronal structure is accompanied with functional recovery (Hoffan and Field Fote 2009; Petersen et al. 2017).

In the light of BCI-FES, both MI/MA and FES have beneficial effect on CNS recovery and FES also directly activates the peripheral nervous system. Their combination has stronger effect than either of these approaches alone.

Two alternative explanations have been provided for the effect of BCI-FES: The first explanation is based on Hebbian learning (Hebb 1949) and the second on motor priming (Siebner 2010), that is, reward based learning (Cervera et al. 2018; McFarland 2018). For the first, a precise timing is crucial (Mrachacz-Kersting et al. 2012, 2019) thus it is based on a template matching of motor-related cortical potentials (MRCPs). The majority of BCI-FES strategies rely on features such as power spectrum density, event-related desynchronisation, common spatial patterns or time domain parameters for which precise timing is not possible (for a review see Cervera et al. 2018). In these studies, motor priming is achieved by technology assisted activation of the motor cortex and subsequent sensory stimulation, assuming that the effect of FES will be larger when the motor cortex has already been active; stronger event-related desynchronisation is related to stronger activation of the motor cortex and spinal motoneurons (Takemi et al. 2015; Daly et al. 2018). A number of studies on people affected by stroke demonstrate cortical reorganisation in both the subacute and chronic stages, following BCI-FES training and provide some evidence that BCI-FES can be used as an effective therapy for post stroke rehabilitation (Cervera et al. 2018). However, the training time in these studies is

typically shorter than the duration of conventional therapy, where mass practice is advocated as the single most relevant factor for recovery (Langhorne et al. 2009). Participants in BCI-FES studies, in particular those who are undergoing inpatient rehabilitation are typically receiving conventional therapy in addition to BCI-FES. Thus, one might argue that the whole BCI-FES training is actually motor priming prior to conventional therapy. This might explain why relatively short duration BCI-FES practice results in cortical reorganisation. It is, however, hard to establish a correlation between these two, because of the often-undocumented amount of conventional therapy which accompanies BCI-FES and lack of consistency in delivering BCI-FES and conventional therapy.

The efficacy of BCI-FES might be further improved by increasing the repertoire of electrical stimulation patterns including goal-oriented movement. Currently most studies concentrate on BCI and use one or two pairs of FES electrodes to produce wrist extension or wrist extension followed by flexion, which is much simpler than FES paradigms used in dedicated functional electrical therapy (Popovic et al. 2006; Kapadia et al. 2014).

Whilst there is not much published evidence that BCI-FES rehabilitation might be effective in people with SCI, the existing evidence suggests that both cortical stimulation and peripheral electrical stimulation used as a primer to physical therapy in people with tetraplegia result in improvements of hand related function that persist at least 30 min after intervention (Gomes-Osman and Field-Fote 2015).

Rehabilitation has the greatest effect in the subacute phase post stroke and post SCI, because that is the time of greatest natural recovery. However, from this reason, it is hard to separate the effect of natural recovery, conventional physical therapy and BCI-FES. In recent years, there is an increasing number of randomised controlled BCI-FES trials on stroke patients trying to address this problem (Cervera et al. 2018).

12.5 Who Should Benefit the Most from BCI-FES Therapy?

As previously mentioned, the majority of published literature includes stroke patients. There are several reasons why studies on SCI population are missing. Firstly, there are much smaller numbers of spinal cord injuries than stroke cases annually, for example, 100 times less in the UK (Stroke Association UK 2019). Secondly, for this kind of research one needs a complex environment including medical as well as engineering knowledge close together, including access to patient population.

A lay person typically imagines a person with SCI sitting paralysed in a wheelchair, having no movement and no sensation in the paralysed part of the body [American Spinal Injury Association (ASIA) Impairment Scale (AIS A)] (Marino et al. 2013). This is a very black and white picture, as half of SCI population has

some sensation and movement preserved below the level of lesion, that is, they have incomplete injury (AIS B, C and D).

The most appropriate candidates for BCI-FES upper limb rehabilitation are people with weak, but partially preserved motor function in upper extremity muscles in the subacute phase post injury [i.e. maximum manual muscle test (MMT) score = 2, active movement with gravity eliminated (Frese et al. 1987)]. Although it is now recognised that the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) is not the best tool to describe the status of the upper extremity it is worthwhile noting that on average only 10% of patients initially classified as AIS A (sensory and motor complete injury) improve to AIS B (sensory incomplete) and further 10% improve to AIS C (sensory and motor incomplete) indicating that some preserved muscle function (MMT = 1 or 2) is a good prognostic factor of recovery (Fawcett et al. 2007).

BCI-FES therapy should be performed early after injury, in subacute phase when natural recovery is largest. The subacute period following SCI lasts about 1 year, though the largest degree of natural neurological recovery is expected within 3–6 months (Petersen et al. 2017). Functional improvements are bit delayed and expected up to 18 months post injury (Fawcett et al. 2007; Field Fotte 2009). This is similar but slightly longer time window for recovery than in stroke patients with functional improvements achieved within 6 months (Jung 2017).

A frequent misconception about people with SCI is that they are all young, under the age of 30. Whilst there is certainly a large proportion of young people, in the last 10 years in industrial countries, there is also an increasing number of people with traumatic and non-traumatic SCI over 60 (Field Fotte 2009; McCaughey et al. 2016). This fact may influence their general health and the adherence to the therapy and would likely influence their acceptance of BCI as an assistive device.

12.6 BCI-FES Assistive Versus Therapeutic Applications at Hospital and at Home

BCI-FES can be used as an assistive device and as a therapeutic tool for rehabilitation. The main difference between these two is in the expected outcome, that is, the context of use, rather than in the BCI-FES system configuration. In this section, we discuss some of these differences and how environmental conditions (hospital or home) may further affect these two applications.

The purpose of an assistive device is to help people with disability or their caregivers to perform the activities of daily living and limit restrictions caused by disability (ISO9999 2016; Bauer et al. 2011). They are designed for long term use and are not necessarily expected to aid recovery. Occasionally, however, as demonstrated by Bockbrader et al. (2019) a prolonged use of BCI-FES as an assistive device may lead to functional improvements. Typically, people with chronic SCI with no voluntary muscle movement against gravity are good candidates for BCI-

FES as an assistive device [see, e.g. MoreGasp project (http://www.moregrasp.eu/)]. Some researchers also advocate that assistive BCI-FES devices should be implantable to minimise setup time and the influence of environmental noise, as people should use them at home and in other noisy uncontrolled environments. They should also be able to perform other activities, such as talking, without affecting the performance of BCI-FES. Although implantable devices are technically superior, patients still prefer non-implantable devices (Huggins et al. 2015). Invasiveness is typically not a point of concern for rehabilitative device. Besides, for BCI-FES used for rehabilitation, high level of concentration to the attempted movements is desirable.

The emphasis of BCI classifiers in assistive devices should be on preventing false positive activations of BCI-FES, for safety purposes. The main purpose of BCI-FES as a therapeutic device is to aid recovery. Therapies are typically organised in safe environment. Classifiers for rehabilitative devices should avoid false negatives to prevent patient frustration. False positive FES activation is similar to passive FES activation and adds to a mass practice.

It has been suggested that 70% is a minimum classification accuracy for BCI systems for communication and control, including assistive devices (Kübler et al. 2014a, b). It is not clear whether the same accuracy would be required for rehabilitation purposes.

A challenge of using BCI in people with chronic SCI is muscle atrophy. Due to years of disuse, muscles are too weak to tolerate FES for a prolonged time and a presence of cortical reorganisation (Shields and Dudley-Javoroski 2009) often leads to motor activation patterns different than in able bodied population. From that reason potential BCI users need to build their muscles for several weeks prior to using BCI-FES. Whilst this might also be an issue in the subacute phase, BCI-FES therapy typically accompanies a conventional therapy, which focuses on preserving muscle strength. Notwithstanding this, the additional problem with FES is that due to activation of muscles in non-physiological manner (Popovic 2014), it causes premature fatigue compared to natural contractions.

We will now look at the influence of the environment on BCI performance. In hospitals, where people receive therapy, the effect of environmental noise can be controlled much better than in the community. Another advantage of BCI used at hospitals is that a skilled person (therapist) is expected to deliver the treatment and to operate BCI. From that reasons it is acceptable to have more complex setup of therapeutic than of assistive BCI-FES, that should be operated by caregivers, that is lay persons.

Whilst hospitals present controlled environment with trained personnel, they have challenges than are not present in the home environment. One of the main challenges is time available for BCI-FES therapy, often limited to an hour a day. Limited time also mandates very short setup (small number of electrodes, active electrodes) and minimum calibration time prior to therapy, ideally of both limbs (Rupp 2014). People at their homes typically have more flexible schedule, should they require additional therapy.

In contrast to people at homes, with chronic SCI who use BCI-FES as an assistive device, people at hospitals, in the subacute stage very frequently have injury related health problems which may impede both conventional and BCI-FES treatment (Rupp 2014). In both stages, medication such as spasmolytic drugs, drugs to treat pain, depression and other problems might cause drowsiness and may also affect the EEG spectrum. Depression is not uncommon in subacute SCI; this may significantly affect persons' motivation to take part in the therapy.

Other problems of a technical nature that may prove an obstacle to using EEG in hospitals in subacute SCI, includes the need for a spinal orthosis, for example, halo or collar preventing the use of an EEG cap or headsets. These are used for several weeks or months, and should not be a problem when using BCI as an assistive device. Cleaning and hygiene are larger issue for therapeutic applications because multiple users might be sharing the device.

In many countries, patients remain in hospitals receiving rehabilitation for several months post injury. They are also advised to continue rehabilitation therapy once they leave home for a number of months. In recent years, the concept of community healthcare is gaining popularity, as an attempt to reduce inpatient hospital stay time, thus reducing cost. This might result in an increased number of home-based self-managed therapies, including BCI. Such applications would have a mixture of requirements for BCI designed for rehabilitation and everyday use. We will present some initial results with such a device in the experimental results section.

12.7 A Brief Overview of Experimental Results

12.7.1 A Hybrid BCI-FES Feasibility Study on Tetraplegic Participants

One of the earliest BCI-FES studies on people with SCI used an EEG power-based time switch to activate FES (Pfurtscheller et al. 2003). A narrow-banded beta synchronisation during imagined feet movements was used as a control signal to activate FES applied to participants' hands. The authors argued that one cannot use MI of the limb to which FES is delivered as a control signal as it would be affected by sensory stimulus caused by the FES. They later improved the design by creating a hybrid BCI consisting of MI and steady-state visual evoked potential (SSVEP) to enable self-paced control of FES (Pfurtscheller et al. 2010).

Inspired by this we tested the feasibility of a hybrid BCI-FES for rehabilitation (Vučković et al. 2015). It was based on the motor attempt of the hand, that is, the limb to which FES was delivered. A cue-based MI served as a control signal to activate the FES on the respective hand (within 10 s post cue) and another naturally produced signal, occipital alpha, served as a self-paced control signal to deactivate FES. The hybrid BCI detected a decrease in the sensorimotor rhythm (SMR) or mu rhythm (8–12 Hz) induced by MI and an increase of the occipital alpha rhythm (8–

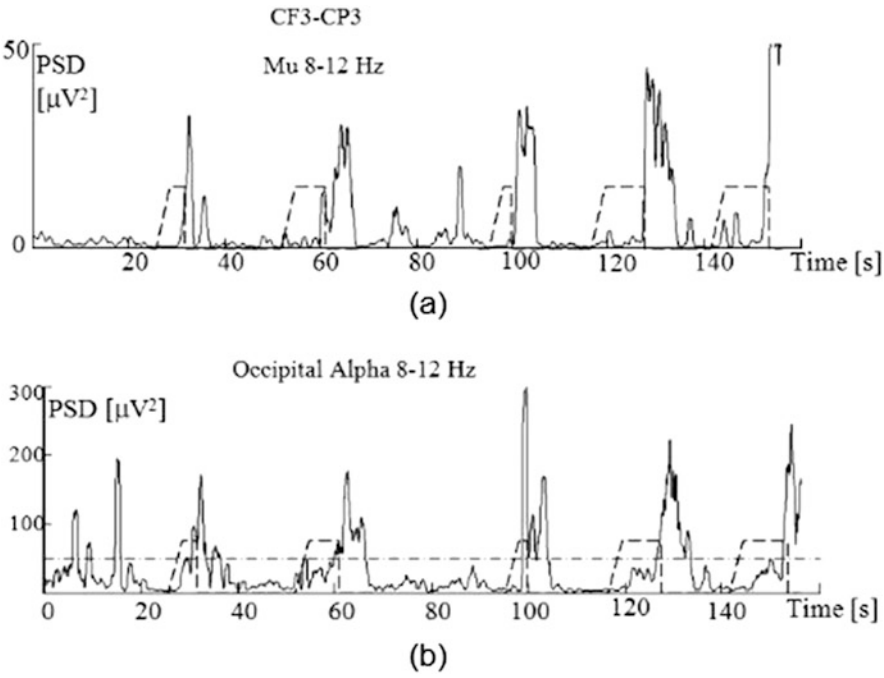

Fig. 12.1 Power spectrum density (PSD) of mu (**a**) and the occipital alpha rhythm (**b**) during self-paced BCI-FES control with hybrid BCI-FES. Trapezoidal shapes represent activation of FES. Dashed dot line in (**b**) represents the deactivation threshold for FES. Activation threshold (0.2 μV^2) could not be presented in (**a**). With permission from J Neurol Phys Ther

12 Hz) in the eyes closed relaxed state to deactivate FES (see Chap. 3 for explanation of EEG rhythms). This allowed patients to complete FES supported movement at their own pace. Only two pairs of EEG electrodes were used to measure the SMR, CP3-CF3 for the right hand and CP4-CF4 for the left hand. Two additional monopolar electrodes recorded the occipital alpha activity at O1 and O2. Two male participants with subacute tetraplegia tested hybrid BCI-FES (Vučković et al. 2015).

Figure 12.1 shows the spectral power density of the SMR/mu (Fig. 12.1a) and the occipital alpha rhythm (Fig. 12.1b) over 2.5 min of BCI-FES control in one participant. The duration of FES stimulus varied as it was participant controlled. The occipital alpha had a much larger amplitude than the SMR. Whilst FES was active, the SMR was low. The occipital alpha was also low, whilst participant had their eyes open, but increased independent of FES when closing eyes.

Recently Likitlersuang et al. (2018) tested a concept of BCI-FES therapy with automatic grasp selection on a single participant with chronic SCI. Similar to Vučković et al. (2015), the movement intention algorithm was based on time switch that measured changes in SMR power over predefined electrodes, with SMR power and time threshold determined heuristically. The novelty was to combine BCI with

computer vision modules to select precision, lateral, palmar or lumbrical grasp thereby achieving an accuracy of 87.5%. Although the intended purpose was therapy, the system was tested on a participant with chronic SCI, and could in principle be also used as an assistive device.

A long-term use of implanted EEG systems with surface FES designed for assistive purposes also may result in functional improvement (Bockbrader et al. 2019). A person with chronic complete cervical injury (C5, AIS A), clinically significantly improved upper limbs functions 1478 days post implant. The improvement was notices with FES switched off also on generalised household tasks not practice during the training. Although these results are promising, a limitation of the study is that the completeness of injury was only measured using the AIS so it is likely that despite being classified as motor and sensory complete, the patient most likely had some spared neuronal pathways.

12.7.2 Randomised Pilot BCI-FES Study on Tetraplegic Participants

In our previous study, we only tested the technical feasibility of repeated BCI-FES sessions in hospital environment. In a following randomised controlled pilot study we tested whether BCI-FES therapy resulted in any neurological or muscle strength improvement (Osuagwu et al. 2016).

Two groups of participants with subacute incomplete SCI, age and injury matched (age 51.7 $\pm$ 18.4 years; min 20, max 75, all male; level of injury: C4–C7, AIS B and C) were recruited. Seven participants in the active group received 20 BCI-FES sessions for both hands (one at the time) and five participants in the control group received 20 sessions of a matched quantity of FES. In the control group the FES devices were computer controlled without BCI. MMT scores were in a range from zero to two in all hand and wrist muscles prior to the therapy. Ethical approvals for the study were obtained from the Regional National Health Service Ethical Committee (ClinicalTrials.gov Identifier: NCT01852279).

Visual feedback in the form of a gauge and audio feedback (a beep) at the beginning of a trial were provided, giving participants 10 s to activate the FES. The BCI was based on time domain parameters and the classifier was based on linear discriminant analysis (LDA) (Osuagwu et al. 2016). A short calibration session using a cue-based MI was necessary before each session.

Only three pairs of bipolar electrodes were used (CF3-CP3, CFz-CPz, CF4-CP4), allowing sessions to take place even when participants were on bedrest in a hospital ward. In this case, participants were also exposed to environmental noises from other patients sharing a hospital room. We used FES with up to four bipolar channels (eight electrodes in total) to achieve wrist flexion and extension, finger extension and thumb flexion/opposition with adequate timing and stimulus duration to mimic a pinch grip.

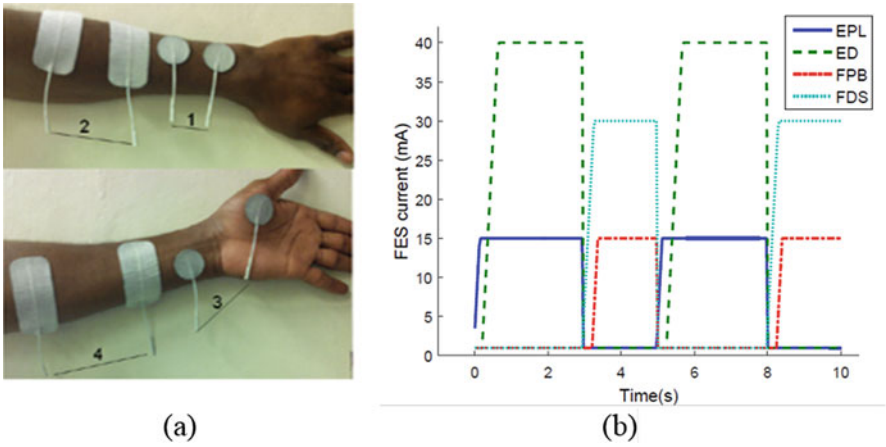

Fig. 12.2 (**a**) Four FES electrodes setup for precision (pinch) grasp, (**b**) order of stimulation and stimulation amplitude to achieve pinch grasp. Electrodes 1 extensor polis longus (EPL) and 2 extensor digitorum (ED), are for finger and wrist extension; Electrodes 3 flexor pollicis brevis (FPB) is for thumb flexion and opposition and Electrodes 4, flexor digitorum superficialis (FDS) are for finger and wrist flexion

Figure 12.2a shows a typical location of electrodes and a typical sequence of activation (from one to four) whilst Fig. 12.2b shows the order and duration of FES activation in order to achieve a precision (pinch) grip. Different hand movements could be achieved by using different combinations of FES electrode placement: for example, channel 2 alone was used for simultaneous wrist and finger extension; channel 2 followed by channel 1 for a gradual wrist and finger extension; channel 2 followed by channel 4 for wrist extension followed by wrist flexion and channels 1–4 for precision grip.

In this study, we wanted to test the effect of active therapy on both neurological and clinical outcome. We used the MMT test (Frese et al. 1987) and the range of wrist movement to measure effects on body structures and functions and the somatosensory evoked potential (SEP) of the ulnar and median nerve (Gugino and Chabot 1990; Curt and Dietz 1999), along with event-related synchronisation (ERS)/event-related desynchronisation (ERD) during cue based motor imagery as a measure of neuroplasticity.

Results: Figure 12.3 shows an example of SEP before and after 20 sessions of BCI-FES therapy, showing a decrease in latency and an increase in the N20 peak following treatment. Although groups did not initially have significantly different MMT scores, the increase of muscles strength was significant in the intervention group only, although improvement in range of movement of both wrists was comparable between groups. The MMT score significantly improved in BCI-FES group not only in hand flexor and extensor muscles but also in upper and lower arm and shoulder muscle. The hand muscles strength improved up to MMT = 3 (full range of movement against gravity without manual resistance) that would allow

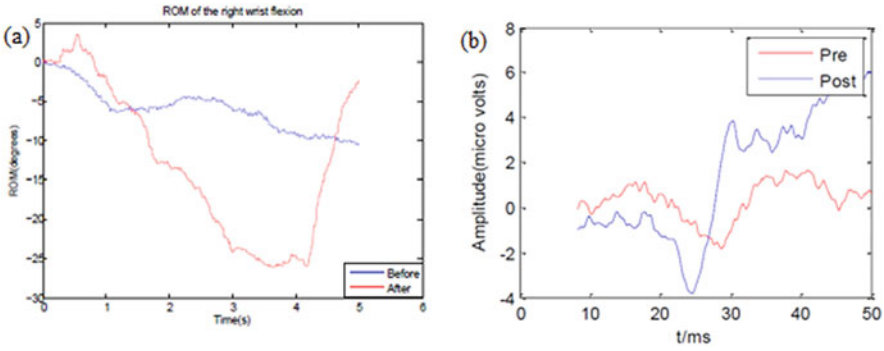

Fig. 12.3 The range of movement (ROM) of a left wrist before and after BCI-FES (**a**) and SEP of the left ulnar nerve before and after BCI-FES (**b**) for a representative participant. Stimulus delivered at $t = 0$ s. Imaged based on averaging 250 stimuli

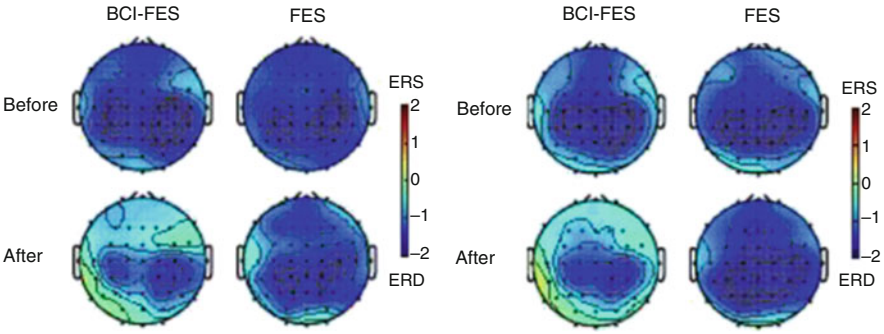

Fig. 12.4 Averaged ERD/ERS maps before and after treatment in active (BCI-FES) and control (FES) groups in the 8–12 Hz SMR band (left) and in the 12–16 Hz SMR band. Significant difference in lateralisation was found in parietal locations for the intervention group only. With permission from J Neural Eng

some activities of daily living (ADL) with the aid of assistive devices. Due to a relatively low MMT score, ADL were not tested. A prolonged therapy might have resulted in further improvement.

Cortical response during MI is shown in Fig. 12.4. Following 20 therapy sessions lateralisation of cortical activity and shift of ERD from the parietal to the central region could be noticed in the intervention group only. This cortical response is indicative of neurological recovery (Nardone et al. 2013; Isa and Nishimura 2014). The parietal shift early after injury is explained by a decreased number of axons from the primary motor cortex (M1) compared to surviving axons from the primary sensory cortex (S1) within damaged corticospinal tracts. Green et al. (1999) showed that in patients who recover function, posterior reorganisation reverses and posterior motor potentials moved to a more anterior position with recovery.

Bilateral activation of the M1 and the ipsilesional activation of the premotor cortex (PM) have also been reported in incomplete cervical subacute SCI (Isa and Nishimura 2014). Lack of lateralisation of M1 has been attributed to unmasking of pre-existing excitatory connections. In a chronic post-injury phase, this bilateral activation has a tendency to lateralise towards the contra-lesional site, accompanying functional recovery (Nardone et al. 2013; Isa and Nishimura 2014; Jurkiewicz et al. 2007). Thus lateralisation of cortical activity during attempted movements in BCI FES is indicative of neurological recovery that has been accompanied by the improvement of muscle strength.

12.7.3 Patient and Caregiver Self-Managed BCI-FES for Home Based Rehabilitation: Feasibility Study

Patients' natural recovery may continue for over a year post injury (Field Fotte 2009). However, the inpatient stay of patients is getting shorter and is less than 2 months in some countries such as the USA (Burns et al. 2017). This might be limiting the functional level the patient may achieve. Therefore, a BCI rehabilitation method is needed, available for patients to use in their homes with the aid of only a caregiver rather than a therapist.

In this study, we adopted a user-centred design approach for BCI, which consist of four main steps: specify the context of use, specify user requirements, design solution and evaluate the solution in terms of efficiency, effectiveness and user satisfaction (Kübler et al. 2014a, b). We created an inexpensive commercially available BCI-FES system (costs of BCI under £1000) for patient and caregiver self-managed therapy that may continue in the patients' home after discharge from hospital.

12.7.4 The Context of Use

For clinical adoption of BCI as a therapy it is necessary to train the therapists to independently use BCI-FES. Furthermore, for home based BCI-FES, therapist have to be able not only to use BCI-FES but also to teach caregivers to use the system, which is an additional skill. In this study we tested the concept of knowledge transfer, first from the researchers to the occupational therapist (OT) and then from the therapist to patients' caregivers. Ethical approval for the study was obtained from the Regional National Health Service Ethical Committee (ClinicalTrials.gov Identifier: NCT03257982) (Fig. 12.5).

Fig. 12.5 A patient practicing BCI-FES (left). Electrodes used for BCI are the two top electrodes on the right, marked with a red bar above and symmetrical electrodes on the left (not clearly visible in the figure). The flow chart of the experimental protocol (right)

12.7.5 User Requirements Specification

A requirement for a home based BCI-FES combined some requirements of clinical BCI-FES for rehabilitation with BCI-FES as an assistive device. Because the system should be operated by non-professionals it should be portable, inexpensive and easy to use by patients and caregivers (Huggins et al. 2015; Käthner et al. 2017; Daly et al. 2014; Deravi et al. 2015). BCI should use non-gel-based electrodes and should ideally be based on a consumer grade device. Overall it should be designed to require minimum changes in the lifestyle of both patient and caregiver, that is, 'burden of treatment' caused by regular use of BCI-FES should be minimised (Gonçalves et al. 2017).

12.7.6 Design Solution

The system consisted of hardware and software. The hardware consisted of a 14 channel EEG device (Epoc, Emotiv, USA), a tablet computer under Windows and a multichannel functional electrical stimulator (Rehastim, Hasomed, Germany). The software consisted of Emotiv proprietary software and a custom made BCI-FES software application written in C++ and a C++ Hasomed proprietary library to control FES. A BCI algorithms based on band power time switch (Vučković et al. 2015).

The same FES electrode configuration was used as in Osuagwu et al. (Fig. 12.2) and participants could select a predefined order of electrodes by pressing a button on the GUI to select (a) wrist extension (b) wrist flexion followed by wrist extension (c) precision grasp.

12.7.7 Solution Evaluation

12.7.7.1 Methods

The evaluation consisted of three stages: In the first stage, researchers trained a group of four OTs over five 1-h sessions; OTs practiced BCI-FES setup on each other. In the second stage OTs thought patients and caregivers how to use BCI-FES over five training sessions, whilst researchers only observed. Each patient had one OT assigned to them, whilst one OT could train several patients. Finally, interested patients and caregivers continued the independent use of BCI-FES within the hospital for up to ten additional sessions.

The second evaluation involved testing usability and outcome measures, presented in terms of efficiency, effectiveness and satisfaction. Effectiveness was measured in terms of the true positive and false positive activation (there was no false negative activation). Because there were only five therapy sessions, the effect on BCI-FES on brain wave patterns and functional outcomes were not measured. Efficacy was measured in terms of donning time during the first and fifth training session (therapists and caregivers), time to activate FES through BCI (patients) and workload (all three groups) (NASA 1986). User satisfaction was measured through focus group meetings (therapists), semi-structured interviews (patients and caregivers), the Quebec User Evaluation of Satisfaction With Assistive Technology questionnaire (QUEST) (Demers et al. 2002), and the level of stress and satisfaction during the first and fifth session (caregivers and patients) measured on the visual numerical scale 1–10 (10 highest level of stress or satisfaction). Interviews were printed verbatim and analysed by two researchers independently, who then agreed on the main themes.

12.7.7.2 Results

Participant demographic information: Four female OTs with an average experience of using FES of 9.2 ± 5.2 years (min 5, max 18), eight participants with incomplete subacute tetraplegia (55.4 ± 16.7 years old, two females) and their caregivers (45.2 ± 15.3 years old, five females) took part in the study. The average time since injury was 12 ± 6 weeks (min 6, max 26). All participants had at least a secondary school education and some basic knowledge of computers. All caregivers lived up to 60 km from the hospital and six were employed.

Effectiveness: Average true positive rate on the first session was 66% ± 25% and it increased to 80% ± 15% by the last training session. The average false positive rate was 11 ± 16% (median 0%) on the first and 7 ± 17% (median 0) on the final session. We did not measure the neurological and functional outcome due to a small number of sessions.

Efficiency: For OTs, the average donning time for was 33.3 ± 0.5 min on the last sessions (they practiced on themselves). The average donning time for caregivers

dropped from 40.3 ± 8.6 min on the first session to 29.1 ± 6.2 min on the last training session, that is, it was similar to the OTs time. In caregivers who continued with self-managed sessions, donning time dropped further to 20.0 ± 7.8 min. The average time for participants with SCI to activate FES by attempting movement did not change, being 3.4 ± 2.0 s on the first session and 3.8 ± 1.0 s on the last session.

Workload, Stress and Satisfaction: OTs were initially trained on separate sessions to use FES and BCI, because they were already familiar with basic concepts of FES. However, they reported similar average workload for FES training session 52 ± 9 (median 49, on a scale min 0 to max 120) and for BCI training session 48 ± 23 (median 46). On the last training session, the average workload for the whole BCI-FES system was 40 ± 30 (median 28).

For caregivers the average workload remained almost unchanged over five sessions, being 37 ± 18 on the first and 38 ± 29 for last, but for participants with SCI it dropped from 53 ± 11 on the first to 42 ± 24 on the last supervised session. The overall stress increased in participants with SCI from the first to the fifth session from 0.2 ± 0.7 (median 0) to 1.6 ± 2.6 (median 0). The overall stress also increased in the caregivers' groups from 2.6 ± 3.2 (median 0) to 3.5 ± 2.9 (median 2.5) possibly because the extent of therapist assistance decreased over sessions. It is of interest to note that the level of stress was much higher for caregivers though their workload was lower than in participants with SCI. Satisfaction also dropped from the first to the fifth training sessions and was of similar level for both groups although their level of stress was different.

Only three pairs decided to take additional self-managed therapy sessions. One pair found BCI-FES too complex to continue whilst for the others, caregivers found it too difficult to come regularly to hospital after working hours. The analysis of results of three pairs who took additional self-managed therapy sessions showed a similar trend from the first to the fifth session as for the whole group. However, their stress levels substantially decreased and the level of satisfaction increased at the end of the last self-managed session (Fig. 12.6). This shows that it takes probably more than five sessions for people to become fully confident in self-managing BCI-FES and also indicates that people are more relaxed when they are not being observed/actively trained by a therapist.

Satisfaction*:* Focus group meetings were organised with OTs after their training and once again after the last patient-caregiver couple was trained. On the first focus group meeting four topics were identified.

- *Knowledge about FES:* All OTs were familiar with FES but used it primarily for muscle strengthening prior to therapy. The main issue for using FES was getting precise timing and electrode location to achieve a natural movement.
- *Active patient engagement in therapy*: In their everyday practice, OTs often encouraged patients to actively attempt a movement produced by FES. However, it was recognised that patients did not always follow the instructions.
- *User friendliness of BCI application software*: The GUI was too `academic'. They preferred learning by doing rather than reading custom made manuals and video instructions.

Fig. 12.6 Average overall workload, stress and satisfaction for three participants with SCI and their caregivers who continue with self-managed BCI-FES treatment. Workload (blue colour) range is from 0 to 120 whilst stress (orange) and satisfaction (green colour) range is from 0 to 10

- *BCI hardware*: The EEG headset was not originally designed to be placed over the central area of the head and was therefore slipping from smaller heads and heads with long hair. Having a purpose-built wearable headset was suggested. On the other hand, after initial training OTs did not find it difficult to get a low impedance with wet electrodes.

The second interview covered the experience of patient and caregivers' training

- *Technical skills and understanding*: Two OTs felt confident to continue BCI-FES training without help from the research team. Most OTs trained caregiver to use only two pairs of electrodes to save time and reduce complexity. A sleeve-like FES setup with multiple electrodes was suggested.
- *Recruitment and session booking*: OTs had to stay after working hours to accommodate working caregivers. Recruitment was difficult because many caregivers were too busy planning and making arrangements at home for the patient discharge from hospital and could not commit themselves to the study.
- *Problem with translation to the home environment*: People getting back home from hospital are frequently overwhelmed as they start to adapt to living in society with a disability. It was suggested that compliance to self-managed therapy therefore might be poor in this period. A suggested solution was to train an outpatient nurse to use BCI-FES. The other suggested solution was to incorporate the activities of daily living in FES training.

Interviews with participants with SCI and their caregivers on the last training session covered the following topics:

- *Learning and understanding*: Learning by doing was preferred than reading/watching instructions. Online instructions within BCI software were suggested.

The main purpose of BCI-FES was understandable to both groups but the underlying principles were less clear. At the end of training caregivers felt moderately confident operating BCI-FES hardware and software on their own (3.7 ± 0.6; 1 min, 5 max confidence level).

- *BCI*: Both groups believed that the EEG headset was acceptable aesthetically and in size to be used at home but one size headset did not fit everybody; initially caregivers found it difficult to achieve a good contact between the electrode and the skin, and to find the right location for the headset but they noticed that they improved by the end of training. Participants with SCI did not find it difficult to control FES through BCI and in general found the system more user friendly than caregivers.
- *FES*: Finding the right placement of FES electrodes on patient's forehands was not a problem for caregivers. In most cases they used stimulation parameters set by the OTs.
- *Main positive aspects*: Feeling connection between thinking to move and seeing hand moving, a caregiver said `I like the fact that I can see his hand working. It's hard to believe these things until you actually see it working'.

The analysis of the QUEST showed that for patients and caregivers ease of use was most important followed by effectiveness. Safety and security, comfort and follow-up service shared third place.

12.8 Discussion

In this chapter, we discussed the basic principles underpinning BCI-FES rehabilitation and some basic differences between requirements for BCI-FES used for rehabilitation therapy and as an assistive device. We looked at the neuronal reorganisation following SCI and how it may affect BCI performance. We also addressed some basic misconceptions related to SCI which might be the cause of a very limited number of studies in this area.

This chapter focuses primarily on the rehabilitation of the upper limb presenting mainly results of studies from our group. It should be however mentioned that similar paradigms could be designed for rehabilitation of the lower extremities, as it has already been demonstrated in studies with stroke population (Mrachacz-Kersting et al. 2019). Most published studies with the SCI population using MI or MA paradigms, concentrate on development of assistive devices (Chap. 13 in this book is dedicated to this topic).

We introduce a novel concept of home based BCI-FES rehabilitation and look at the feasibility of the transfer of knowledge not only from researchers to therapist but also from therapist to patients and caregivers. Results of this study might also be relevant for studies on assistive BCI-FES. The technical complexity of BCI was not the greatest barrier to translating BCI to community. A major barrier was the involvement of caregivers, most of whom were employed. A limitation was that

only people living close to hospital could be included in the study and that their number was too small to perform statistical analysis of data. In real life, involvement of professional caregivers and outpatient nurses would be necessary to keep good adherence to therapy, in particular during transition from hospital to home. In our recent study, we recruited 15 people with SCI and chronic pain who used the same wearable device as in our former study within their homes for up to 2 months (Al-Taleb et al. 2019). The two mains factor for good adherence in the pain study were that participants have been offered a treatment (rather than taking part in a feasibility BCI FES study) and had chronic injuries living in the community with their lives already organised around their disability.

A positive result of this BCI-FES study was that it showed that family caregivers could learn to operate BCI-FES on their own and that using BCI imposed a low workload on patients. Two OTs who spent most time with patients felt confident that they could teach caregivers to use BCI-FES in the future. Thus, we demonstrated that transfer of knowledge is possible.

The main issue with BCI studies with the SCI population remains low recruitment numbers, which calls for multicentre studies.

12.9 Conclusions

People with SCI may benefit from BCI-FES both as a therapeutic and assistive device through different stages post injury. The number of studies focused on BCI-FES rehabilitation with SCI is low due to the low incidence of SCI and frequent misconceptions about the SCI within the BCI research community. Both, SCI in the subacute and chronic stage, may have an impact on EEG activity, which has to be taken into account when designing BCI. Limited number of studies show first encouraging results of the effectiveness of BCI-FES as a therapeutic tool for upper limb rehabilitation in subacute SCI. Patient and caregiver self-managed BCI-FES is feasible but requires organised support network. Stroke patients are a larger population, thus more people might benefit from this concept. The way forwards in therapeutic BCI-FES studies with SCI population would be multicentre trials to ensure statistically significant participant numbers to enable collecting strong evidence of the effectiveness of the treatment.

Frequent Misconception about SCI and BCI-FES

- *People with SCI are wheelchair users who have no voluntary movement and no sensation below the level of lesion.*

More than 50% of people with initial SCI have an incomplete injury (AIS B, C, D) with preserved sensation and/or movements below the level of injury.

(continued)

- *BCI is not adequate therapy for SCI patients because they have an injury to the spinal cord rather than to the brain.*

Therapies targeting brain indirectly target the spinal cord. SCI affects the nervous system on all levels.

- *Therapy should finish when people leave inpatient rehabilitation.*

Most of neurological natural recovery after SCI takes about 6 months whilst functional recovery might take up to a year. In most developed countries rehabilitation is on average 4 months whilst in the USA it is less than 2 months (Burns et al. 2017). This is much shorter than a period of natural functional recovery.

- *SCI patients are young.*

This is true mainly for developing countries. In industrial countries, however, the age distribution in SCI patients is bimodal, there are many younger people and many people over 60 (McCaughey et al. 2016).

- *Cortical activity in SCI patients early after injury is the same as in able bodied because they do not have injury to the brain.*

Not entirely true, though SCI and its complications affects the brain to much smaller extent than a stroke.

- *In chronic SCI, EEG activity during movement imagination and attempt is weaker than in able bodied, due to disuse reorganisation.*

Partially true, EEG activity might actually be stronger than in the able bodied in people with SCI who suffer from injury-related central neuropathic pain.

- *People with complete SCI do not feel FES.*

Not always true, people might feel the strong afferent stimuli caused by FES. In some cases, hypersensibility in the stimulated body parts might not permit the application of FES.

- *People with complete tetraplegia are not candidates for (BCI) hand therapy.*

Only partially true. Many people with complete SCI have a few level of zones of partial motor and sensory presentation below the level of injury.

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Chapter 13
Non-invasive Brain–Computer Interfaces for Control of Grasp Neuroprosthesis: The European MoreGrasp Initiative

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Abstract Restoration of grasping has the highest priority for people with cervical spinal cord injury (SCI). This chapter describes the non-invasive brain–computer interface (BCI)-controlled grasp neuroprosthesis developed within the European Horizon 2020 project MoreGrasp. Based on former projects of the collaborators, several innovative technologies were developed within the MoreGrasp project with the aim to achieve an intuitive thought-controlled restoration of hand function in end users with tetraplegia for supporting activities of daily living. The end users in the focus of this project have been people with sufficiently preserved elbow and shoulder movements, but missing hand and finger functions.

In particular, within MoreGrasp a novel, closed-loop upper limb grasp neuroprosthesis was developed which could be controlled by different multimodal control options, namely user-friendly BCIs based on gel-less electrodes and wireless electroencephalogram (EEG) amplifiers using natural movement attempt strategies,

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a shoulder joystick and instrumented objects. All these control modalities could be tailored to the end users' needs and capabilities. Furthermore, a web-based service infrastructure for registration, assessment, and training of end users was developed. It assisted experimenters as well as end users in prototype assessment and operation. Finally, a clinical study involving end users with tetraplegia evaluating the MoreGrasp technology at their homes was initiated. The first results obtained and the lessons learned are provided at the end of the chapter.

Keywords Spinal cord injury · Electroencephalogram · Hybrid brain–computer interface · Movement-related cortical potential · Grasp neuroprosthesis · Non-invasive · Closed-loop · Array electrode · Web-based services · Industrial uptake

13.1 Introduction

Individuals with spinal cord injury (SCI) are affected by a substantial loss of motor functions. Depending on the level and severity of the injury, activities of daily living such as personal hygiene, eating, and drinking, or getting dressed represent serious challenges. In the worst-case scenario, an individual with SCI is not able anymore to perform these essential daily tasks autonomously without the help of others. For obvious reasons, people with severe motor impairments of the upper extremity seek for interventions to regain at least partial personal independence. Asking a person with tetraplegia about his/her highest priorities in respect to improvement of motor functions, three quarters rate regaining arm/hand function their first priority choice (Anderson 2004; Snoek et al. 2004). For some persons, hand and grasping function can partly be restored through muscle and tendon transfers. Within this surgical intervention, transfer of still voluntary controllable muscles or parts of them to other non-functional muscles is performed to allow basic arm/hand functions such as elbow flexion or regaining functional grasping (Leclercq et al. 2005). Recently, it has been shown that combinations of transfers of nerves and muscles under voluntary control result in a high functional gain (van Zyl et al. 2019). When surgical interventions are not applicable because of too few muscles under voluntary control or exceedance of the time window for nerve transfers, technical solutions such as non-invasive motor neuroprostheses represent an alternative to improve upper extremity motor functions.

This chapter summarizes the current state of the non-invasive brain–computer interface (BCI)-controlled grasp neuroprosthesis developed in the European Horizon 2020 collaborative project MoreGrasp (www.moregrasp.eu). Based on former projects of the collaborators, within the MoreGrasp project several innovative technologies were developed with the aim to achieve an intuitive thought-controlled restoration of hand functions in end users with tetraplegia for use in activities of daily living. The user group in the focus of this project has been people with sufficiently preserved elbow flexion and shoulder movements, but missing or very weak hand and finger functions.

Fig. 13.1 Overview of the components of the MoreGrasp system. It consists of a central computational unit, a wireless EEG-amplifier and water-based electrodes placed in a cap, inertial measurement units (IMUs), a shoulder joystick, an FES stimulator, a personalized textile forearm sleeve with integrated (partly array) electrodes, and a tablet computer for setup and operation of the complete system

For this, within MoreGrasp a novel, closed-loop upper limb grasp neuroprosthesis was developed which could be controlled by different multimodal control options, namely user-friendly brain–computer interfaces based on gel-less electrodes and wireless EEG amplifiers using natural mental movement attempt strategies, a shoulder joystick, and instrumented objects (Fig. 13.1). All these control modalities could be tailored to the end users' needs and capabilities. Furthermore, a web-based service infrastructure for trial registration, trial inclusion, and documentation of the assessments and of the training of end users was developed. It assisted clinical experts as well as end users in prototype assessment and operation. Informed consent was obtained from all individual participants included in the studies presented below.

13.2 Functional Electrical Stimulation for Grasp Restoration

Functional electrical stimulation (FES) of paralyzed muscles in a coordinated manner forms the core part of the non-invasive BCI-controlled neuroprosthesis developed within the MoreGrasp project. With this neuroprosthesis, the two grasp patterns

mostly used for activities of daily living can be restored, namely the lateral and the palmar grasp pattern: In case of the lateral grasp pattern, the flexing thumb is moving toward the flexed fingers to grasp a key, a fork, a spoon, or other small objects. With the palmar grasp, in which the thumb is placed in opposition to the index finger, larger objects such as a glass can be grasped.

The most important prerequisite for a successful restoration of the grasp function by FES is a low degree of denervation of the muscle groups relevant for grasping. Denervation of arm muscles in the context of a cervical SCI is caused by additional damage of lower motor neurons at the lesion level (for details see Chap. 2). Even if muscles are innervated and can be activated by electrical stimulation, the FES-generated contractions need to be sufficiently strong to perform tasks of daily life. This might not be the case in end users with tetraplegia, whose muscles were often not activated for months to even years. This inactivity results in a reduction of muscle mass (disuse atrophy) and in an increased fatigability of muscles. Both can be reversed by an electrical stimulation conditioning program over weeks to months. The longer the period of inactivity persists, the more stimulation sessions are required to achieve a sufficient fatigue resistance. Beside the FES-related issues, there are other factors that might prevent a successful restoration of a grasp pattern such as limited passive range of movement (ROM) due to shortened muscles or joint contractures resulting in very limited passive hand opening or closing.

With this in mind, the MoreGrasp consortium focused their efforts not only on the technical development of a customizable grasp neuroprosthesis, but also on the establishment of standardized screening procedures together with a clinical algorithm to support end users in the stimulation training.

13.2.1 Screening and FES Training

As a first step, potential grasp neuroprosthesis end users need to undergo a screening procedure, during which the preserved upper extremity functions, that is, sensation and motor functions, are assessed. For quantification of the functional status, standardized assessments such as ISNCSCI (ASIA and ISCoS International Standards Committee 2019), MRC 1943), and passive ROM (neutral-0-method) are performed and general inclusion and exclusion criteria are evaluated (see Fig. 13.2). In a second step, the presence of severe denervation in the relevant arm and hand muscle groups is systematically assessed by applying electrical stimulation (ES). Special precaution needs to be taken to distinguish between fast fatigue and denervation. Eventually, a test using long pulse widths (see Chap. 2) capable of stimulating denervated muscles is recommended.

All evaluation assessments are supported by a customized tablet software kit, the MoreGrasp Mobile Evaluation Toolkit (MET). The MET allows immediate digitalization of all evaluation parameters listed above. Based on these outcome parameters, clinical experts in the MoreGrasp consortium decide whether to perform further assessments or to exclude the candidate because of the presence of exclusion criteria.

Fig. 13.2 MoreGrasp screening at a potential end user's home. (Left and Center) The clinical expert assesses residual voluntary motor functions using standardized tests (ROM). (Right) The tablet-based Mobile Evaluation Toolkit (MET) allows direct digital documentation of all assessment parameters

After it has been confirmed by the clinical experts that a person with SCI will most probably benefit from the MoreGrasp neuroprosthesis, upper limb muscle training is initiated. As already mentioned, long-term paralyzed arm, hand, and finger muscles of persons in the subacute or chronic phase after the SCI can be substantially atrophied. By applying low-frequency (2–20 Hz) electrical stimulation for up to 1 h on a daily basis, strength and fatigue resistance can be improved to a degree where the FES can be used for activities of daily living. The MoreGrasp clinical training algorithm estimates a training period of 8–12 weeks, during which end users train for up to 1 h at least 5 times a week (see Fig. 13.3).

13.2.2 Personalization of the MoreGrasp Neuroprosthesis

The two grasp patterns (lateral and palmar grasp) can be generated with seven different surface electrodes placed on the forearm (Rupp et al. 2015). The electrodes are activated in a coordinated manner with one single degree of freedom. This has been implemented by a grasp-pattern-specific pulse width node map for each stimulation channel. The pulse widths of the channels in this stimulation map are set in dependency of one signal ranging from 0% to 100%, which might originate from different control sources, such as a shoulder joystick.

One of the biggest problems of non-invasive FES systems is the complex handling of the electrodes, especially with regard to electrode location. To overcome this, a textile forearm sleeve has been developed for the MoreGrasp neuroprosthesis in which the FES electrodes are pre-mounted and do not need to be placed individually (Fig. 13.4a). The textile sleeve is made of stretchable cloth and is individually customized to the end user's forearm anatomy to ensure proper electrodes-skin contacts (Fig. 13.4b). Measurements of the end user's forearm are taken earliest 4 weeks after the start of the ES muscle training, since the forearm diameter might change as a consequence of the training. In addition, further adaptations can be done

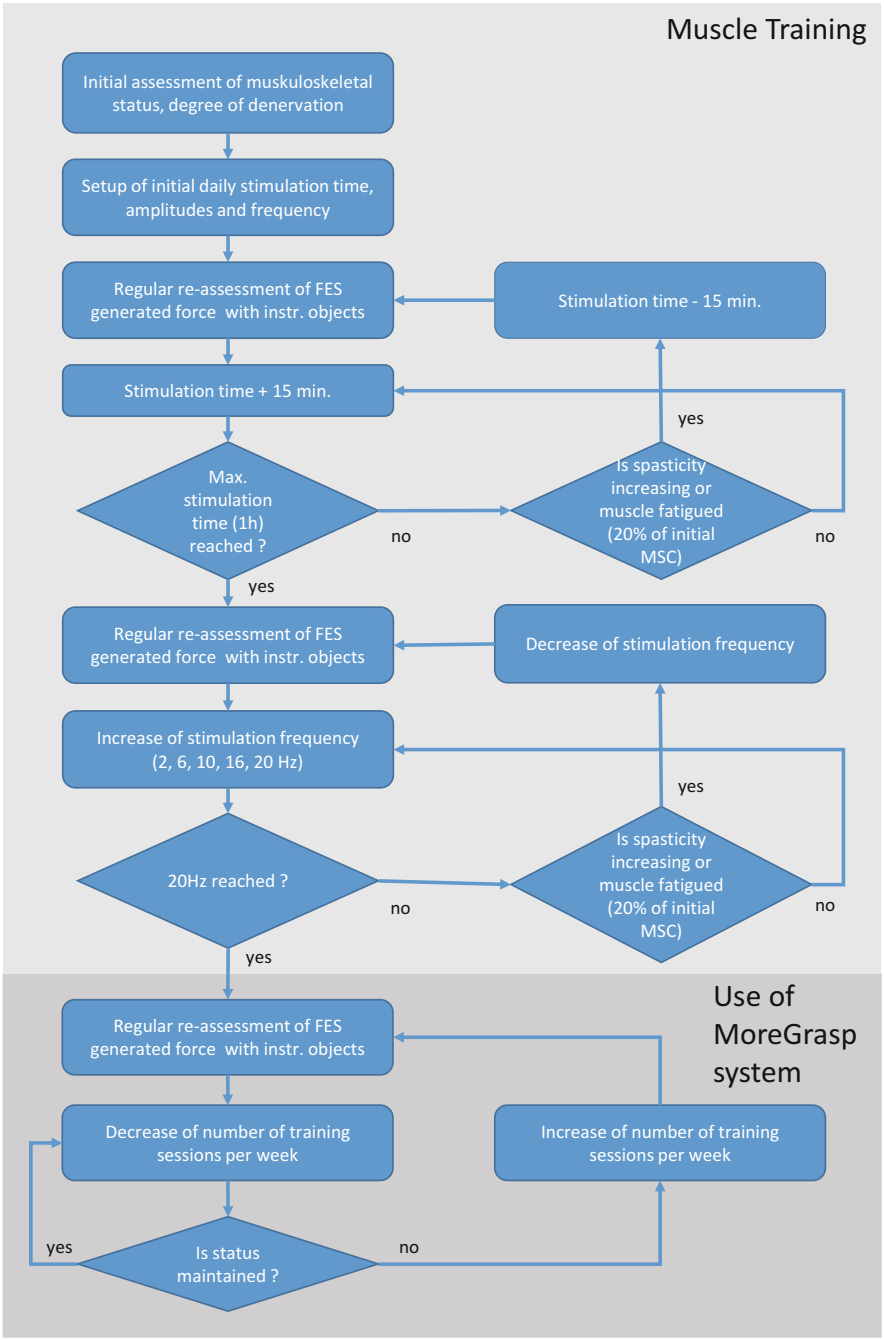

Fig. 13.3 The MoreGrasp Stimulation Training Clinical Algorithm. The light gray shaded area displays the stimulation training procedure before the actual neuroprosthesis is applied. The initial stimulation time is carefully adapted to the status of the muscles. In most end users with tetraplegia, an initial stimulation time of 30 min is possible right from the start. This time can be increased

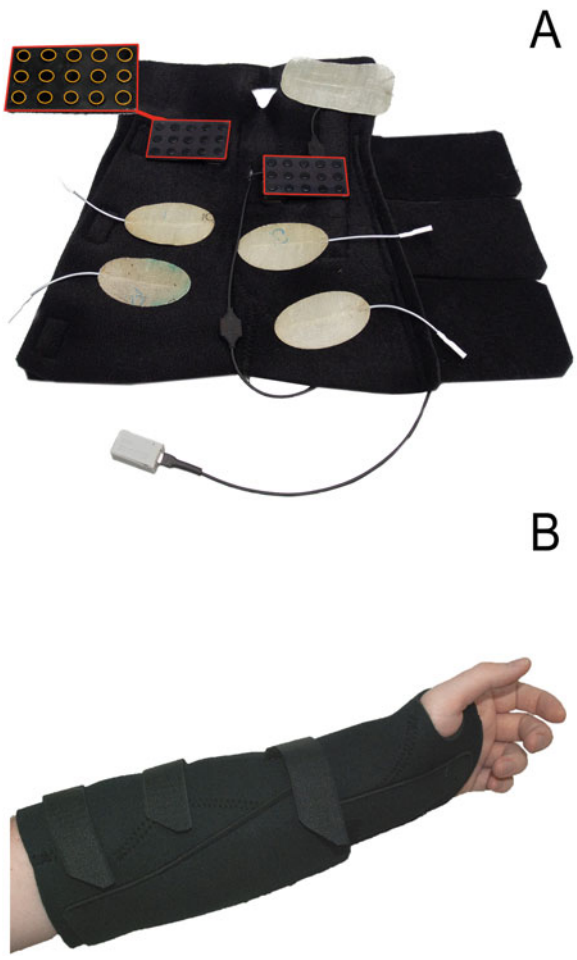

Fig. 13.4 The MoreGrasp FES-sleeve. (**a**) The personalized textile forearm sleeve with final electrode layout (two electrode arrays (red frames) for stimulation of thumb extensor/opposition muscles; two pairs of traditional gel electrodes for stimulation of finger extension and thumb/finger flexion). The large rectangular electrode serves as a common anode for the electrode arrays. (**b**) The electrode sleeve mounted on an end user's arm. The sleeve is individually manufactured according to the dimensions of an end user's arm

to the sleeve, for example, integration of a wrist stabilization splint made of aluminum to keep the wrist in neutral position during grasping in end users with strong ES-generated wrist flexion.

Gel electrodes, the type of surface electrodes routinely used in FES applications, are attached within the forearm sleeve and individually positioned over motor points of muscles relevant for grasping. The main drawback of surface electrodes is the strong dependency of muscle activations on the positions of the electrodes. This

Fig. 13.3 (continued) through the training sessions, depending on the progress of each user. An increase of stimulation frequency is also possible. The dark gray shaded area shows the procedure after functional use of the neuroprosthesis with the aim of reducing the additional training time to zero

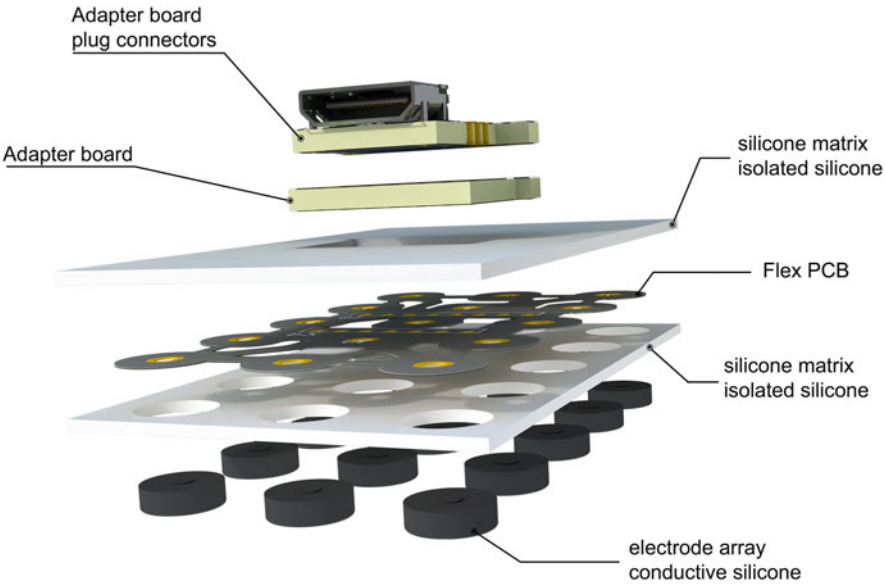

Fig. 13.5 Schematic of the surface array electrode (Version 3.0). The array (60 mm × 35 mm) holds 15 individual surface electrodes (5 mm diameter, 5 mm distance) embedded within a 3 × 5 isolated silicone matrix. The array is flexible to fit the curvature of the forearm

relates to static placement of electrodes, that is, position changes which occur due to variations in donning of the sleeve, but also to dynamic conditions when, for example, an end user rotates the wrist. As a consequence of the wrist rotation, the stimulation current distribution may change and motor nerves may change their orientation in the electrical field beneath the surface electrodes. Both conditions result in altered muscle activation patterns and accordingly in changes of grasp patterns. As a consequence, end users who hold an object, for example, a glass, firmly in their hand, could lose the grasping force as soon as they start to rotate the hand to drink from the glass.

To counter these effects, the MoreGrasp consortium developed a new type of surface electrode, a so-called array electrode (Fig. 13.5). The array electrode consists of a matrix of up to 15 single electrodes which can be electrically merged by an electronic multiplexer to virtual larger electrodes. Similar to standard surface electrodes, the electrode array is positioned over the motor point of the muscle(s) of interest. But instead of the need for mechanically repositioning the electrode for finding the optimal stimulation location, an electronic "repositioning" is possible by switching between subsets of electrodes within the array. In a dynamic setup, the array electrode allows for compensation of electrode shifts caused by hand rotations by rotation-angle dependent, closed-loop switching of electrodes.

To show that the surface array electrode allows for a wrist-position independent FES-generated extension of the thumb, a proof-of-concept experiment was performed. Due to the small muscles, thumb movements are most prone to changes

of electrode position. For determination of the wrist rotation angle, two inertial measurement units (IMUs) were integrated into the forearm sleeve. The measured wrist rotation angle was fed into the FES control module as an input signal. A stimulation node map was defined at the beginning of the experiment, where the set of electrodes was identified with maximum selectivity for thumb extension as part of the manual screening process in neutral position, in maximal pronation and in maximal supination position of the wrist. Linear interpolation of the stimulation electrode positions in the stimulation map of the FES control module was done after the manual screening process based on the Manhattan-distance to fill in missing values in the input–output matrix. The stimulation frequency was fixed to 20 Hz and a current level was set and kept constant during all conditions that caused a strong thumb extension.

The experiment was performed with two conditions: In a first control condition the most selective electrodes in neutral rotation position of the wrist were constantly stimulated with a fixed current during rotational movements of the wrist toward maximum supination and pronation. In the second condition the electrodes in the array were electronically shifted according to the linear interpolation map based on the calculated wrist rotation angle in real-time. The results of the experiment are shown in Fig. 13.6. In the control condition with fixed stimulation positions, the thumb flexes and adducts toward the palm of the hand when the arm is pronated. In contrast, with wrist-rotation dependent selection of the electrodes, a stable thumb extension independent from the rotation angle can be achieved (cf. Fig. 13.6f, i).

Although a short calibration period is required every time the sleeve with the electrode array(s) is donned, the possibility for dynamic re-positioning of electrode positions without the need for doffing and donning of the sleeve contributes to a large amount to the user-friendliness and to the stability and robustness of the stimulated grasp patterns (G. R. Müller-Putz et al. 2019).

13.3 EEG-Based Neuroprosthesis Control

The MoreGrasp neuroprosthesis was designed to be controlled by a number of different input modalities. One of these modalities is a non-invasive EEG-based BCI.

From the EEG recording technology point of view, the MoreGrasp final objective was to develop wearable and ergonomic EEG recording systems that could be used by end users over extended periods at their homes and that are easy to set up for the end users' relatives or caregivers. The EEG recording technology is one of the main barriers to transfer and deploy EEG-based applications out of the laboratory. To allow this transfer, the specifications of this technology were defined in the early stages of the project with two main principles in mind: (1) guarantee good signal quality to allow reliable EEG recordings needed for the BCI control (comparable to standard gel-based electrodes) and (2) increase the usability and ease the application in daily life (e.g., high aesthetics and short donning and doffing time).

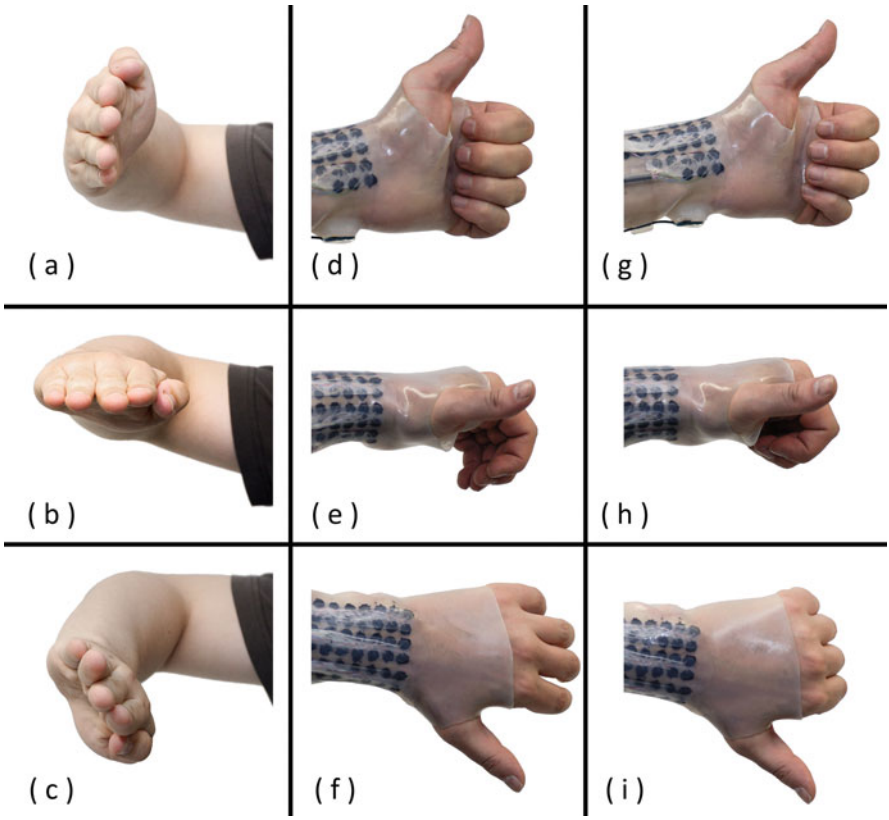

Fig. 13.6 Grasp patterns during three different rotation angles of the wrist. (**a**, **d**, **g**) Neutral position; (**b**, **e**, **h**) 90° supination; (**c**, **f**, **i**) max. pronation; (**a**–**c**) no stimulation; (**d**–**f**) with fixed stimulation electrodes; (**g**–**i**) with wrist-angle adjusted stimulation electrode selection. It can be seen that with active compensation the extended position of the thumb remains stable during rotation of the wrist

We considered two alternatives to the usual gel-based Ag/AgCl electrodes which represent the gold standard regarding signal quality: water-based electrodes and dry electrodes. Water-based electrodes present a viable compromise between signal quality and usability. In comparison to gel-based electrodes, water-based electrodes provide improved usability (e.g., do not require washing the hair after its use) with only low deterioration of the signal quality. Dry electrodes can further improve usability since they do not require any conductive medium and can be set up faster than gel- or water-based systems. However, they are usually more sensitive to artifacts and have a worse signal-to-noise ratio. Within the MoreGrasp project, two types of EEG systems were developed: (1) a water-based system with 32 or 16 channels for the evaluation and training phases, respectively; and (2) a dry headset concept with 12 channels optimized for motor tasks and exploring more user centered designs. Signals recorded with the amplifiers of these systems are transmitted to the MoreGrasp computational unit via Bluetooth wireless technology.

13.3.1 Water-Based EEG System

The water-based system was developed to fulfill two different types of tasks: first, it was used for EEG screenings and evaluations by experts, which required an extensive evaluation of the EEG patterns at specific time points. Second, it was used by the end users with the help of their caregivers or relatives during the training phase and, ideally, after that in their daily activities. Therefore, two different versions of the amplifier system were developed: a 32-channel system for screening and evaluation and a 16-channel amplifier for the use of end users at home. Both EEG amplifiers were battery powered and could be easily placed on the cap or on the end user's wheelchair, thereby minimizing the length of electrode.

Another important aspect of the water-based system was how long the water-soaked sponges below the electrodes retained enough humidity to keep the signal-to-noise ratio at a low level. The shape of the sensor and the material of the sponges are the two main factors at play. By using absorbent materials and keeping them inside a closed sensor case, it was possible to record EEG with high quality for more than 4 h given a proper preparation of the system.

The two versions of the water-based systems are shown in Fig. 13.7a, b. Table 13.1 shows their specifications in detail, and the differences between both systems.

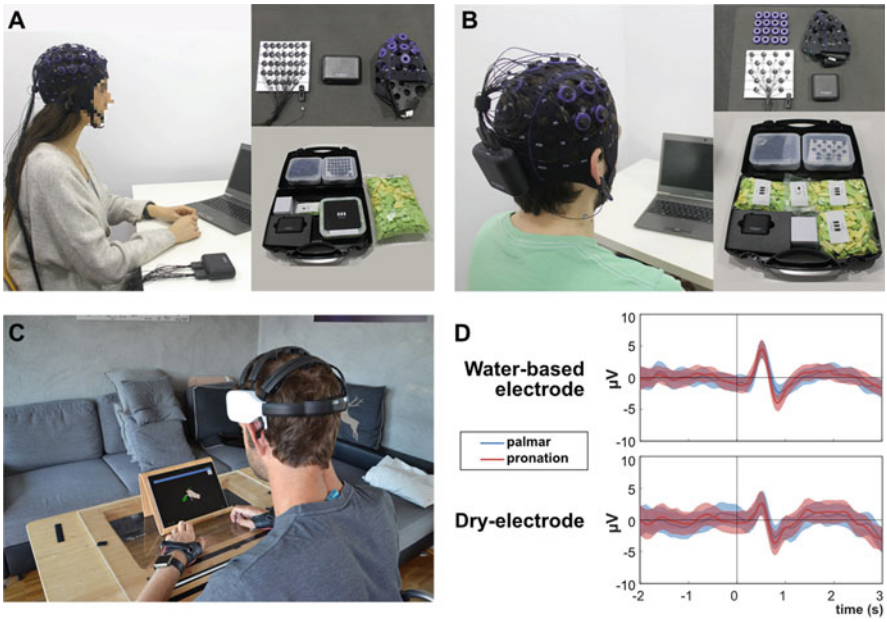

Fig. 13.7 The MoreGrasp EEG recording systems. (**a**) The water-based 32 channel EEG system. (**b**) The water-based 16 channel EEG system. (**c**) End user of the MoreGrasp project equipped with the dry headset and performing the training phase. (**d**) Movement-related cortical potentials averaged across subjects for the water-based (top) and dry electrode recordings (bottom) at channel location Cz. The mean and confidence intervals (alpha = 0.05) are displayed

Table 13.1 Amplifier specifications for the water-based EEG systems

	16 ch EEG recording system	32 ch EEG recording system
Dimensions	78 × 72 × 31 mm	107 × 74 × 32 mm
Weight	121 g	162 g
Inputs	16× EEG + REF + DRL 1× Photodiode 1× IMU 16 bit (9 ch.)	32× EEG + REF + DRL 2× bipolar ExG 1× Photodiode 1× IMU 16 bit (9 ch.)
Sampling Frequency	256 Hz	256 Hz
Input range	±100 mV	±100 mV
Bandwidth	0–40 Hz	0.40 Hz

In addition to the EEG signals, they also provide data from a cap-mounted IMU, a digital and a photodiode input (to synchronize with external visual cues at sample level).

13.3.2 Dry Headset Concept

Dry electrode sensors were considered as an alternative for the final system to be used at the end users' homes. A 12-channel prototype was built to illustrate and evaluate the potential of this technology in an everyday setting. When designing this concept, we also took into account the most consistent feedback from end users regarding neurotechnology: the need for better aesthetics and their reluctance to use the established standard systems due to this issue. With these design guidelines, we opted for a 12-channel layout over the motor cortex. The electrodes were made from sintered silver (Ag/AgCl) with pivoting four legs contact points that allowed the electrodes to bypass hair and to contact the scalp. The electrodes are fixed to an elastic band which adapts to the form of the end users' head. The prototype does not allow for any kind of cabling to promote aesthetic appearance.

13.3.3 Performance of Water and Dry Electrodes

In preliminary system tests, both systems have been compared in a small study based on six non-disabled persons who performed palmar grasp or wrist pronation movements during a cue-based paradigm. The water-based system (32 channels) allowed to record more pronounced movement-related cortical potential (MRCP) pattern and expectantly also achieved a higher movement decoding accuracy than the dry headset (11 channels).

In a larger follow-up study consisting in total of 45 non-disabled study participants, we assessed the performance of both water and dry electrode-based systems as

well as a gel-based system which is considered the "gold standard" for EEG recording. In this study, participants executed reach-and-grasp actions on a glass (palmar grasp) or a spoon (lateral grasp). Results confirmed that recordings using the water-based system provided more pronounced MRCPs than the dry electrode system. However, on group level, the difference in decoding performance was less than 6% compared to both water- and gel-based systems. Encouragingly, both morphology of MRCPs and decoding performance were similar between the water-based and gel-based systems (Schwarz et al. 2020a, b, c).

13.4 Discrimination of Movement-Related Cortical Potentials From EEG

Previous attempts for implementing a BCI for neuroprosthesis control strongly relied on the imagination of movements (Pfurtscheller et al. 2003; Rohm et al. 2013; Kreilinger et al. 2013; Rupp et al. 2013; Gernot R. Müller-Putz et al. 2005). In Purtscheller et al. (2003), the participant with SCI was asked to imagine repeated plantar flexion and extension of both feet, while subsequent studies introduced imagining squeezing a stress ball repeatedly. Eventually, studies on mental strategies revealed a multitude of mental strategies suitable for generating brain signals which machine learning algorithms can discriminate (Friedrich et al. 2013). Unfortunately, these modalities require a form of repeated or continuous imagination, which inevitably leads to a delay to perform the designated task. Additionally, the mental imagery tasks are mostly counterintuitive to the task at hand: performing repeated motor imagination of plantar flexion/extension of both feet (Pfurtscheller et al. 2003) for opening or closing the right hand is rather abstract and feels unnatural to the user. Clearly, a more natural and intuitive form of control had to be found, ideally the imagined or attempted movement should match the final intended action.

13.4.1 MRCPs in Non-disabled People

Recent studies have shown that the MRCPs might hold sufficient information for decoding single attempted or executed movements (Dremstrup et al. 2014; Ofner et al. 2017, 2019; Schwarz et al. 2018, 2019; Pereira et al. 2017; Yang and Yao 2018; Oda and Moritani 1995; López-Larraz et al. 2014; Niazi et al. 2011; Omedes et al. 2017). In the EEG, the MRCP is represented as a negative shift in amplitude over premotor areas, supplementary motor area, and the primary motor cortex during movement preparation (cf. Bereitschaftspotential (Kornhuber and Deecke 1965), starting already up to 2 s before the actual movement) which reaches its maximum negativity right before the movement onset is detectable via EMG (called the motor potential). Thereafter, several potentials can be identified but are not consistently

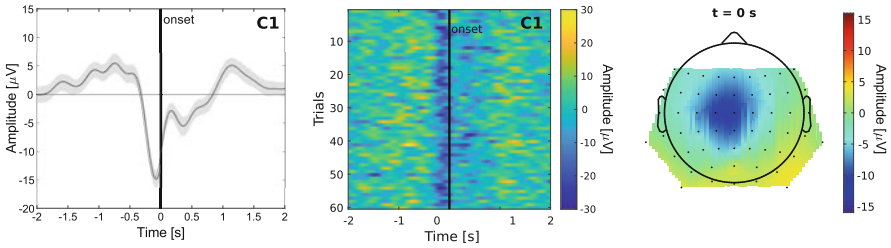

Fig. 13.8 Movement-related cortical potential of one non-disabled participant, for explanatory purposes. Left: Channel C1, Grand average of 60 reach-and-grasp movement trials (palmar grasp, executed with the right hand). The black perpendicular line shows the movement onset, measured with a photoresistor placed on the start position. Center: Single-trial image representing all movement repetitions and the respective potentials at channel C1: the negative deflection can be found consistently over all trials around the detected movement onset at 0 s. Right: Topographical map representing the spatial distribution at the detected movement onset ($t = 0$ s): a fronto-central and broad negative deflection occurs, slightly contralateral to the movement, with higher amplitudes on the electrodes over the motor areas

defined in the literature (Shibasaki and Hallett 2006). In Fig. 13.8 we provide an example of a movement-related cortical potential elicited during the execution of a reach-and-grasp movement.

The advantage of using MRCPs compared to modulations in the, for example, mu band, is twofold: first, a single executed movement is sufficient for eliciting an MRCP, making repetitive (imagined) movements as in classical BCI paradigms obsolete. Second, an MRCP is also elicited when a movement is attempted or even imagined. Thus, a natural and intuitive association between the attempted movement and the desired movement can be made. Exemplarily, the end user attempts to grasp a glass, and subsequently, the BCI detects the evoked MRCP, and the neuroprosthesis performs the palmar grasp. In previous studies, it has already been shown that MRCPs encode, for example, the grasp kinematics (Agashe et al. 2015), different levels of grasp force and speed (Jochumsen et al. 2013) or different reach and grasp movements (Iturrate et al. 2018; Schwarz et al. 2018, 2019). To verify the potential of MRCPs for neuroprosthesis control, two studies in non-disabled participants were conducted (Ofner et al. 2017; Schwarz et al. 2018).

In a first study (Ofner et al. 2017) we investigated whether different upper limb movements could be discriminated using MRCPs. Fifteen non-disabled participants volunteered to participate in the experiment. Their task was to execute six different upper limb movements according to the instructions presented on a screen: elbow flexion, elbow extension, wrist supination, wrist pronation, hand closing, and hand opening. In a second session, participants were asked to just imagine these movements. In the offline analysis, we discriminated the six different executed movements against each other with an accuracy of 55%, and any movement against no movement with an accuracy of 87%. Whereas in the session where participants imagined the movement, 27% and 73% were achieved for movement versus movement and movement versus rest, respectively. For both sessions, the chance level

was lower than 20% when classifying movements. Detailed analysis showed that movement conditions involving different joints (e.g., hand opening vs. wrist supination) are better to discriminate, which might eventually be beneficial for independently controlling movements of different joints with the neuroprosthesis. Details on paradigm and results are given in Fig. 13.9a.

In a second study (Schwarz et al. 2018), we investigated whether executed reach-and-grasp actions could be discriminated against each other. Fifteen non-disabled participants volunteered to participate in the experiment and were asked to execute reach-and-grasp actions on objects of daily life: a glass (palmar grasp), a key (lateral grasp), and the pin of a needle (pinch grasp). We could also show that better than chance classification of these tasks was possible with an accuracy around 66% for all involved reach-and-grasp tasks including a no-movement condition. Additionally, we could show that the first second after start of the movement held the most information for discrimination. Nevertheless, better than chance discrimination could already be performed one second before the actual movement. Details on paradigm and results are given in Fig. 13.9b.

13.4.2 MRCPs in People with High SCI

Based on the findings in the previous studies with non-disabled participants (Ofner et al. 2017; Schwarz et al. 2018), we conducted an EEG study (Ofner et al. 2019) including also end users with tetraplegia. The study consisted of two parts: first, we investigated in an offline analysis whether attempted arm and hand movements of participants with SCI could be classified from low-frequency time-domain EEG signals. Second, we introduced a proof-of-concept of an MRCP-based online classifier for self-paced hand movements in one participant with SCI.

For the first part, we measured ten participants with cervical SCI (see Table 13.2 for details on the status of participants) while they attempted or executed the following non-repetitive movements: wrist pronation, wrist supination, palmar grasp, lateral grasp, or hand open. The paradigm is described in Fig. 13.10. Note that in this study we asked the participants to execute or to attempt the movement, instead of using movement imagination. This change in mental strategy had three main reasons: first, the results of our previous study in non-disabled participants (Ofner et al. 2017) have not been promising regarding the discrimination of imagined non-repetitive single movements. As already mentioned, classification accuracies were substantially smaller when compared to the discrimination of executed movements. Second, MRCPs evoked by attempted movements have been observed in persons with SCI—despite being altered when compared to subjects without disabilities (Xu et al. 2014). Third, it has been shown in people with tetraplegia that attempted movements were generating more pronounced patterns than MI in the frequency-domain (Blokland et al. 2012).

In (Ofner et al. 2019), we could show for the first time that MRCPs of people with SCI are different depending on the attempted arm/hand movement (Fig. 13.10b). In a

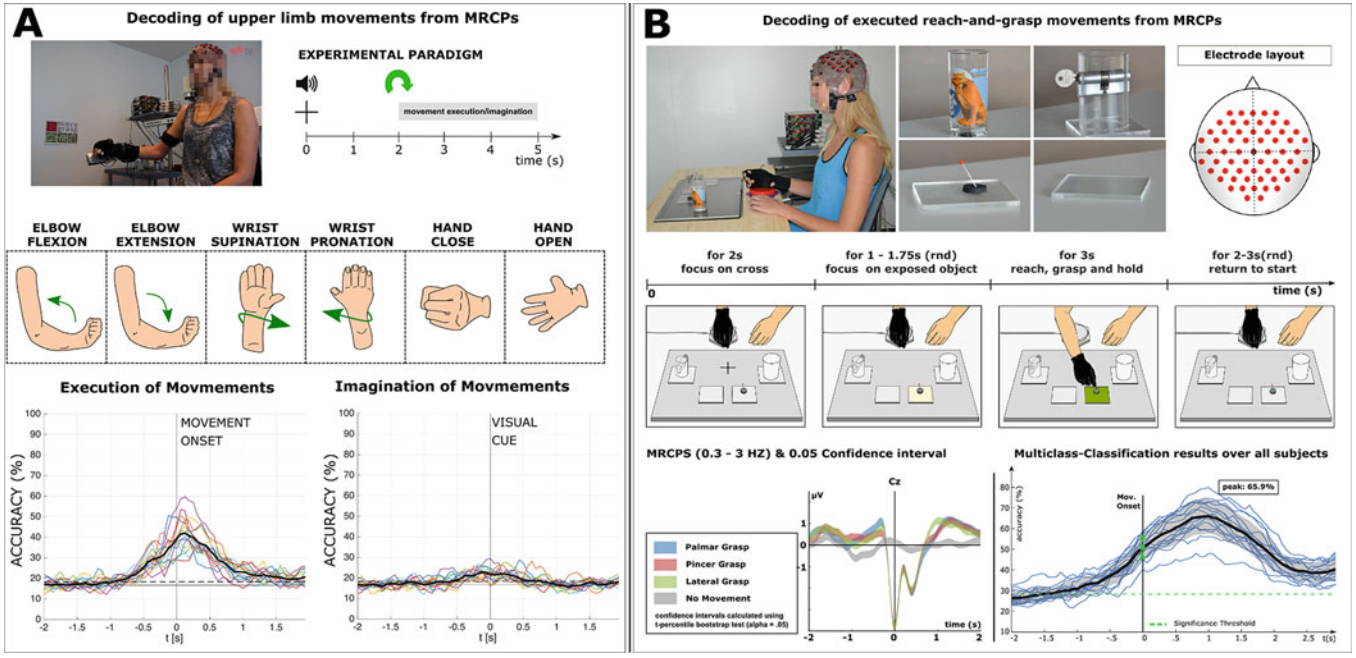

Fig. 13.9 (**a**) Experimental paradigm and performance results for decoding upper limb movements. Participants were asked to execute six different movements in a cue guided paradigm (top right). In a second session, the participants were asked to imagine the same set of movements. Grand average results over all subjects (bottom, bold black line) indicate better than chance accuracy peaking at 55% for executed movements. However, for imagined movements, the performance was lower, peaking at 27%. Figures taken and modified from (Ofner et al. 2017). (**b**) (Top) Experimental design and performance results for decoding reach-and-grasp actions. Objects of daily life were chosen for the experiment, representing three different grasp types which are commonly used most: palmar, lateral, and pincer grasp. Participants were asked to reach and grasp the objects on the table, highlighted by an inbuilt screen. (Bottom left) MRCPs of all three reach-and-grasp conditions including a no movement condition (gray). (Bottom right) Multiclass classification results. Figures taken and modified from (Schwarz et al. 2018)

Table 13.2 Characteristics of the participants measured in (Ofner et al. 2019)

Participant	Sex	Age [years]	Tested hand	Time since lesion [months]	AIS	NLI
P01	Male	35	Right	11	B	C6
P02	Male	42	Right	10	D	C1
P03	Male	62	Right	7	B	C5
P04	Female	20	Right	9	B	C5
P05	Male	57	Right	9	A	C4
P06	Male	78	Right	7	D	C5
P07	Male	27	Left	4	C	C4
P08	Male	69	Right	0	B	C7
P09	Male	53	Right	2	A	C4
P10	Male	55	Right	11	A	C6

AIS American Spinal Injury Association Impairment Scale, *NLI* Neurological Level of Injury. Explanation of AIS grades: *A* complete, *B* sensory incomplete, *C* motor incomplete, *D* motor incomplete

multiclass classification scenario (5-class, chance-level performance at 20%), a grand-average accuracy of 45.3% was obtained around 1 s after the class cue presentation (Fig. 13.10c). Similar to our findings in non-disabled participants (Ofner et al. 2017), the discriminability depended on the joints involved in the movement. Concretely, movement classes of closely related joints (e.g., wrist supination vs. pronation) were less discriminable than movements of more independently controlled joints (e.g., wrist supination vs. hand open).

It is important to note that the preserved motor functions of the participants were not homogenous. For this reason, we analyzed a subset of participants with no active hand movement (ISNCSCI motor score of 0 or 1 for finger flexors and little finger abductor). In this analysis, we selected hand open, palmar and lateral grasp movement classes, and performed a 3-class offline classification. Grand-average classification accuracy peaked with 53% at 1 s after class cue presentation (chance level was at 33.3%). This result was of particular importance, because it showed that the movement classes could be successfully discriminated against each other, even if the movement was only attempted.

These results motivated the first proof-of-concept of an MRCP-based BCI to discriminate between hand open and palmar grasp, and an additional rest class, also published in (Ofner et al. 2019). Participant P09, who had a complete SCI with no preserved hand function (see Table 13.2), participated in two additional sessions on 2 consecutive days.

Regarding the performance of the movement versus rest classification, a true positive rate (TPR) of around 30% (i.e., correctly *detected* movements, independent of the movement class), with more than three false positives (FP) per minute (i.e., false movement detections) were obtained. MRCPs for both training and test paradigms of the proof-of-concept are in Fig. 13.10c, d, respectively. Classification of hand open versus palmar grasp was possible with a classification accuracy of 68.4% (which was analyzed only on the true positives of movement vs. rest). While the online classifier performance in this proof-of-concept is not sufficient to be used for

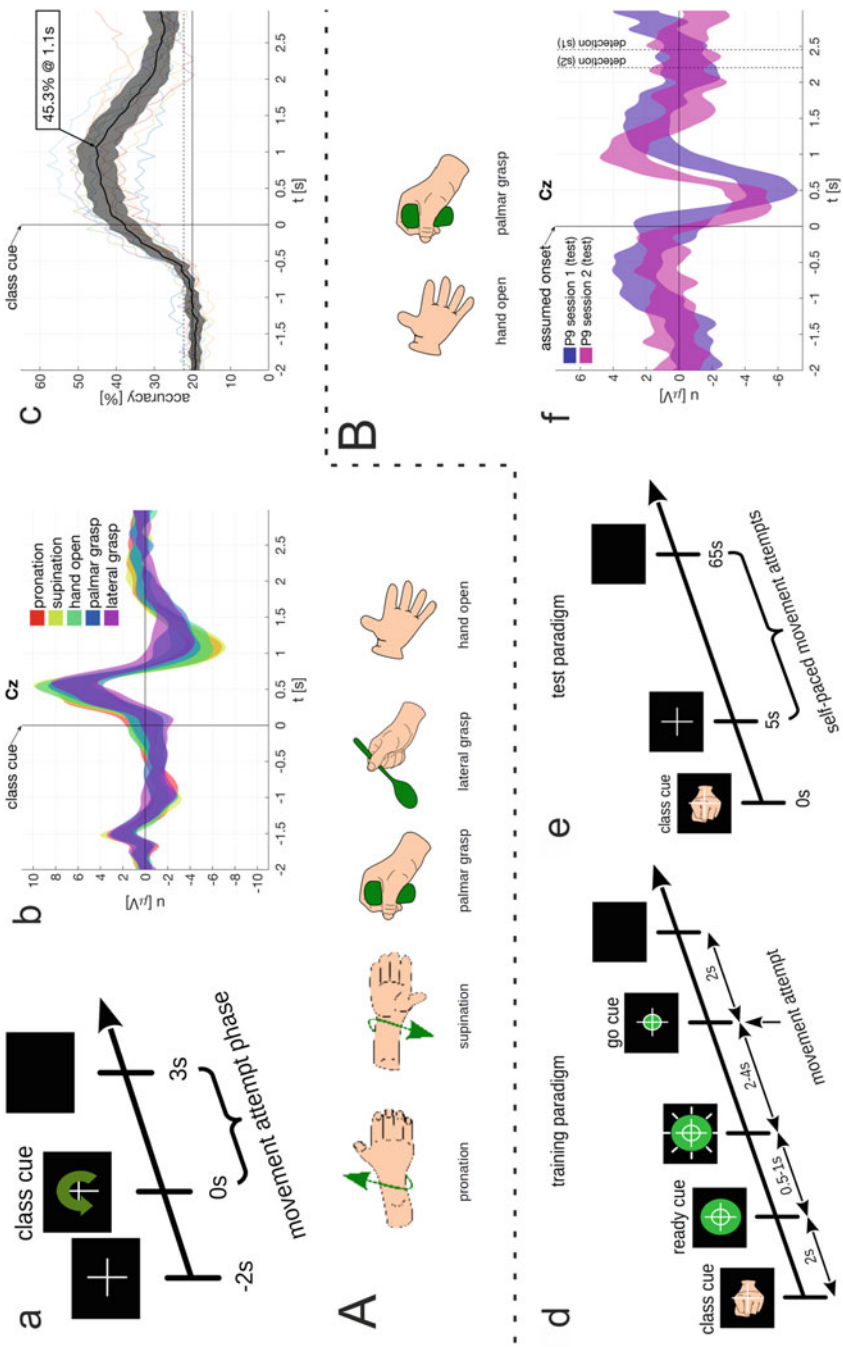

Fig. 13.10 (**a**) Offline study in SCI population. (*a*) Paradigm for screening of attempted movements in people with SCI. The class cue was different for each of the movements: wrist pronation, wrist supination, palmar grasp, lateral grasp, and hand open. (*b*) Grand-average MRCPs for the movements screened. (*c*)

Fig. 13.10 (continued) Grand-average classification accuracy through time (think black line). Subject-specific accuracies are plotted in thinner lines. Images were adapted from (Ofner et al. 2019). (**b**) Proof-of-concept for online control in one user with SCI. (*d*) Training paradigm, (*e*) test paradigm, (*f*) MRCPs in electrode Cz on the training paradigm for both sessions, (*d*) MRCPs in electrode Cz on the test paradigm for both sessions. Figure modified (Ofner et al. 2019)

neuroprostheses control, we show for the first time the general feasibility of discriminating different upper-limb movements online in an end user with SCI.

13.5 Instrumentation of Everyday Objects

Awareness of the environment a user operates in can provide supporting evidence for user intention. Depending on the object that is closest to the end user's hand the system could, for example, make an informed guess of the intended grasp type and grasp force for a future grasping action. In the MoreGrasp project, we explored this idea via instrumented objects, everyday objects that are instrumented with sensors. Specifically, we built movement and touch-sensitive sensors as shown in Fig. 13.11. With this, touch or nudging events can be detected. These events can be used as a control modality to adjust the grasp type if the hand is opened, and to adjust the grasp pressure if the hand is grasping. In addition to supporting neuroprosthesis control, sensor data from instrumented objects can be useful for (continual) quantitative

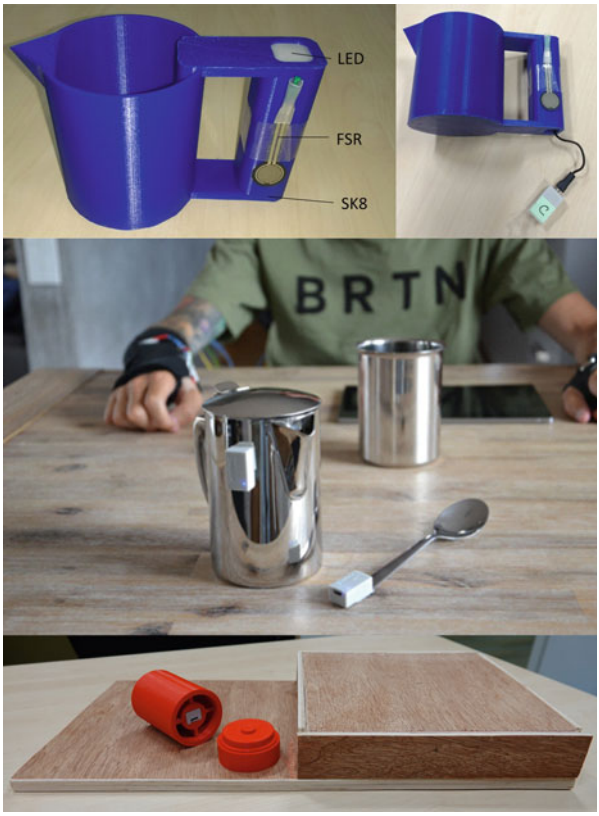

Fig. 13.11 Instrumented objects of daily life. (Top) The plastic can prototype was sensorized using a force sensitive resistor and a wireless IMU. (Center) Battery operated IMUs can be mounted on any object. They transmit any event wirelessly via Bluetooth to the computational unit. (Bottom) Sensorized cylinder from the Grasp and Release test

assessment of grasping performance, for example, during the standardized Grasp and Release test (GRT) (Wuolle et al. 1994).

13.6 Multimodal Control Principles

Successful FES-supported grasping requires continuous, real-time control. Existing neuroprostheses are driven by low-bandwidth constrained input channels such as an EEG-based BCI or a shoulder position sensor. Efficient interfaces are required that maximize the control of these channels with minimum effort and allow the user to decide which input modality to use depending on preference, context, or fatigue. Environmental sensing can be helpful for inference of user intent (e.g., which type of grasp to use) by capturing broader contextual information about reaching and grasping tasks. This has the potential to empower users to conduct everyday tasks through the limited control channels available.

13.6.1 Shared Control Principles and Architecture

In the scope of the MoreGrasp project, we developed a concept of shared control for the MoreGrasp neuroprosthesis. Shared control is a control method in which a human and a machine conduct a task by being able to delegate elements of the control loop between each other (Williamson and Murray-Smith 2012; Sheridan 2002; Tonin et al. 2010; Carlson et al. 2011; Pohl and Murray-Smith 2013). This can include automatic delegation of control tasks from human to machine in cases where the human is certain that the machine can cope with the situation, is tired of controlling the system through a particular modality (e.g., muscle cramps in shoulder control, or mental fatigue with BCI) or needs to focus on something else in the environment.

The development of our shared control architecture was driven by the following principles: the system should be able to reason under the uncertainty of noisy and ambiguous input, to gracefully handle sensor failure, and to respond safely to emergency situations. The shared control architecture has a set of loosely coupled, configurable elements as illustrated in Fig. 13.12. A sensor encoder unit estimates the probabilities of binary events such as “is the hand close enough to an object to grasp?”, “is the user activating the shoulder joystick?”, and “is the BCI indicating a grasping intent?” from sensor feature vectors. A Bayesian network with binary nodes estimates the intention of the user (e.g., “switch to palmar grasp” or “increase grasp pressure”) in terms of discrete functional electrical stimulation outcomes, and the certainty of that estimate. User feedback from this unit indicates prediction of user intentions. An action-state-machine monitors the probability of actions, and switches between activity states (e.g., “begin open grasp fully now”) when probability thresholds are crossed. Outputs affecting the estimation of intention (e.g., “the

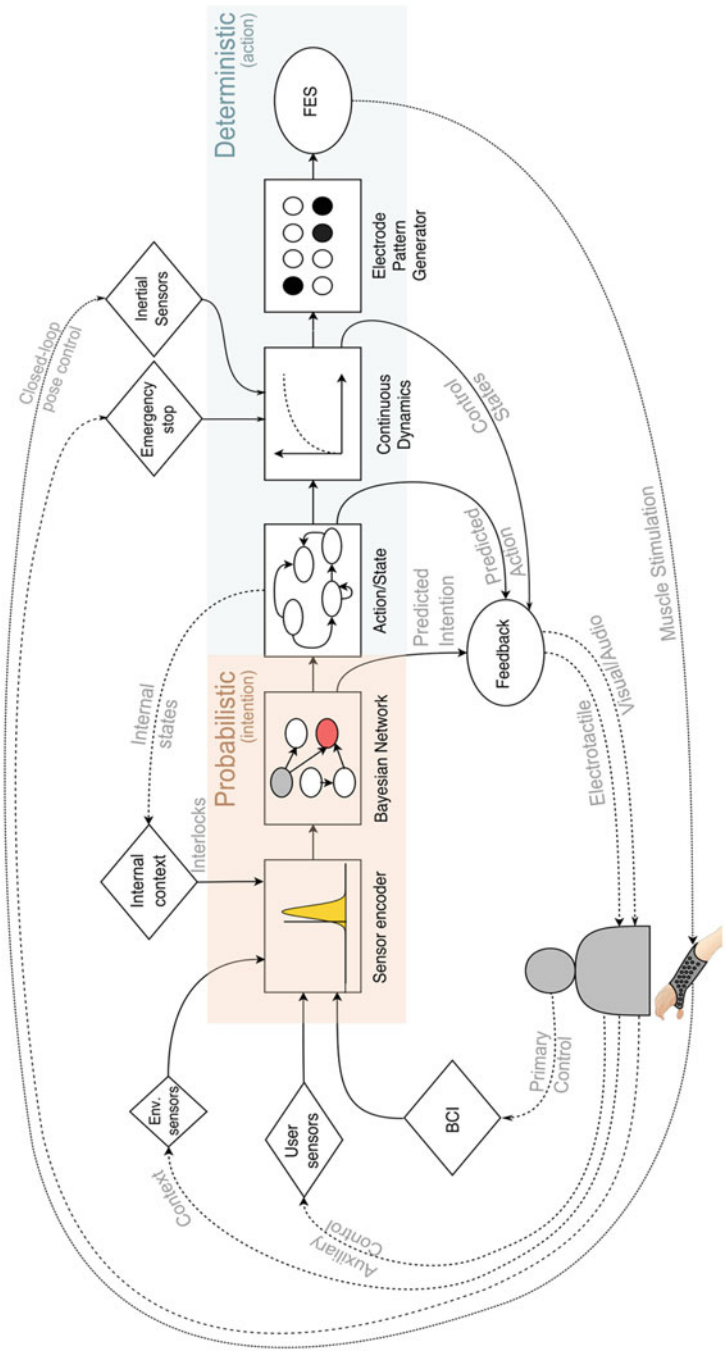

Fig. 13.12 Shared control structure, showing the internal processing pipeline and the user in the loop. A probabilistic intention decoder is connected to a deterministic action synthesizer

user is unlikely to release grasp 5ms after opening it") are fed back to the Bayesian network. User feedback from this unit indicates prediction of future actions. A continuous dynamics module generates the signals to open, close, or reconfigure the hand smoothly over time when the action-state-machine indicates a change of state, separating the synthesis of continuous values from underlying discrete states. Direct feedback from the sleeve inertial sensing will be used for closed-loop control in this module. The "emergency stop" estimator overrides all pattern generation and ensures safe and quick return to a neutral state. The electrode pattern generator generates appropriate FES patterns across the electrode array to satisfy the continuous dynamics required.

The system is fully probabilistic between the sensor input vectors and the action-state-machine, which makes it practical to support sensors with widely varying reliability and also to provide meaningful feedback about inferred user intentions. It is feasible to reason about the intention decoding process because of our simplifying assumptions that (i) intention can be mapped onto a set of (unknown) latent binary variables, (ii) that actions can be seen as transitions in a finite-state machine, and (iii) continuous closed-loop physical output can be generated from discrete internal transitions. This framework is flexible enough to support interaction spread over time. For example, a grasp may be triggered by the BCI in advance but only executed when the probability of being close enough to an object is sufficiently high. Alternatively, the BCI could immediately issue commands, but be "locked out" by holding the shoulder high (measured by a shoulder joystick) to suppress control. Estimates of both local reliability (per-command) and general reliability (e.g., tiredness detection) can be encoded as rules in the Bayesian network to support control across the full spectrum of signal quality.

13.6.2 Adaptability and Customization

The factorization of the decoding/control process allows different elements of behavior to be implemented by altering the Bayesian Network, without interfering with the optimization of electrode patterns or the continuous-time dynamics. Each of the pipeline elements can be customized with a significant degree of independence, even after the system has been delivered to the end user. Sensor encoders can be activated, deactivated, or reconfigured, for example, to support different control modalities. The Bayesian Network intent inference logic can be adapted to user preference. Finite-state-machines can be reconfigured, for example, to change transitions between hand configurations. Continuous dynamics can be adjusted to account for varying muscle responses.

13.7 Feedback to the End User

End users with SCI who require FES stimulation to actuate their muscles necessarily have an impairment of the sensation in their hands, and do not adequately perceive how they are grasping objects. Furthermore, when an intelligent system is in-the-loop assisting users with grasping functions, it is essential that users can understand and predict the actions that assistance will take.

There are many modalities available to deliver feedback. Tailoring the choice of modality, taking into account the perceptual effects, physical constraints (e.g., wiring requirements, screen placement, power draw), social acceptability, and overall aesthetic design is critical to the MoreGrasp platform being effective. Visual feedback is the most obvious display modality. However, a traditional visual display requires a screen, such as a monitor or tablet. This must be placed somewhere in the environment, and adds to the setup complexity and limits the scenarios in which the neuroprosthesis can be used. Critically, it also draws visual attention that would normally be diverted towards the object being manipulated.

Alternative options, such as head-mounted displays were rejected as infeasible due to excessive complexity and ergonomic constraints. As a compromise between ergonomic feasibility and display fidelity, we developed a simple body-worn display using a smartwatch platform (see Fig. 13.13). This provides a small, unobtrusive display that can be worn comfortably on the wrist by end users for long periods or can be unobtrusively mounted at the wheelchair. We designed simple visual displays for action feedback to be shown on this display. The main idea for this type of feedback is to ensure the end user aligns his/her conceptual model of the system with the current state of the system, enforcing understandability and usability.

The information about the action variables that need to be fed back contains the current type of grasp and the intensity applied via the FES. This is communicated using a picture to encode the type of grasp and a color code to show the amount of

Fig. 13.13 All possible visual feedback modalities presented on the smartwatch. The key symbolizes the lateral grasp and the cup symbolizes the palmar grasp. The color coding conveys the intensity of the FES stimulation, red for high, yellow for medium and green for low

stimulation exercised. The smartwatch display can be queried at any time, allowing the user to verify the state of the system in a glimpse.

13.8 Web-Based Technology and Toolkits

Right from the start, the MoreGrasp project required a battery of different evaluation and training tools which assisted not only MoreGrasp experts in their decision making, but also guided MoreGrasp end users through the various stages of training.

13.8.1 Toolkit System Architecture

The MoreGrasp service combined various hardware and software elements in a complex exchange of information (see Fig. 13.14).

Mobile tools had two major requirements to ensure reliability: first, hardware operation and control should not be hindered by setup and presentation of the user interfaces, and second, data collection should be independent from internet connectivity. The former implied that the used hardware needed to provide sufficient performance to smoothly run both the user interface and all MoreGrasp prototype related processes. For this reason, a powerful laptop computer with mechanically robust Solid-State-Drives (computational unit, CU) is used, which can be stored in a

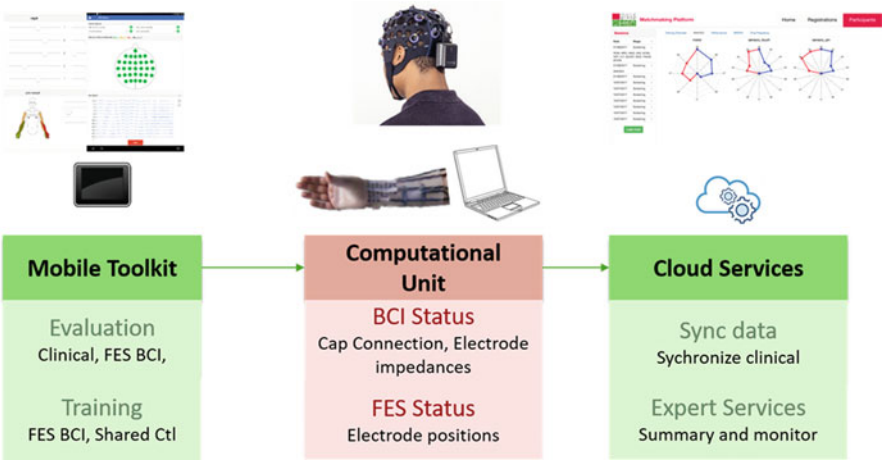

Fig. 13.14 Overview of the MoreGrasp system modules. Toolkits installed on a tablet communicate via WiFi with the computational unit (CU), a PC which is mounted in a backpack on the end user's wheelchair. Whenever a stable internet connection can be established, the CU connects to MoreGrasp cloud services and synchronizes training data, which in turn can be analyzed by MoreGrasp experts

backpack behind the wheelchair. An Android-based tablet computer was used as a mobile user interface. This made it possible to separate computing and communication equipment from the devices with which the user directly interacts. The mobile equipment communicated via a proprietary WiFi network, allowing it to operate independently without connection to the internet. As soon as a connection to the Internet was established, a cloud service synchronized the local data with the MoreGrasp server.

13.8.2 MoreGrasp Registration Platform

Potential end users interested in participation in the MoreGrasp clinical study could use a web-based registration platform found on the project website (www.moregrasp.eu). The registration platform consisted of a number of online questionnaires and forms to gather basic personal information, but also asked for information of, for example, the type accident which led to the SCI or basic residual motor skills ("can you move your hand to your mouth?", "can you bend your elbow?"). In addition, applicants were also able to upload videos to demonstrate their residual movement capabilities.

Once an applicant completed the online registration, the system notified MoreGrasp experts who evaluated the gathered data and videos and decided whether the applicant fulfilled the basic requirements to allow a further introduction to the study. The developed graphical interface allowed experts to apply interactive filters on the information as well as comparisons between different applicants.

13.8.3 Functional Assessment: The MoreGrasp Mobile Evaluation Toolkit (MET)

The main purpose of the screening was to evaluate whether a study applicant fulfills all requirements and is eligible for the MoreGrasp clinical study program. For this, not only the neurological and musculoskeletal status was assessed, but also first EEG sessions were performed to assess BCI-capabilities. The MoreGrasp Mobile Evaluation Toolkit (MET) provided experts a convenient platform for assessment. For the clinical evaluation, it provided interactive digital forms to assess inter alia (i) International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI), (ii) Range of Motion (ROM), (iii) Medical Research Council (MRC) or (iv) Modified Ashworth Scale (MAS).

In addition the MET also provided an interface for FES based assessments. The FES assessment has three purposes: First, to identify denervated muscles caused by a SCI-associated damage of lower motor neurons at the level of the lesion. The degree of denervation might result in an inability of using the neuroprosthesis. Second, to

find the optimal electrode positions for selective stimulation of single muscles or muscle groups which are necessary to generate different grasp patterns. The third purpose of the screening is to obtain information on the characteristics of the muscle groups to be stimulated and to define the initial training parameters.

Lastly, the MET provided functionality to assess the BCI capabilities of a person. Via the MET, experts are capable of checking the EEG-signals and electrode impedances and could configure a BCI paradigm which is tailored to the users capabilities.

13.8.4 At the End Users Homes: The Mobile Training Toolkit (MTT)

Once end users were accepted for inclusion in the study, the end user training was performed at their homes with the help of caregivers. As such, a control interface was necessary to allow non-experts to operate the MoreGrasp prototype.

The Mobile Training Toolkit (MTT) consisted of minimalist interfaces so that inexperienced users can quickly learn to operate the MoreGrasp system in order to start training. The FES training required observing the proper assembly of the neuroprosthesis which included correct positioning of the electrodes and starting the training. The BCI training also required observing the correct assembly and mounting of the equipment and control of electrode impedances. BCI training required the user to choose a training protocol and a classification model. Once the protocol is initiated, the interface displays the graphic stimulus to generate the signals.

13.8.5 Matchmaking Platform

The matchmaking platform consolidated all data collected from participants. It was used by experts to define steps in the progress of a user towards independent use of the MoreGrasp neuroprosthesis. As every end user took part in different examinations, a large body of heterogeneous data was collected. The matchmaking platform provided interfaces for a BCI and neurophysiological expert to get a clear overview of the end user's status and progress. As data was synchronized from the mobile toolkits, the platform generated visual reports for experts, including visualizations of clinical data.

The matchmaking platform displayed these data as radar graphs as shown in Fig. 13.15. The graphs (i.e., motor scores, light touch and pin-prick sensation scores) were organized in circular layers and represented the spinal segments from C2 to T1 from top to bottom. The left half-circle represents the left side of the body and the right half-circle the right side, respectively. At each spinal level, the motor/sensory

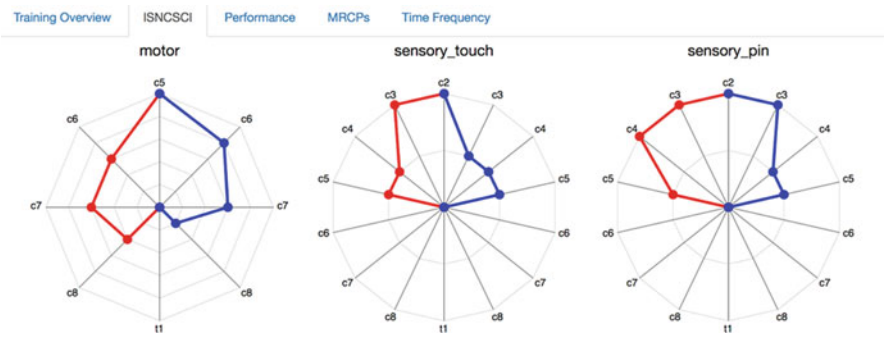

Fig. 13.15 Radar graphs to visualize clinical test data, in this case ISNCSCI motor and sensory scores of cervical and highest thoracic spinal segments

score was marked as a dot, with a larger distance to the center indicating a higher score.

For BCI data, the matchmaking platform illustrated movement classification accuracy over time. The accuracy incorporated several classes, depending on the recorded session (Fig. 13.16, left). Additionally, it was also possible to inspect MRCPs for the different movement attempts for each session (as seen in Fig. 13.16, right).

13.9 The MoreGrasp Clinical Feasibility Study

The primary goal of the pilot study was to test the usability and feasibility of the MoreGrasp neuroprosthesis prototype in cooperation with end users with tetraplegia and their relatives and caregivers at their homes. This section focuses on the description of the protocol of the MoreGrasp clinical study, and first results are presented on the neuroprosthesis and BCI use.

13.9.1 The MoreGrasp Study Protocol

Potential end-users had the possibility to express their interest in participating in the MoreGrasp clinical feasibility study using the web-based registration platform on the project website (www.moregrasp.eu). Upon registration, the potential MoreGrasp end users are asked about basic information regarding their injury pattern and residual motor functions. Since MoreGrasp is a multicenter trial, both Germany and Austria were possible countries of recruitment. The clinical trial has been registered at the DRKS with ID DRKS00013785 (more details can be found at www.drks.de). MoreGrasp clinical experts receive an alert every time a new

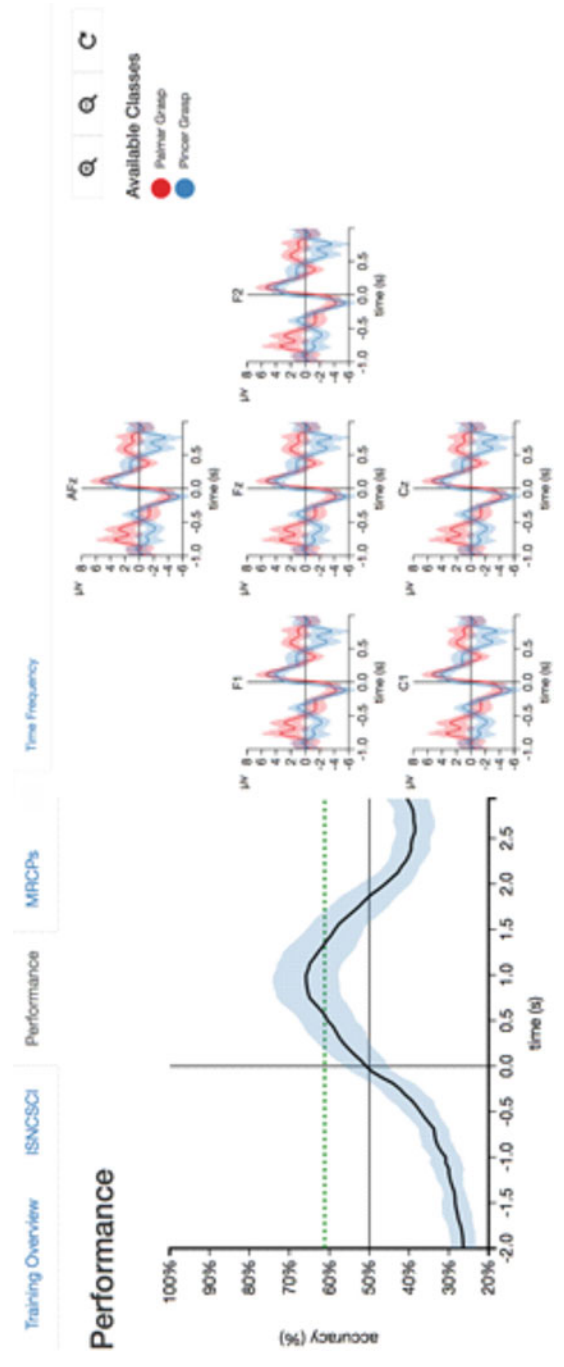

Fig. 13.16 Left: Performance overview of the classification accuracy. Right: MRCPs in selected channels for two different movement attempts (palmar and pincer grasp)

Table 13.3 Inclusion and exclusion criteria of the MoreGrasp clinical study

Inclusion criteria
– Gender: Both, male and female
– Minimum Age: 18 Years
– Subacute to chronic cervical SCI with time since injury ≥6 months and missing or weak grasp function
– Sufficient voluntary shoulder movements and elbow flexion on one side, preferably on the dominant side
– Capacity to consent
Exclusion criteria
– Severe restrictions in the passive range of movement of the joints of the upper limb (>30% of physiological range of motion)
– Severe spasticity in the upper limbs
– Skin diseases like infections, psoriasis, burns. at the upper limbs
– Hyperesthesia of the upper limbs (upper and lower arm), which would not allow to increase FES intensity to a sufficient level of contraction force
– Cardiac pacemaker, other active implants like medication pumps, phrenic pacemaker.
– Metal implants in the direct area of current flow under the stimulation electrodes
– Plexus paresis or other injuries/diseases that lead to extensive denervation of muscles of the upper limbs
– Known history of epilepsy
– Severe cognitive impairment or psychiatric conditions that restrict the use of a neuroprosthesis
– Pregnancy

registration on the project website was made, and the candidates were prescreened for study eligibility based on predefined inclusion and exclusion criteria (see Table 13.3). Table 13.4 shows a list of the study participants included at the time of writing.

If candidates have been evaluated as potential study participants, a first in-person visit was scheduled, in which the candidate has been introduced to the nature of the clinical study. After informed consent has been obtained, initial neuro-musculoskeletal and BCI screenings were performed. The first neuro-musculoskeletal screening consisted of an ISNCSCI exam, testing of restrictions of passive ROM, voluntary muscle strength according to MRC, grading of spasticity with the MAS, and a testing of the FES-generated grasp strength. The latter is of utmost importance because people have to be excluded in case of severe denervation of muscles. Due to its importance it was in fact the first assessment performed in a potential MoreGrasp candidate.

Details about the BCI screening are given in the section below. After inclusion in the clinical study, users performed FES and BCI training separately (Training 1 in Fig. 13.17), first with the help of experts and at later stages only with the help of caregivers. After this initial training phase, which takes ideally around 8 weeks, the second training phase (Training 2 in Fig. 13.17) started, in which end users are free to use the system for activities of daily living at their homes without supervision with their preferred control modalities (i.e., BCI control, shoulder joystick, instrumented objects, or combinations of the previous modalities).

Table 13.4 Characteristics of the MoreGrasp study participants

Participant	Sex	Age [years]	Tested hand	Time since lesion [months]	AIS	NLI
GRZ001	Male		Left	20	B	C4
GRZ002[a]	Female		Right	2	C	C4
GRZ003	Male		Right	5	B	C4
GRZ004[b]	Female		Right	24	B	C4
GRZ005	Male		Left	7	A	C2
GRZ006	Male		Right	5	B	C2
GRZ007	Male		Left	2	A	C4
GRZ009[b]	Male		Left	Missing	B	C4
UKLHD002	Male		Left	7	A	C5
UKLHD003[a]	Male		Left	4	A	C3
UKLHD004[b]	Male		Right	1	A	C3
UKLHD005[b]	Male		Right	35	A	C4
UKLHD006[b]	Female		Right	2	A	C4
UKLHD007[b]	Female		Right	2	B	C5
UKLHD008[a]	Male		Right	4	A	C5
UKLHD009[b]	Male		Right	2	B	C4

AIS American spinal injury association impairment scale, *NLI* neurological level of injury. Explanation of AIS grades: *A* complete, *B* sensory incomplete, *C* motor incomplete, *D* motor incomplete
[a]Dropped out by own decision
[b]Excluded after first screenings due to denervated muscles

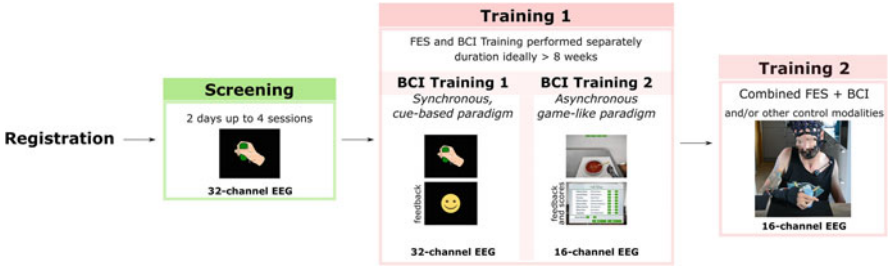

Fig. 13.17 MoreGrasp screening and training protocols

13.9.1.1 BCI-Controlled MoreGrasp Neuroprosthesis

Earlier in this chapter, we have already presented several studies that showed that different executed (in non-disabled participants (Ofner et al. 2017; Schwarz et al. 2018)) or attempted (in SCI participants (Ofner et al. 2019)) movements can be discriminated from the low-frequency time-domain of the EEG. In the MoreGrasp clinical study, we evaluated the applicability of the BCI technology for neuroprosthesis control in end users at their homes. For this, BCI screening and training protocols were developed and included in the MoreGrasp system's Mobile Evaluation and Training Toolkits. In this section we present both protocols and we show the initial BCI screening sessions results (G. R. Muller-Putz et al. 2019), in

which different non-repetitive movements of the upper-limb were screened and it was then determined, offline, whether they were discriminable. All data obtained was recorded using the MoreGrasp system, including its water-based EEG system.

BCI Screening

The experimental paradigm of the BCI screening sessions was a cue-based paradigm which is very similar to the paradigms used in (Ofner et al. 2017, 2019). The timing and visual cues used are shown in Fig. 13.18a. At second 0, a cross appeared on the tablet display, together with an auditory beep to get the participant's attention. At second 2, a cue indicating the type of movement to be attempted was shown. This consisted of a hand icon with different postures corresponding to the four movements (wrist rotation, palmar, lateral, and hand open) and a rest cue (stop sign). As soon as the movement cue appears, the participants were instructed to perform a movement attempt, starting from a neutral and slightly opened hand position. The cues were displayed for 3 s, followed by a 1-s break in which participants could perform eye blinks or other artifacts. A total of 75–80 trials per class were recorded. For these sessions, the 32-channel EEG setup of the water-based system was used.

Figure 13.18b shows the grand-average MRCPs on channel Cz for six participants on the first screening session relative to the palmar and lateral grasp movement attempts. From these first results, we could already conclude that there is a high inter-individual variability of MRCPs, with respect to their morphology and also timings relative to the cue presentation.

BCI Training

After screening, we continued using the cue-based paradigm so that the participants could train their designated movement tasks. Aside from that, we also found it necessary to communicate the importance of reducing artifacts on the EEG and the

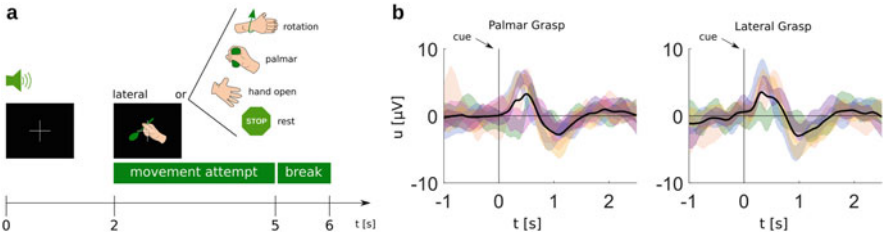

Fig. 13.18 BCI screening in the clinical study. (**a**) Cue-based paradigm, which is used for screening but also for training stages. As soon as the cue is presented, the participant is instructed to perform the corresponding movement attempt. After 3 s, there is a short break and the next trial starts. (**b**) Grand-average MRCPs on channel Cz for palmar and lateral grasp (thick black lines). Individual subjects are plotted in colored lines. Adapted from (G. R. Muller-Putz et al. 2019)

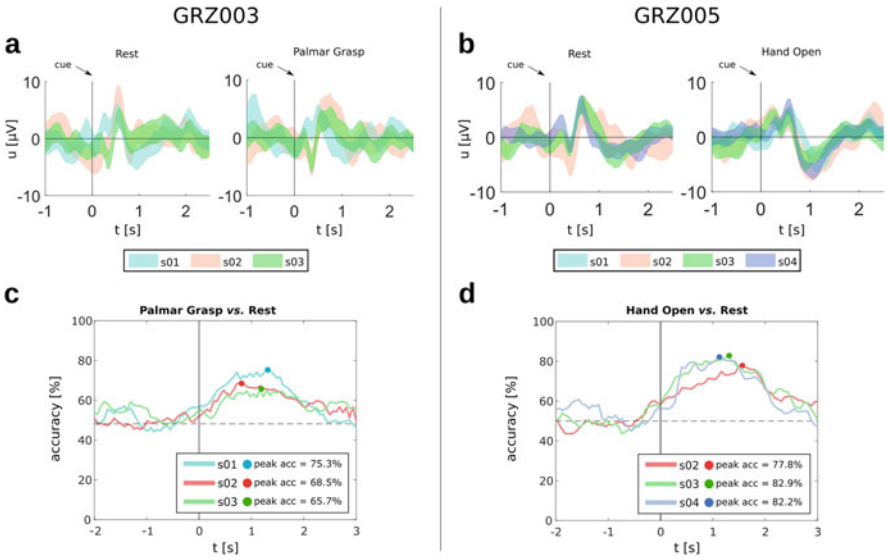

Fig. 13.19 Multi-session results with the cue-based paradigm. (**a**) Grand-average MRCPs on channel Cz for GRZ003 (palmar grasp and rest conditions). (**b**) Grand-average MRCPs on channel Cz for GRZ005 (hand open and rest conditions). (**c**) Classification accuracies through time with respect to the movement cue for palmar grasp versus rest for GRZ003. (**d**) Classification accuracies through time with respect to the movement cue for hand open versus rest for GRZ005. Adapted from (G. R. Müller-Putz et al. 2019)

negative impact of eye movements and muscular artifacts specifically during the period of the movement attempt (since it contaminates the features necessary for the classifier calibration). In these sessions we investigated whether there is an inter-session variability in terms of MRCPs duration and shape, but also on whether there was a change in offline classification performance. In Fig. 13.19 we show the MRCPs for the participants GRZ003 and GRZ005 in multiple sessions. Figure 13.19a shows the MRCPs for palmar grasp in GRZ003 and Fig. 13.19b the MRCPs for hand opening in GRZ005. For comparison, we also show the rest class for both participants. For rest and movement conditions, it is possible to observe a positive peak at around 500 ms after cue presentation. For GRZ005 we additionally observed a negative deflection on the movement condition, while for GRZ003 there is no negativity. Figure 13.19c, d shows the classification accuracies of movement versus rest for the respective sessions through time, with respect to the cue (second 0). For all sessions and both participants, we observed accuracies above chance-level after cue-presentation, reaching peak accuracies of 75/69/66% for sessions s01/s02/03 for GRZ003, and higher peak accuracies for GRZ005 of 78/83/82% for sessions s02/s03/s04. The potentials observed for GRZ005 more closely resemble the typical MRCPs shape, and this was most likely reflected in the higher classification accuracies of this participant. It is also important to mention that for GRZ003 the reduced 16-channel EEG setup was used for sessions s02 and s03, and

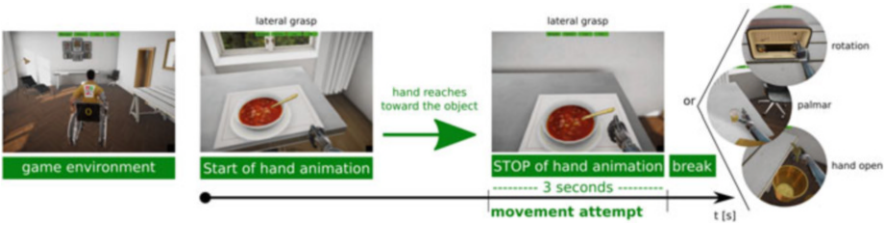

Fig. 13.20 BCI game paradigm for BCI training. The participant was instructed to start the movement attempt as soon as the hand stopped in front of the object which is the final target of the movement. In the current example, the hand approached the spoon. When it stopped the participant should immediately attempt a lateral grasp. As with the cue-based paradigm, the participant has 3 s to perform the non-repetitive movement attempt. After a 3-s break, a new trial starts

session s02 was conducted by the participant's caregiver who operated the system independently from the support by technical experts.

As we have seen in the screening sessions but also in (Ofner et al. 2017, 2019), the recordings of these cue-based paradigms contained not only MRCPs but also superimposed potentials likely related to the perception and cognitive processing of the visual cues. This affects the features necessary for calibration of the classification model. For that reason, we developed a game-like paradigm which intended to counter the negative effects of the presentation of discrete cues, as well as to mimic a more realistic control scenario. This paradigm is described in Fig. 13.20. Aside from avoiding the discrete cues so that the training data more closely resembles the free-control scenario data, we also aimed to make BCI-training more engaging and appealing to the user. After calibrating the classification model, the participant could decide to test it with performing some game trials with feedback. If feedback was selected and in the case of a correct movement classification, the complete action is executed, for example, for the palmar grasp the glass is grasped if the correct movement was classified. This classification model can also be used to directly control the neuroprostheses, without the need of any paradigm or cue display on the tablet.

13.9.2 MoreGrasp Neuroprosthesis Application

Up to this point, two (GRZ003, UKLHD002) MoreGrasp study participants have completed FES training and have been provided with their individualized MoreGrasp neuroprosthesis. The grasping performance was tested with the Grasp and Release test (GRT) (see Fig. 13.21) (Wuolle et al. 1994).

For the test, both participants were seated in front of a table. The MoreGrasp neuroprosthesis was already attached to their limb. For controlling the neuroprosthesis, they used a shoulder-operated joystick which was mounted on the opposite body side of the hand equipped with the electrode sleeve.

Fig. 13.21 Schematic of the Grasp and Release test: Within 2 min, the study participants had to grasp the designated object, transfer it on the podium and release it for as often as possible. In each 2 min run, only one type of object was used (cylinder, paper weight, VHS tape)

A testboard was positioned in front of the end user in a comfortable reaching position. One half of the testboard was elevated and acted as a podium (see Fig. 13.21). On the opposite side, test objects were placed by the experimenter. Different types of test objects were equally weighted and had to be grasped with different grasps: a cylinder and a VHS tape using the palmar grasp, a paper weight with a lateral grasp. For each test run, only one object type was used.

Participants were instructed to grasp the object on the board, transfer it on the podium of the board and safely release it (see Fig. 13.22). In a total of 9 runs (3 per object type) each lasting 2 min neuroprosthesis users were requested to complete as many grasp-transfer-release cycles as possible. The number of fully successfully performed cycles was recorded as outcome measure. To compare to a baseline, the test was also performed without the MoreGrasp neuroprosthesis.

Figure 13.22 shows participant GRZ003 performing the GRT for all three test object types. Results (see Fig. 13.23) indicate that with the MoreGrasp neuroprosthesis, which was controlled in this case via the shoulder joystick, the number of successfully completed grasp-transfer-release cycles increased when compared to baseline (i.e., no FES). Especially for participant UKLHD002, the use of the neuroprosthesis resulted in a considerably higher performance compared to baseline. Both participants also used the neuroprosthesis in daily life activities. Figure 13.24 (top row) shows participant GRZ003 during a meal: Using the shoulder-joystick-operated neuroprosthesis, he grasped the fork using a lateral grasp. The force of the thumb was strong enough to allow normal use of the fork. The bottom row shows participant UKLHD002 holding a 330 mL bottle (full) with the palmar grasp and drinking from it. Again, the force applied by the fingers was strong enough to hold the bottle safely during lifting and tilting it towards his mouth.

13.10 Discussion

In this chapter, we showed the technology developed in the European Horizon 2020 project "MoreGrasp", together with initial results of the associated clinical study. The development of the web-based infrastructure and the MoreGrasp neuroprosthesis prototype has been finalized, and first results on usability and feasibility were obtained in the MoreGrasp clinical study.

Fig. 13.22 MoreGrasp study participant GRZ003 performing a Grasp and Release test. (**a**) The end user grasps the cylinder (blue object) with a palmar grasp and transfers it to the podium. (**b**) For the paperweight, a lateral grasp is used. (**c**) The videotape was the most difficult to grasp for him due to its size

Within the MoreGrasp project, the consortium was able to develop a neuroprosthesis prototype which can be fully individualized to end users' needs and priorities. The newly developed surface array electrodes allow for easy and fast calibration of the grasp pattern after donning. In addition, the dynamic adaptation of stimulation locations inside the array increases the robustness of the generated grasp patterns during for example wrist rotations.

Furthermore, a structured screening and training procedure has been established to identify potential MoreGrasp end users and to prepare them for home-based use of the system for activities of daily living. For the training procedure, a standardized muscle training clinical algorithm was implemented which can be adapted to the musculoskeletal status of end users. Provided their motivation and compliance, the muscle stimulation training conditions them to the best of their ability for neuroprosthesis use.

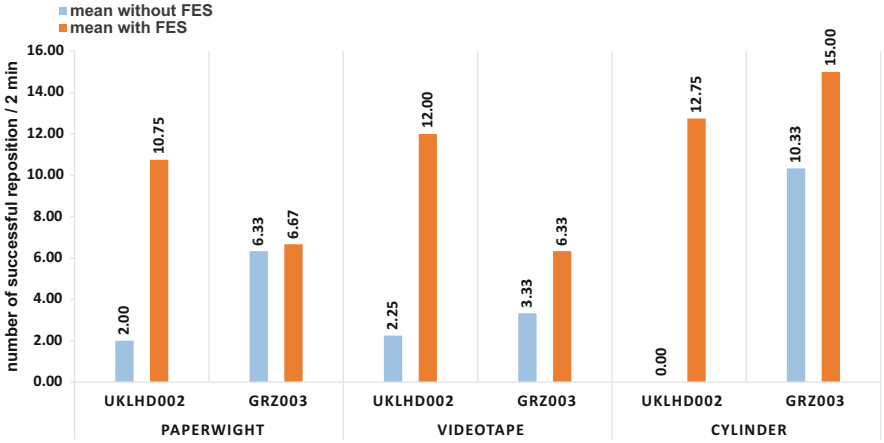

Fig. 13.23 GRT results for MoreGrasp end users UKLHD002 and GRZ003. The bars represent the mean of the successfully completed grasp-and-release cycles for 3 runs. Blue bars show the results when performed without the neuroprosthesis, orange bars for using the neuroprosthesis

Fig. 13.24 Neuroprosthesis application in daily life settings (Top Row): Participant GRZ003 is using a fork to eat spaghetti. (Bottom Row) Participant UKLHD002 is drinking from a bottle. Both participants use a joystick mounted on the contralateral shoulder to control the MoreGrasp neuroprosthesis

13.10.1 Neuroprosthesis Control Modalities

Decisive efforts were made to study and explore possibilities for a natural BCI-based control of the grasp neuroprosthesis. Several studies in non-disabled participants as well as in end users with SCI could show that in a controlled laboratory environment, singular upper limb movements can be decoded from the low frequency time domain of the EEG (Ofner et al. 2017, 2019; Schwarz et al. 2018, 2020b, c; Pereira et al. 2017). However, BCI decoding results, both calculated offline as well as from experiments with real-time feedback, indicated that the achieved performance is not sufficient to allow a robust control by BCI alone. In addition, the step to a real-time asynchronous control, in which the movement intention of the user is self-paced, represents a serious challenge and needs to be further explored. Furthermore, initial results already obtained in MoreGrasp end users suggest that there is a high individual variability in terms of MRCP morphology and timings, which makes it very hard to obtain a stable classification model on a recurrent daily basis.

The MoreGrasp prototype as a whole was designed with multimodal control in mind. This includes establishing control of the neuroprosthesis using the BCI together with a shoulder joystick mounted on the contralateral shoulder and instrumented objects: A potential application scenario for a hybrid BCI (Pfurtscheller 2010; G. Muller-Putz et al. 2015) combining the BCI with the shoulder joystick could be to decode the intended grasp type with the BCI and use the shoulder joystick to control the degree of hand opening and closing (Rohm et al. 2013). Instrumented objects are intended to further reduce the workload of end users of the MoreGrasp system. They allow for semiautomatic selection of the most appropriate grasp pattern for this object when being touched. Evaluations with end users showed that all components of the MoreGrasp prototype can be individually set up in respect to the status and needs of each end user in a way that their manipulation skills are improved. This has been proven by the quantitative results obtained in many evaluation sessions in multiple end users. The MoreGrasp consortium undertook substantial efforts to achieve a level of reliability and usability of the MoreGrasp prototype sufficient for everyday use over 2–3 h/day without the help of technical experts. However, the long-term experiments with end users using the system at their homes showed that this aim was only partially achieved. While the BCI approach of the MoreGrasp prototype offered the most intuitive way of control, its decoding performance was not yet sufficient to allow for everyday use. Although the shoulder joystick provided reliable control for some hours, end users and their caregivers reported problems with the fixation. Additionally, a functionality is needed so that end users can recalibrate the range of motion needed for control of hand opening and closing. The structured feedback collected from end users revealed that further improvements, such as an ergonomic joystick housing, wireless connections, and low weight of the shoulder joystick will further increase user acceptance and most probably control reliability. Although the concept of the instrumented objects was shown to be feasible, further developments in respect to battery lifetime, wireless charging concept, and general usability aspects such as

waterproofness will improve their acceptance in daily life activities. Nevertheless, all this information could only be collected because a comprehensive assessment scheme has been used in the MoreGrasp study. This highlights the importance of implementation of a user-centered design process into any assistive technology trial.

13.10.2 From the Controlled Laboratory Environment to the End Users' Homes

The transition from experimental laboratory prototypes operated and supervised by researchers to an easy to use, robust system which is intended for everyday use by non-experts is complex and challenging. Within the MoreGrasp project, a number of novel technologies attempted to ease this transition, in order to make the technology not only better approachable by end users and caregivers, but also to assist experts in their work.

One of the more salient technologies developed were the water-based EEG systems. The wirelessly operated EEG system established skin contact between electrodes and scalp via moistened sponges and were easy to apply. The amplifier was attached to the EEG cap itself which kept cabling to a minimum. As part of the MoreGrasp clinical study, the caregivers of GRZ003 were instructed in mounting the EEG system by themselves and were eventually able to operate the EEG system and check signal quality and channel impedances with only minimal assistance. In this way, they also recorded BCI training sessions completely on their own.

The tablet-based mobile toolkits for evaluation and training represented the core parts of the MoreGrasp project. All data from clinical and FES-based evaluations (this included the generation of complex stimulation maps of the arm to form basic grasp patterns) were digitized. It formed also the basis for the BCI evaluation and could act not only as an interface to check signal quality and electrode impedances, but also as a display to present BCI paradigms. Eventually, all data, either instrumented data or data manually entered with the app of the MoreGrasp Mobile Toolkit, were stored on a secured MoreGrasp server for further evaluation and processing. From a technical point of view, the MoreGrasp prototype is designed as a distributed system, which is highly dependent on wireless communication—a necessity for minimizing any cable connections. However, the use of the system at end users' homes showed that not every end user's home was equipped with a high-bandwidth internet connection with an unlimited data transfer volume allowing a permanent connection to the MoreGrasp cloud. In out-of-the-laboratory environments, this is not an uncommon situation and is often encountered also in hospitals, where data protection (patient sensitive data) is imperative. The solution of the MoreGrasp experts was to rely within the distributed system on wireless connections via Bluetooth and WiFi, but was not in demand of a permanent internet connection. Only when a connection was available and agreed by the end users, the system connected to the cloud for data exchange.

13.10.3 The MoreGrasp Clinical Feasibility Study

So far, two end users have completed FES training and were fitted with customized MoreGrasp neuroprostheses. The initial evaluation results from the Grasp and Release test have shown that an improvement in grasping function can be reached on an individual basis. However, we also saw strong differences in these results between both tested participants: for instance, while participant UKLHD002 was not able to grasp the cylinder with the bare hand, participant GRZ003 was able to put the cylinder on average more than 10 times on the podium. Eventually, participant UKLHD002 was able to reposition the cylinder on average 12 times with neuroprosthesis support (GRZ003 average, 15 times). These variations between participants result from different grasping strategies, but foremost from different physiological parameters such as the grade of muscle denervation or residual voluntary motor functions. Nevertheless, in limited field tests, both participants were able to perform tasks of daily life, using a fork for eating spaghetti or holding a full bottle and drink from it. The individual results indicate that it is important to include assessments that quantify the individual success of participants and their subjective impression rather than only focusing on standardized quantification on a group level.

Regarding the handling of the MoreGrasp prototype, both study participants and their caregivers were able to perform FES-based stimulation training for several weeks completely on their own. In the later stages of the study, GRZ003 and his caregivers were even able to perform BCI training with only limited assistance via video chat.

Single components, such as donning the neuroprosthesis, attaching a shoulder joystick or even mounting the BCI headset did not pose extraordinary problems to end users and their caregivers or relatives. However, the operation of the prototype independent from technical experts was perceived by end users as challenging. The feedback from users shows that the interplay between individual components of the prototype introduced an additional layer of complexity. The usability of the MoreGrasp prototype can be substantially improved by further integration efforts combining the FES, computing, and user interface components into a single system. However, due to limited budgets in a research project, off-the-shelf components such as standard laptop computers, wireless interfaces, and FES-stimulators had to be used, which resulted in a large size, high weight, and limited usability. As an example, with several standard components simple functionalities like a central power switch to turn the whole system on and off or a central charge connector are technically not feasible.

13.10.4 Industrial Uptake Scenario

The MoreGrasp consortium included industrial partners to define scenarios and identify requirements for a potential future industrial uptake. To transfer a prototype like the MoreGrasp prototype into an industrial application—a product—is a complex challenge in many ways. Industrial uptake is where most of the promising solutions developed in research projects fail. The main issue with respect to the MoreGrasp prototype is—given the assumption that the outcomes of the clinical study show a substantial functional benefit in end users:

> How can such a highly complex and multimodal system designed for a comparatively small target patient group be successfully marketed?

In our opinion, the industrial transfer of the technology developed in MoreGrasp can only succeed if several stakeholders cooperate successfully. In our view, the most likely way of industrial uptake is that the MoreGrasp technology will be made available through a network of partners, rather than imposing the responsibility to a single company. A cooperation of industrial and clinical partners is able to contribute individual parts to the product, while simultaneously reducing the economic risk for a single company.

On top of this cooperation, MoreGrasp representatives are needed for the control and the communication between the partners, but also for many other important tasks. This group of experts represents MoreGrasp externally and is responsible for the essential cooperation with rehabilitation clinics. These clinics are the first points of contact for the end users of the MoreGrasp system and have the competence to identify potential users, to inform them and to carry out the screening procedure. Before end users can use the entire system, BCI and FES training is required. This process takes a few weeks though there are possible solutions to support the training without professional support, there is an obvious need for personal attention at least at the beginning of the training period. The start of the training must be monitored and supervised by professionals from rehabilitation clinics. To make this procedure possible, MoreGrasp representatives visit the participating clinics and train their staff. The adaptation, use and maintenance of the system (screening, training, and application) are explained in workshops. The physicians and therapists working in the clinics need to be convinced of the additional value of the developed solution so that a partnership-based cooperation can develop. Arguments for cooperation are, of course, the benefits for the end users, the expansion of the service portfolio with an associated increase in attractiveness and the financial remuneration of their work by healthcare payers.

In addition, distribution partners have to be found in the form of specialized medical supply stores, so that a comprehensive supply can be achieved. A large number of such companies with field service points sell rehabilitation technology and are usually also familiar with the use of high-priced aids (e.g., electric wheelchairs to which the MoreGrasp system is to be attached). Furthermore, these distribution partners need to be intensively trained and can later instruct end users,

relatives, and caregivers in the use of the system and training. Appropriate economic incentives must be offered for such cooperation.

A task that should not be underestimated will be to convince healthcare payers of the added value of the desired solution. It is not only a question of the healthcare payers bearing the costs for the arising and not insignificant costs, but also of informing the insured person in the best case scenario, should the MoreGrasp system be a suitable help. In this regard, efficacy studies with the MoreGrasp prototype are necessary to unveil the potential of the technology. Based on the outcomes of these studies, potential savings for the health care systems can be estimated, which is an important argument for healthcare providers. The following list shows a simple calculation example for the costs of a caregiver. The assumption is that an end user regains enough independence using the MoreGrasp system to reduce the necessary daily care time of the caregiver by 20%.

Savings for health system:

Reduced necessary care time by caregiver:	20%
Approximate salary per month:	4000 €
Resulting savings per caregiver/month:	800 €
Reduced additional costs due to better health	
condition (per month):	100 €
Reduced cost per year and product:	**10,800 €**

This admittingly rough estimate highlights only the caregiver dimension and does not take into account other dimensions such as a reduced need of healthcare appliances or a potential income for health insurance companies through contributions to health insurance funds due to a possible part-time employment.

The future success of technology such as the MoreGrasp system and the transfer of innovative research results into clinical practice will depend on the successful collaboration of several parties and the clarification of regulatory and reimbursement issues in such a way that potential end users can ultimately be provided with a solution that has been developed not only for them but with them.

13.11 Conclusion

Within the European MoreGrasp initiative we were able to develop a closed-loop upper limb grasp neuroprosthesis which can be tailored specifically to end users' needs and capabilities. For the neuroprosthesis, we developed novel, surface-based arrays electrodes which allow optimal stimulation of motor points even when the arm position changes (e.g., wrist rotation) leading to an increased reliability in daily life situations.

We assessed the feasibility of several control modalities, such as BCIs, shoulder joysticks, and sensor-equipped daily life objects. In respect to BCIs, we explored brain patterns associated with single upper limb movements such as grasps or wrist

rotations in order to utilize these for an intuitive neuroprosthesis control. We could show that these movements were represented in the low frequency time domain of the EEG. Evaluations with end users showed that the FES and control modalities of the MoreGrasp prototype can be individually set up in respect to the status and needs of each end user in a way that their manipulation skills are improved. Though our investigations showed that BCI-based decoding of movement attempts was possible in a controlled laboratory environment, it needs to be shown in the clinical study if the performance is sufficient to allow for reliable neuroprosthesis control.

The feedback from end users collected in the user-centered design process of the MoreGrasp project allowed us to identify aspects of the prototype which need further improvement. A high level of usability is a prerequisite for acceptance by end users.

The initial results of the MoreGrasp feasibility study revealed that the autonomous use of the prototype by end users is challenging and needs to be further streamlined and simplified. A starting point may be the multimodal control approach: while multimodal control offers the end user a variety of input modalities, it is also a source of additional complexity. A viable approach would be to quantify the end users performance using all control modalities in an "intermediate screening session," for example, shortly after the completed FES training period. Including only the best performing and most reliable control modality, experts could closely tailor a simplified prototype to the end user.

On the plus side, the supporting infrastructure such as the cloud-based platform and the tablet-based toolkits for evaluation and training exceeded expectations. Although further streamlining regarding usability is necessary, the toolkits proved to be a reliable tool during the evaluation sessions. Especially the app-based clinical assessment forms proved to be invaluable and could be an addition for any electronic hospital information system.

The results of the FES screening process of the MoreGrasp clinical trial showed that the extent of denervation of upper limb muscles was higher than initially expected, which led to an unexpected high exclusion rate. At this point, it is unclear if this is a general characteristic of the end user target group, which developed in recent years, or our comparatively small recruited end user population was biased in an unfavorable way. Hence, additional efforts have to be undertaken to systematically investigate the severity and extent of denervation of upper limb muscles within the target population on a large scale.

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Part V
Outlook

Chapter 14
Therapies of the Future

Thomas Stieglitz

Abstract Current developments and trends in research might contribute to potential therapies of the future. However, user preferences vary with age, lifestyle, social status, and societal changes. This overview outlines different aspects that are crucial for successful implementation of prospective clinical therapies. It presents innovative technologies and cutting-edge research developments, while focusing on those with a high level of technological maturity. Micromachined electrode arrays, optoelectronic probes for light stimulation of genetically modified nerve cells, and "thought-control" of assistive devices are presented and discussed. Aspects of translational research and some personal thoughts conclude this view in the crystal ball of brain–computer interfaces for individuals with spinal cord injury toward human applications in daily life.

Keywords Neural implant · Electrode · Optogenetics · Bioelectronics medicine · Shared control · Translational research · Emerging technologies

14.1 Desires and Needs for the Future

Prediction of future therapies must somehow bridge the expectations between a look in the crystal ball and reality. When we imagine future therapies, we might wonder why devices are not available that we have seen in the movies from Disney, Pixar, and the Marvel studios. Science fiction and phantasy movies suggest metal armors that let humans act with superhuman forces and let us become avatars that safe virtual worlds just by the power of their thoughts. Humans have flown to the moon and the Internet knows answers to every question. In reality, assistive devices look much simpler. How to prevent false expectations on promises that cannot be met and

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to prevent disappointment in persons that are desperately looking for solutions at any monetary and personal cost? Key for the definition of future treatments after spinal cord injury (SCI) is how and to which degree a new technology can increase independency in activities of daily living and how much effort is needed to use this technology on a daily basis. Second question covers the accessibility of a technology or treatment. How many institutions competently offering an effective therapy are available and at which average distance to the persons in need of these treatments? Third, are there any restrictions in use, for example, is this treatment only available in the context of a research project or is there support for its long-term daily use? Is there any restriction with respect to the environment? Must it be dry or does it also work under wet conditions, for example, under the shower? Is any additional equipment or support necessary like high-speed computers, experts that help in calibration or something related to this? Fourth, how mature is the technology brought to the user? Is it "brand new" or is there already some experience and history with the devices, their longevity, and the approval as medical device?

This paragraph will put some light on different aspects of future therapies. Who is defining wishes and desires of these potential treatments, for example? Who does transfer and test them in clinical practice and in-home use? Is there any reimbursement possible when the user is lucky enough to live in a country where public healthcare exists at a decent level? How many persons are in need of such an assistive technology and will the number be large enough to develop a business model that pays off for entrepreneurs and investors? Who is driving and funding research in this field? It is impossible to give answers to all of these questions in this chapter, but it will provide some insights in fundamental and translational research lines in neuroscience and neural engineering that might be able to contribute to future treatments. Critical comments will accompany the presentation of novel developments to highlight general challenges such as time lines, market size of treatments, and necessary investments as well as hurdles in translation of basic research results into approved medical devices for assistance in activities of daily living in people with after SCI.

14.2 The Push of Emerging Technologies

The microelectronic revolution started some decades ago and created new consumer electronic devices that changed daily life and communication dramatically. Internet and smartphones allow to exchange photos, videos, and voice messages, instantaneously all over the world. Cars are rolling computers and resemble game consoles. Today's average cell phone has more computing power than the computers in Apollo 11 that performed the first crewed landing on the moon in 1969. Active implantable medical device (AIMD), which is the technical term for stimulation and recording implants, however, still look similar to their ancestors of the 1970s. While electronic circuits inside implants approved for routine clinical use represent state-of-the-art technology, allow complex online signal processing, detect movements by

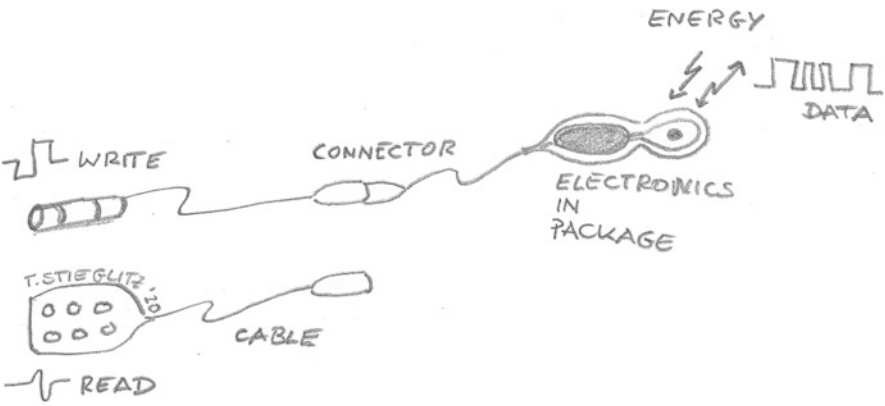

Fig. 14.1 Components of an active implantable medical device for biosignal recording and stimulation

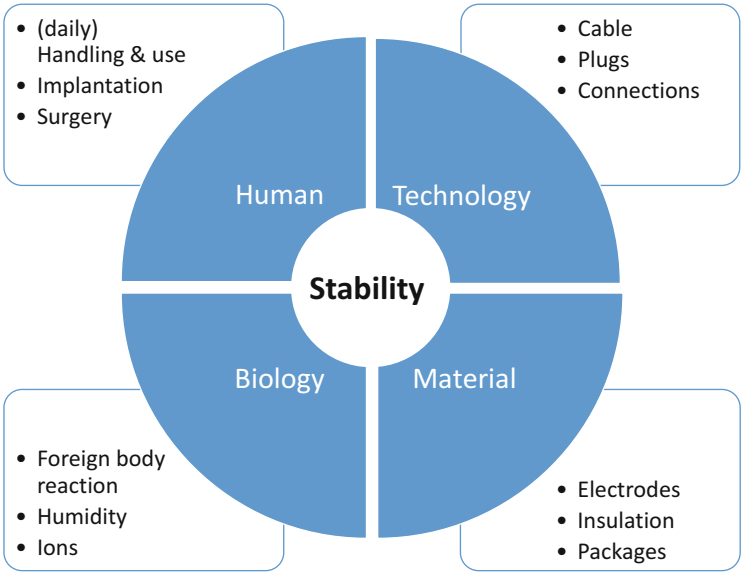

Fig. 14.2 Aspects contributing to implant stability

miniaturized accelerometers, and are able to send out data streams or receive information to generate and adapt stimulation pulses at high speed, packages, cables, connectors, and electrodes still look quite "old-fashioned" (Fig. 14.1).

Safety and reliability demands (Fig. 14.2) as well as comprehensive test and documentation requirements from legal authorities lead to rather evolutionary refinements and conservative design choices than to revolutionary changes. Researchers are continuously shifting the technological limits.

Governmental funding programs have guided and facilitated research by focus topics. Examples are the "Revolutionary Prostheses Program," the "Haptx" for delivering sensory feedback, or the "Brain Initiative" in the USA. Recently, the significant increase of channels to interface with neuronal target tissue is in focus of a US Defense Advanced Research Projects Agency (DARPA) program. Micro- and nanotechnologies together with information technology and artificial intelligence are expected to create disruptive implants. These implants shall be able to acquire nerve signals at high spatial and temporal resolution, to extract information out of huge data streams, to decipher the neural code and ultimately result in novel treatment options (Robinsonlab 2018). Academic researchers as well as newly founded companies compete with brilliant mind-blowing concepts for money and promise to conduct the first-in-human clinical trials soon.

However, in the end, end user acceptance and market penetration will be the true indicators of sustainable success rather than early high impact journal publications. To better understand innovation and the rationale of technology-driven research, some neuroscientific aspects will be introduced in the following paragraph before presenting examples of cutting-edge technological developments.

14.3 The Pull of Neuroscientific Research

A better understanding of the neurobiology of the brain is obviously needed to develop better treatment options in the future. Neuroscientists work hard on the discovery of anatomical details, functional connections of cells, networks, and networks of networks. They try to decipher the neural code, model functional connectivity, and describe the interplay between different regions of the brain in response to tasks or under "freely running" conditions. Tools and methods are developed to investigate these processes on variant time scales of different spatial resolution. Sophisticated imaging systems (Fig. 14.3) (Kim et al. 2015) exist for diagnosis that display anatomical (computer tomography (CT) and magnetic resonance imaging (MRI)) or functional, that is, metabolic (positron emission tomography (PET), single photon emission CT (SPECT), and functional MRI (fMRI)) information at high spatial resolution. Some methods are excellent for diagnosis or observations while the subject is at rest like magnetoencephalography (MEG) or MRI. Their applicability in individuals with SCI needs to be checked on an individual basis due to potential artifacts caused by metal implants for spine stabilization.

Although noninvasive brain research tools such as (f)MRI or MEG provide excellent spatial and temporal resolution, operating conditions like the use of liquid helium for cooling prevent their use for mobile applications. The recording of the electroencephalogram (EEG) for analysis of brain activity is very common due to its noninvasiveness, ease of use, and high temporal resolution (see Chap. 3). However, EEG-based systems provide only a limited spatial resolution and are only capable to record the summed electrical activities from many thousand neurons. This can be improved by more invasive techniques (see Chap. 9). Approaches to record signals

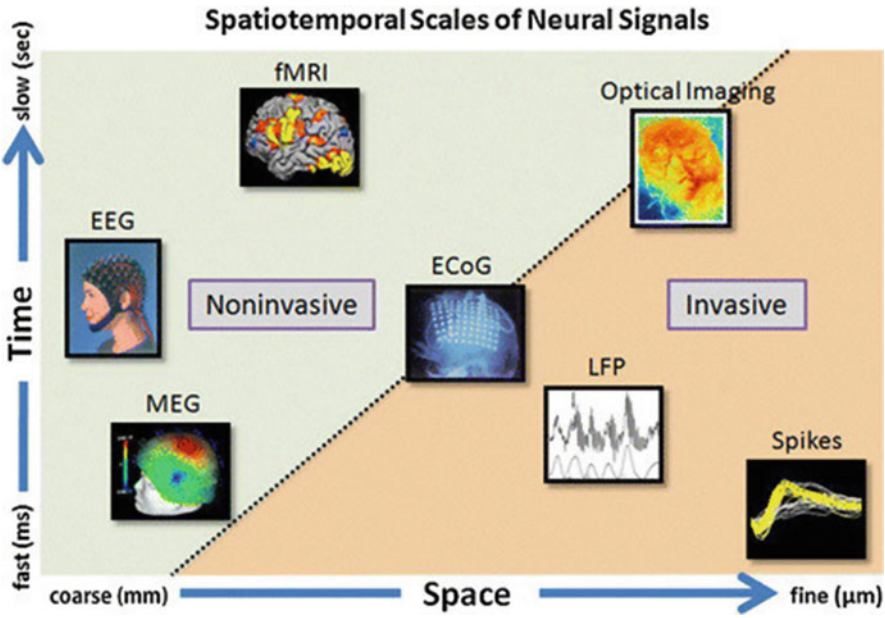

Fig. 14.3 Overview of neural activity imaging technologies of the brain with respect to spatial and temporal resolution (Kim et al. 2015). Achieving high spatial and temporal resolution requires implantable systems to record brain activity

at the single cell level work well in basic research, for example, in rodents in acute experiments or even up to some months in freely behaving animals. However, these approaches can be hardly transferred into clinical applications due to limited lifetime of recording devices and percutaneous connectors. These inherently carry a risk of infection along the parts that penetrate the skin, bone, and meninges. Interactions with neural target tissue in fundamental neuroscience mainly serve the purpose to probe certain neural circuitries to better understand brain functions or changes under pathophysiological conditions. Traditionally, direct probing of nerve cells was mainly done electrically by applying electrical voltage and current and recording the electrical responses. Changes of the membrane potential change signal transfer properties, shift postsynaptic potentials and might elicit or suppress the generation of action potentials. Patch clamping experiments with glass micropipettes allow single cell access but need vibration- and movement-free preparation. Therefore, transfer to high channel approaches in freely behaving subjects does not work.

An electrical stimulation (ES) using extracellular electrodes excites cells with respect to their distance to the electrode and their axon diameter (see Chap. 2) but not by their functional type. Therefore, inhibitory and excitatory cells in spinal cord and brain circuits cannot be selectively activated by ES, and suppression of activity requires activation of inhibitory neurons and circuits instead.

Since the noughties of the last century, a paradigm change took place with the invention of optogenetic modification of cells. Here, light instead of electrical

current is used to suppress or elicit cell type specific activity and overcome shortcomings of ES. The probing of neuroscientific research hypotheses is evaluated either by neurophysiological recordings or by changes in behavior. Prominent animal models are rodents, mainly mice. When it comes to cognitive or complex movement tasks, sensor fusion or attention, experiments are conducted with nonhuman primates. Even though fundamental brain mechanisms are species independent, tools for nonhuman primates need to be more reliable for chronic applications. They might be close to those for first-in-human proof-of-concept studies but still do not meet the requirements for medical device approval and widespread clinical use.

The following paragraphs give an exemplary overview of research approaches that reflect trends in miniaturization of implantable neural interfaces. These include ways to electrically interact with the brain as well as the principle of optogenetics with its opportunities and challenges in probe development. The use of neural signals in combination with assistive devices is often termed "thought control." This principle will be discussed exemplarily for the closed-loop control of robotic arms and exoskeletons for individuals with tetraplegia due to high cervical SCI.

14.4 Electrical Probes

Thought control of assistive devices (see Chaps. 6 and 9) or neuroprostheses based on ES (see Chap. 5) has become a popular research focus over the last two decades. Nerve cells communicate via electrical action potentials caused by ion shifts at the nerve membrane. The changes in the electrical field can be measured more reliably than the underlying chemical signals. In addition, temporal resolution is high, which forms the basis for driving an assistive device like a speller or other activities. Intuitive voluntary control of complex devices with several degrees of freedom like a robotic arm needs multiple control signals, all with sufficient temporal resolution. Electrical recordings offer highest spatial and temporal resolutions, with the EEG being the most commonly used signal at the noninvasive level (Zijlmans et al. 2017). The skull with the scalp, however, acts—electrically spoken—as a low pass filter. The high resistivity together with the capacitive properties of bone and skin filter out high frequency components and blur out spatial origin of the signals (see Chap. 3). Invasive electrodes and electrode arrays offer better spatial and temporal resolution at the cost of a surgical intervention and a permanent implant. While cardiac pacemakers, cochlear implants, as well as implantable pulse generators for deep brain or spinal cord stimulation have entered clinical practice with approved devices, fully implantable recording systems with more than a single channel approved as medical device are scarce. However, large experience with recording cortical signals exists from fundamental neurosciences in rodent and nonhuman primate models to study and understand brain functions and in the field of presurgical epilepsy monitoring. A very active research community currently develops implantable probe arrays with an increasing number of contact

sites while decreasing their size to minimize tissue damage and foreign body reaction. More and more (start-up) companies are founded and promise to develop the next generation of brain–computer interfaces (BCIs) for everyday use in patients for various application scenarios. The advertisements range from "thought-control" of robotic arms via mind-controlled type-writing to up- and downloading information to and from the human mind. Usefulness and feasibility are left at the reader's discretion and the future will tell the success stories.

This overview highlights general lines of research with different philosophies but does not go into details of technologies and neuroscientific hypotheses. Intention is to present latest research concepts with respect to the intended use and to assess the translational potential into clinical settings in predictable time periods. Classification of implantable probe arrays will be done according to the implantation site and the system concepts.

14.4.1 Probe Array Concepts

Invasive probe arrays are either placed on the surface of the brain, i.e., epicortically or inside the cortex, that is, intracortically (Fig. 14.4). Epicortical arrays represent established systems for presurgical epilepsy diagnosis (Zijlmans et al. 2017). They are made out of silicone rubber with embedded metal electrodes for recording of the electrocorticogram (ECoG). The better they adapt to the curvature of the brain, the higher the signal-to-noise ratio they achieve. Thinner and thereby more flexible arrays have been developed with smaller electrodes diameters and denser arrangements using laser manufacturing (Fig. 14.4a). Micromachining technologies allow even smaller dimensions and higher integration densities (Fig. 14.4b) (Rubehn et al. 2009). Substrate and insulation layers are very thin and result in conformable adherence to the brain surface. Not only mass signals and local field potentials but also spikes can be detected with some of those surface arrays (Galindo-Leon et al. 2019; Khodagholy et al. 2014) when they tightly adhere to the underlying brain structure. Connections of these arrays to cables, connectors, and wireless systems represent a major challenge. Another one is reliable prognosis of their life-time. Experience from chronic preclinical studies in fundamental neurosciences is promising (Bosman et al. 2012), but the data basis is still very small and diverse.

The spatial and temporal resolution of the signals recorded by the ECoG arrays is sufficient for sophisticated BCI-control (Volkova et al. 2019). Integration of amplifiers using organic (Khodagholy et al. 2014) (Fig. 14.4c) or silicon-based (Wise et al. 2004; Ruther and Paul 2015) microelectronics allows amplification of the small ECoG signal amplitudes and the selection of meaningful electrodes by multiplexers while reducing the number of interconnection lines.

Intracortical probes have been used in fundamental neurosciences for decades. Metal wires with varnish insulation have been cut, implanted, and fixed with dental cement with surprisingly good success. Chronic recordings about 7 years (Krüger et al. 2010) have been published for studies in nonhuman primates. Micromachining

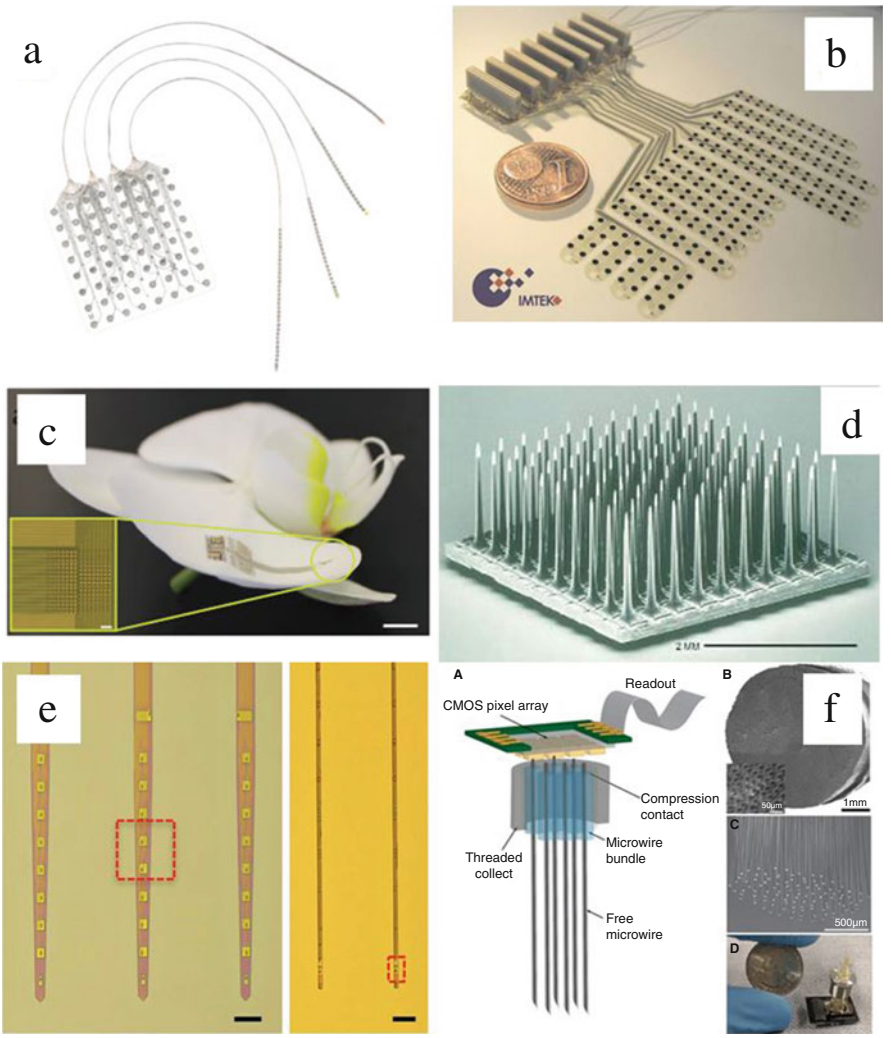

Fig. 14.4 Overview of electrode array approaches to interface with the brain. Epicortical: (**a**) Laser structured arrays in AirRay technology with FDA clearance (Cortec GmbH, Freiburg, Germany), electrode spacing: 10 mm; (**b**) micromachined finger array with 252 contact sites (Rubehn et al. 2009); (**c**) array with integrated organic transistors for 256 sites (Khodagholy et al. 2014). Intracortical: (**d**) Silicon based "Utah Arrays" (Hochberg et al. 2006); (**e**) ultra-slim polymer shafts (Luan et al. 2017) with a width of about 50 µm (left: scale bar 100 µm) and about 10 µm (right: scale bar: 50 µm); (**f**) high density array with 800 microwires (Obaid et al. 2020)

technologies and integration of electronics into microsystems resulted in many tools used in neuroscientific experiments (Gosselin 2011; Seymour et al. 2017; Stieglitz 2019, 2020). However, the only one that has achieved medical device approval for use in clinical applications is the so-called Utah-Array (Campbell et al. 1991;

Hochberg et al. 2006) (Fig. 14.4d) with its investigational device exemption in the USA. It is made out of a 1.4 mm thick block of silicon and consists of a 10 × 10 needle array with one electrode at the tip of each needle. It is injected into the cortex with the help of a pneumatic inserter. A tiny bundle of wires leads from the array to a pedestal that is fixed to the skull bone. This percutaneous socket allows connection to external recording (and stimulation) systems. Such a system has been implanted in a few dozens of paralyzed individuals with, for example, SCI or brain stem stroke. After training, these people were able to control assistive devices like computers or robotic arms and hands with these BCI systems. The lifetime of the electrodes is currently of about 5 years. Cable bond connections to electronics have been exchanged by wireless systems, but the percutaneous socket is still in place even in the most recent version. Main limitations come from the performance of the array due to drop-out of channels. Foreign body reactions to the stiff array and perpetuous (micro-) movements cause chronic inflammation, scarring, and degeneration of neurons around the needles. Reduction of size and increase of flexibility are research directions to cope with these issues. Proof-of-concept studies showed that carbon fibers of about 6 µm diameter showed no scaring in the brain (Kozai et al. 2012). Probes as thin as 1–2 µm of polymers (Fig. 14.4e) were even able to follow the motions of the brain (Luan et al. 2017) due to blood pulsation and respiration. While the increase in electrode density to record as many single nerve cells as possible (Fig. 14.4f) with nearly no foreign body reaction (Obaid et al. 2020) is one of the driving forces in current neuroscience research, only few approaches address the question whether these probes might be suitable for human clinical studies or even daily home use. Companies like Blackrock (Salt Lake City, UT, USA), Cortec (Freiburg, Germany), Neuralink (San Francisco, CA, USA), and Paradromics (Austin, TX, USA) (to name a few in alphabetical order) address the development of invasive BCIs for human use but do not yet have approved medical devices available for regular use in clinical application.

14.4.2 Implant System Concepts

The system concept of most implants is derived from the cardiac pacemaker. So far, the separation of electrode arrays, cable, an optional connector, and a hermetic package to protect electronics has limited complexity. However, the high robustness and reliability of these rather simple systems set the standard against which novel concepts have to compete. One of these rather novel concepts is the idea of distributed systems that communicate with each other and with devices outside the body. With distributed systems one of the major drawbacks of current active implants, which are cable breakdowns, can be overcome. “Smart dust” has been a buzzword in the noughties in microsystems engineering and has made it into Michael Chrichton’s dystrophic novel “Prey” about autonomous “nanobots” (Crichton 2002). Wireless inductive powering and data transfer are well established principles. Single channel systems with small size have been developed to record

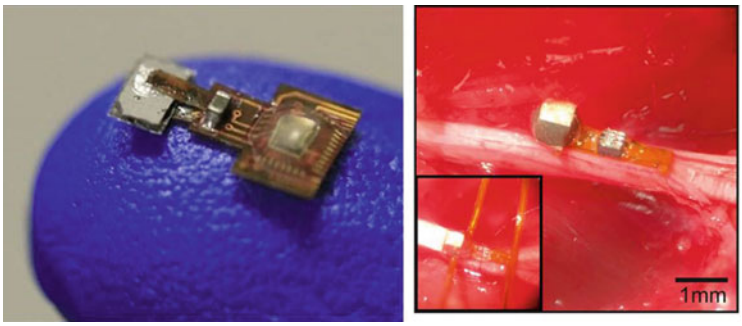

Fig. 14.5 Concepts of distributed neurotechnical microimplants. One channel implant with magnetic transmission (Yu et al. 2020) (left); "neural dust" (Seo et al. 2016) with ultrasonic power supply and data transfer (right) as single channel recorder

biosignals, to amplify them on site, and to transmit the digitized signal via radio frequency. Nowadays, novel concepts address transmission principles for powering beyond electromagnetic near field to be more efficient at small scale (Seo et al. 2016). Magnetic fields allow implants of sizes below a coffee bean (Fig. 14.5a) (Yu et al. 2020). "Neural dust" (Seo et al. 2016) makes use of the piezoelectric effect and ultrasound as powering source to develop motes smaller than 1 mm^3 to record electrical signals and to stimulate nerves.

The basic proof-of-concept in-vivo study in animals of the neural dust has been performed in the peripheral nervous system but the general concept is intended for use in BCIs. Extension to multiple implants and increasing longevity are currently the most important aspects during commercialization of this concept at Iota Biosciences (Berkeley, CA, USA).

14.5 Electrical and Optical Stimulation for Afferent Feedback

While recording of electrical signals from the brain is used to "read out" information for control purposes, electrical stimulation seems to be the natural counterpart for "writing in" signals into the brain. This is important for provision of afferent including proprioceptive feedback in people with impaired sensory function (Cronin et al. 2016; Lee et al. 2018) or for neuromodulation purposes (McCormick et al. 2020).

While some functional aspects are discussed below in the context of "thought control of assistive devices," one electrophysiological aspect has to be stressed out here: electrical stimulation is hardly able to selectively activate nerve cells that have similar distance to the electrodes or have similar size of their axons or cell bodies. In addition, electrical stimulation preferably *activates* neurons; *inhibition* is nearly impossible or comes with high energy and instrumental costs. As a consequence,

light as a substitute to electrical stimulation has been explored for stimulation of neural tissue. Although laser have been successfully applied in the infrared range to elicit action potentials (Chernov and Roe 2014), the underlying mechanisms have been controversially discussed. In any case, energy densities were high and selectivity not superior to electrical stimulation.

A paradigm change came with the advent of optogenetics that was selected as the "Method of the Year" by Nature in 2000 (Nature 2011). In this method (Fig. 14.6), the deoxyribonucleic acid (DNA) of light sensitive ion channels from algae was isolated, decoded, and transferred into a viral vector that allowed expression of these ion channels in nerve cells of mammals. Depending on the particular genetic design, the target nerve cell type could be selected. DNA sequences were found and designed for excitation and inhibition (Yizhar et al. 2011). These opsins are wavelength specific. Blue light at 470 nm activates channelrhodopsin (ChR2) and causes nerve action potential generation by Na^+ influx in the cell, while halorhodopsin (NpHR) activation with yellow light at 589 nm causes nerve cell inhibition by Cl^- influx.

Opsins with different light response dynamics and biophysical principles (channels, pumps, and transmembrane proteins) have been genetically engineered. This method has been originally developed to investigate fundamental neuroscientific questions about functions, connections, and interdependencies in brain networks (Zhang et al. 2010).

Optoelectronic probe development experienced a boom from "Do-it-yourself" approaches to commercially available toolkits for neuroscientific research, mainly in rodents (Fig. 14.7). Microsystems engineers equipped electrical microprobes with miniaturized waveguides, light-emitting, and laser diodes (Alt et al. 2017; Rudmann et al. 2018) (Fig. 14.8). By these, activity of transfected cells can selectively be suppressed or elicited by light.

Tools came first from the neuroscience laboratories: glass waveguides were inserted into murine brains to investigate behavioral changes, for example, in relation to anxiety (Tye et al. 2011). Translational studies for clinical treatments have been performed in many disciplines. Optoelectronic approaches have been published to cure blindness (Simon et al. 2020). Optical cochlear implants (Dieter et al. 2020) promise better hearing. Applications for cardiology (Boyle et al. 2018) as well as for peripheral nerves (Xu et al. 2020) are reported beside treatments of neurological disorders. While questions on efficacy, side effects, longevity of transfection as well as alternatives to direct viral transfection are under investigation (Richter and Bruegmann 2019; Ordaz et al. 2017), translational research on the engineering side is not yet meeting all of the requirements (Fig. 14.9) of active implantable device regulations worldwide (Alt et al. 2017; Rudmann et al. 2018).

Therefore, electrical stimulation is currently still the only technology with sufficient level of maturity to "write in" sensory information into the brain for clinical applications.

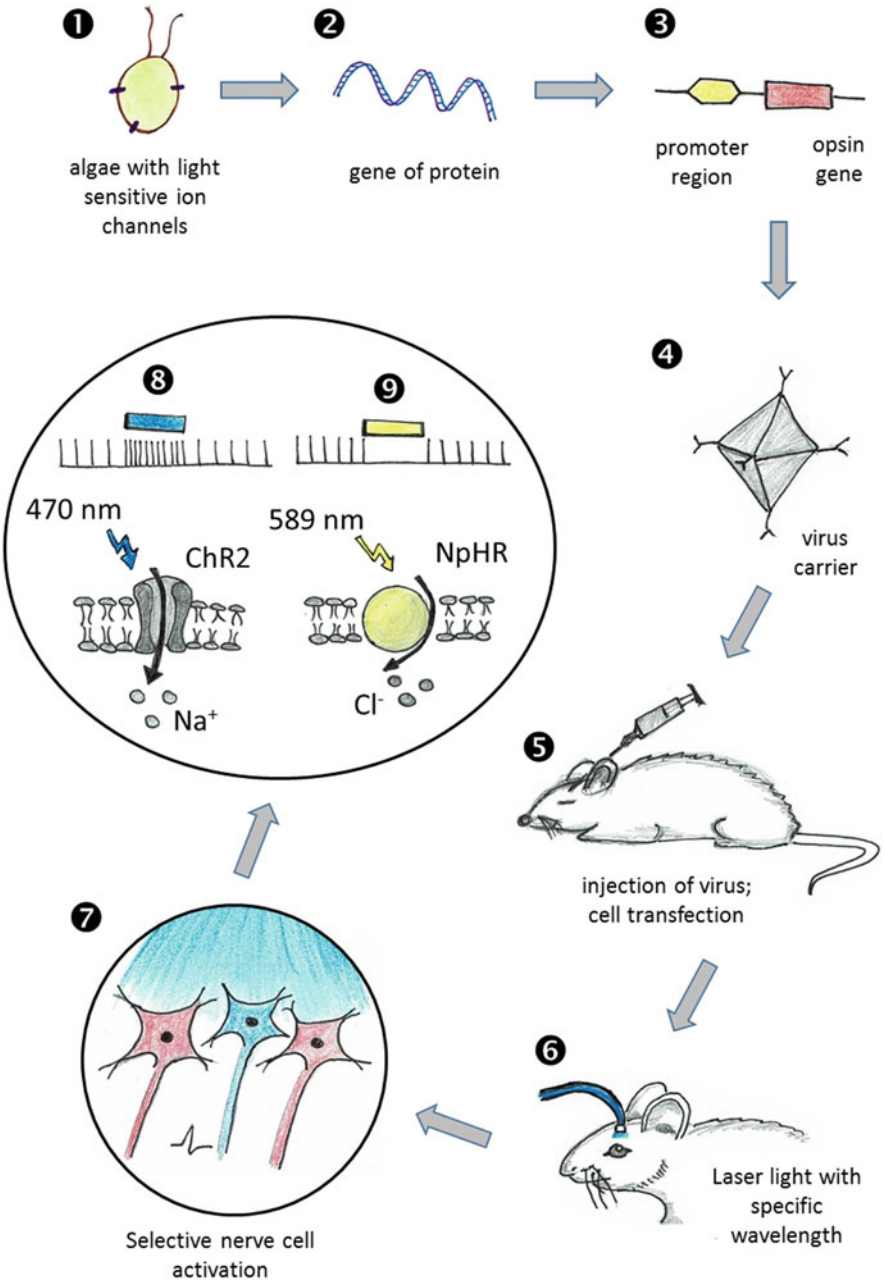

Fig. 14.6 The working principle of optogenetics (Sketch: T. Stieglitz)

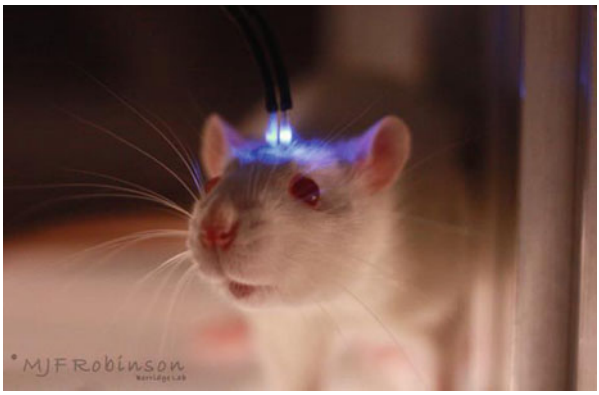

Fig. 14.7 Optogenetic setting in a murine model (Robinsonlab 2018)

14.6 Thought Control of Assistive Devices

The use of robotic arms or exoskeletons is one option to substitute or replace lost functions after SCI or paralysis of other incidents, for example, brain stem stroke. The more functionality is lost, the more complex the assistive device and its control has to be, while residual functions for operating a human–machine interface are often not present anymore. Independent of the underlying brain signals, every form of brain control is often sold as "thought control." Three types of scenarios will be outlined here to give an overview of very different research lines. However, they all have in common that they are very impressive but probably not close to everyday applications.

The thought control of robotic arms and hands with intracortical needle arrays in the motor cortex goes back to the noughties (Hochberg et al. 2006). Single cell activity is recorded and directional sensitivity and firing rates of these neurons are used to continuously predict the intended movement direction over time. The temporal course of these intended directions results in the trajectory of movement. When microstimulation is provided to the somatosensory cortex with a second electrode array, sensory feedback about the outcome of the movement task improves control (Lee et al. 2018). One challenge beyond probe functionality and longevity is the calibration of the encoding software (Brandman et al. 2017, 2018). For translation of the brain signals into correct and precise movements of the robot arm, a calibration needs to be done more or less on a daily base by technical experts. Systems work sufficiently reliable in research laboratories but none of them has been validated for permanent home use. This applies to each component of the systems including the robotic arm, the control hardware, the software as well as the usability by the end users and their caregivers.

Safety and security features need to be considered that end users unintentionally hurt neither themselves nor others. Performance rates of about 90% are good enough for research papers but not for safe use and consequently for medical device approval.

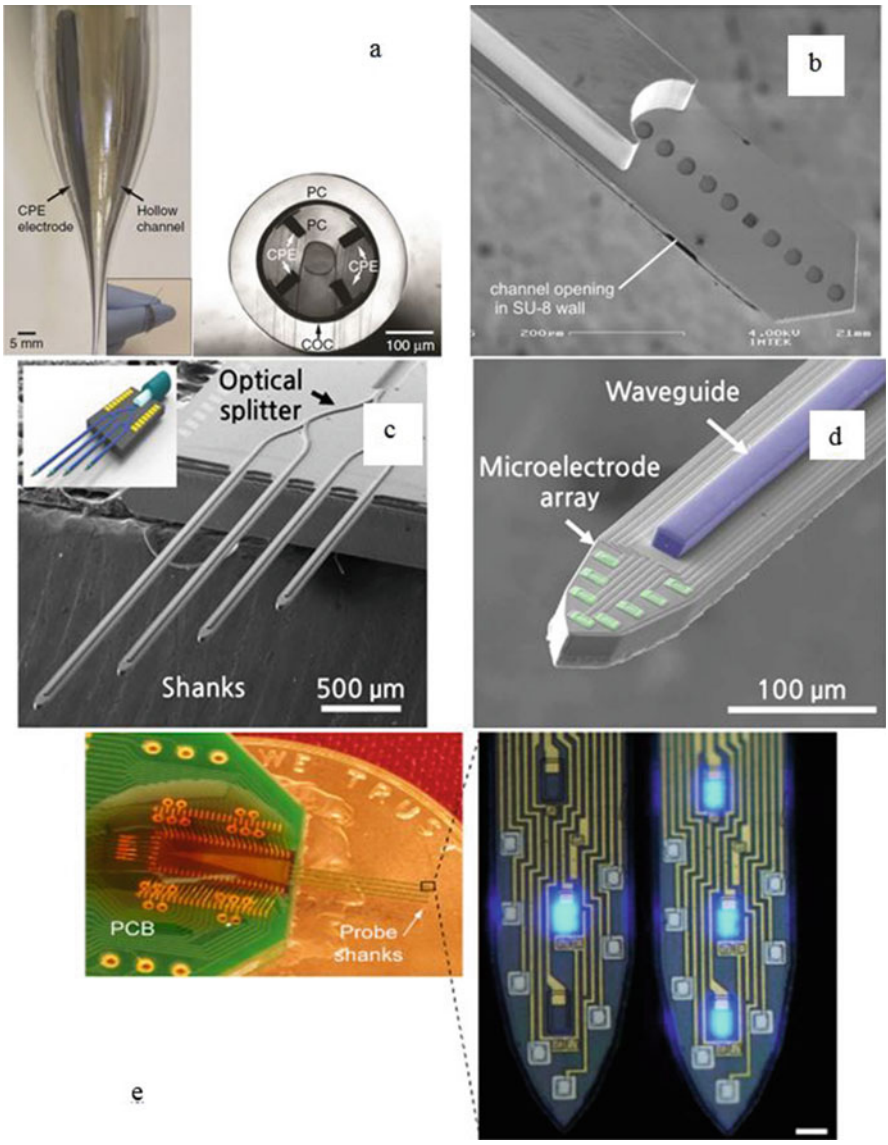

Fig. 14.8 Micromachined optoelectronic probes. (**a**) Advanced optical fiber-based system with multiple integrated electrodes (Canales et al. 2015); (**b**) Optrode based on flexible polyimide substrate, SU-8 waveguide, and fluidic channels (Rubehn et al. 2009); (**c**) Replacement of the single implanted optical fiber with a microfabricated planar optrode with microwaveguides (Son et al. 2015); (**d**) Detail view of one shaft (Son et al. 2015); (**e**) Planar optode with directly integrated LEDs that can be controlled individually (Wu et al. 2015)

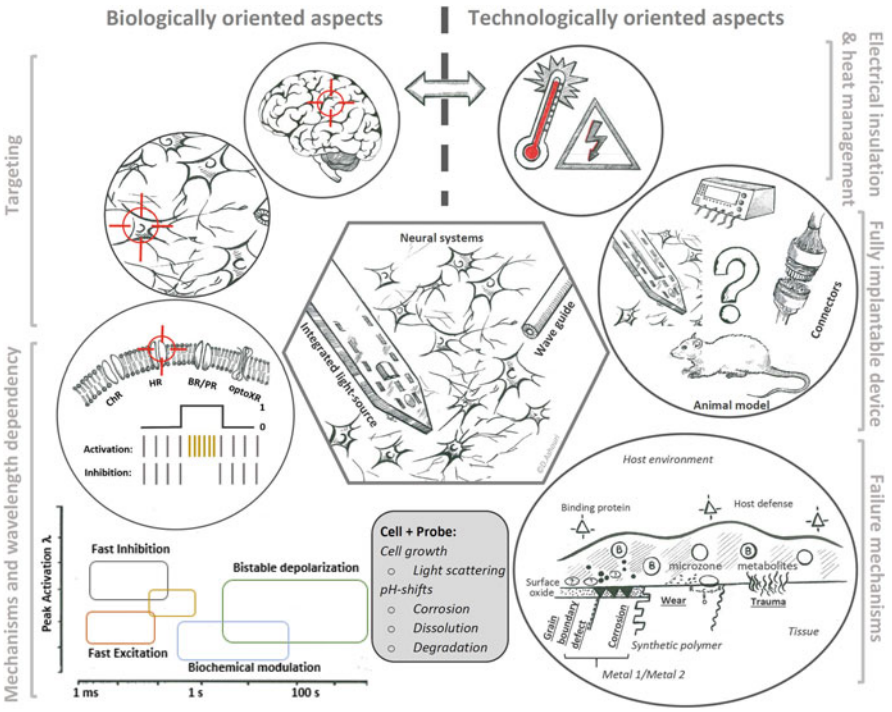

Fig. 14.9 Multiple handling, application, and material science aspects contribute to the design, application, and longevity of optoelectronic probes (Rudmann et al. 2018)

Exoskeletons are not completely new in rehabilitation of people with SCI. With reciprocal gait orthoses (RGOs) (Whittle et al. 1991; Bernardi et al. 1995), individuals with paraplegia were able to walk by voluntarily induced changes in the center of mass. However, due to nonphysiological walking pattern, overloading symptoms such as pain was induced by their use (Arazpour et al. 2015). Combination of an RGO with surface muscle stimulation has been investigated and showed beneficial effects on exercise and mobility aspects (Hirokawa et al. 1996). Modern commercial exoskeletons use several motors to move lower extremity joints and muscles. These active actuation mechanisms result in improved performance and usability (Arazpour et al. 2016). Movement is initiated by leaning forward, for example. Arm and hand functions with sufficient force are still needed to compensate for instabilities of the trunk by use of a walking frame or crutches. Additionally, users need to fulfill many other prerequisites such as sufficient bone density, low level of spasticity, and the absence of autonomic dysreflexia (see Chap. 1). The use of exoskeletons is still demanding, for example, getting into and out of an exoskeleton take substantial time and help from caregivers. So far, exoskeleton systems have not achieved a wide acceptance in the clinical environment as well as from end users.

Initiation and selection of movement tasks by brain signals with a fully implantable system in combination with an exoskeleton have been presented with the

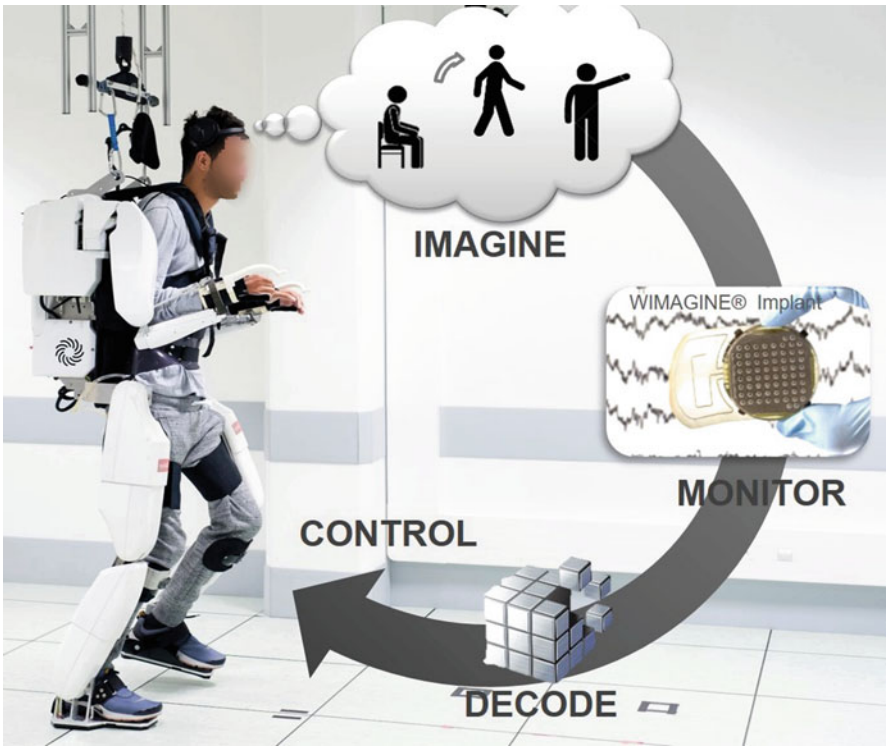

Fig. 14.10 The WIMAGINE system combines epicortical implants with an exoskeleton to generate motor control signals out of brain activity

WIMAGINE system (Mestais et al. 2015) (Fig. 14.10). Two wireless recording implants with integrated epicortical electrode arrays have been implanted over the left and right motor cortex of an individual with complete tetraplegia. The complete implant development was conducted directly toward human applications and was in compliance with European legal requirements for active implantable medical devices. Movement initiations are decoded and translated in control commands of the exoskeleton to drive one or two arms with four degree of freedom and two legs with three degrees of freedom each. The research center Clinatec in Grenoble (France) founded by Prof. Benabid, one of the French inventors of deep brain stimulation, has got approval to run first-in-human clinical trials with this system in 2015.

Arm (but not hand) and walking movements controlled by a "brain-switch" were successfully demonstrated (Benabid et al. 2019).

As a next step, combined movements, patient variability, and reliability under various conditions need to be investigated. Performance comes at the cost of a relatively bulky exoskeleton and the surgical intervention with two implants. Even if everything looks ready for routine clinical application, it is on the discretion of

future users to take the risk of the intervention to potentially increase the amount of activities of daily living. Numbers are currently too low to assess usability and increase of subjects' autonomy.

The third line of research combines BCI (noninvasive as well as invasive) with autonomous robots in a shared-control approach. This hierarchical control scheme can be applied for either artificial limbs or stationary robotic arms as well as in combination with autonomously driving vehicles at home. The user's intention has to be detected by any BCI decoding paradigm (e.g., motor imagery) and an adequate communication user interface. Imagine Paula has a SCI at level C4. She wants to drink cold lemonade. She drives the cursor on a computer screen with her BCI system to the menu "beverages" and selects the desired cold drink. By pressing the ENTER button, the autonomy is transferred to the robotic system that drives to the fridge, takes the beverage, pours it into a jar and brings it back to her mouth to let her drink (Kuhner et al. 2018). While the described task might be beneficial, handling of objects or eating in shared-control might be irritating when one "start" signal initiates complex movements without any voluntary control and without any feedback. Knowledge from autonomous driving needs to be transferred not only for safety and security but also with respect to psychophysical and psychological effects of this approach.

14.7 Novel Concepts for Noninvasive Neurotechnology

While noninvasive neurotechnologies can be used without any surgical intervention, their spatial and temporal resolution, size and mobility as well as usability might be limiting factors in daily life. DARPA has launched its next-generation nonsurgical neurotechnology (N^3) program and awards six research groups that attempt to overcome these limitations. The aim is to build BCIs that reach the level of performance achieved with implanted electrodes, but with approaches that do not need any surgical intervention. Within a timeline of only 4 years, ideas should be developed, proven in animal models and transferred into first-in-human clinical studies (DARPA 2019). Recording of neural activity as well as intervention by nerve stimulation shall be performed within a turn-around time of less than 50 ms. Latest technologies using ultrasound, magnetic nanotransducers, genetic engineering to create magnetosensitive nerve cells, coherent light interaction, optically pumped magnetometers, and diffuse optical tomography shall help to achieve the desired spatial and temporal resolution. The program is highly challenging in its timeline and DARPA's statements about the purpose of this program are unambiguous. "If N^3 is successful, we'll end up with wearable neural interface systems that can communicate with the brain from a range of just a few millimeters, moving neurotechnology beyond the clinic and into practical use for national security," said program manager Al Emondi. "Just as service members put on protective and tactical gear in preparation for a mission, in the future they might put on a headset containing a neural interface, use the technology however it's needed, then put the

tool aside when the mission is complete." Even though, technology could also be used for medical purposes, military use is in the driving force for these developments. While these use cases are in focus of DARPA's mission, researchers all over the world and funding agencies are well advised to take ethical and societal considerations into account, promote a "responsible neurotechnology" approach, and discuss dual use within the scientific community as well as in the general public. While rights of privacy, identity, agency, and equality of BCI users have been already addressed (Yuste and Goering 2017), potential applications beyond medical use should be based on a societal consent and not on minority interests of private or public investors.

14.8 The Translational Gap

The number of research articles in respect to neural technology is rising nearly exponentially and interest in neural engineering is huge. Research programs in the USA and also Europe have supported many groups and consortia, not only in the "decade of the brain" (2000–2010) but also in the decades before and after. One might ask question why research that makes it into Nature and Science does not result in medical products that can be used to increase the quality of life, for example, of individuals with SCI.

Future therapies will be based on fundamental knowledge and science that has been discovered today. However, brilliant minds who materialize their thought in proof-of-concept studies in animal models or even in first-in-human clinical trials do quite often neither have the mindset, the experience, and the mandatory skills to transfer that idea into a successful product on the market. The "translational gap" has become a technical term summarizing all hurdles between research and market success (Stieglitz 2020). The technology readiness level (TRL) has been originally invented by the NASA to assess the maturity level of developments for military and spacecraft applications. The European Commission (EC) has adopted the levels for civil use (Table 14.1) (EU 2014).

Conceptual and proof-of-concept studies are on a relatively low level in this scale that is not linear at all. Resources of time and money rise nonlinearly with higher TRLs. Since the market of medical devices is regulated, developments have to comply with regulatory requirements that already have to start in the conception and design phases of a medical device. If researchers do not adequately document their developmental processes according to the rules, this process might have to start from the scratch when an idea is taken up by a company. Parameters need to be verified and validations have to be done under quality management conditions. The number of validation samples already reaches numbers of a small series production for first-in-human studies.

When researchers are willing to walk this rocky road, they have to find adequate funding programs to perform this kind of research first. Funding agencies like to point toward private–public–partnerships and founding of start-up companies, while

Table 14.1 Technology readiness levels (TRLs) according to the definitions of the EC

Level	Description
TRL 1	Basic principles observed
TRL 2	Technology concept formulated
TRL 3	Experimental proof of concept
TRL 4	Technology validated in lab
TRL 5	Technology validated in relevant environment (industrially relevant environment in the case of key enabling technologies)
TRL 6	Technology demonstrated in relevant environment (industrially relevant environment in the case of key enabling technologies)
TRL 7	System prototype demonstration in operational environment
TRL 8	System complete and qualified
TRL 9	Actual system proven in operational environment (competitive manufacturing in the case of key enabling technologies; or in space)

investors want to see more evidence—preclinical or even clinical data—or want to get more shares when entering such an endeavor. Even with running prototypes or market entry, a success story is not yet written. A well-designed business plan already considers "the valley pf death" (Fig. 14.11) (Osawa and Miyazaki 2006) that describes the period of time after the product launch before it becomes an economic success. This period needs a lot of financial resources. Knowledge about market size and predicted patient acceptance, clinical networks with educated experts as well as swift service and maintenance are key factors to be considered. And do not forget the person with business experience in the management team or a start-up company!

14.9 Conclusions

Today's neuroscience research tools will lead the development of future therapies. The unknown of course is which ones and for what purpose. In this chapter, some lines of research are highlighted and summarized that include miniaturized implants, genetic engineering for optical excitation of nerves, and shared-autonomy scenarios to control artificial limbs and robots. What is in focus of research today might get proven useless tomorrow, while unspectacular devices might serve millions in the future. False predictions of the future of cars and personal computers in the early days are iconic. Translational research bridges the fundamental discoveries with clinical applications and future therapies. This research and career path is very regarding and should be appreciated to attract the right stakeholders. Thus, more

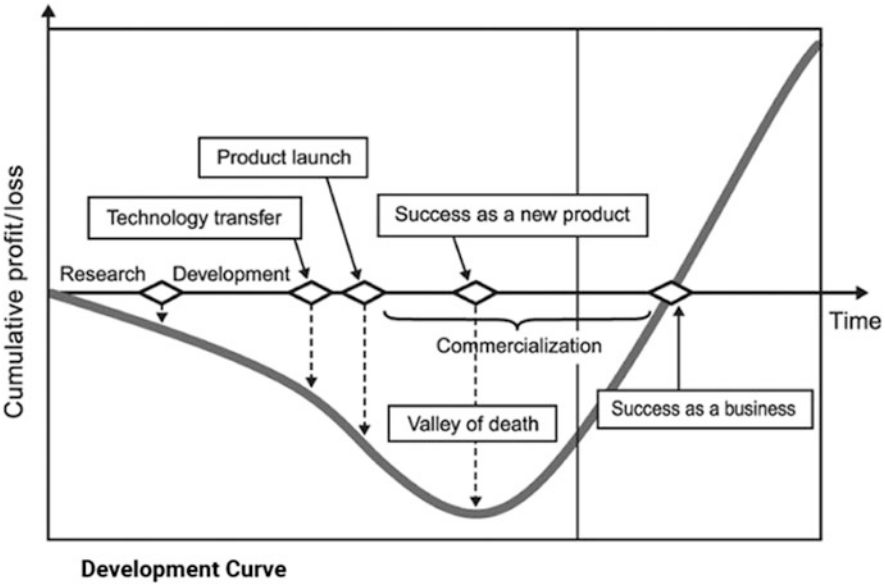

Fig. 14.11 Success in translational research needs enough investment to bridge the time between the launch of a product and its success on the market, known as the "valley of death" (Osawa and Miyazaki 2006)

brilliant ideas can be transferred into applications that serve users' needs and offer individuals with SCI treatments and rehabilitation devices that make a real difference in respect to a better autonomy and independency in activities of daily living.

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