INTRODUCTION TO NEURAL ENGINEERING FOR MOTOR REHABILITATION
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INTRODUCTION TO NEURAL ENGINEERING FOR MOTOR REHABILITATION

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Neural engineering is an interdisciplinary research area that brings to bear methods from neuroscience and engineering to analyze neurological functions and to design solutions to problems associated with neurological limitations and dysfunctions (definition by the Editorial Board of the Journal of Neural Engineering [Durand, 2007]). Despite neural engineering’s being a relatively new research area, the field is developing rapidly. This development requires continuously updated didactic material for the increasing number of undergraduate, graduate, and Ph.D. courses on the topic. The applications of neural engineering to rehabilitation of movement cover a broad range of engineering challenges, from electrode design to signal processing and from the neurophysiology of movement to robotics.

The three main approaches of neural engineering used for rehabilitation of impaired motor functions are restoration, replacement, and neuromodulation. Restoration consists in retaining existing neural and anatomical structures and in controlling them for reestablishing a motor function. An example of such an approach is functional electrical stimulation (FES). Replacement consists in substituting the impaired motor apparatus with an artificial one, controlled by residual, but still functional, neural or muscular structures. An example of these methods is the control of artificial limbs (active prostheses). The aim of neuromodulation is (re)training the central nervous system to induce plasticity through artificial stimulation of afferent pathways and/or by artificial enhancement of efferent neural and muscular signals provided as feedback. Examples of such an approach are the application of patterned peripheral electrical neuromuscular stimulation (e.g., transcutaneous electrical nerve stimulation, TENS), mechanical stimulation using robots.
or repetitive transcranial magnetic stimulation for retraining the diseased central nervous system.

The aim of this book is to present the state of the art in technologies for motor neurorehabilitation and to give an overview of the current challenges and recent advances within neural rehabilitation technology. The book is intended for undergraduate, graduate, and Ph.D. students as well as senior researchers who work in the field of biomedical engineering, and it is organized in five parts. Part I reviews aspects related to injuries of the nervous system that determine motor impairments. It is considered as a prerequisite that the reader is familiar with the physiology of the neuromuscular system, which is not included in this book. Part II reviews engineering methods for interfacing the neuromuscular system and for conditioning and processing neural and muscular signals. The methods described in Part II are also used in the last three parts of the book, which describe examples of neurotechnologies within the areas of restoration, replacement, and neuromodulation. The topics in each part are collected with the focus on the application (e.g., replacement of function) rather than on the principle on which such application is exploited. Therefore, for example, the principle of brain-interfacing is used in applications described in both Parts III (replacement) and V (neuromodulation), according to the different uses of brain-interfacing in these two sections. Each part begins with a short introduction that serves to put into perspective the topics addressed in that part and to guide the reader to the research areas detailed there. The book’s parts comprise introductory chapters, which provide a broad perspective (review chapters), and chapters with a strong focus on more specialized topics (focused chapters), as indicated at the beginning of each chapter.

The book is intended to provide a broad perspective within the field of motor neurorehabilitation engineering by including several topics that in most other books are treated separately. At the same time, the book does not intend to provide an exhaustive treatment of all methods and approaches for motor neurorehabilitation. Rather, the topics presented have been selected to be representative of the field and thus to provide the reader with a general broad overview and understanding of the research area. Readers who approach neural rehabilitation engineering for the first time will find the review chapters as an overview of the state of the art, whereas senior researchers or experts within the field may have further interest in the focused chapters that provide a detailed analysis of specific topics with recent solutions. As indicated, the physiology of the neuromuscular system is not presented in this book, which has as its starting point the injuries of the system. Therefore, readers approaching neural engineering for the first time are advised to first consult references on human physiology.

The editors are very grateful to all the contributing authors for enthusiastically accepting the invitation to contribute to this project and to Dr. Antonietta Stango (University Medical Center Göttingen, Germany) for the important contribution of assisting with the editorial tasks.
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Metin Akay

REFERENCE

PART I

INJURIES OF THE NERVOUS SYSTEM

Part I contains three chapters that examine the type of neural injuries that may lead to sensory–motor impairment, as well as aspects of plasticity, as a relatively novel conceptual theme in the field of neural rehabilitation. Damage to the nervous system is typically associated with the loss of motor drive and of afferent input to the central nervous system. The severity of the neural damage depends on the location of the injury, which may lead to adaptation of the movement pattern, paresis, or complete paralysis. Plasticity has been defined as changes in the strength, number, and location of synaptic connections in response to either an environmental stimulus or an alteration in synaptic activity in a network; our fundamental understanding of what underlies neural plasticity is believed to be one of the key elements in devising strategies for rehabilitation or repair of injuries.

Chapter 1, by Popović and Sinkjaer, provides a review of the incidence and the pathology of major diseases and injuries within the central nervous system that lead to impairment of the sensory–motor system, such as stroke and spinal cord injury. The chapter also briefly introduces the types of injuries that lead to loss of sensory–motor functions at the peripheral level.

Chapter 2, by Navarro, more specifically examines injuries at the peripheral level that may result in partial or total loss of motor, sensory, and autonomic functions. Functional deficits may be compensated by reinnervation of denervated targets by regenerating the injured axons, by collateral branching of
undamaged axons, or by remodeling of nervous system circuitries. Plasticity of central connections may compensate functionally for the lack of adequate target reinnervation; however, plasticity has limited effects on disturbed sensory localization or fine motor control after injuries, and it may even result in maladaptive changes, such as neuropathic pain and hyperreflexia.

Obtaining evidence for spinal or cortical plasticity in the human is very difficult without using invasive recording techniques. Chapter 3, by Ivanenko and collaborators, reports on motor primitives to provide a novel perspective on how the neural control system operates under locomotion in healthy subjects and in patients. They find that building blocks with which the central nervous system constructs motor patterns can be preserved in patients with various motor disorders despite the fact that they often modify their muscle activity and adopt motor equivalent solutions. Our understanding of these motor primitives may be useful in driving neuroprostheses or entraining locomotor circuits in disabled people in the future.
1

REVIEW CHAPTER

DISEASES AND INJURIES OF THE CENTRAL NERVOUS SYSTEM LEADING TO SENSORY–MOTOR IMPAIRMENT

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SUMMARY

Damage to the central and peripheral nervous systems is associated with a loss of motor drive and a defective afferent input to the central nervous system (CNS). Depending on the location and severity of the neural damage this leads to anything from a complete paralysis to a paresis and a maladaptation of the movement pattern. This chapter starts with a presentation of neuron injury. Such injuries are categorized based on the extent and type of damage to the nerve and the surrounding connective tissue. This chapter addresses sensory–motor deficits that are caused by neuron injury or disease: (a) cerebrovascular accident (CVA), or stroke, which causes impairments due to changes in blood supply to the brain; (b) spinal cord injuries (SCIs), which result in total or partial obstruction of flow of both sensory and motor information between the peripheral and central nervous systems; (c) nontraumatic disorders of the CNS (amyotrophic lateral sclerosis and multiple sclerosis); and (d) cerebral palsy. At the end of the chapter we present the incidence of CNS diseases.
NEURON INJURY

A neuron injury is categorized based on the extent and type of damage to the nerve and the surrounding connective tissue (Fig. 1.1): neuropraxia, a nerve injury in which the nerve remains intact but with its signaling ability damaged; axonotmesis, in which the nerve remains intact but there with an interruption in conduction of the impulse along the nerve fiber; and neurotmesis, which follows a severe contusion, stretch, laceration, or similar damage. In this case both the axon and the encapsulating connective tissue lose their continuity.

In some injuries, the presynaptic neurons that synapse on the damaged cells are also affected. Transneuronal changes of various kinds are important in explaining why a lesion at one site in the central nervous system (CNS) can have effects on sites distant to the lesion, sites that are distributed according to the connections that the lesion interrupts.

The zone of trauma is a place where a bundle of axons is cut, either by sectioning of a tract within the CNS or by sectioning a peripheral nerve. The part of the axon still connected to the cell body is the proximal segment, and the part isolated from the rest of the cell is the distal segment.

At a zone of trauma in the CNS, the axon and myelin sheath undergo rapid local degeneration. Because a lesion usually interrupts blood vessels, macrophages from the general circulation can enter the area and phagocytose axonal debris. Astrocytes and microglia proliferate and act as phagocytes. In the CNS, however, the proliferation of fibrous astrocytes leads to the formation of a glial scar around the zone of trauma. Scarring can block the course taken by regenerating axons and establish an effective barrier against the reformation of central connections.

The degeneration spreads in both directions along the axon from the zone of trauma, but only for a short distance in the proximal segment, usually up to the point of origin of the first axon collateral. After few days, a retrograde reaction is seen in the cell body. If the entire cell body dies, then degeneration spreads from the axon hillock down along the remainder of the proximal segment. In the distal segment, outside the zone of trauma, the degeneration

![Figure 1.1. Sketch of nerve injury.](image-url)
first appears in the axon terminal about one day after the occurrence of the lesion. In approximately two weeks, the synapses formed by the distal segment degenerate completely. The process is called terminal degeneration. Degeneration of the distal axon, termed Wallerian degeneration, takes place over a period of about two months. Sometimes cells that are prior postsynaptic to the injured neuron may also be affected.

The term **motor unit** refers to the motor neuron in the spinal cord and the population of muscle fibers that it innervates. The motor unit has four functional components: (1) the cell body of the motor neuron, (2) the axon of the motor neuron that runs in the peripheral nerve, (3) the neuromuscular junctions, and (4) the muscle fibers innervated by that neuron.

Most diseases of the motor unit cause weakness and wasting of skeletal muscles. These diseases may differ in other features, however, depending upon which of the four components of the motor unit is primarily affected. A disease can be functionally selective by affecting only the sensory systems or only the motor systems. Motor diseases are regionally selective. They affect only one component of the neuron (e.g., the axon, rather than the cell body).

The clinical consequences of neurogenic disease are most obvious when a peripheral nerve is cut. The muscles innervated by that nerve are immediately paralyzed and then waste progressively. Tendon reflexes are lost immediately, as is the sensation in the area innervated by the nerve because the nerve carries sensory as well as motor fibers. In neurogenic diseases, similar effects of denervation appear more slowly, and the muscles gradually become weak and wasted.

**CEREBROVASCULAR ACCIDENT**

There is a large population of humans that suffer from impairment caused by changes in blood supply of the brain. Blood flow to the brain is highly protected, yet the brain remains highly susceptible to disturbances of the blood supply, as reflected in the high incidence of symptomatic cerebral vascular disease. The term **stroke**, or **cerebrovascular accident** (CVA), refers to the neurological symptoms and signs, usually focal and acute, which result from diseases involving blood vessels.

Strokes are either occlusive (due to closure of a blood vessel) or hemorrhagic (due to bleeding from a vessel), as sketched in Figure 1.2. Insufficiency of blood supply is termed ischemia; if it is temporary, symptoms and signs may clear with little or no pathological evidence of tissue damage. Ischemia reduces blood supply, thereby depriving tissue of oxygen and glucose, and prevents the removal of potentially toxic metabolites such as lactic acid. When ischemia is sufficiently severe and prolonged, neurons and other cellular elements die; this condition is called infarction.

Hemorrhage may occur at the brain surface (extraparenchymal). Alternatively, hemorrhage may be intraparenchymal (e.g., from rupture of vessels
damaged by long-standing hypertension), causing a blood clot or hematoma within the cerebral hemispheres, in the brainstem, or in the cerebellum. Ischemia or infarction may accompany hemorrhage. The mass effect of an intracerebral hematoma may compromise the blood supply of adjacent brain tissue; subarachnoid hemorrhage may, by unclear mechanisms, cause reactive vasospasm of cerebral surface vessels, leading to further ischemic brain damage. Infarcted tissue may also become secondarily hemorrhagic.

Each cerebral hemisphere is supplied by an internal carotid artery, which arises from a common carotid artery beneath the angle of the jaw, enters the cranium through the carotid foramen, traverses the cavernous sinus (giving off the ophthalmic artery), penetrates the dura, and divides into the anterior and middle cerebral arteries (Fig. 1.2 and Fig. 1.3).

Interconnections between blood vessels (anastomoses) protect the brain when part of its vascular supply is compromised. The anterior communicating artery connects the two anterior cerebral arteries; the posterior cerebral arteries are connected to the internal carotid arteries by the posterior communicating arteries.

**Middle Cerebral Artery Territory Infarction**

Infarction in the territory of the middle cerebral artery (cortex and white matter) causes the most frequently encountered stroke syndrome with contralateral weakness, sensory loss, and visual field cut, and, depending on the hemisphere involved either language disturbance or impaired spatial perception. Weakness and sensory loss affect the face and arm more than the leg because of the somatotopy of the motor and sensory cortex (pre- and post-central gyri): the face and arm lie on the convexity, whereas the leg resides on

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**Figure 1.2.** Sketch of the hemorrhagic (left) and ischemic (right) cerebrovascular accident. The right panel shows a magnetic resonance imaging (MRI) scan of a brain after an ischemic stroke.
the medial surface of the hemisphere. Motor and sensory losses are greatest in the hand, as the more proximal limbs and the trunk tend to have greater representation in both hemispheres. Paraspinal muscles, for example, are hardly ever weak in unilateral cerebral lesions. Similarly, the facial muscles of the forehead and the muscles of the pharynx and jaw are represented bihemispherically and are therefore usually spared. Tongue weakness is variable. If weakness is severe (plegia), the muscle tone is usually decreased initially and is gradually increased over days or weeks to spasticity with hyperactive tendon reflexes. A Babinski sign, reflecting upper motor neuron disturbance, is usually present from the outset. When weakness is mild, or during recovery, there may be clumsiness or slowness of movement out of proportion to loss of strength; such motor disability may resemble Parkinsonian bradykinesia or even cerebellar ataxia.
Acutely, there is often paresis of contralateral conjugate gaze because of damage to the convexity of the cortex anterior to the motor cortex (the frontal eye field). The reason why the gaze palsy persists for only one or two days, although other signs remain severe, is controversial.

Sensory loss tends to involve discriminative and proprioceptive modalities more than affective modalities. Pain and temperature sensation may be impaired or seem altered, but they are usually not lost. Joint position sense, however, may be severely disturbed, causing limb ataxia, and there may be loss of two-point discrimination, astereognosis (inability to recognize a held object by tactual sensation), or failure to appreciate a touch stimulus if another is simultaneously delivered to the normal side of the body (extinction).

Visual field impairment (homonymous hemianopsia) is the result of damage to the optic radiation, the deep fiber tracts connecting the thalamic lateral geniculate nucleus to the visual cortex. Destruction of left opercular cortex in humans causes aphasia, which may take a variety of forms depending on the degree and distribution of the damage. Frontal opercular lesions tend to produce particular difficulty with speech output and writing with relative preservation of language comprehension, whereas infarction of the posterior superior temporal gyrus tends to cause severe difficulty in comprehending spoken speech and reading. When the damage is widespread, there is severe language disturbance of mixed type (global aphasia). Left-hemisphere convexity damage, especially parietal, may also cause motor apraxia, a disturbance of learned motor acts not explained by weakness or incoordination, with the ability to perform the act when the setting is altered.

Right-hemisphere convexity infarction, especially parietal, tends to cause disturbances of spatial perception. There may be difficulty in copying simple pictures or diagrams (constructional apraxia), in interpreting maps or finding one’s way about (topographagnosia), or in putting on one’s clothes properly (dressing apraxia). Awareness of space and the subject’s own body contralateral to the lesion may be particularly affected (hemi-inattention or hemineglect). Subjects may fail to recognize their hemiplegia (anosognosia), left arm (asomatognosia), or any external object to the left of their own midline. Such phenomena may occur independently of visual field defects and in subjects otherwise mentally intact.

**Anterior Cerebral Artery Territory Infarction**

Infarction in the territory of the anterior cerebral artery causes weakness and sensory loss qualitatively similar to that of convexity lesions, but affects mainly the distal contralateral leg. There may be urinary incontinence, but it is uncertain whether this is due to a lesion of the paracentral lobule (medial hemispheric motor and sensory cortices) or of a more anterior region concerned with the inhibition of bladder emptying. Damage to the supplementary motor cortex may cause speech disturbance, considered aphasic by some and a type of motor inertia by others. Involvement of the anterior corpus callosum may
cause apraxia of the left arm (sympathetic apraxia), which is attributed to disconnection of the left (language dominant) hemisphere from the right motor cortex.

**Bilateral Anterior Cerebral Artery Territory Infarction**

Bilateral infarction in the territory of the anterior cerebral artery (occurring, e.g., when both arteries arise anomalously from a single trunk) may cause a severe behavioral disturbance, with profound apathy, motor inertia, and muteness, attributed variably to destruction of the inferior frontal lobes (orbitofrontal cortex), deeper limbic structures, supplementary motor cortices, or cingulate gyri.

**Posterior Cerebral Artery Territory Infarction**

Infarction in the territory of the posterior cerebral artery may include, or especially affect, the following structures: the thalamus, causing contralateral hemisensory loss and sometimes spontaneous pain and dysesthesia (thalamic pain syndrome); the subthalamic nucleus, causing contralateral severe proximal chorea (hemiballism); or even the midbrain, with ipsilateral oculomotor palsy and contralateral hemiparesis.

**SPINAL CORD INJURIES**

Spinal cord injuries (SCIs) or diseases are a frequent reason for disability and result in total or partial obstruction of flow of both sensory and motor information instrumental for normal life. Spinal cord injuries are most often caused by trauma, especially following motor vehicle and sports accidents. The resulting syndrome depends on the extent of direct injury of the cord or compression of the cord by displaced vertebrae or blood clots. In extreme cases trauma may lead to complete or partial transection of the spinal cord. Knowledge of the anatomy and physiology of the spinal cord helps in recognizing spinal cord disease and localization of the disease to a particular segment or region of the spinal cord. This allows identification of the nature of the disorder.

Lesions of the spinal cord give rise to motor or sensory symptoms that are often related to a particular sensory or motor segmental level of the spinal cord (Fig. 1.4). Identification of the appropriate level of the motor or sensory loss (called a motor or sensory level) is important for understanding the disability.

When motor roots are involved, or when motor neurons are affected focally, clinical findings may indicate the spinal level of the injury. This clinical evidence would include the typical lower motor neuron signs: weakness, wasting, fasciculation, and loss of tendon reflexes. Because it is clinically difficult to relate the innervation of muscles of the trunk and thorax to specific spinal
segments, however, the motor level may not be evident. For instance, a lesion anywhere above the first lumbar segment may cause signs of upper motor neuron disease in the legs. Under these circumstances, sensory abnormalities are more valuable for localizing the lesion.

The characteristic pattern of sensory loss after a transverse spinal cord lesion is loss of cutaneous sensation below the level of the lesion, contralateral to the damaged spinothalamic tract if the lesion is unilateral. The sensory level is often more evident than the motor level. However, sensory loss due to spinal lesions must be differentiated from the pattern of sensory loss caused by lesions of peripheral nerves or isolated nerve roots. In multiple symmetrical peripheral neuropathy (polyneuropathy), there is a glove-and-stocking pattern of impaired perception of pain and temperature. This pattern is attributed to “dying-back” or impaired axonal transport; the parts of the axons most severely affected are those most distant from the sensory neuron cell bodies in the dorsal root ganglia. In injuries of single peripheral nerves, the distribution of sensory loss is more restricted and can be recognized by reference to sensory charts that were originally generated by studies of the long-term effects of traumatic nerve injuries incurred during war.

Nerve root or segmental sensory loss and spinal sensory levels can be identified by the dermatomes typically affected. The spinal cord ends at the base