Translational Neurorehabilitation

Brain, Behavior and Technology

Rocco Salvatore Calabrò
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Introduction to Translational Neurorehabilitation

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Rocco Salvatore Calabrò

Population is aging worldwide, especially in the western countries, with a great burden on the social and economic system. Neurological diseases increase with age, especially neurodegenerative ones, including Alzheimer's Disease and Parkinson's Disease.

The Global Burden of Disease Study estimated that in 2016, there were more than 80 million stroke survivors in the world, 43.8 million people with dementia, 45.9 million patients with an active epilepsy, and 6.1 million individuals with Parkinson's disease. Globally, in 2016, neurological disorders were the leading cause of disability (276 million disability-adjusted life-years) and the second leading cause of deaths (9 million) in the world [1].

Moreover, people who survive a brain injury are rising, thanks to the improvement of intensive acute care; then, the need for neurorehabilitation will double in the next few years. Motor, cognitive, and behavior approaches have changed over years and novel tools to treat brain and spinal cord injury should be validated before translating into the clinical practice.

Translational Neuroscience is aimed to integrate basic research of brain morphology and functional activity in vivo, with the needs of patients suffering from disorders of the Central Nervous System. The study of these disorders is a subject of Neurology, Psychiatry, and Neurosurgery, as well as Neurorehabilitation. In fact, Translational Neurorehabilitation is an interesting new field that seeks to produce more meaningful, applicable rehabilitation results that directly benefit human health, performance, and quality of life.

Robotics and virtual reality (VR) are the most promising tools of the last decades in the rehabilitation area [2, 3]. Robotic devices have been developed to reduce the

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required labor and time, improve the reproducibility of the kinematics of different movements and gesture, and increase the volume of the motor exercises. They can also accurately and objectively measure patient's output in terms of joint kinematics and kinetics. The current rehabilitation robotic devices can be grouped into two main groups: exoskeleton (that fits to the patients' joints and move them through predetermined patterns) and end-effectors (moving the limb from the more distal part).

VR is the multisensory and interactive simulation of real scenarios, mainly presented in a three-dimensional way, with which the patient can interact [4, 5]. VR devices use specific software with input-output peripherals that make the experience complex and engaging, promoting the improvement of patients with motor/cognitive disabilities, as well as their well-being and participation. VR allows being at the center of rehabilitation training, through two perceptive conceptions, i.e., immersion and presence "Immersion" is the objective perception of a sense of "sensory absorption" in the three-dimensional environment, whereas "presence" is a subjective psychological state whereby the user is consciously involved in the virtual context [6, 7].

The application and implementation of robotics and VR in clinical practice is the best example of translational neurorehabilitation of the last decades. Indeed, many devices (for either rehabilitative or assistive purpose) have been developed and the way neurological patients are trained is really changing with positive results on their outcomes.

Moreover, understanding the neurophysiological underpinnings of functional recovery is also fundamental, and to this aim advanced electrophysiology and neuroimaging could be of help. The former is used within translational neuroscience/neurorehabilitation as a means of studying the electric properties of neurons in animal models as well as to investigate the properties of human neurological dysfunction and the basis of functional recovery. Neuroimaging involves a variety of techniques, including fMRI, DTI, PET/SPECT, used to observe the activity or the structures of, or within, the nervous system [8, 9].

Finally, the use of neuromodulation (TMS and tDCS), alone or combined to other innovative tools, may boost neural plasticity and therefore, improve patients' recovery and quality of life [10].

The stages of translational neurorehabilitation, as well as all the other fields of translational medicine, neuroscience research are as follows:

- S0: Basic science research
- In the neurorehabilitation field, this could be aimed at finding/experiment compounds able to improve neuroplasticity, reduce/slow neurodegeneration, and then improve functional recovery
- S1: Preclinical research
- Preclinical applications of task-specific rehabilitation include skilled reaching tasks. Skilled reaching tasks can be applied to experimental models to investigate motor behavior and sensorimotor integrations in post-injury recovery. Preclinical studies may also involve proof-of-concept works on robots/VR tools.

- S2: Clinical research
- Once a device has been made by bioengineering, this should be validated in clinical practice. First, feasibility and safety can be investigated in healthy subjects; then, pilot studies could address this issue in neurological patients, and finally RCT and real-life clinical studies must evaluate the efficacy, as compared to traditional methods.
- S3: Clinical implementation.
- This involves studies aimed at applying diagnostic or treatment devices to other patients than those for whom the tool was initially designed, approved, and commercialized.
- S4: Public health
- The device could become fundamental within a service or pathway in neurorehabilitation, especially for patients suffering from chronic disability. Politicians, CEO, and all stakeholders are fundamental at this stage.

This summary of the transitional stages allows to better understand how the approach to this new field is complex and integrated, involving several disciplines (such as biomechanics, engineering, neurology, physiology, physiotherapy, neuropsychology, biochemistry, physical and rehabilitation medicine) basic researchers, clinicians, and other non-healthcare professionals.

The book provides useful information concerning brain–behavior interactions to basic neuroscientists, neural engineers, clinical neurologists, and physiatrists.

It is aimed to expand current understanding of brain function and disease by evaluating preclinical and clinical trials on neural plasticity and functional recovery after nervous system disorders, and disseminate the knowledge coming from novel therapies, including advanced robotic and ICT/AI-based applications.

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Brain Injury, Neural Plasticity, and Neuromodulation

2

Antonino Naro and Rocco Salvatore Calabrò

2.1 Introduction

Any brain structural damage, with regard to stroke and traumatic brain injury, can impair behavioral skills and the correlated motor skill learning, i.e., the process of optimizing sequences of action for accomplishing specific tasks [1]. Such an impairment mainly depends on the deterioration in connectivity between sets of corticospinal neurons following changes in synaptic efficacy [2], whose spatial and temporal organization is known as the "connectivity map."

Both connectivity maps and behavioral skills can at least be partially restored through intense motor practice and rehabilitation [3], ultimately aimed at restoring functions essential to independence in daily activities. Actually, motor training triggers the principles-pillars governing the organization of connectivity maps, including fractured somatotopy (i.e., the representation of any individual skill is highly distributed across different cortical regions), interconnectivity (i.e., adjacent cortical areas are densely interconnected via white matter bundles), and area equals dexterity (i.e., the more demanding the skill, the larger the proportion of the map is involved in the skill's representation) [4, 5], as a strong correlation between connectivity maps and its synaptic plasticity and performance of skills exists through a learning-dependent motor cortical map organization [6]. Therefore, motor training affects plastic changes in synaptic efficacy within the motor cortex, with consequent changes in map topography and, eventually, behavioral skills. Particularly, motor recovery through rehabilitation strategies (including neuromodulatory pharmaceutical agents and stimulation techniques such as exercises, pharmacological interventions, and brain stimulation) is achieved by activating a variety of neuroplastic

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processes (including synapse strengthening, neural circuit rewiring, axonal sprouting, spinogenesis, and neurogenesis) that comprehensively allow the brain to change and adapt its functions to brain damage [7–11].

To achieve such neurobiological changes, motor practice must be intensive to induce effective brain reorganization, according to an experience-dependent neuroplasticity principle [12]. This consists in the entrainment of long-term potentiation (LTP) and inhibition of long-term depression (LTD) mechanisms, which both promote behavioral motor learning [12, 13]. These are hallmarks of recovery processes as compared to simple compensation processes, which do not entrain plasticity mechanisms, as well as the activation of some biochemical cascades, including myokines, neurotrophic factors, neuropeptides, growth factors (GF) and GF-like molecules, and cytokines, which have all been recognized as crucial for recovery. Interestingly, all such mechanisms can be further potentiated by adding external stimuli through brain stimulation devices, including repetitive transcranial magnetic stimulation (rTMS) and transcranial current stimulation (TCS). Finally, the use of technological devices, as robots, has been of significant help to let the patient to perform an intensive, repetitive, assisted-as-needed, and task-oriented motor training, which are all essential factors to modify synaptic efficacy within the motor cortex, with consequent changes in map topography and, eventually, behavioral skills.

This chapter provides an overview of the neuroplasticity mechanisms related to brain injury and neuromodulation, focusing on how motor practice and brain stimulation can drive neural plasticity processes to facilitate functional recovery, also paving the way for next-generation strategies for brain injury rehabilitation.

2.2 Brain Injury

The acute disruption of brain tissue by a cortical contusion, ischemia, hemorrhage, or axonal injury [14] often causes irreversible damage to the central nervous system (CNS) [15]. Focal brain damage determines a degeneration process initiated by unrestrained neuronal depolarization (excitotoxicity) [16], increasing the likelihood of neuronal dissolution [17], axon disintegration [18], cell lysis and neuronal necrosis (19), apoptosis and postsynaptic receptor modification [14]. These neuronal damages trigger an inflammatory process and an accumulation of reactive oxygen species [19], with consequential DNA fragmentation and lipid peroxidation, all causing further neuronal disconnection [20] and a future harmful effect on neurogenesis [21].

Secondarily to this damage, a cascade of events can be triggered (including metabolic processes [22], decrease in energy transduction and lack of adenosine triphosphate [23], excitotoxicity and inflammation processes, vasogenic and cytotoxic edema (the former resulting from BBB damage, the latter from cell metabolic derangements) [21, 24], disruption of the blood–brain barrier (BBB) [21], damage to the vasculature (which favor pro-inflammatory processes and release excitatory

amino acids, creating a more vulnerable environment) [25–27], and white matter destruction, ultimately leading to a collapse of brain tissue [14, 28], implying impairment of cell functions, cell death [29], and consequent dissemination of damage [24]. In addition, owing to neuroinflammation and BBB loss of autoregulation, cerebral blood flow (CBF) results impaired, placing the brain at an increased risk of ischemic injury during the first hours after the injury.

All these changes can affect the connectivity of thousands of neurons, resulting in an impairment of their functional interactions. In this way, a relatively localized injury can result in widespread damage to the brain [30]. All these aspects determine the degree and magnitude of long-term deficits [22].

2.2.1 The Role of Plasticity in Brain Damage Recovery

Plasticity is defined as the intrinsic property of the nervous system to reorganize itself in response to an injury [31, 32], beyond its role in neural development and homeostasis [33]. Brain plasticity may be neuronal (synaptic or non-synaptic) or non-neuronal [34], as well as activity- or time-dependent [35], including modulation of synaptic transmission [36], integrative properties of individual neurons [37] and neuronal networks [38], neurotransmitters and ions [39, 40], gap junctions [41], and glial cells [42, 43]. All these mechanisms ultimately result in anatomical and functional modifications [44].

Brain damage recovery develops through three main stages: activation of cell repair [45], including subsidence of inflammation and edema, functional cell plasticity changes (including changes in the amount of excitation or inhibition induced and in the strength of specific synapses, also known as short-term plasticity), and anatomical plasticity changes [46–49]. Rehabilitation strategies therefore aims at targeting activity-dependent synaptic plasticity [50] (mainly based on long-term potentiation (LTP) and long-term depression (LTD) phenomena) [51, 52] that has a significant role in brain injury recovery [53–58] through the induction of anatomical neuronal changes [59–62], including using redundant connections or forming new connections among residual neurons, which all support functional recovery [63–65]. However, such plastic changes can also have negative effects, potentially leading to maladaptive outcomes (including spasticity [34], pathological pain [66, 67], schizophrenia [68, 69], dystonia [70], cognitive impairment [71, 72], and seizure foci [73]. It is therefore essential in the rehabilitation processes to suppress functionally maladaptive changes while enhancing favorable processes (and their related outcomes), leading to a better recovery of motor and cognitive function thus decreasing disability burden. To this end, artificially coupling neuronal pool discharges in a spiking time-dependent plasticity manner through brain stimulation, so to eventually modify functional and/or structural network connectivity (i.e., through activity-dependent plasticity), represents a promising therapeutic intervention in the rehabilitation setting [5].

2.3 Brain Stimulation

Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) use, respectively, magnetic field to induce electric fields (consistently with the principle of electromagnetic induction) [74] and direct low-intensity currents in cortical tissue to affect cortical excitability with potentially relevant neuroplastic effects consistently with LTP and LTD phenomena [75, 76] and, eventually, functional and structural changes of neuronal networks [8, 77, 78]. Magnetic stimuli can either directly or indirectly (by interneurons) depolarize cortical neurons [79], depending on stimulus configuration (including intensity, frequency, pattern, and morphology) and the different thresholds to electrical stimulation of neuronal populations [80].

The electric current yields, first, ionic changes around targeted neurons by flowing ions through the cell membrane, mostly at axonal-soma and axonal-bouton boundaries [81], thus inducing neuronal depolarization or hyperpolarization [82], and then a stimulation-induced storage of charge, which ultimately lead to modifications in neural excitability [83–85]. The repeated application of magnetic stimuli corrupts the ongoing neuronal activity, whose summatory effects result in an increase or a decrease in cortical excitability, which is when the after stimulation neuromodulatory effects occur. Generally, low frequencies (below 1 Hz) tend to decrease cortical excitability probably due to preferential stimulation of GABAergic neurons [86, 87], while high frequencies (above 5 Hz) have the opposite effect [88]. Both approaches can induce both local and distant aftereffects, harnessing large scale cortical networks, as also suggested by specific changes in CBF, which are not however necessarily coherent with excitability changes direction (i.e., cortical excitability increase, CBF increase) [79].

Neuromodulation may affect cortical plasticity by providing peripheral stimuli when timilgly collimated each other (namely, Paired Associative Stimulation—PAS), consistently with a spike-timing dependent plasticity principle [89–91]. Additionally, stimuli can be timingly sequenced in specific patterns, for example, low-frequency pulses can be preceded by a short train of high-frequency pulses (i.e., priming), leading to a stronger inhibitory effect [92]. Alternatively, brief simple or patterned trains of stimuli (three 50-Hz stimuli at 5 Hz) can have relevant consequences on cortical excitability whether administered continuously (cTBS, GABAergic-dependent excitability decrease) [93, 94] or intermittently (iTBS, excitability increase) [95]. The duration of TMS aftereffect is variable depending on the individual's physiology and the stimulation setup. It can range from minutes to weeks [96, 97]. It has been proposed that the repeated modulation of cell polarization (namely, short-term effects) can affect the modulation of NMDA glutamatergic receptors [98, 99], which could account for LTP/LTD induction. These effects, in turn, pave the way for long-term effects, including early genes expression associated with neuronal activation (including c-Fos) [100–102] and neurotrophic factors (such as brain-derived neurotrophic factor), which altogether account for structural plasticity changes (which is proposed to the most relevant for the neurorehabilitation aftereffects) [100].

Less information is available for tDCS aftereffect. The weak direct currents employed in tDCS paradigms can modify the resting membrane potential, which impacts the level of spontaneous neuronal excitability and activity [103, 104]. Noteworthy, tDCS does not interrupt neuronal activity like TMS does; in other words, it does not induce action potentials through a rapid depolarization of neurons, like TMS does, but it rather modulates neuronal membrane excitability [103]. The direction of tDCS effects depends on the stimulation setup adopted, particularly including electrode polarity (i.e., anodal stimulation increases cortical excitability, whereas cathodal stimulation decreases it) [105–111], besides current intensity, stimulation duration, and current density, i.e., the quotient of current strength and electrode size. Polarity changes (without determining action potential) is achieved by changing the activity of transmembrane proteins and hydrogen ions [107, 110, 111] at the interneuron level [112, 113], as well as sodium and calcium channels [107, 110, 111], whereas NMDA, $GABA_A$, and glutamate-dependent mechanisms seem less relevant [107, 110–112, 114]. Interestingly, a significant polarization of neuronal membrane can result in the inactivation of voltage-gated channels, thus reverting tDCS aftereffects [107, 110, 111].

Prolonging current exposure can then induce ionic changes and modifications in transmembrane proteins, which in turn cause long-lasting changes of neural membrane function [115], calling into account synaptic mechanisms (contrarily to what observed for the immediate effects of tDCS), which likely involve GABAAergic and glutamatergic synapses [93, 94, 112, 113] related to LTP- and LTD-like mechanisms [116]. Particularly, the activation of NMDA receptors by glutamate entrains LTP phenomena [117, 118], whereas cathodal stimulation may be able to contribute to the development of LTD-like phenomena.

2.4 NBS as a Therapeutic Tool

A brain injury can yield a variety of neurobehavioral consequences, including seizures [119, 120], headache [121], movement disorders, motor impairment, language and visual deficits, sleep [122], memory [123, 124], and attention disorders as well as concentration impairment [125]. These can occur soon after a brain injury as well as up to months. Similarly, the course of recovery may last months to years. This means that specific interventions at different time periods can be used in the attempt to foster brain function recovery, mainly depending on the phase (acute, subacute, and chronic) of brain damage. Basically, we can try (i) to limit the extent of the initial injury to minimize further neurological deficits, and (ii) to promote reorganization of neural networks, allowing for the relearning/vicariation of lost functions [12, 126–128].

Modifying cortical excitability by using NIBS could help to counteract the acute inflammatory phenomena of a brain lesion and to favor an adaptive rewiring of damaged neural connections, thus ultimately enhancing behavioral recovery [129–133]. Specifically, NIBS aims at reducing the excessive glutamatergic activity resulting from neuronal damage and the loss of surround inhibition mechanisms through

enhancing residual inhibition mechanisms, ultimately resulting in a suppression of cortical excitability. In this regard, daily cathodal tDCS, low-frequency rTMS, and cTBS may prove to be useful, as suggested by the remodulation of the glutamatergic and GABAergic systems in murine models [134]. Moreover, NIBS can limit the oxidative stress and apoptosis process following brain injury [135]. Finally, NIBS can modulate plastic changes even in the acute phase, to avoid maladaptive consequences, including effects on axonal sprouting and synaptogenesis [136]. Following glutamatergic-mediated neurotoxicity, a prevailing inhibitory tone takes step, which both silence neural networks [137] and affect LTP/LTD plasticity processes [137, 138]. Therefore, facilitatory interventions such as high-frequency rTMS or anodal tDCS could increase cortical excitability and counteract GABAergic inhibition, so to facilitate, for example, motor function recovery as shown in stroke models [139].

Consistently with the issue that function recovery occurs through a series of distributed cortical activation in different brain areas of both hemispheres, the strategy of contemporary modulating both hemispheres seem reasonable. Indeed, the modulation of interhemispheric balance using a combination of NIBS parameters has been shown promising [107, 110, 111, 140–149], with particular regard to motor learning [147] by using high-frequency rTMS, iTBS, and anodal tDCS [88, 107, 110, 111, 140, 144] over the affected hemisphere or low-frequency rTMS, cTBS, and cathodal tDCS on the contralesional hemisphere [150, 151] by modulating transcallosal inhibition [152]. To enhance NIBS aftereffects, coupling with Physical Therapy Motor training involving skill learning (as opposed to simple exercises) may be critical to induce plastic changes in the CNS via increased synaptogenesis, LTP/LTD-like mechanisms, and reorganization in the thalamo-cortical motor maps [53, 153, 154]. NBS and motor learning seem to share similar mechanisms for inducing neuroplasticity; thus, their individual therapeutic effects may be enhanced by their combination. For instance, physical exercise can improve motor and cognitive outcomes by improving motor cortical representations [55, 155]. NBS delivered prior to a motor task may prime neuronal networks in the cortex, whereas simultaneous application may recruit specific sets of synapses involved with motor performance. In this regard, physical therapy coupled with high-frequency rTMS on the injured hemisphere [156] or low-frequency stimulation on the contralesional hemisphere [157], as well as CIMT coupled with active tDCS or cathodal tDCS of the intact M1 and anodal stimulation of the affected M1 [158], induce structural neuroplasticity changes and a modulation of transcallosal inhibition from the undamaged to the affected hemisphere sustaining functional outcomes after ischemic stroke compared to sham stimulation. However, the specific anatomic and neurophysiologic derangements of each patient, the time elapsed after brain injury, the severity of paresis, the type of intervention, the technique of NIBS used and its parameters, the target area, the type of physical training performed, and its timing in relation to stimulation [116] may all influence the success of treatment [159], as different tDCS setups coupled to robotic therapy showed non-significant outcome difference. All such above-mentioned factors must be thus individually tailored and the need for further research in the field is obviously emphasized.

2.5 Conclusions

The knowledge of the complex mechanisms and timing of neuroplasticity processes developing after a brain injury are the fundamental prerequisite to build a patient-tailored rehabilitation program. This would help enhance recovery and decrease the burden of disabling sequelae after the injury. Although plasticity processes sustain functional recovery, they might also lead to additional injury and negative outcomes if developing as maladaptive. Targeting plasticity processes in an adequate manner becomes therefore critical to enhance the former while suppressing the latter. This has been demonstrated as possible through rehabilitation strategies which are furthermore fostered by NIBS, so to precisely target specific neural networks and potentiate plasticity processes aftereffects. However, further research is needed to understand the mechanistic interaction between the aforementioned techniques, as well as to establish their safety and define optimal stimulation parameters.

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