

## Chapter 3

# Stroke and potential benefits of brain-computer interface

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### Abstract

To treat stroke and, in particular, to alleviate the personal and social burden of stroke survivors is a main challenge for neuroscience research. Advancements in the knowledge of neurobiologic mechanisms subserving stroke-related damage and recovery provide key data to guide clinicians to tailor interventions to specific patient's needs. How does the brain-computer interface (BCI) fit into this scenario? A technique created to allow completely paralyzed individuals to control the environment recently introduced a new line of development: to provide a means to possibly control formation and changes in the brain network organization. In a sort of revolution, similar to the change from geocentric to heliocentric planet organization envisioned by Copernicus, we are facing a critical change in BCI research, moving from a brain to computer direction to a computer to brain one. This direction change will profoundly open up new avenues for BCI research and clinical applications. In this chapter, we address this change and discuss present and future applications of this new line idea of BCI use in stroke.

## ISCHEMIC STROKE PATHOGENESIS

### Lesion core and penumbra

Cerebral ischemia results from obstruction of blood flow to a portion of the brain due to three main causes: small vessel disease, atherothrombosis, or cardio-embolism. This classification nevertheless is clearly not adequate since it does not cover up to 30% of strokes whose cause remain unknown (Amarenco et al., 2009).

Following ischemia, brain tissue is deprived of oxygen supply with detrimental effects on energy-dependent processes in neuronal cells. Energy loss particularly affects the transmembrane ionic gradient and cellular homeostasis. This elicits several processes that lead to cell death: excitotoxicity, oxidative and nitrative stress, inflammation, and apoptosis (Khoshnam et al., 2017). These pathophysiologic processes are interlinked, involve neurons as well as glial and endothelial cells, and evolve through time. Overall, a very complex picture, with an evolving mosaic of severe damage across time and space, arises. The lesion core, in which irreversible immediate damage is present

because of necrotic cell death, is surrounded by areas where suffering but metabolically active cells are present, which eventually will face cell death. The death signals will spread throughout the anatomical and functional network determining metabolic changes and eventually even cell death also in far distant areas (Weishaupt et al., 2016). Indeed, stroke pathogenetic mechanisms are present well beyond the lesion core and the penumbra areas.

Most stroke treatment approaches developed in the laboratory have focused on protecting neurons from the different ischemia induced processes, such as inflammation and apoptosis, particularly in the areas outside the central core, the so-called penumbra, where neuronal damage is delayed and death mechanisms are sensible to different drug treatments. Different good and very recent reviews are available on this topic (Khoshnam et al., 2017). Much less attention has been paid to pathogenetic mechanisms outside the core and penumbra areas, the so-called remote damage mechanisms whose importance for recovery is well established and which may be of relevance for brain-computer interface (BCI) approaches to stroke.

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### Remote damage

Although not directly related to ischemia, remote cell death mechanisms are complex, involving many different phenomena. Signaling cascades observed in remote damage are partially similar to those present in the core and penumbra regions. Excitotoxicity, derived from oxidative and nitrative stress, inflammation, autophagy, and apoptosis are all mechanisms involved in both delayed and remote responses (Viscomi and Molinari, 2014). The study of remote cell death damage mechanisms is in its infancy. However, considering the importance of remote damage in sustaining network changes in stroke, it is easy to predict that more expansive understanding of remote cell death will help to improve recovery by addressing and guiding poststroke circuit reorganization.

Remote cell death does not occur because of hypoxic/ischemic damage but because of delayed, secondary degeneration affecting cells not directly involved in the initial damage (Block et al., 2005). Cells degenerate because of different destructive downstream events sustained by active, independent mechanisms. These events are thought to be activated by unknown signals conveyed through anatomical and/or functional networks reaching the primary site of damage. This flow of death signals can last for days, weeks, or months and may result from damage of axonal processes (Carmichael et al., 2017) involved in the ischemia or penumbra areas or from transneuronal effects. Morphologic and physiologic effects on parent cell body from axonal damage are well known and documented (Sears, 1987; Titmus and Faber, 1990). Less is known about transneuronal (or transsynaptic) effects. The importance of these effects after focal lesion has been clearly demonstrated in the cortico-cerebello-cortical circuit. Although no monosynaptic links exist between the cerebral and cerebellar cortices, stroke involving the cerebral cortex, even with sparing of subcortical structures, influences both the anatomical and the functional organizations of the cerebellar cortex and vice versa. Focal lesion in the cerebral cortex not only alters the functionality of the contralateral cerebellum (Lin et al., 2009) but also induces gross anatomical changes (Gold and Lauritzen, 2002). Similarly, damage limited to cerebellar structures produces long-lasting structural and functional effects in the cerebral cortex, contralateral to the cerebellar stroke site (Clausi et al., 2009; Vico Fallani et al., 2016).

Retrograde transneuronal degeneration or “dying backward” is a degeneration that involves neurons that lose their projection target. Conversely, “dying forward” refers to anterograde transneuronal degeneration because of loss of inputs. These transsynaptic degeneration mechanisms have been described in different animal models (Viscomi et al., 2015) and confirmed in many CNS

diseases in humans (Nakane et al., 1997; Rehme and Grefkes, 2013; Umarova et al., 2017). Remote cell death severity is related to several factors, such as type, distance from and extent of the primary insult, and type of connectivity involved. These factors are not equally distributed across networks with specific circuits characterized by intrinsic vulnerability differences (Sofroniew and Isacson, 1988; Faden, 2002). The general picture of remote damage sensitivity is even more fragmented if neuronal cell types are considered. Specific cell populations not only differ in their vulnerability, but also apparently, similar cells may react quite differently to remote damage insults. Models of axotomy of central neurons, such as homogeneous neurons of the dorsal lateral geniculate nucleus (Hendrickson et al., 2012) and the inferior olive and pontine nuclei (Viscomi et al., 2015), clearly indicate that this is the case. The reasons for this variability remain unknown (Buffo et al., 2003; Di Giovanni, 2009).

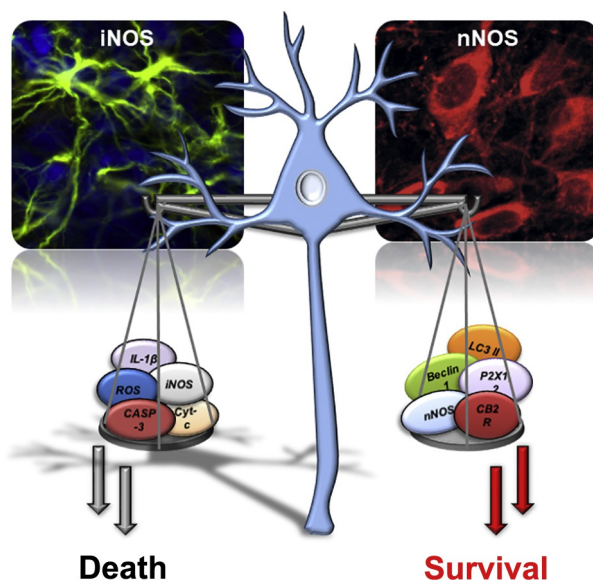
Taken together, these data indicate that stroke pathogenetic mechanisms are present well beyond the lesion core and the penumbra areas. The remote effects, once considered mainly of transitory nature, the so-called “diaschisis phenomenon” as defined by Von Monakow (1914), are sustained by long-lasting structural and biochemical changes. Overall, stroke damage has to be considered in its complexity and its far-reaching effects on CNS function to correctly support poststroke recovery of the function.

### STROKE RECOVERY BETWEEN MYTH AND REALITY

As mentioned earlier, cellular and molecular mechanisms activated by ischemic stroke are extremely complex, involving, since the beginning, a cascade of events not only in the lesion core but also, if not prominently, in the perilesional tissue. In this latter area, both degenerative and protective responses are intermingled and are very difficult to disentangle from one another. The same mechanisms involved in cell death are also the starting points for removing irreversibly damaged tissue. This step is the cornerstone to allow repair and reorganization of surviving structures. Changes in perilesion brain areas are also considered to establish a particularly sensitive period of enhanced plasticity (Zeiler and Krakauer, 2013). Example of the double edged attitude toward recovery is the inflammatory response since the early phase of ischemia (Khoshnam et al., 2017). Neuron glial cross talk interacts with inflammatory mechanisms allowing spread of the lesion as well as changes in the extracellular matrix. In specific restricted time windows, these changes allow the neural tissue to become permissive, supporting sprouting of axonal processes and dendritic remodeling.

Research to improve stroke recovery mostly focused on preserving neurons and circuits in the penumbra area. A number of neurotrophic and neuroprotective agents have been identified and tested (Demuth et al., 2017). In spite of the large research effort and the promising results in animal models, none of the proposed neuroprotective agents succeeded in developing a clinically effective treatment (Onwuekwe and Ezeala-Adikaibe, 2012). Recently, more attention has been given to remote changes as potentially effective therapeutic targets to support stroke recovery. To this aim, both pharmacologic agents (Viscomi et al., 2015) and rehabilitation protocols (Zeiler and Krakauer, 2013) targeting CNS areas remote to those primary damaged areas have been developed.

Besides the core and penumbra regions, even in remote areas, the degenerative and recovery mechanisms are highly intermingled with survival and degeneration factors (Fig. 3.1). Within this scenario it is conceivable



**Fig. 3.1.** Schematic of the molecules so far characterized in the hemicerebellectomy (HcB) remote degeneration model playing a key role in determining death/survival fate of axotomized neurons. Survival molecules (*right side*): upregulation of neuronal nitric oxide synthase (nNOS), cannabinoid receptor type 2 (CB2R), and purinergic receptor X1, X2 (P2X1, 2), and Beclin 1 and LC3II conversion—these latter two as markers of autophagic machinery—promote neuronal survival. Death molecules (*left side*): cytochrome *c* release (cyt *c*), caspase-3 activation (casp-3), inducible nitric oxide synthase (iNOS) upregulation, and IL-1 $\beta$  and reactive oxygen species (ROS) production cause neuronal death. From Viscomi MT, Molinari M (2014). Remote neurodegeneration: multiple actors for one play. *Mol Neurobiol* 50: 1–22, with permission from Springer Nature.

that a better understanding of the changes in the remote areas will greatly help our understanding of poststroke organization, particularly at network level.

The same rodent models critical for discovering cell mechanisms and signaling associated with remote damage have shed light on the mechanisms underlying neuronal network remodeling. Functional connectivity is affected brain-wide with alterations in both hemispheres (Calautti and Baron, 2003; De Vico Fallani et al., 2013) well beyond the infarcted area.

On the other hand, in spite of the focus on core and penumbra areas, once the primary damage is stabilized, functional recovery and rehabilitation approaches take advantage of areas that are remote but functionally linked to the primary site of damage (Coleman and Perry, 2002; Viscomi and Molinari, 2014) rather than address changes in the primary lesion site. This approach is in line with network-based models of brain functioning, which stress the importance of information flow across networks, in contrast to traditional localist models, which lay emphasis on functions localized in specific defined brain regions (Roy, 2012). Therefore, according to the network-based function model, functional deficits arise not only because of the local effects of the damaged region but also because of the dysfunction of functionally connected anatomically intact areas (Zhang et al., 2012). There is much debate over the nature of these remote region dysfunctions: how intact remote regions are, how important the remote regions are in determining the clinical picture, and their relevance for recovery (Viscomi and Molinari, 2014). This latter aspect has also been addressed by different groups in the attempt to develop biomarkers of potential recovery (Grefkes and Fink, 2011; Yin et al., 2014; Weishaupt et al., 2016). This remote, network-based approach would be of particular interest for the development of more effective strategies for stroke rehabilitation.

## FUNCTIONAL RELATED PLASTICITY

Neural plasticity is a widely used definition to address the capacity of the neural system to modify its structure and function in response to various stimuli from changes in external world requests as well as from modifications of the CNS microenvironment or functionality (Macchi and Molinari, 1989). Sporadic indications on the capacity of the adult CNS to change its structure can be found very early at the beginning of the history of Neuroscience (De Felipe and Jones, 1991). Nevertheless, it has been only in the 1970s that consensus developed on the idea that structural as well as functional brain organization is not fixed after development has ended, as stated by Cajal at the beginning of this century (Jones, 2004). Nowadays, it is well established that brain connectivity

is continuously adapting, driven by highly interacting functional as well as structural changes (Jones, 2004; Monday and Castillo, 2017). Of particular interest for stroke rehabilitation is the concept of functional or activity-related plasticity (Cesa and Strata, 2007; Svensson et al., 2014). In particular, all experience-dependent adjustments of brain function are based on synaptic plastic changes. These changes might affect the organization of microcircuits as well as long-distance connections involving both presynaptic and postsynaptic activities (Monday and Castillo, 2017). After stroke, activity changes interact with those induced by lesions, possibly in a highly sensitive milieu, affecting a substantial reorganization of the spared areas and pathways. Overall this reorganization is often associated with limited, spontaneous restoration of function, and the rehabilitation activities are directed to support adaptive and to counter maladaptive rewiring of circuits (Alia et al., 2017).

The most common and widely recognized impairment caused by stroke is motor impairment, which can be regarded as a loss or limitation of function in muscle control or movement or a limitation in mobility (Wade, 1992). Motor impairment after stroke typically affects the control of movement of arm and leg of one side of the body (Warlow et al., 2008) and affects about 80% of patients. Therefore, much of the focus of stroke rehabilitation, and in particular the work of physiotherapists, is on the recovery of impaired movement and the associated functions.

Motor recovery after stroke is complex and confusing. Many interventions have been developed to try to aid motor recovery (and associated functions), and many randomized controlled trials and systematic reviews have been done (Sandercock et al., 2009), although most trials were small and had some design limitations. Constraint-induced movement therapy (CIMT), for example, has emerged as a promising intervention in subacute and chronic stroke (Kitago et al., 2012). In CIMT, the unaffected arm is restrained for a majority of waking hours, while the affected arm undergoes task-based practice. The mechanisms underlying the functional improvement seen with CIMT are not well understood at either the neural or the behavioral level. Functional improvement in the affected arm after CIMT in patients with chronic stroke appears to be mediated through compensatory strategies rather than a decrease in impairment or return to more normal motor control.

A wide range of strategies and devices have been developed for promoting motor recovery by taking advantage of the brain's ability to reorganize its neural networks after injury.

Direct evidence that adjacent regions of the cortex might function in a vicarious manner after injury can be traced to studies in the mid-20th century (Glees and Cole 1949). Monkeys were subjected to focal injury to

the thumb representation. When brains were remapped following behavioral recovery, the thumb area reappeared in the adjacent cortical territory. However somewhat different findings were observed by Nudo et al. in the 1990s. Small, subtotal lesions were made in a portion of the distal forelimb (DFL) representation in squirrel monkeys, and the animals were allowed to recover spontaneously (i.e., without the benefit of rehabilitative training) for several weeks. In contrast to earlier findings, the remaining DFL was reduced in size, giving way to expanded proximal representations (Nudo and Milliken, 1996). However, in animals that underwent rehabilitative training with the impaired limb, the DFL was preserved or expanded (Nudo and Milliken, 1996).

Moreover, the importance of exercise characteristics in determining beneficial or detrimental effects is provided by studies on dystonia (Guehl et al., 2009). Experimental exercise characterized by rapid reversal of agonist–antagonist muscles, based on stereotypical movements with stressful end-range motion that induce cutaneous stimulation across broad surfaces have been shown to induce dystonia in animal models (Byl et al., 1996). Along with experimental data, it is a well acknowledged clinical fact that precise repetitive behaviors that involve nearly coincident inputs and outputs are those most prone to develop task-specific dystonia (Breakefield et al., 2008; Torres-Russotto and Perlmutter, 2008). Interestingly, the knowledge of the mechanism sustaining dystonia also provided the means to develop a specific effective treatment based on disrupting the inputs and outputs overall as well as the strictly imposed synergies. Thus, a sensory motor-returning therapy has been tested for focal task-specific dystonia. Exercise is based on single digit movements with immobilization of the other digits, on extensive practice of dystonic digits, and in coordination with other digits (Candia et al., 2002). These exercises induce motor changes that are associated with neurophysiologic changes at cortical and network levels (Tinazzi et al., 2003; Coynel et al., 2009).

Dystonia is thus a good example of how exercise can drive reorganization of brain circuits. As in dystonia, it must be stressed that better understanding of this plastic remodeling is crucial to develop more effective strategies for stroke rehabilitation, avoiding possible maladaptive responses. This is quite a critical aspect; indeed, it is generally believed that fixed repeated motor patterns at high possible strengths are the target of effective task-oriented exercise. Further, it is widely reported that greater intensity of practice is generally associated with improved functional outcomes not related to the type of treatment. On the other hand, evidence from rehabilitation clinical trials enhance the idea that treatment should be personalized considering individual patients' problems and preferences (Rodgers and Price, 2017).



In this search for personalized rehabilitation approaches, we are still lacking cues to direct our interventions and pragmatism dominates.

Some guiding lights can be derived from a better comprehension of poststroke reorganization of connectivity (Dijkhuizen et al., 2014). Advances in computational neuroscience and brain imaging techniques have been instrumental in making possible supervision of in vivo connectivity changes (Bullmore and Sporns, 2009; Stam, 2014). In particular, the application of graph theory derived approaches is quite effective in evidencing organizational and system-level changes after stroke. Observed connectivity changes include (i) altered interhemispheric connectivity, (ii) critical deviation from efficient processing of segregated and integrated information (supported by the so-called optimal network “small-world” topology), and (iii) abnormal region centrality in the ipsilesional and contralesional hemispheres (De Vico Fallani et al., 2013; Rehme and Grefkes, 2013). Thus, topology of brain interactions, both at local and global scales, is affected by stroke. Furthermore, modern signal processing techniques provide different indexes whose validity as indicators of functional coupling between different areas are at present at the stage of testing in humans and animal models of stroke (Alia et al., 2017). Connectivity changes after stroke are often associated with recovery (Wu et al., 2015); nevertheless, that poststroke network changes might be maladaptive should also be considered (Taub et al., 2002). Considering the variability of network changes, the importance of functional plasticity in affecting connectivity, as well as the close link between brain organization and functional recovery, the need for indexes capable of monitoring connectivity changes is critical. Such indicators would help in scoring synaptic reorganization and plasticity at the system level in relation to recovery after stroke helping to disentangle maladaptive vs adaptive mechanisms as well as more effective vs less effective therapies (Saleh et al., 2017).

### **THE BCI COPERNICAN REVOLUTION: FROM ENVIRONMENTAL CONTROL TO SCOUTING BRAIN CHANGES**

Stroke-related brain function changes are heterogeneous and often unpredictable and, thus, hard to cope with apt treatment. The development of a correct rehabilitation program requires various motor and cognitive assessments to develop the patient-specific approaches that are needed (Rodgers and Price, 2017).

The question then arises: how can we improve the capacity to customize rehabilitation interventions needed for the specific lesioned brain? To answer this question,

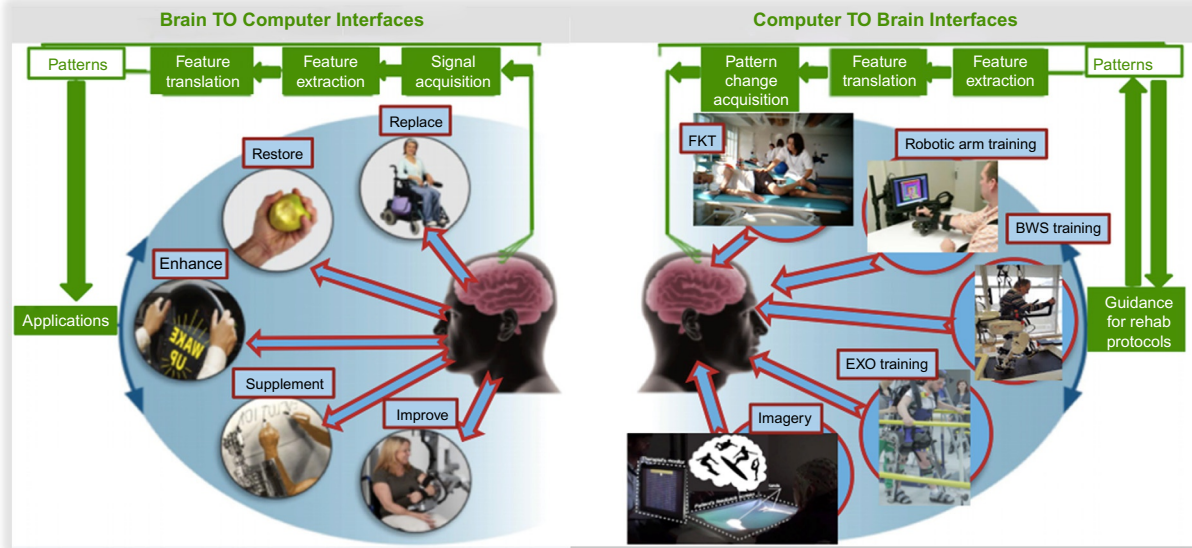
we need to monitor brain connectivity changes, i.e., plasticity, not only serially but also ideally in real time so to avoid maladaptive changes that seem potentially positive changes at the time they occur. At present, we do not have such a tool. Can BCI technology help in tackling this complex scenario? First, we have to consider some changes in the classical BCI setup. In a neurorehabilitation setting, at least three different actors need to be considered. Brain activity information should be provided not only to the patient, as in the classical BCI closed loop, but also to the physician to decipher potential intervention modalities according to network functionality, and to the physiotherapist to allow direct online interactions between imposed exercise or treatment and network changes. Positive effects of such an approach are manifold. Patients respond differently to any specific rehabilitation exercise. The therapist has to recognize any maladaptive response to train the subject to avoid them. The added knowledge of ducting exercise-related network changes would greatly help this process. On the other hand, when positive functional effects are present, the online observation of the plasticity of the brain changes would help in monitoring the extent and timing of the exercise. This scenario implies a radical change in our view of BCI (see also Chapters 9 and 13).

BCI technology could be instrumental in opening an instantaneous window into brain activity and mechanisms that underpin functional recovery. The vision is that BCI not only allows for a direct control of a (e.g., robotic) device to restore or to improve patients' performance, but it also feeds back (to patients and therapists) the ongoing brain changes related to/induced by the BCI-driven exercise itself. Accordingly, BCIs can be twofold devices: device to rehabilitate and device to help the decision-making process for guiding and shaping the intervention (Fig. 3.2).

Such an approach would not be limited to the guiding of the rehabilitation therapy. BCI technology would also allow for continuous monitoring of brain activity during recovery, providing a sort of window “into the brain functions” and, consequently, a powerful tool to provide an objective quality check of rehabilitative interventions.

With this perspective in mind, different groups are investigating various new directions within BCI for neurorehabilitation based on patients', physicians', and physiotherapists' perspectives (Millán et al., 2010; Pichiorri et al., 2016). This research paves the way for a better translation of the BCI, opening possible exploitation of the technology outside the assistive domain into the daily clinical practice.

Accordingly, BCIs can be twofold devices: device to rehabilitate and to help the decision-making process for guiding and shaping intervention. Different noninvasive



**Fig. 3.2.** The BC Copernican revolution. *Left side:* Classical design and operation of a brain-computer interface (BCI) system as proposed by Wolpaw and Wolpaw (2012). Brain activity signals are recorded and analyzed to correlate with the user's intent to control application devices that replace, restore, enhance, supplement, or improve natural CNS outputs. *Right side:* Design and operation of a computer-brain interface. In this case, devices and environment that induced changes in brain activity are recorded and analyzed to guide patient, therapist, and devices activity to improve recovery.

(EEG) BCI-based approaches were developed to promote functional motor and cognitive recovery after stroke. For example, an Italian multidisciplinary team (neuroscientists, bioengineers, and rehabilitation experts) was successful in designing and implementing a sensorimotor rhythm-based BCI combined with realistic visual feedback of upper limb to support hand motor imagery practice in subacute stroke patients (Cincotti et al., 2012; Morone et al., 2015). Moreover, a BCI system based on movement-related cortical potentials combined with functional electrical stimulation for lower limb motor rehabilitation was introduced (Mrachacz-Kersting et al., 2012) and its clinical efficacy in a cohort of chronic stroke patients was also demonstrated (Mrachacz-Kersting et al., 2016).

The dual aspect that often emerges in the context of BCI technology to boost neurologic rehabilitation after stroke is the following: should future efforts to improve efficacy of BCI-driven approaches/interventions address the design toward either the development of the most effective decoding algorithms or the integration of evidence-based clinical principles that harness brain plasticity through task-dependent experience? Most probably, a “hybrid” approach will best fulfill the complexity of the rehabilitation requirements. In particular, the deployment of optimal solutions to decode motor/cognitive “intentional” signals should rely on neurophysiologic determinants of brain reorganization after stroke damage (physiologically driven vs data-driven approach

in designing new classes of decoding algorithms) and on their relationship with altered functions. Motor learning principles should guide the design of BCI systems, taking into account the growing knowledge on how these principles are maintained or deranged after stroke.

We expect that synergic advancements in these neuroscientific questions will have a direct impact on the translational aspects of BCI technology such as to identify determinants of response-to treatment and to tailor/shape intervention according to patients' clinical and neurophysiologic characteristics (stratification of target population). At the same time, clinical transfer of the current successful BCI systems (and future ones) requires to answer crucial questions regarding the timing of intervention, adaptability to patient compliance (not to harm), integration with conventional treatment (secondary effect on usual care), and follow-up of intervention efficacy.

The improved BCI capacity of online monitoring of brain activity will hopefully have a significant impact on the daily clinical routine of neurologic rehabilitation, modifying today's gym rehab scenario into a technology empowered environment in which human-machine interaction capabilities could be used at their full potential.

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