New technologies to treat neurodisorders: neuroprosthetics

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New technologies to treat neurodisorders: neuroprosthetics

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SESSION 3
RESTORING AND ENHANCEMENT OF COGNITIVE FUNCTION

Presentation

Silvia Misiti

Head of IBSA Foundation for Scientific Research

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The Forum "New technologies to treat neurodisorders: neuroprosthetics" was a successful, highly inspiring meeting. The Forum brought together experts from all over the world to discuss the current understanding of the mechanisms underlying motor and cognitive dysfunctions in neurodisorders and to present the state of the art of technologies that interface with both the central and peripheral nervous system to restore and enhance the lost or impaired functions.

The meeting was opened by Sandro Mussa-Ivaldi from the Rehabilitation Institute of Chicago, one of the most recognized expert in motor learning. He discussed the ability of the central nervous system to learn new and complex sensorimotor mappings through practice in different scenarios and how this aptitude can be leveraged with rehabilitation purposes. Lena Ting gave an interesting talk on neuromechanical principles and their importance to gain insights into the patterns of neural activity that generate movements, with a focus on how such patterns are affected by rehabilitation in patients with motor deficits. Motor rehabilitation was also the main topic of Robert Riener's talk, which focused on robot-assisted training for stroke patients. He provided an overview of the current state of the art and presented the key challenges for future developments in the field of rehabilitation robotics.

The second session of the Forum addressed function restoration through neural interfaces with the peripheral nervous system and the spinal cord. More specifically, Professor Micera gave a lecture on the importance of the peripheral nervous system in the treatment and rehabilitation of a variety of pathological conditions and he presented the details of a bidirectional neurocontrolled hand prostheses able to read commands from the motor nerves and stimulate sensory nerves to return proper sensory feedback. Professor Courtine enraptured the audience with detailed descriptions of the development and testing phases of an electrochemical neuroprosthesis designed to restore locomotion in animals and, ultimately, in human subjects.

The speakers of the last session illustrated different techniques to restore and enhance cognitive function. More specifically, Friedhelm Hummel tackled the ability of non-invasive brain stimulation (NIBS) techniques to modulate brain plasticity and treat symptoms in stroke patients. He illustrated the successful results of several clinical studies and outlined important future challenges for the optimization of NIBS-based treatments. Andre Brunoni's talk addressed the use of transcranial direct current stimulation (tDCS) in clinical psychiatry. He gave a detailed overview of the evidence for tDCS efficacy in the treatment of depression, bipolar disorders, schizophrenia, and alcohol dependence. Frank Scharnowski presented the use of neurofeedback to non-invasively and non-pharmacologically improve brain function and treat dysfunctions, such as neglect syndrome. He showed that, through such technique, human subjects can gain control over specific brain activity, with positive consequences in terms of perceptual, motor, and memory enhancement.

Jose Carmena closed the Forum with a brilliant plenary lecture. He provided the audience with an exhaustive overview of brain-machine interfaces, from early studies, to current work aiming at inducing neuroplasticity via closed-loop control, all the way to future technological challenges.

The meeting represented a unique and comprehensive opportunity to approach the field of neuroprosthetics from different points of view. Indeed, neuroprostheses include a plethora of techniques, encompassing both invasive and noninvasive approaches acting at the central or peripheral level of the nervous system, with the common aim of improving or restoring both motor and cognitive function. Notwithstanding the great extent of this topic, the Forum managed to address neuroprosthetics in all its different aspects.

Overall, although the results accomplished over the last years are astonishing and the first translational programs on human subjects have started, more time is needed before neuroprostheses will be considered as clinically viable solutions to help patients. However, psychologists, neuroscientists and engineers are currently working together to yield additional insights into how the nervous system works and to discover new ways to effectively interface with it. The evolution of such technical and clinical capabilities has the exciting potential to develop life-changing devices within the future years.

Introduction

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The World Health Organization (WHO) defines "impairment" as "a problem in body function or structure", while uses the term "disability" to refer to "a complex phenomenon, reflecting the interaction between features of a person's body and features of the society in which he or she lives".

In this framework, the primary goal of neuroengineering, an interdisciplinary research area that encompasses neuroscience and engineering, is to study the mechanisms underlying impairments and to use this knowledge to alleviate patients' disability. Depending on the scenario, different approaches can be adopted to maximize the recovery of a lost, or compromised, physical, psychological, and social function. For instance, *replacement* consists in the substitution of the impaired portion of the motor system with an artificial part. Instead, we refer to *restoration* when the existing anatomical and neural structures are retained and exploited for the recovery of the lost function. While these terms can be broadly applied to any type of impairment, *neurorehabilitation* specifically targets the nervous system using various neuromodulation approaches to recover lost or altered neural functions.

As researchers gain new insights into the organization and functions of the central and peripheral nervous system, new approaches are emerging that effectively interact with the human nervous system. Over the last years, this new knowledge, together with the evolution of efficient technology, fostered the development of neuroprostheses namely *neural interface* technologies. These devices supplant the input and/or output of the nervous system to restore physical, cognitive and mental functions and improve the quality of life for impaired individuals.

Although the field of neuroprosthetics covers a broad range of systems, two macro-categories can be distinguished. The first group consists of neural recording systems, which *retrieve information* from the nervous system through electrophysiological recording tools. This category includes technologies used to record the brain activity (but also peripheral nerves or spinal cord activity): Brain Machine Interfaces (BMI). These signals are then used to establish a direct communication between the nervous system and external devices such as robotic arms, or computer cursors to improve the quality of life or rehabilitation therapies outcomes in individuals with motor disabilities caused by stroke, spinal cord injury (SCI), amputation, degenerative neurologic disorders and other pathologies.

The second group consists of both invasive and noninvasive functional neural stimulation systems that *feed information* to the nervous system by modulating neural activity with the aims of providing assistive technologies to restore sensation, and to promote neural plasticity. In the recent years, researchers have focused on enhancing the functionality of neuroprostheses by integrating these two categories, thus creating bidirectional intuitive interfaces, like prosthetics hand providing somato-sensory feedback. Currently, fully integrated bidirectional systems are close to demonstrability but still far from clinical use by amputees and disabled patients. However, tireless research and significant progress in the field of a new generation of implantable micro-technologies bodes well for the future of this highly-vibrant and young field of research.

SESSION 1

UNDERSTANDING AND RESTORING MOTOR CONTROL

The engineering of motor learning: from basic neuroscience to clinical applications

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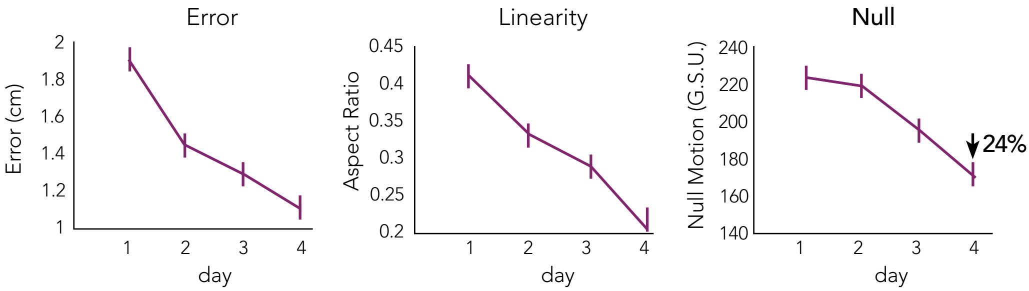
A commonly accepted view posits that there are two types of learning. On one hand, explicit (or declarative) learning is a conscious operation, through which we form concepts and ideas that are then used to create representations of the world. On the other hand, implicit (or procedural) learning has been regarded as mere acquisition of sequences and procedures as distinguished from forming abstract concepts and representations. Lacking awareness, implicit learning is usually considered a "lower-level" learning. Motor learning, that is the acquisition a new skills and the adaptation of existing skills within new environments, has been considered a form of implicit learning. However, in the last two decades we have begun to see motor learning also as a process through which the brain forms representations, internal models and acquires "actionable knowledge" about the properties of the world, about physics and dynamics, and about the fundamental structure of the space in which we live and operate.

The ability of developing an intuitive representation of the space while learning new ways to move can be observed when a spinal cord injury (SCI) patient is asked to control a cursor on a screen through the movements of his shoulders. He learns a new representation of the space, the monitor where the cursor moves, and a mapping between movement of his shoulders and movement of the cursor.

The ordinary space in which we move is Euclidean and, even a toddler who starts to explore the world, implicitly knows the Euclidean laws, such as Pythagoras' theorem, that rule the space where he moves. However, our brain signals (e.g. motor, visual, etc.) do not share the same Euclidean properties and we are still struggling to understand where and how our central nervous system (CNS) may be able to encode these properties.

Notwithstanding our lack of knowledge, several experiments showed that the structure of space in perception and movement is learned through practice and can be remapped when our ability to move is altered by accidents or experiment. In 2005, Mosier

• **Figure 1.** Learning of a new mapping with practice



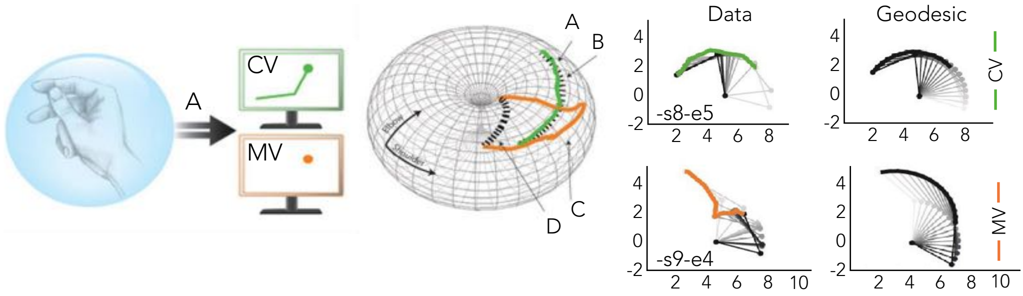
Left: Reaching error, Middle: Linearity. The ratio of maximal lateral deviation to the start-end distance. Right: Null Motion (in glove signal units). This is the total signal variation that did not cause any cursor movement.

Source: Mosier *et al.*, 2005 [1].

and colleagues [1] carried out an experiment to investigate the ability of the motor system to learn a counterintuitive mapping of hand configurations into the 2D position of a cursor on a screen. The performance error decreased with practice, demonstrating the subject's ability to learn the new mapping. Even more interestingly, also without explicit instructions, participants showed the tendency to straighten their trajectories and to reduce the extent of null space motions (i.e. motions that did not contribute to the movement of the cursor) (• Figure 1). This important finding was an early evidence that the human CNS is able to learn Euclidean structures simply from practice and without explicit instructions.

In a more recent experiment, Danziger and colleagues [2] studied the ability of the CNS to learn a static nonlinear mapping with the same data-glove apparatus used in [1]. To do so, they asked participants to control the end-point of a 2-Degree of Freedom (DOF) virtual arm by controlled hand gestures. The method was the same as in [1]. Subjects wore a data glove but in this case the glove signals controlled the two joint angles of the virtual arm, They were divided into two groups. Both groups controlled the same mechanism with the same gesture-to-angles mapping. One group (CV) received visual feedback of the entire virtual arm, while the other (MV) was provided only with information of the end-point position. Results (• Figure 2) showed that the participants who received feedback of only the cursor learned to move along straight lines, which are geodesics on the Euclidean plane. In contrast, participants who saw the entire arm learned to move along curved lines, which corresponded to geodesics over the torus surface representing the kinematics of the 2-joint arm. geodesic lines. These findings demonstrate the ability of the brain to capture the geometric structure of the space in which it operates.

● **Figure 2.** Learning curved geometries



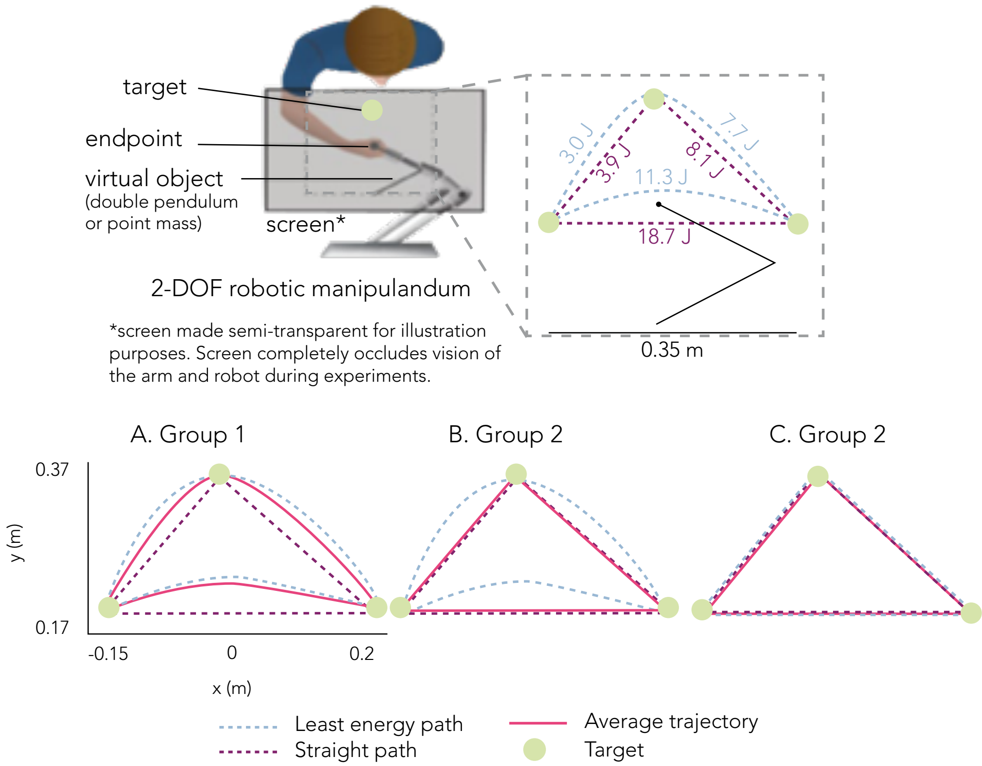
Source: Danziger *et al.*, 2012 [2].

In a more recent study Farshchiansadegh and colleagues [3] found that practice allows subjects to learn the dynamics of the objects they are handling. The investigators asked participants to execute reaching movements between three targets while holding a robotic manipulandum. The manipulandum was programmed to emulate two virtual objects: a point mass or the free extremity of a double-pendulum (similar to the mechanism simulated graphically in [2]). During task execution, participants, who were divided into three groups, were provided with haptic or visual feedback of the virtual object or both. Only one group received coherent haptic and visual feedback reflecting the actual double-pendulum dynamics, the other two groups were provided with non-coherent feedbacks: haptic feedback reproducing a double-pendulum and visual feedback representing a point mass, or vice versa. Results showed that only the subjects who received mutually consistent feedback were able to move along the paths of minimum kinetic energy, while the other participants learned to move along straight paths (● **Figure 3**). This finding demonstrates that we are able to learn the complex dynamics of an object by manipulating it when the visual and haptic information are present concurrently and congruently. Otherwise, we adopt a default solution that we are most familiar with: motions along smooth straight trajectories, that is along geodesics of the Euclidean space where we are used to move and transport isolated rigid bodies.

Noise is another key element of motor learning. Indeed, evidence has shown that the brain is able to solve the redundancy underlying the execution of a motor action by choosing the solution that minimizes noise [4]. This tendency of the CNS to strive for noise minimization can be leveraged to drive subjects towards desired motor solutions.

A recent work [5] investigated the use of noise penalization to teach healthy subjects a specific mapping between high-dimensional hand gestures and 2D location of a computer cursor. To do so, participants, who were grasping inertial sensors with the two hands, were divided into two groups: a control group and an experimental group for which a hand posture-dependent jitter was introduced to penalize specific

Figure 3. Learning curved geometries



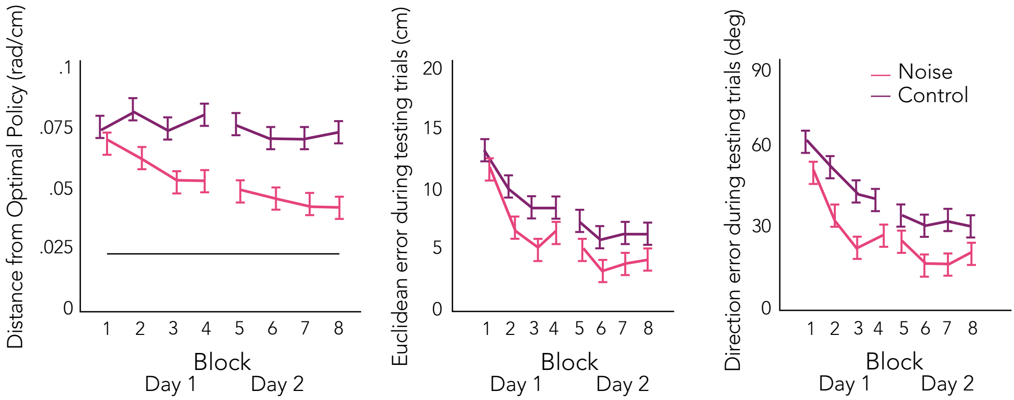
Source: Farshchiansadegh *et al.*, 2016 [3].

hand postures. Results of this work showed that the introduction of noise did not significantly impaired the learning process. On the contrary, compared to the control group, the experimental group got closer to the optimal policy and showed the ability to achieve a better performance when asked to make movements without visual feedback of the cursor (**Figure 4**).

Injection of engineered noise to guide motor learning toward desired coordination patterns may lead to new therapeutic approaches for the recovery of movement skills following stroke and other disabling neurological conditions.

Body-machine interfaces can be programmed to achieve concurrently assistive and rehabilitative goals. In a recent study [6], while testing kinematic-based control of virtual external devices in SCI patients, an alteration of the mapping between movement of the shoulders and movement of the external device was introduced with the aim of promoting symmetrical recovery. To induce training of the most impaired side,

● **Figure 4.** Subjects learned to reduce the noise and performed better in blind trials



Source: Thorp *et al.*, 2016 [**5**].

the gains of the system were modified to allow the most impaired side to gain more authority during control. As expected, the intervention caused an initial decrease in the quality of the control. However, with practice, the patient was able to recover the original quality of control while significantly improving motor symmetry.

In summary, through learning we form internal representations of physical and geometric properties of the world we are interacting with. These representations allow us to go beyond the experienced sensory-motor events and form predictions in novel circumstances. When multiple motor patterns can perform a given task, signal dependent noise can be exploited to guide motor learning toward the selection of desired patterns. Interfaces based on overt motions can be tuned to accommodate recovery goals as their disabled users perform functional tasks.

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Principles of neuromechanics and their implications for rehabilitation*

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Biomechanics, per se, is insufficient to determine movements. Indeed, the way we move is shaped by neuromechanics, which is the study of interactions between neural, biomechanical, and environmental dynamics. As a consequence, neuromechanical principles are key to understand patterns of neural activity that generate movements in expert and novice healthy subjects and in patients with motor deficits, and how these patterns change through rehabilitation.

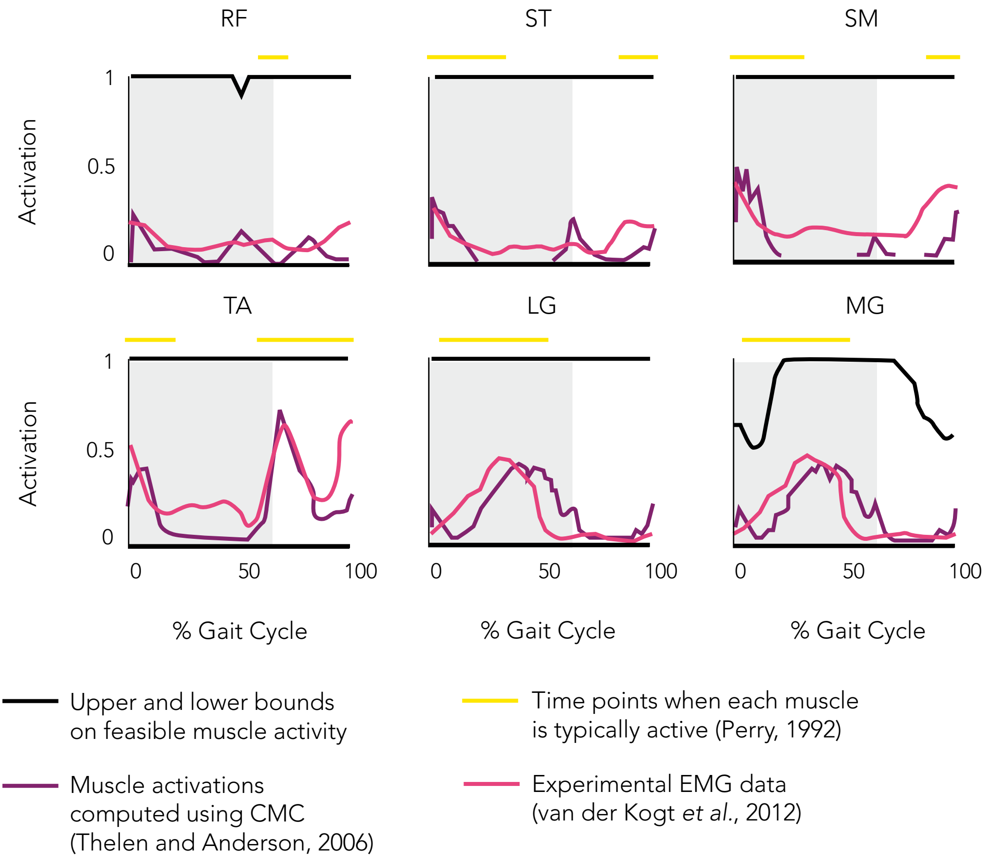
The first of these principles is the concept of motor abundance, meaning that, for any given motor task, there are several motor solutions. Although some of these available options may be less desirable in terms of biomechanics and energetics, the number of motor equivalent solutions that can produce functionally-equivalent behaviors is significant, meaning that there is no single correct or optimal motor pattern.

According to the principle of *motor structure*, the biomechanical affordances and constraints of the body shape the allowable structure of motor patterns. However, an important point is to understand to which extent biomechanics determines muscle activity.

In a recent work, Simpson and colleagues [1] compared the real activity of six lower limb muscles recorded during gait, with the "optimal" activity obtained by an OpenSim model based on energy optimality constraints. They found that actual and "optimal" muscle activity mostly overlapped but that, during specific time intervals, muscle activity of one or more muscles did not follow the ideal one (● **Figure 1**). Notwithstanding these differences, the motor task could still be achieved, provided that the activity of the other muscles changed accordingly. This finding supports the idea that, during walking, muscle activity is shaped but not uniquely constrained by biomechanics.

* Ref. Ting LH, Chiel HJ, Trumbower RD, Allen JL, McKay JL, Hackney ME, Kesar TM. *Neuromechanical principles underlying movement modularity and their implications for rehabilitation.* Neuron 2015;86:38-54. PMCID: PMC4392340.

• Figure 1. How far can muscle activity deviate from an "optimal" solution?



Source: Simpson *et al.*, 2015 [1].

A key point in motor control is *motor variability* and the concept that different underlying neural control signals of the muscles can result in similar movements. Indeed, many muscle activation patterns can generate the same force. Based on the hypothesis that the nervous system only controls task-relevant motor outputs, variations and variability in motor control also depend on biomechanical constraints. As a consequence, biomechanical models can be used to determine the degree to which variability can occur without corrupting the motor performance.

The concept of *multifunctionality* arises from the inability to interpret motor output by merely looking at the single muscle's activity. Indeed, motor actions result from the combination and coordination of several different muscles.

More specifically, if one considers the simple on/off combinations of muscle activation patterns among n muscles, one obtains 2^n possible joint torque patterns (the number of possibilities increases even further if the level of muscle activation and relative timing of activations are also taken into account). Because of this high dimensionality, a large set of motor modules (i.e. combinations of muscle activity that result into specific biomechanical functions) may facilitate multifunctionality, allowing the same muscles to perform different functions in different behavioral contexts. As a consequence of having so many muscles that can be combined, it is likely that multi-muscle combination patterns may be remembered through practice.

Motor individuality, that is the concept that individuals express different motor styles that depend on evolutionary, developmental, and learning processes, has recently emerged as a principle of motor control. Developmental processes, motor exploration, experience, and training all play a role in shaping individual movement patterns which do not necessarily follow engineering rules or optimality constraints. This concept illustrates that biomechanics is not sufficient to determine motor patterns, allowing for many functionally-equivalent solutions.

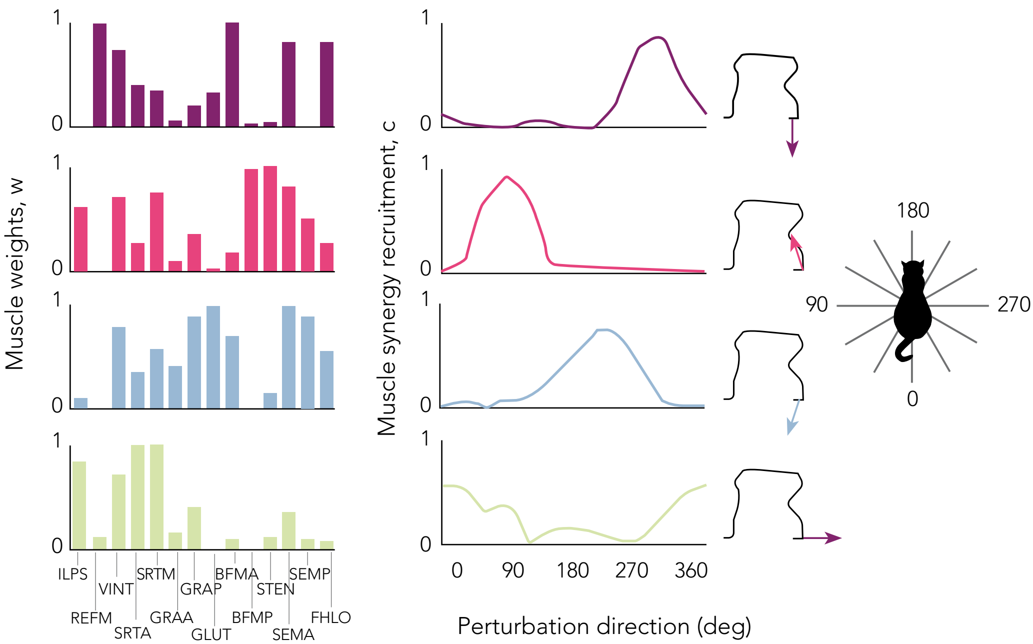
Motor modularity, that is the idea that the central nervous system exploits a reduced number of very specific patterns of multi-muscle coordination rather than using all different random combinations of muscle activity, allows to gain insight into neural control of balance and walking, by explaining individual differences, variability, and generalization across tasks. Modular control is useful from a neurocontrol point of view. Indeed, rather than controlling each muscle independently, the recruitment of motor modules over time allows to structure control at a task-level, thus consenting a rapid decision making process. A rapid decision making is an important feature of motor control.

For instance, when studying balance perturbation in cats, Ting and Macpherson [2] reported that motor module recruitment was correlated to the production of a particular end-point force, since each module was recruited to restore balance in a specific direction (● **Figure 2**). As a consequence, the recruitment of these motor modules can theoretically be predicted through engineering principles of energy optimization.

However, what really happens is that each single animal expresses his own individual structure of how to produce movement. Indeed, when analyzing motor synergies across different animals, Torres-Oviedo and colleagues [3] reported consistency in the presence of specific muscles due to biomechanical constraints, but flexibility in the recruitment of some other muscles, meaning that the animals tested produced the same motor output but adopted slightly different ways to implement it. This finding suggests that the nervous system favors habitual and reliable solutions, rather than picking the ones that are considered optimal (● **Figure 3**).

When a similar analysis is run on human subjects, it can reveal trial-by-trial differences in muscle activity which are not random, but reflect flexible recruitment of motor modules based on task demand and adaptation. For instance, during walking,

• **Figure 2.** Motor module recruitment is correlated to an endpoint force vector



Source: Ting and Macpherson, 2005 [2].

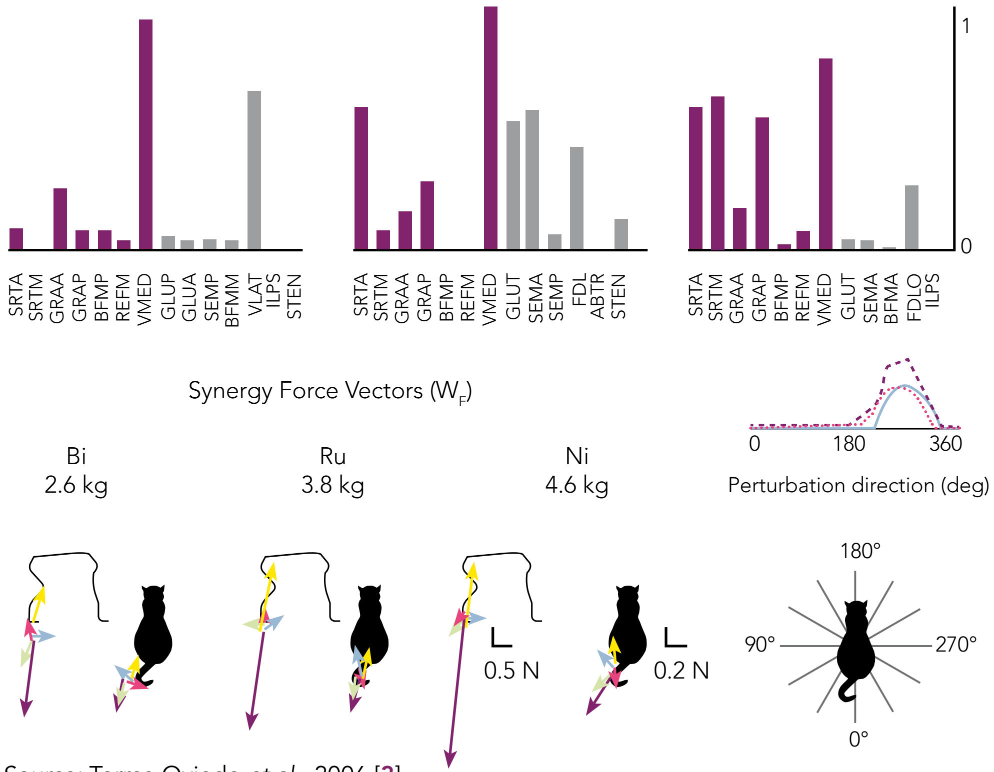
trail-by-trial variability was reported also within the same subject, depending on the strategy he was adopting (e.g.: hip or ankle strategy) [4].

An important feature of factorization analysis is that it can be applied on the single subject, thus allowing to take into account subject-specific patterns of coordination and, at the same time, study possible changes in muscle patterns of the same individual over time. This feature is particularly important when monitoring patients' status during rehabilitation.

Synergy analysis on humans [5-8] also reported a generalization of common motor modules across different motor tasks, such as walking perturbation to walking, anticipatory stiffening of leg, reactive balance with feet in place, reactive stepping. The recruitment of these common modules generally reflected the desired direction towards which one wants to move his center of mass. Task-specific neural plasticity is a key element when studying changes in motor modules induced by either training or rehabilitation.

To answer the question of how professional dancers can be easily recognized from the way they walk, a recent study [9] analyzed how ballet training refines motor mod-

• **Figure 3.** Individualized motor structures

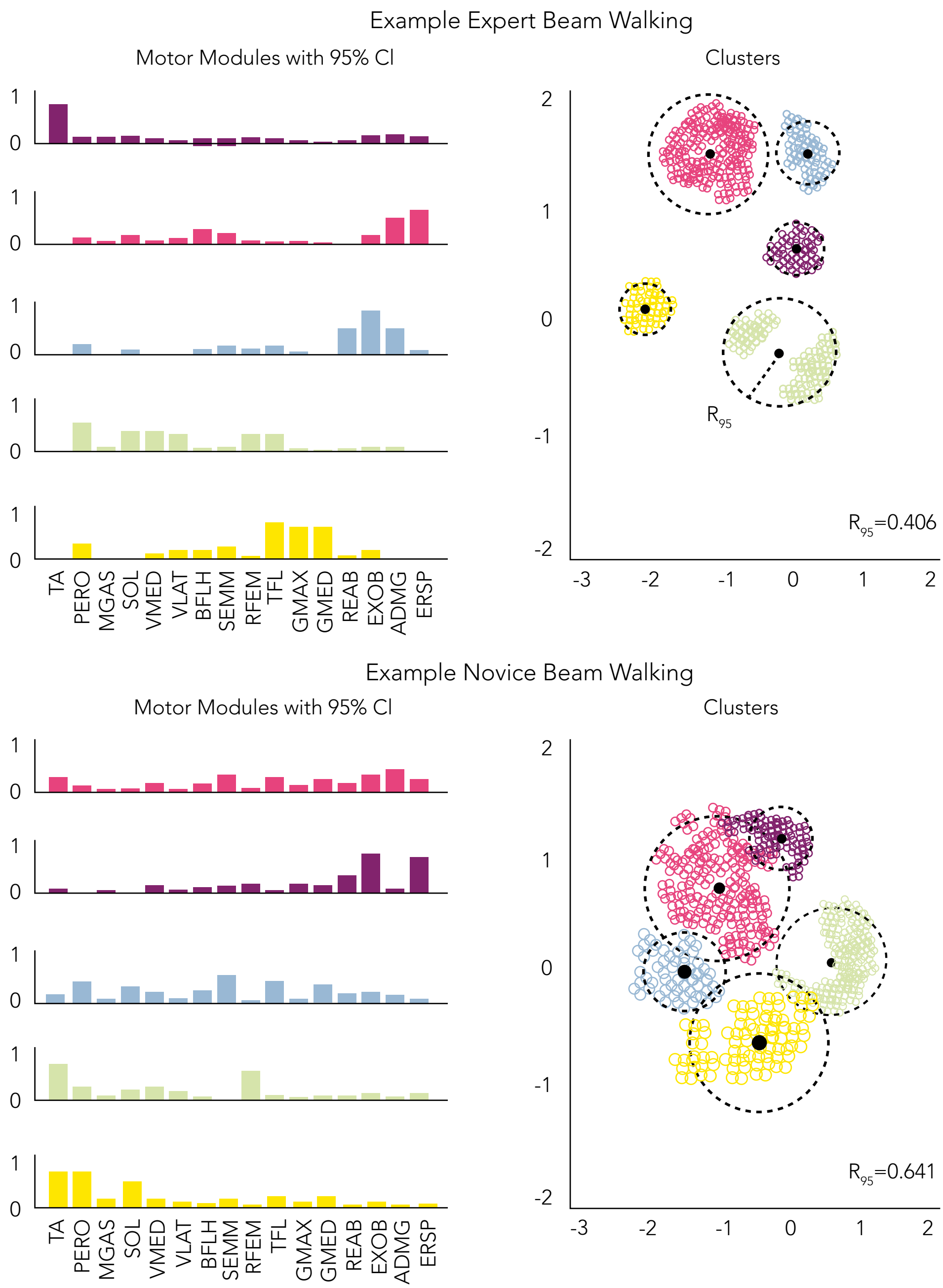


Source: Torres-Oviedo *et al.*, 2006 [3].

ules for walking. Results from this study showed that, when walking across the beam, dancers achieved a better performance compared to novices, although the kinematics was fairly similar between the two groups. Importantly, results showed that the long-term ballet training increases how consistently different motor modules are recruited and coordinated. Indeed, experts showed to use very well-learned and distinct motor modules, while novices seemed to explore the space of motor solutions (• **Figure 4**). Other between-group differences showed that the experts presented lower levels of muscle co-activation.

Following the same principle, we can study changes in motor modules induced by adapted tango rehabilitation in Parkinson's disease (PD) patients. A recent study (unpublished data) [10] showed that, in these patients, within-behavior variability in motor modules can be reduced following successful adapted tango rehabilitation. Results also showed that PD patients first needed to learn the appropriate motor patterns, before being able to refine co-activation. The above mentioned neuromechanics principles and the concept of modular control should be considered when designing neurorehabili-

● **Figure 4.** Ballet training increases the consistency of muscle coordination



Source: Sawers *et al.*, 2015 [9].

tation solutions. Indeed, all possible engineering-based interventions have to consider the abundance of motor patterns and the presence of individualized motor solutions across different subjects. Only by leveraging this abundance of motor solutions, engineering-based interventions able to help a wider range of people and conditions can be successfully developed.

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The future of rehabilitation robotics

Robert Riener

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Stroke is the third most common cause of disability and second most common cause of death worldwide; it strikes about 16,000 people each year in Switzerland and 1 million in China. Stroke is an age-related disease that results in severe secondary complications, including osteoporosis.

The traditional rehabilitation approach for stroke patients is still represented by caregiver-assisted manual training, which is money and time demanding and implies several disadvantages, both for the caregiver and for the patient. Indeed, manual training is physically exhausting for the operator and is non-ergonomically optimal; as a consequence, training has a limited duration in time, resulting in decreased rehabilitation efficacy.

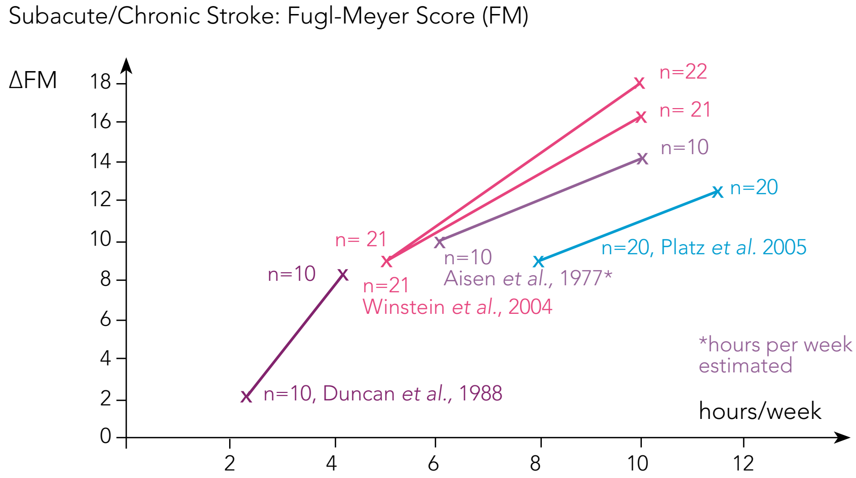
Nowadays, patients suffering a stroke spend only the 10% of their time engaged in therapy (occupational, speech, etc.). The amount of inactivity is extremely high (90%), with negative consequences for the rehabilitation outcome. Indeed, it has been shown that a relationship exists between the time duration of the training and the improvement in motor function which, for stroke patients, is typically expressed as change in the Fugl-Meyer (FM) score (● **Figure 1**).

A solution to the time requirement can be represented by robot-assisted training, which helps increasing the intensity and the duration of training.

Over the past years, a number of robot-assisted solutions have been developed both for the lower (Lokomat, LOPES, Alex, G-EO, Haptic Walker, etc.) and the upper (Armeo, MIT-Manus, MGA, Bi-Manu-Track, etc.) limbs. Among the upper-limb exoskeletal robots, ARMin III [1-3] is a 7-Degree of Freedom (DOF) device that allows movement of elbow, wrist and hand grasping.

Using this device, Klamroth-Marganska and colleagues [4] ran a multicenter randomized controlled clinical trial on 73 patients with moderate to severe chronic stroke

• **Figure 1.** Effect of intensive training

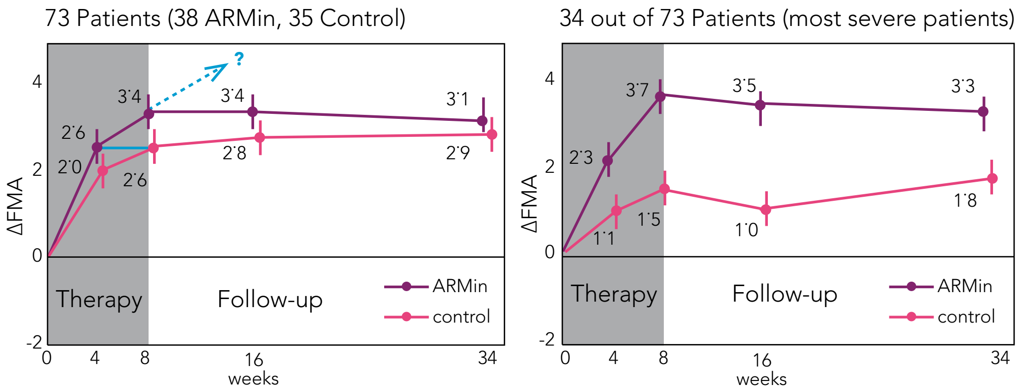


to test the effectiveness of robotic-assisted training with respect to conventional therapy. After 8 weeks of training, the study reported a significantly greater improvement for the robot-assisted group (• **Figure 2**). Interestingly, the gap between the two groups was even wider when considering only the most severe cases, showing that the most severe patients seemed to be the ones who most benefited from robot-assisted training. However, it is worth noting that, although a significant difference in the motor improvement induced by the two therapies was reported, the gap between robot-assisted and manual training seems not to be wide enough to be considered clinically relevant.

In the future, to significantly outperform conventional manual therapy, robot-assisted training should address a number of needs. Among them, the key factor would be to increase the training intensity, which not only means to increase the training duration and the number of repetitions of the task, but also to require the user to exert physical effort during training. To do so, it would be important to introduce and implement strength training and to assist the patient only when needed in order to have him to actively participate as much as possible. Another important factor is to stimulate the patient's mental effort by providing him with challenging tasks that keep him constantly motivated and rewarded. To this aim, robot-assisted therapy can be associated with virtual reality and games that mimic challenging daily-life tasks. To further favor participation and social reward, robot-assisted training can leverage collaborative gaming performed in remote or physical cooperation between two or more patients.

An important challenge for the future is the transfer of rehabilitation from clinical to home environment. To allow at-home use of training and assistive robotics, pow-

• Figure 2. Conventional *vs* robot-assisted therapy



Source: Klamroth-Marganska *et al.*, 2014 [**4**].

ered-orthoses must become simple, cheap, non-cumbersome, and wearable. Over the past years, many companies and institutes have developed a number of powered-orthoses to assist gait (MIT Exos, Rewalk, Honda, Parker, etc.). However, current solutions remain heavy, stiff and with power supply limited in time.

To address these limitations, the new approach proposed by the Wyss Institute (Walsh *et al.*) is the creation of a soft exoskeleton which is light, comfortable, avoids joint-misalignment and can be used in the wheelchair. Indeed, this new approach mainly targets wheelchair users who present residual muscle function and aims to allow them to independently achieve simple daily tasks with limited duration in time. An important feature of this method is the use of only one actuator per leg.

The Sensory-Motor Systems Lab (ETH Zürich) has developed a first prototype of such a soft, robotic device, named MAXX (Mobility Assisting teXtile eXoskeleton). The robot primarily consists of functional textiles and lacks rigid structures. Anti-gravitary action is achieved by the combination of a passive element at the knee and a distally-placed tendon actuator allowing hip and knee extension.

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SESSION 2

INTERFACING WITH THE PERIPHERAL NERVOUS SYSTEM AND THE SPINAL CORD

Reading and writing the peripheral nervous system: from bionic limbs to bioelectronic medicine

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The Nervous System (NS) is an extremely complex and multilayer network of fibers that starts in the brain and spinal cord and branches out to the rest of the body. Typically, most of the attention is devoted to the Central Nervous System (CNS) because of its key and vital role. However, in recent years, the peripheral nervous system (PNS) has been gaining more and more importance among neuroscientists.

More specifically, a burgeoning field is represented by peripheral neuroprosthetics, which aims at restoring the lost function by reading from and providing signals to the PNS. One of the most successful examples in this field is represented by cochlear implants, which exploit the tonotopic organization of the cochlea to restore auditory function. Auditory restoration is a typical example that shows how solutions targeting more central levels of the NS, such as the auditory brainstem, result in a deterioration of the performance. The reasons underlying this poor performance lay in a still non-optimal technology and, most importantly, in the fact that these solutions cannot rely and leverage the most peripheral structures of the NS and are therefore required to compensate for them.

Using the "peripheral approach", recently, Bouton and colleagues reported promising results for the restoration of cortical control of functional hand grasping in quadriplegic patients through the use of matrices of stimulation electrodes placed on the distal segments of the upper limb [1].

Likewise, over the past years, approaches addressing the PNS have also been used to tackle the challenging goal of restoring the lost function in transradial amputees by providing them with effective approaches for the control of hand prostheses. In this framework, currently available solutions are characterized by a number of limitations, including inadequate dexterity, complex control strategies for multi-degree of freedom (DOF), absence of sensorization which in turn results in the lack of embodiment with the prosthesis.

Sensorization is therefore a key factor for reinstating the full complexity of the human hand in an artificial device. To this aim, over the past years, fairly intensive research has been devoted to the study of efficient approaches to provide amputees with sensory feedback. Targeted Muscle Reinnervation (TMR) represents one of the most promising approaches in this field [2].

TMR is a surgical procedure to reassign nerves that once controlled muscles that no longer perform a useful function to residual pectoral muscles that can be used as biological amplifiers to control a prosthesis. Importantly, sensory nerve fibers from transferred nerves can grow through the muscle and reestablish functional connections, thus allowing patients to feel as if their missing hand or arm is being touched (transfer sensation). Although very promising, this techniques still requires refinement mostly in terms of closing of the loop.

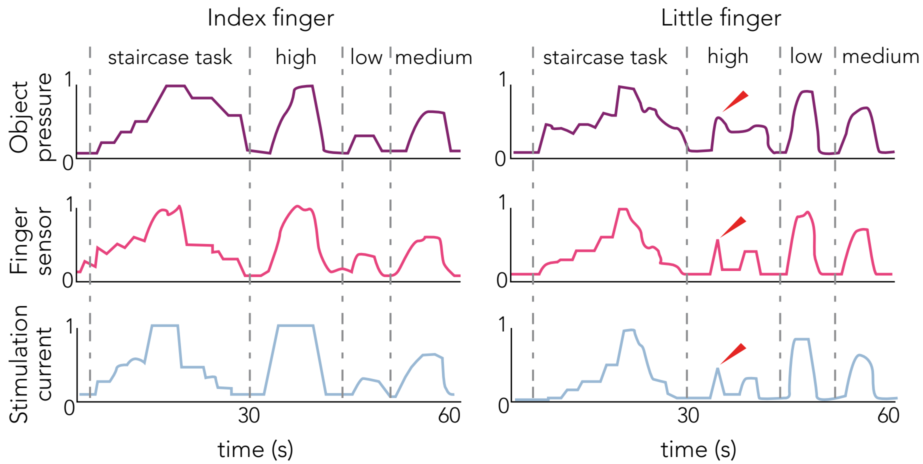
A different approach, Intracortical Sensory Feedback, is instead obtained by implanting stimulation electrodes in the somatosensory cortex. The first experiments were run on macaque monkeys which were instructed to perform different tasks according to stimulus intensity [3]. Most recently, Schwartz and colleagues were able to test this technique on human subjects [4]. These studies show the high potential of intracortical sensory feedback even though, for now, the richness of the elicited sensations is far distant from the natural ones.

Over the past years, our group has been actively working on the development of bidirectional neurocontrolled hand prostheses able to simultaneously extract brain commands from the motor nerves and stimulate sensory nerves to return proper sensory feedback. To this aim, the first necessary step was the identification of a neural interface able to satisfy the trade-off between high selectivity and reduced invasiveness.

To this end, transverse intrafascicular multichannel electrodes (TIME) [5] able to transversally penetrate the peripheral nerve and selectively activate subsets of axons in different fascicles within the nerve were selected and successfully tested on animals. The following step was to test the feasibility of a short-term implant on a pilot human subject. The patient, a 35-year-old transradial amputee, underwent a relatively simple surgery and was implanted with four TIME electrodes on medial (two electrodes) and radial (two electrodes) nerves above the elbow for a period of four weeks. The multiple active sites over the four electrodes were stimulated to elicit different sensations at multiple sites of the hand. The patient reported a large variety of sensations (e.g.: waving on the skin, touch, pressure, hot/cold, proprioception, vibration) prevalently localized on palm, thumb, index and little fingers.

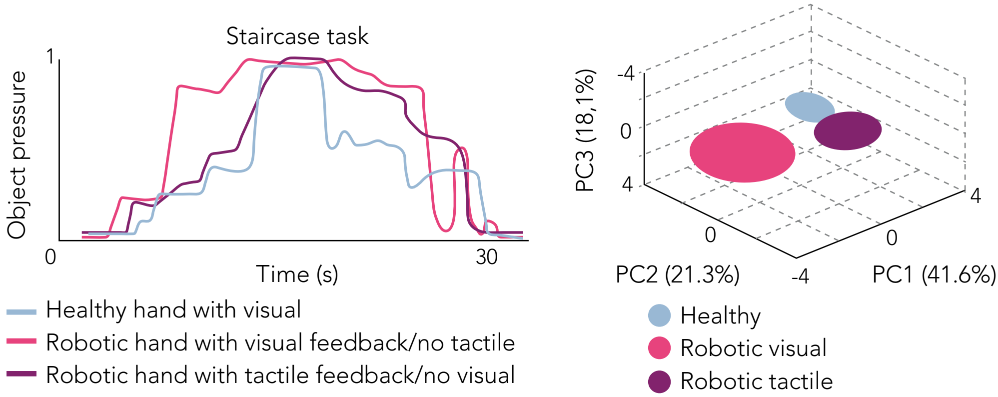
In addition, our group was able to estimate the curves of the relationship between injected charge and reported sensation strength, where they showed that stronger sensations can be induced by simply modulating the amplitude of the stimulation current. We also characterized the elicited sensation to verify its repeatability over time and reported excellent stability of the evoked sensation without the need for a daily calibration of parameters or electrodes. Closed-loop control based on sensory feedback was then tested on

• Figure 1. Grasping force modulation



Source: Raspopovic *et al.*, 2010 [6].

• Figure 2. Force modulation: natural *vs* artificial hand

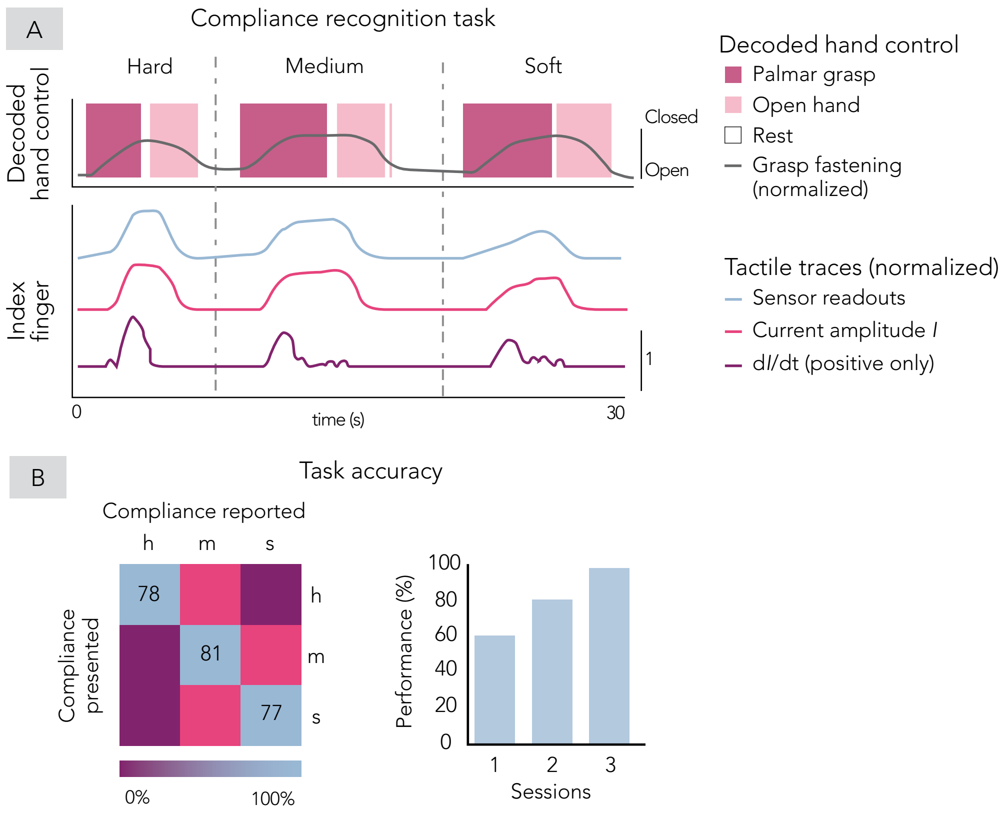


Source: Raspopovic *et al.*, 2010 [6].

the patient by embedding sensors in the prosthesis to record the force exerted at the fingers. After proper processing, the force information was fed back to the TIME electrodes to stimulate the nerves. The subject showed a surprisingly good ability to modulate the grasping force in a variety of ways (staircase modulation, low, medium, and high levels of force) and to achieve very rapid online movement corrections (• **Figure 1**) [6].

Grasping force modulation was then compared with the one accomplished with the residual hand. The patient was asked to perform the same force modulation task in three condition: with the residual hand, with the prosthetic hand without visual

● **Figure 3.** Compliance and shape recognition



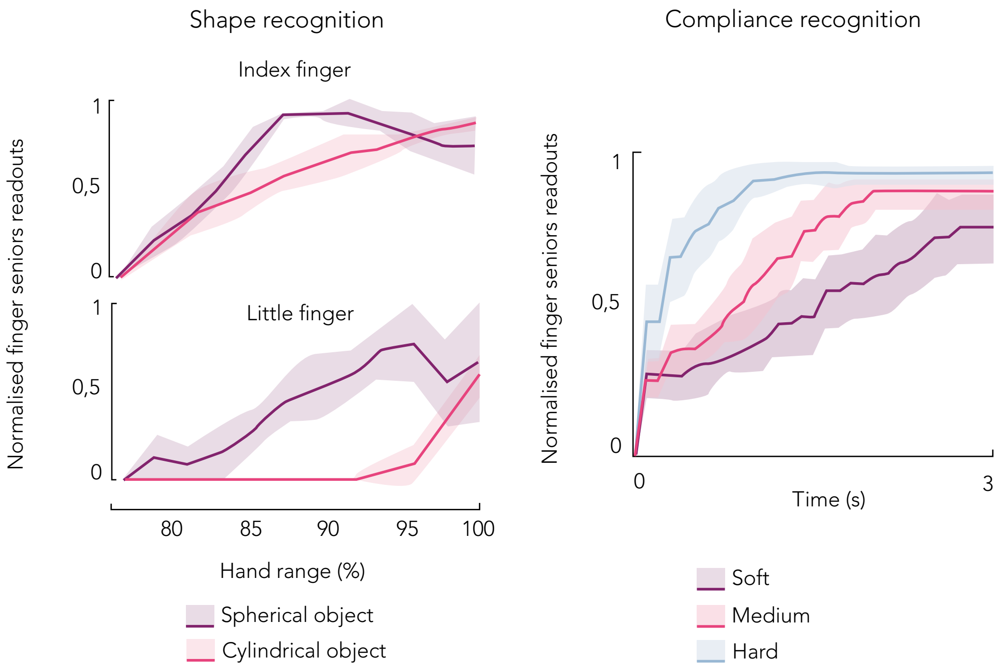
Source: Raspopovic *et al.*, 2010 [6].

feedback (only tactile), and with the prosthetic hand without tactile feedback (only visual). As shown in ● **Figure 2**, the artificial sensory feedback allowed the user to achieve performance close to the natural ones, while visual feedback led to a control that was not easily modulated (on-off trend).

The patient also underwent compliance and shape recognition tests where he was asked to distinguish objects characterized by three different levels of stiffness (hard, medium, and soft) (● **Figure 3**, **Panel A**) and three different shapes (small and big spheres, and cylinder) (● **Figure 3**, **Panel B**). In both cases, the patient's performance showed remarkable results.

The quality of the performance in all tests described above ultimately depends on the grasping force profiles provided to the patient. Differently to other techniques, the sensory feedback here implemented is not an on-off sensation and, by analyzing

• **Figure 4.** Force time profiles



Source: Raspopovic *et al.*, 2010 [6].

the time profiles of the force (• **Figure 4**), it can be hypothesized that the patient is experiencing a force sensation whose dynamics is similar to the natural one.

Another important step is the evaluation of whether texture discrimination can be artificially provided in human subjects by implementing mechano-neuro-transduction. To this aim, Oddo and colleagues [7] modulated the temporal pattern delivered to the nerves via percutaneous microstimulation in four healthy subjects and via implanted intrafascicular stimulation in the transradial amputee. Both approaches allowed the subjects to reliably discriminate spatial coarseness of surfaces. Moreover, EEG activity induced by mechano-neuro-transduction showed physiologically plausible responses similar to the ones elicited by a natural mechanical tactile stimulation.

Based on the successful results of the above mentioned studies, testing of long-term implants is currently ongoing on three amputees and preliminary results support the long-term feasibility of this approach. Evidently, more work is needed to systematically assess the chronic usability of TIME electrodes and to provide solutions that allow to test the ability of this approach in improving the amputees' quality of life in ecological conditions (e.g.: domestic environment with no wires). Future work in this field should also be aimed at increasing the understanding of the ability of the current approach in terms of fine texture discrimination, potential restoration of proprioception, and induction of embodiment.

Altogether, the above-mentioned novel techniques show the astonishing strong potential of the PNS in the restoration of lost functions. The successful results provide the rationale for leveraging the PNS in the treatment (or in the rehabilitation) of a variety of diseases and pathological conditions. In this framework, it is likely to expect that advancing technologies able to exploit the pervasive role of the PNS will bring about a real "peripheral revolution" in the fields of bioengineering and neuropharmacology.

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Motor ecoprosthetics

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The control of the leg involves not only the cortex, but a wider and exquisitely well-organized network which includes, in addition to cortical areas, brainstem circuits able to activate core circuits located in the spinal cord which are in turn modulated by movement feedback circuits.

This complex – still perfect – organization matrix completely scatters as a consequence of Spinal Cord Injury (SCI), although it is known that, most of the time, the key circuits that control muscles are located below the injury level. After the lesion, these circuits are still intact but non-functional, leaving the subject completely paralyzed. The paralysis can be ascribed to two main causes, namely lack of serotonin and loss of the excitatory drive; the latter is essential to steer the system.

As a consequence, when aiming at restoring the lost gait function, the natural approach should be to mimic these two lost sources of information to provide the spinal cord circuits with the drive that they are lacking after the lesion. Thus, the first attempt at creating an electrochemical neuroprosthesis to restore the missing sources of excitation and modulation in decerebrated and spinalized animals leveraged the use of serotonin agonists to tune spinal cord cells and electrical stimulation to mimic the excitatory drive. Although motivation and excitation are key factors of active gait, it is important to incorporate conscious intent of the animal as a third element.

To this aim, a 4-Degree of Freedom (DOF) robotic suspension system was designed to provide gravity and safety support but, at the same time, force the animal to use the dormant hind limbs to gain voluntary control over the direction of movement. The combination of these three essential building blocks led to the development of an electrochemical neuroprosthesis incorporating active training which was successfully tested on rats [1]. Indeed, after an intensive and quite challenging training of two months, the paralyzed rat was able to stand and initiate voluntary locomotion (motivated by chocolate rewards). When investigating the mechanisms underlying the restoration of voluntary control of locomotion, anatomical examinations highlighted an extensive remodeling of cortical projections particularly towards various brainstem motor areas. These areas contain reticulospinal neurons that contribute to initiating and sustaining locomotion. This finding suggests that active training promoted a multilevel reorganization of the motor circuits matrix aimed at regaining control of the paralyzed limbs.

These astonishing results provided the rationale for a translational program aiming at optimizing the experimental steps in order to target locomotion restoration in non-human primates and, ultimately, in human subjects. To this aim, the first essential step was the optimization of the non-ecological electrical stimulation which, in the first version, consisted of two electrodes placed on the dorsal aspects of the spinal cord and exerting maximum intensity to stimulate the lumbar circuits as a whole. As a consequence, the goal of the optimization process was to inject current at the ideal location with the proper timing to reproduce the natural dynamics of motor circuits activation during walking. To this aim, it was essential to design a neuroprosthesis able to achieve both spatial selectivity, namely releasing stimulation at the exact locus, and temporal structure, namely delivering stimulation at the correct timing. To achieve such a challenge, it was key to rely on the proper technology; to this end, flexible electrode made of silicon and platinum were used. These electrodes allow to stimulate both electrically and chemically for extensive periods of time without causing any foreign body reaction.

To make sure the electrodes where placed in the proper loci in the spinal cord, our group recorded the rat's muscle activity during walking, decomposed and projected it into the location of the cells in the spinal cord, thus obtaining a reconstructed spatiotemporal map of motoneuronal activation during walking; this technique allowed us to identify which neurons needed to be activated (where and when) [2]. However, to gain insights into the stimulation process, computational modeling was leveraged to better understand what was exactly activated through current injection. To this end, a finite-element model of the spinal cord was built to understand the electrical field induced by the epidural electrical stimulation. Results showed that, rather than penetrating into the spinal cord, the current was flowing around it and was reaching the cerebrospinal fluid [3].

In addition, the superposition of this finite-element model with an anatomically-realistic model of the spinal cord showed that the stimulation was reaching the thick myelinated fibers running in the side dorsal horn, meaning that muscle spindles feedback circuits were activated [4]. More specifically, each pulse of stimulation induced a monosynaptic response and, at the same time, recruited a couple of thinner fibers through the interneurons (polysynaptic response). An additional computational step consisted in a dynamic model that added one inhibitory interneuron. To investigate the changing length of the muscle, such inhibitory reciprocal network was embedded within the previous combined model and was linked with a Simulink model of the animal's hind limb. In this way, the changing length of the muscle was associated with a model of muscle spindle to understand the interaction between natural flow of activity on the muscle spindles feedback circuit and the epidural stimulation. Results reported comparable in silico and in vivo activity, meaning that the model was able to predict the different patterns of stimulation. The stimulation was then optimized to stimulate the muscle synergies that activate flexion and extension. Finally, to identify the proper stimulation timing, the kinematic data recorded from the rat during locomotion was used to build an algorithm able to estimate in real-time the biomechanical state of the limb (i.e.: phase of the gait cycle). This piece of information, highly-accurate in time, was then used to trigger the stimulation. The optimized neuroprosthesis was successfully tested on a group of rats. Importantly, a linear correlation between the stimulation frequency and the overall muscle activation was reported. Based on this finding, a proportional integral controller that tuned the simulation frequency to maintain the foot trajectory within the reference band was implemented [5].

An intermediate step before the translation to human subjects consisted in the testing of the neuroprosthesis on primates who present a CNS more similar to the human one. To this aim, our group developed a wireless platform and adjusted the neural interface to the primate's spinal cord. To meet real-time constraints, we used a neurostimulator provided by Medtronic which performed control with a 100ms latency. The entire implant was then tailored on primates and, rather than using movement feedback as for rats, stimulation was controlled through brain signals (recorded through a wireless neurosensor that recorded spiking activities from the leg motor cortex). We thus obtained a brain-spine interface able to decode the flexion/extension motor states from brain signals and link this motor intention to the spinal cord stimulation through the neurostimulator. The implant was first tested on intact monkeys for optimization purposes before translating to primates in the acute phase following spinal cord hemisection [6].

The very last step before translation to human subjects was the design of a very specific and customized robotic support system with force applied to the trunk in 3 DOFs which allows to maximize the interaction between body and gravity. The clinical trial testing the electrochemical neuroprosthesis on humans is currently ongoing.

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SESSION 3

RESTORING AND ENHANCEMENT OF COGNITIVE FUNCTION

Use of non-invasive brain stimulation in stroke rehabilitation

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Studying stroke is particularly important from both scientific and clinical points of view. Indeed, from a scientific perspective, the presence of a very focal lesion, as in the case of stroke, allows to investigate well the brains' ability of neuroplastic changes to restore function. On the other hand, this disorder has a strong relevance and clinical impact because of the very high incidence and prevalence; indeed, e.g., in Germany, around 270,000 people per year or in Switzerland, 16,000 people per year, suffer a stroke and almost one fourth of this group is younger than 55 year-old and active in professional life. All these points support the crucial role of efficient rehabilitation treatments. Moreover, on average, only two out of nine patients successfully recover from stroke. Therefore, although some fruitful and promising treatments such as thrombolysis and mechanical revascularization are currently embraced to treat stroke, evidently there is still room for improvement in the field of rehabilitation for stroke patients to bring more of the patients back to their normal life.

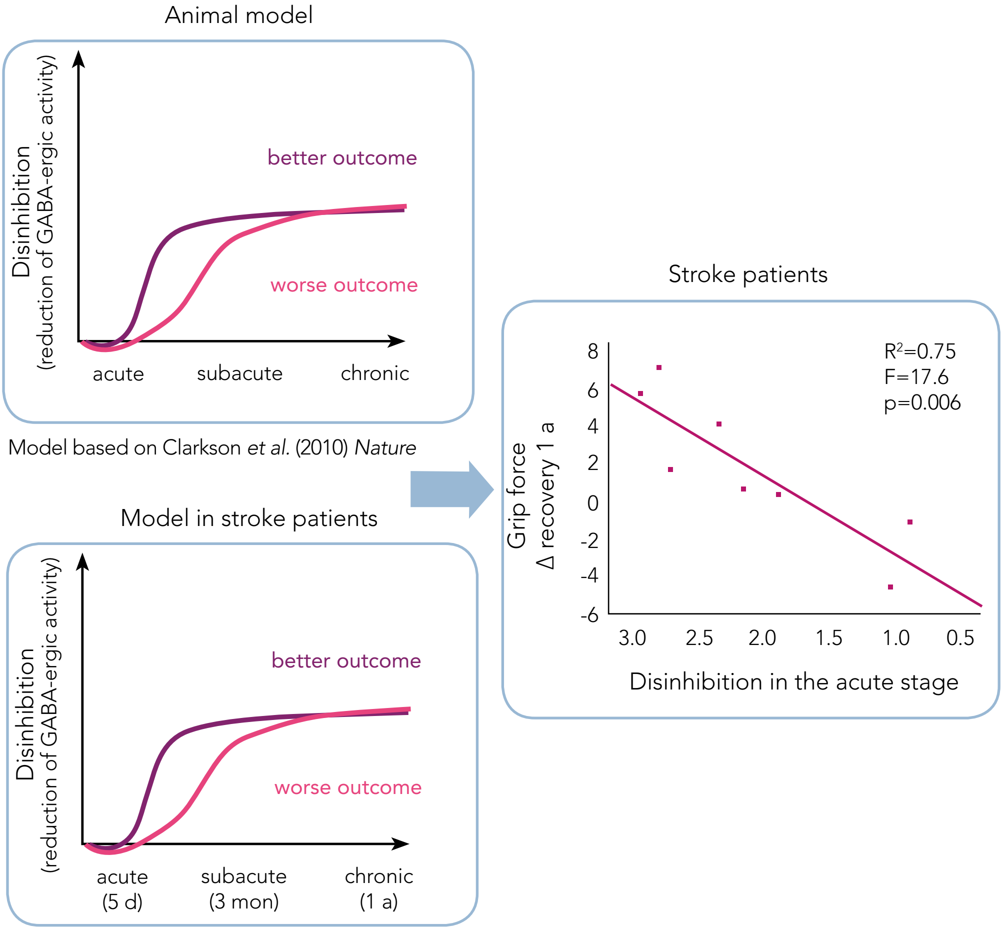
In addition, recovery is extremely heterogeneous and variable across patients; as a consequence, understanding the underlying mechanisms of the recovery process and its heterogeneity is a necessary piece of knowledge to develop novel innovative interventions and to target rehabilitation in a more efficient fashion.

A key factor in the recovery process of stroke is represented by neuroplasticity, which is the brain's ability to reorganize itself by forming new neural connections to (re-)gain function. Indeed, it is widely accepted that effective rehabilitation interventions should support and impel the natural reorganization process of the human brain.

The first convincing evidence for this process were shown in animal models. More specifically, Frost and colleagues [1] showed that in monkeys the ventral premotor cortex was able to take over the role of the damaged primary motor, leading to recovery of the impaired motor functions. The study of stroke animal models also highlighted the important role played by neurotransmitters in the recovery process; indeed, the reduction of the excessive GABA-mediated inhibition typically occurring right after stroke was able to enhance functional recovery in rodents [2].

In humans, the level of activity of inhibitory neurons in the motor cortex can be investigated through noninvasive methods, such as Transcranial Magnetic Stimulation (TMS). Using such technique, Liuzzi and colleagues [3] found that, in stroke patients, an earlier reduction of GABA-ergic activity in the motor cortex resulted in a

• **Figure 1.** Changes in local inhibitory (GABA-ergic) activity in the motor cortex in stroke patients



Source: adapted from Liuzzi *et al.*, 2014 [3].

more successful recovery (● **Figure 1**). This study thus confirms that novel interventions for stroke should leverage and modulate brain neuroplasticity.

Nowadays, technology advances allow us to use non-invasive brain stimulation (NIBS) techniques in a well-controlled fashion. In this field, the two main techniques are transcranial direct current stimulation (tDCS) and repetitive TMS. The importance of both methods is due to the ability of regulate activity of cortical areas and modulate plastic changes. Importantly, the effect of these techniques can be both inhibitory or excitatory and can also persist for a reasonable amount of time after the end of the stimulation. This last feature allows to use NIBS to enhance the effect of (neurorehabilitative) training. Although the underlying mechanisms are still not completely clear, they seem related to the modulation of glutamate-ergic and GABA-ergic neurotransmission.

To understand the behavioral impact of NIBS, a double-blind placebo-controlled cross-over study was conducted to investigate whether the use of tDCS to induce excitatory neuroplasticity in the motor cortex controlateral to the training hand could enhance motor learning in healthy elderly [4]. After a short learning session, subjects who received stimulation during training showed an improved performance compared to subjects provided with a placebo stimulation. Notwithstanding the promising result, such improvement was limited to a short period of time and vanished the following week. However, in a following study, Zimerman and colleagues (unpublished data) extended the training protocol over a 5-day period and showed that elderly subjects who received stimulation while exercising reached a significantly greater level of learning compared to the group who performed training without stimulation and, most importantly, that the improvement was still present after 60-day follow-up after the training.

The first promising experiment supporting the potential of NIBS in manipulating the behavior of stroke patients was conducted by our group in 2005 [5]. We carried out a double-blind sham-controlled cross-over study to compare the effects of tDCS and sham stimulation on motor performance during daily-life activities. Results showed that, while the group who received sham stimulation did not present any improvement in performance, the tDCS group was able to accomplish motor tasks faster. However, likely due to the short protocol, subjects did not report any long-term effects. Over the past years, several other studies on the same pathological population reported similar results, confirming the potential of NIBS in enhancing the effect of the recovery process in stroke patients [6, 7].

To provide a more robust evidence of the efficacy of NIBS treatment for stroke, an important randomized controlled trial (Neuroregeneration Enhanced by Transcranial DC stimulation in Stroke, NETS) aiming at recruiting 160 subacute patients is currently ongoing. Results from such a big pool of subjects should provide a strong and reliable proof supporting the use of NIBS in the recovery of stroke patients in daily clinical life.

Beneficial effects of NIBS have been shown also for other domains affected by stroke, such as aphasia and neglect.

Although quite intensive research claims the positive effect of NIBS for a number of conditions, these studies still present some limitations, mostly related to the relatively low effect size and to the presence of non-responders. This suggests that there is still a long way to go to optimize NIBS-based treatments. In particular, it would be key to understand the factors responsible for the heterogeneity of the results in order to predict the treatment outcome and to customize the cure. In addition, future work should aim at increasing the accuracy and the focus of the stimulation.

A crucial factor to consider is the increase of the training time; to this aim, devices to be used at home are a necessary requirement. For instance, previous studies have shown the effectiveness of a home-based rehabilitation treatment which required the patient to wear a hand-orthosis for one hour a day training over 50 weeks. The possibility to combine such domestic rehabilitation devices with remotely-controlled NIBS is key for the future of neurological rehabilitation.

Future work should also investigate the effects of multi-site stimulation; indeed, as shown by evidence from functional imaging, stroke is a network disease which involves many areas other than the primary motor cortex. As a consequence, multi-site stimulation should lead to additive beneficial effects. For instance, motor learning studies have shown that, while stimulation of the primary motor cortex results in an improved performance with decreased movement time during training, stimulation of the cerebellum positively affects so called offline learning effects by improvement of the behavior between the training sessions, extending the effect of treatment over longer periods. A final last step should test the combination of different interventions by testing e.g., NIBS together with botulinum injections and robot-aided therapy to achieve additive, longer lasting effects.

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Use of transcranial direct current stimulation (tDCS) in clinical psychiatry

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The burden of psychiatric disorders is huge; indeed mental and substance use disorders represent almost 25% of the burden of all non-communicable clinical conditions [1]. Common mental disorders include major depression, obsessive-compulsive disorders (OCDs), and schizophrenia. Unfortunately, current available treatments have low efficacy and a relevant number of cases are treatment-resistant (e.g.: major depression: 33%; schizophrenia: 40%; drug addiction: 40-60%). As a consequence, the development of novel strategies to treat mental disorders is a key requirement. Current neuromodulatory techniques adopted in psychiatry include invasive interventions, such as vague nerve stimulation (VNS) deep brain stimulation (DBS), and electroconvulsive therapy (ECT); as well as non-invasive brain stimulation (NIBS) techniques, such as transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (TES).

TES methods involve the application of weak electrical currents (~1-2 mA) using electrodes placed over the scalp. These currents generate an electrical field able to modulate neuronal activity according to the modality of the application, which is direct in the case of transcranial direct current stimulation (tDCS). Early studies on animals showed that the use of direct current stimulation in the animal's brain was able to induce cortical excitability changes. Over the past fifteen years, the use of non-invasive technologies, such as tDCS, allowed to modulate also the human's brain excitability, inducing both inhibition and facilitation [2]. More specifically, anodal stimulation is known to facilitate motor cortex excitability, while cathodal stimulation is typically applied to inhibit motor cortical excitability. The popularity of tDCS in the treatment of mental disorders is due to its features which include affordability, portability, low maintenance, simplicity, and safety. In terms of safety, possible adverse effects, which include discomfort, itching, and headaches, are typically mild and well-tolerated by patients [3].

Depression is a complex disorder characterized by two main symptoms, namely depressive mood and anhedonia, and a plethora of accessory symptoms, which include anxiety, weight changes, decreased attention, and sleep problems. Although the underlying mechanisms of depression are still not clear, evidence shows that it is related to hypoactivity of the prefrontal cortex and hyperactivity of subcortical regions [4]. Therefore, the use of NIBS in the treatment of depression aims at restoring the interplay between cortical and subcortical regions through excitatory modulation of cortical activity in specific areas, such as the prefrontal cortex, which in turn induces the inhibition of subcortical activity through top-down modulation.

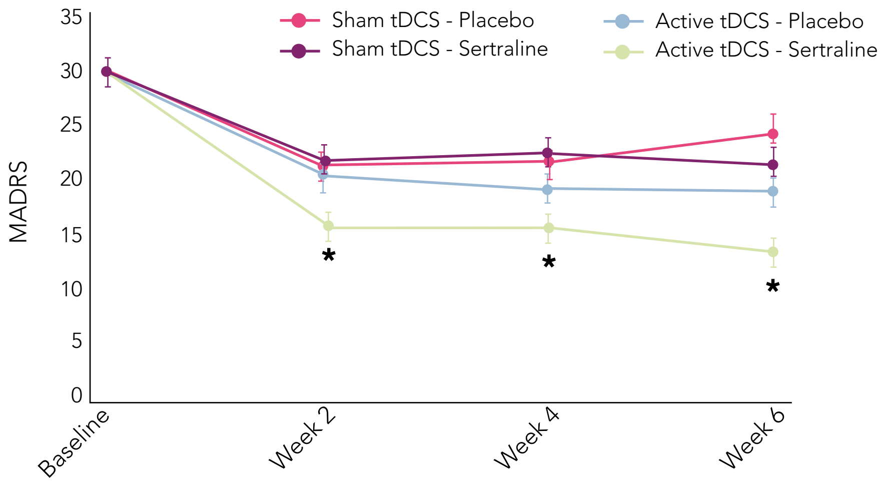
Up to now, the efficacy of tDCS in the treatment of depression has been investigated in ten randomized clinical trials. Results from six of these ten studies (gathering about 300 patients) are collected in an individual patient data meta-analysis [5] which reported greater response rate and lower remission for patients who underwent tDCS compared to patients who received sham stimulation. Similar results have been reported for TMS and antidepressant drugs, although with a larger sample size (about 3,000 and 10,000 patients for TMS and pharmacotherapy, respectively).

One recent study aimed at comparing the results of drug therapy using sertraline and tDCS in the treatment of depression [6]. The study recruited 120 patients with moderate-to-severe depression and treat them over a 6-week period by applying a factorial design which included factors stimulation (tDCS or sham) and drug (sertraline or placebo). The most efficient results were reached with the combined treatment (tDCS-Sertraline) which led to strong reduction in the Montgomery-Asberg Depression Scale (MADRS) and significant response and remission rates. Interestingly, data at 6-week showed that, differently from subjects who underwent treatment with sham tDCS (both sham-sertraline and sham-placebo), patients who received tDCS alone (tDCS-placebo) retained the effect of treatment, suggesting the delayed effect of tDCS (● **Figure 1**).

A similar study investigated the effect of tDCS in the treatment of post-stroke depression (PSD) [7]. PSD is a common complication of stroke characterized by high morbidity and mortality. Pharmacological treatments for PSD present side effects and show mixed results; as a consequence, the need for novel useful interventions is strong. Comparable to studies on depression [6], tDCS treatment reported better results in terms of response, compared to sham stimulation. Similarly to previous cases, tDCS showed a somewhat delayed effect that appeared at the endpoint evaluation (● **Figure 2**).

A necessary step in the analysis of tDCS therapy for depression is to investigate the potential of tDCS in substituting antidepressant drugs. To this aim, an ongoing clinical trial is currently establishing the efficacy of tDCS versus sham stimulation and full-dose escitalopram (antidepressant drug) [8]. A secondary, yet important aim of this study is the identification of predictors of response, such as genetics, peripheral markers, neuroimaging, cortical excitability, to understand whether tDCS and pharmacotherapy exert distinct biological antidepressant effects.

• **Figure 1.** Sertraline *vs* tDCS for treating depression



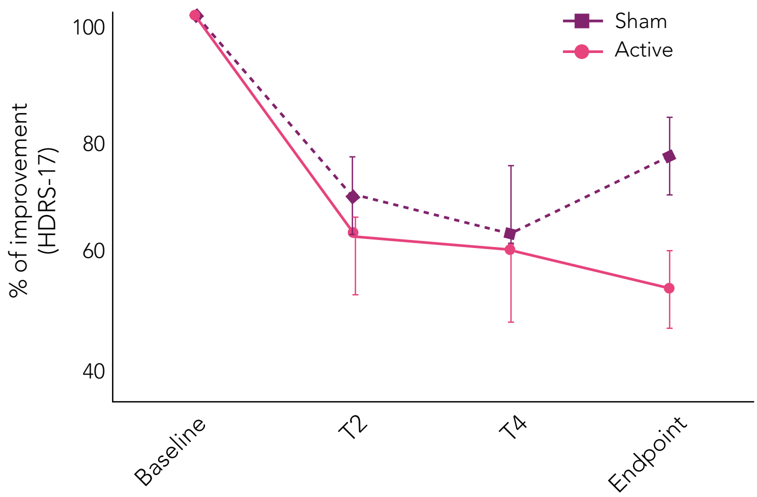
Source: Brunoni *et al.*, 2013 [6].

The use of tDCS to treat bipolar disorders (BD) is still at its early stage. Indeed, up to know, only one non-controlled trial has tested tDCS on fourteen BD patients, reporting fairly promising results [9]. However, the quality of evidence is low and requires further work. For this reason, a controlled clinical trial is currently ongoing.

An additional challenge is the use of tDCS as a maintenance treatment for depression. Indeed, while pharmacotherapy can be extended for quite long periods showing retained effects for up to 2 years, works on the use of tDCS as a maintenance treatment are not very promising, showing a high percentage of refractoriness after 6 months [10]. These findings suggest that more work is needed before being able to extend tDCS treatments over longer periods. To this aim, a necessary achievement is the implementation of home-based NIBS devices. To this end, while adequate technology is present and available, a weak point is represented by the lack of efficient training and robust guidelines for domestic use of NIBS devices.

The use of tDCS treatment has also been extended to other mental disorders, such as schizophrenia. The symptomatology of schizophrenia encompasses both positive and negative signs. Almost 30% of patients with schizophrenia present auditory verbal hallucinations that are refractory to antipsychotic drugs. To target this severe symptom, Brunelin and colleagues tested, on 30 patients with schizophrenia, the effect of 10 sessions of tDCS over 5 consecutive days [11]. This study tested inhibitory stimu-

• **Figure 2.** tDCS for post-stroke depression



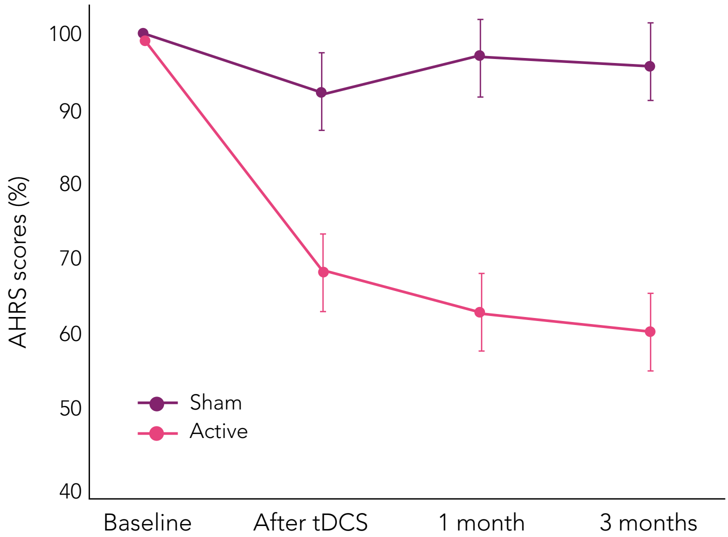
Source: Valiengo *et al.*, 2016 [7].

lation over the left temporoparietal junction and excitatory stimulation over the left dorsolateral prefrontal cortex to affect hallucinations and negative symptoms, respectively. Results showed that auditory verbal hallucinations were robustly reduced by tDCS compared to sham stimulation and that the beneficial effect on hallucinations lasted for up to 3 months (• **Figure 3**). An improvement of other negative symptoms was also reported.

The use of tDCS has also been explored to treat 35 patients with alcohol dependence [12]. Bilateral tDCS reduced relapse probability in severe alcoholic subjects and resulted in improved perception of quality of life, compared to sham stimulation. However, because of the reduced sample size, more studies are needed to claim for a strong beneficial effect of tDCS over alcohol dependence.

Overall, the use of brain stimulation is key in clinical practice for psychiatry (• **Figure 4**). The two main techniques currently in use are ECT and TMS. While ECT presents strong limitations, such use of sedation and high rate of refractoriness, TMS is a well-established therapy in the treatment of mental disorders, due to reasonable cost, safety, noninvasiveness and beneficial results. In this framework, tDCS is a low-cost emerging intervention that has shown a number of promising results in the treatment of depression and other mental disorders, also in combination with other treatment options (e.g.: pharmacotherapy) and providing the possibility for home-based application.

• **Figure 3.** Effect of tDCS on auditory verbal hallucination in schizophrenia



Source: Brunelin *et al.*, 2012 [**11**].

• **Figure 4.** Integrated levels of care neurostimulation

Primary attention

tDCS → low cost, ease of use, home use, augmentation to pharmacotherapy

Secondary attention

rTMS → medium cost, efficacy comparable to drugs

Tertiary attention

ECT → refractory patients, higher costs, needs sedation

Quaternary attention

DBS → super-refractory patients, few centers, very high costs, should have very high efficacy

Source: Brunori AR (personal files).

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Improving human brain function and dysfunction with neurofeedback

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Neuroplasticity is the brain's ability to reorganize itself by forming new neural connections and represents a key factor for learning and restoration of function. Neurofeedback, which consists in providing feedback about one's own brain activity, is an emerging technique able to leverage brain plasticity to improve or restore functions.

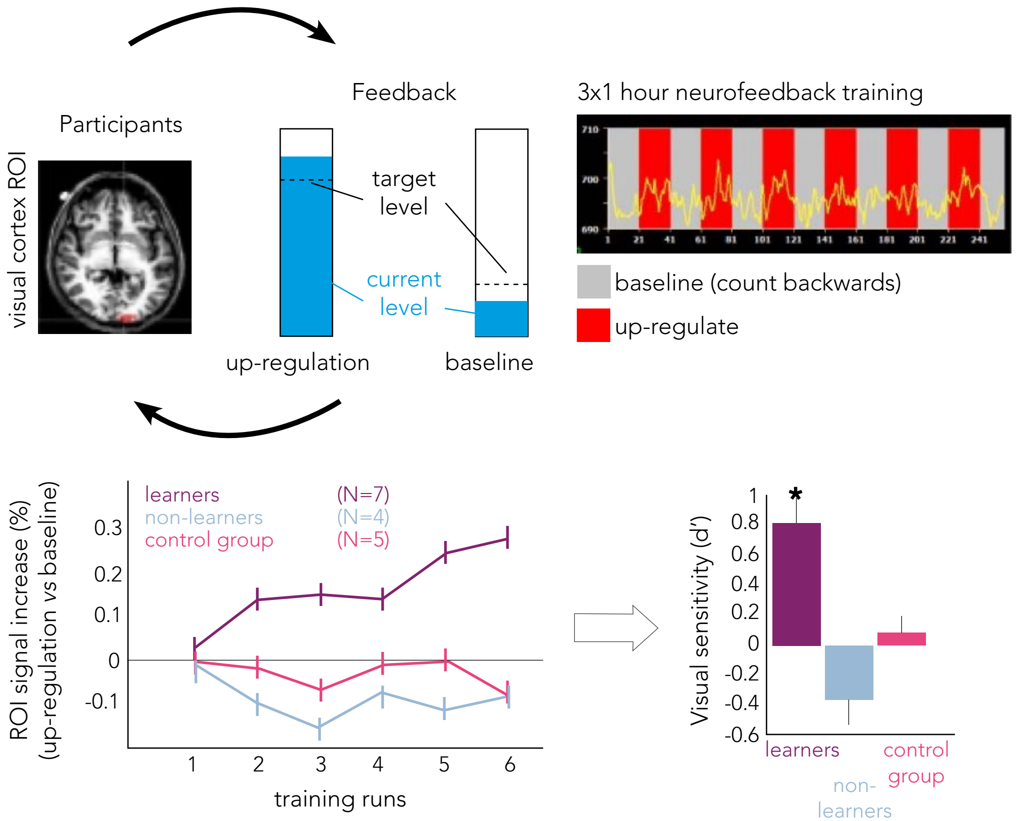
The first studies on neurofeedback date back in the 60s [1] and trained rodents and cats to gain voluntary control of single neurons. In a more recent work from Carmena's group [2], rodents learned to control the pitch of an auditory cursor to reach one of two targets by modulating activity in primary motor cortex irrespective of physical movement. Applications of neurofeedback on humans require the use of less invasive techniques to measure brain activity, such as EEG or fMRI, but the overall mechanism remains constant and basically consists in extracting some sort of signal from the user's brain, process it, and feed it back to the participant to allow him to modulate the signal and ultimately gain control over brain activity.

During fMRI-based neurofeedback, the user receives visual feedback of the brain's activation directly inside the scanner in the form of a vertical bar which indicates the level of the user's brain activity and the target level to reach. Through a trial-and-error process, the user learns to gain control over brain activity. Once training is successfully accomplished, the interesting question is to understand how voluntary control over brain activity affects perception and behavior.

To this aim, a number of studies have investigated neurofeedback of different brain areas (primary motor, primary sensory, motosensory, emotion processing, and memory regions). Interestingly, they showed that achieving control over a specific area results in behavioral changes correlated with the function for which the brain area is accountable.

For instance, our group [3] trained human participants to control ongoing spontaneous activity in regions of the retinotopic visual cortex using fMRI-based neurofeedback. Each participant underwent three 1-hour training sessions composed by baseline blocks interleaved with up-regulation blocks of the same duration. During the baseline blocks the target level indicator was low to indicate the participant to maintain a stable baseline activity. During up-regulation blocks, the target level indicator moved up. At the end of training, seven participants successfully learned to control the neurofeedback signal (learners), while four participants did not learn to increase visual cortex activity (non-learners). Five participants (controls) underwent the same training procedure but received feedback from an area not involved in visual processing, and they did not learn to control visual cortex activity. Perceptual sensitivity was significantly enhanced only for the learners group (• **Figure 1**). This study shows the potential of the neurofeed-

• **Figure 1.** Neurofeedback of visual cortex to improve visual perception



Source: Scharnowski *et al.*, 2012 [3].

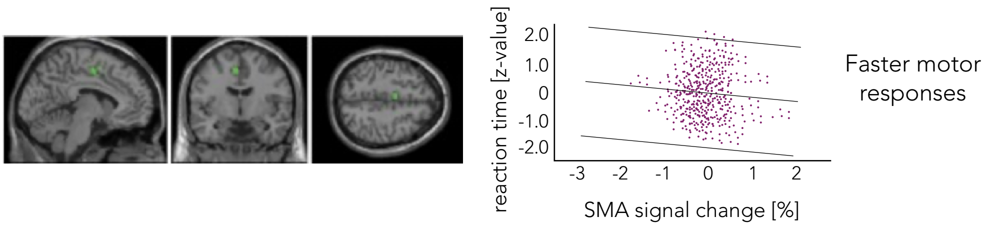
back approach to non-invasively and non-pharmacologically manipulate specific brain activity, thus training the brain to deliver particular perceptual enhancement.

Similarly, other studies have shown improvement in motor performance and memory for those subjects who were able to successfully up-regulate the supplementary motor area (SMA) and down-regulate the parahippocampal cortex (PHC), respectively (• Figure 2).

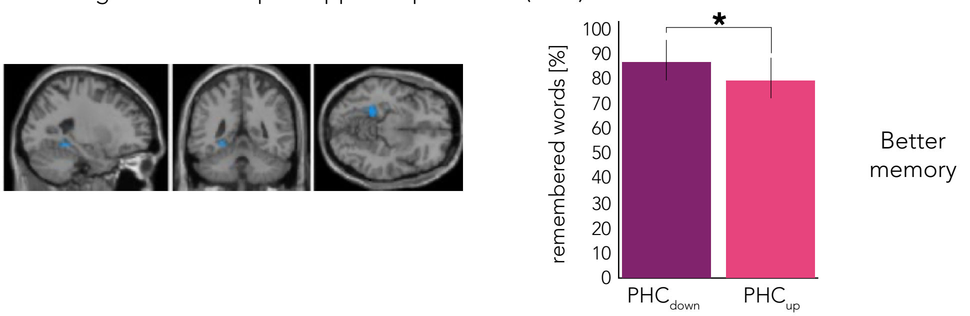
Moving to clinical applications, a recent pilot study (unpublished data) has tested neurofeedback on 6 hemispatial neglect patients who presented a damage in the right parietal lobe. Neglect patients are characterized by lack of awareness for the contralesional side of space. Indeed, since parietal cortex is involved in visual processing enhancement, the absence of such parietal influences due to the lesion causes attention-dependent pathological changes in the intact visual cortex. This pilot study tested the use of neurofeedback to train neglect patients to increase visual cortex activity, thus boosting visual processing and alleviating their symptoms. Results reported that after three 1-hour training sessions patients learned to up-regulate the right visual cortex and, most importantly, showed a significant decrease in neglect severity.

• Figure 2. Improving motor performance/memory through neurofeedback

Up-regulation of the supplementary motor area (SMA)



Down-regulation of the parahippocampal cortex (PHC)



Source: Scharnowski *et al.*, 2015 [4].

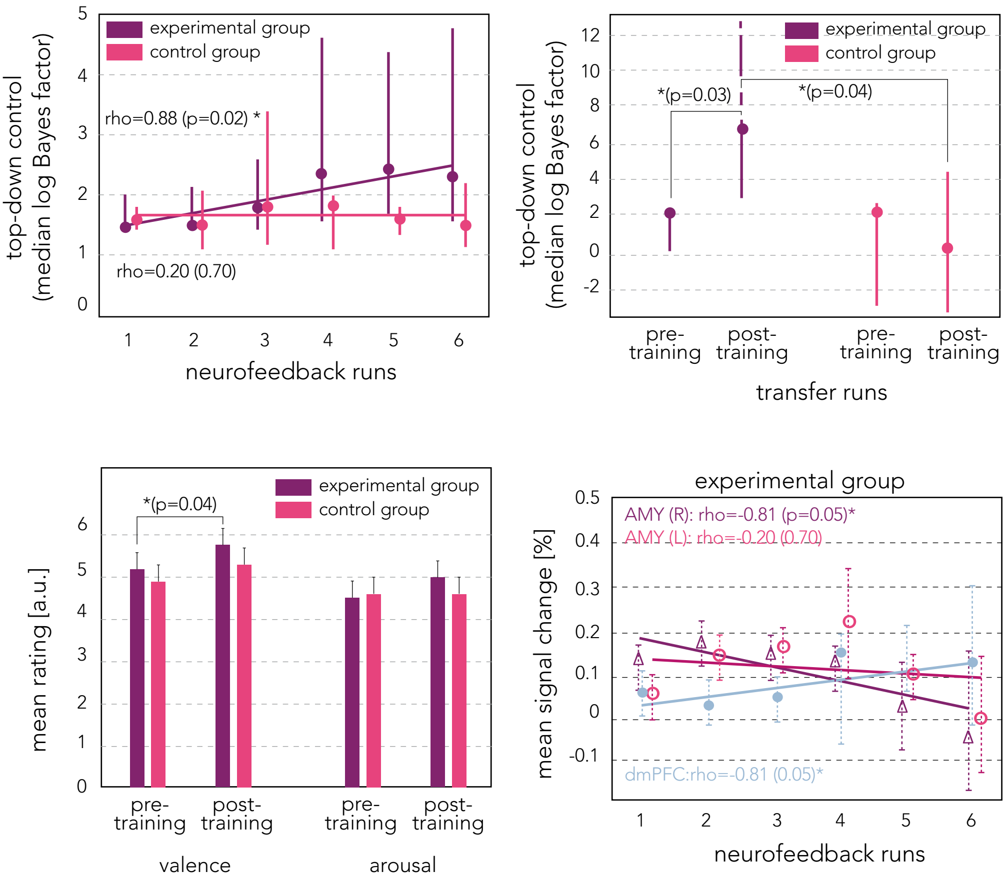
Currently available solutions in the treatment of neglect patients, which include caloric vestibular stimulation, neck vibration, TMS, prism adaptation, aim at compensating the altered inter-hemispheric asymmetries that characterize the disorder. Using neurofeedback, the same approach can be accomplished through differential feedback which provides the user with a signal representing the difference between two brain regions to gain control over the interhemispheric balance between the left and right visual cortices. This approach has been tested in a pilot study in which 14 healthy participants trained for three 1-hour sessions. Participant successfully learned to control the interhemispheric visual cortex balance and this ability was retained for about one year. Notwithstanding the promising results on healthy subjects, this novel approach has not yet been successfully applied to neglect patients.

Evidence shows that most mental functions and disorders are not simply associated with a specific and restricted brain area, but rather with activity of entire functional brain network. For this reason, our group has been implementing connectivity-based neurofeedback with the aim of manipulating and gaining control over connectivity of both the healthy and the pathological brain. One of the first applications has been to achieve control over the network that regulates emotions. Emotion regulation allows us to adaptively cope with negative and positive events and constitutes an important aspect of our personal well-being and social interactions. The disruption of this network can result in burdening affective disorders. Neurofeedback of the emotion networks was implemented through a simplified connectivity model that takes into account the control of stimulus-driven bottom-up responses from the limbic cortex through cognitive top-down processes originating in the prefrontal cortex.

The goal of the first pilot study on 15 healthy subjects was to increase cognitive top-down control of the prefrontal cortex over the amygdala [5]. Results showed that, contrary to subjects who received sham feedback, after only three training sessions participants who received connectivity-based neurofeedback learned to achieve top-down control; interestingly, such ability was subsequently maintained in the absence of neurofeedback (• Figure 3). In addition, we found that voluntarily increasing top-down control caused improved valence ratings. Finally enhanced control was correlated with decreased amygdala, and increased prefrontal cortex activity. Future work should transfer this approach to patients affected by emotion regulation disorders.

Another interesting area of application of neurofeedback is the modulation of activity in neurotransmitter centers which allows to indirectly gain control over neurotransmitters' release. Studies have shown that asking the user to up-regulate dopamine releasing brain areas results not only in increased activation of the ventral tegmental area, but also in co-activation of other dopaminergic regions, such as substantia nigra, hippocampus, and prefrontal cortex. This suggests a possible spread of activation through dopaminergic innervations. The ability of controlling neurotransmitter centers has a strong potential as a therapy for addiction. Indeed, a pilot study trained 25 cocaine users and 28 control subjects to up-regulate the ventral tegmental area

• **Figure 3.** Neurofeedback to learn control over emotion networks



Source: Koush *et al.*, 2015 [**5**].

using neurofeedback, and showed that cocaine users have the ability to learn control over activity in dopamine releasing brain areas. Future work should aim at gaining insights into the behavioral effects of neurofeedback training in these patients.

To conclude, in the framework of available techniques that aim at improving or restoring brain function, neurofeedback represents a recent and emerging method that counts several advantages, such as non-invasiveness, safety, production of lasting effects and ability to target both psychological and biological factors. Importantly, neurofeedback is based on learning, which is a fundamental human ability.

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Large-scale neural circuit dynamics during neuroprosthetic skill learning

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Brain-Machine Interfaces (BMIs) and neuroprostheses include a plethora of techniques, encompassing both invasive and noninvasive approaches acting at the central or peripheral level, with the common aim of improving or restoring function, such as communication, and lower or upper limb control. Among the number of options, the choice will be established based on the single patient and his personal needs. A common underlying requirement for the success of these techniques is the fact that the brain should be at least partially aware of the device.

The first studies on BMIs date back in the early 2000s. Such works showed that, in the absence of task-relevant movement, primates could modulate neural activity to control external devices and, most importantly, they were able to improve with training as a result of the ability to learn something about the specific device. After fifteen years of intensive research, a number of techniques have been designed and tested on different species all the way to humans.

However, BMIs are not yet a clinically viable solution to help patients and the gap between academic and industry state of the art is significant. To bridge this gap, future research should address two main metacategories that run in parallel. The first challenge consists in the optimization of the neural interface, which should ideally be small, long-lasting and allow efficient bidirectional communication. The optimization of the design encompasses many sub-challenges, such as the optimization of the biophysical interface, the choice of the proper material to avoid the degradation process, and the improvement of the communication modalities. The second metacategory concerns the scaling up in functionality with the aim of allowing patients to gain back independence and easily perform daily-living tasks. This category includes several fields, such as the optimization of control strategy and sensory feedback.

In the framework of BMI, our group tackles mainly three points. The first important line of research investigates neuroprosthetic skills, meaning the proficient, readily-recalled control of artificial actuators irrespective of natural physical movements. The main hypothesis underlying BMIs is that neuroprosthetic learning occurs through the selection of specific neural patterns via feedback and reinforcement. Neuroprosthetic skills are typically investigated through center-out reaching tasks, where a cursor on the screen is a simple, yet efficient actuator to investigate the principles of how brain learns. More generally, the working loop consists in the recording of volitional control signals as spike trains of neurons which are then input to a decoder that controls a N-Degree of Freedom (DOF) virtual or physical actuator. The decoder achieves a dimensionality reduction from many inputs to a lower number of outputs and does not have to meet excessive biomimetic requirements. A crucial point in the design of the system is to leverage the brain's ability to learn something about the BMI. We demonstrated such brain's capacity when training animals over multiple days [1]. Once accomplished the necessary requirement of obtaining stable neural recordings, animals underwent multiple BMI sessions and their performance improved with time, reaching a plateau after an average of 6-7 days. The key finding of the experiment was that the tuning of neurons changed with learning. Indeed, as performance improved, the patterns of neuron activity became more stable and remained constant once the animal reached the plateau.

This finding indicates that the animal can learn and use this piece of knowledge day after day, at the beginning of each session, showing that the brain can consolidate neuroprosthetic motor skills to be readily-recalled, stable over time and robust to interferences as for natural learning.

Another important observation of our work is that learning is state-dependent. More specifically, we showed that cortical neurons can flexibly switch between manual and brain control modes after learning and that the brain learns to specifically modulate task-relevant units [2].

Gaining insights into the dynamics of neural exploration is a key requirement to optimize BMI design. To deal with high variability, the brain has two options: either learning how to control each single neuron independently, or reduce the dimensionality of the problem and achieve shared layered control. To address this question, we used factor analysis to decompose variability during learning into two sources: shared and private. Our results suggest that brain starts exploring the high-dimensional space through private inputs and, as it learns and achieves better control, it switches to co-modulated activity. In other words, private signals are noisier and results in low-quality performance but are useful for the fundamental initial space exploration.

BMI can be interpreted as a two-learner system consisting of brain and decoder. Ideally, the system should simultaneously harness the brain's ability to learn from the decoder and the benefits of machine learning to optimally choose when and how update the decoder's parameters.

Therefore, to improve performance, our group achieved closed-loop decoder adaptation using a SmoothBatch algorithm that updated decoder parameters on a 1-2 min time-scale [3]. The algorithm was successfully tested on one nonhuman primate, suggesting that closed-loop decoder adaptation involves a co-adaptation process between the subject and the decoder. Notwithstanding these positive results, decoders based on Kalman filters do not model the spikes directly, and therefore may limit the processing time-scale of BMI control and adaptation. Thus, a new promising method applies point process filtering to allow for neural processing, control and decoder adaptation with every spike event and at a faster time-scale with respect to previous decoders [4]. Our results shows that the high control rate results in a significant improvement in performance (up to 30%) [5]. To date, BMI learning and control have primarily been studied in laboratory-controlled settings where users control a BMI isolated from other tasks. However, real world is noisy and neuroprostheses will ultimately be used for a number of behaviors in coordination with existing motor and cognitive functions. Consequently, tasks that activate brain areas near (or overlapping) with those used for BMI control may cause degradation of performance. In this framework, we claim that neuroplasticity and skill formation are critical for reducing disruptions from native motor networks. To prove this hypothesis, our group developed a behavioral paradigm that required a non-human primate to simultaneously control arm and BMI cursor [6]. The subject simultaneously performed an isometric force task with the arm contralateral to the units used for BMI decoding and a center-out task with the BMI cursor. Results showed that the isometric force task significantly disrupted BMI performance but, most importantly, did not alter skilled control of the BMI. This finding supports the hypothesis that neuroplasticity and skill formation are key requirements for the robustness of the BMI system.

All the BMI principles described above can also be leveraged with a rehabilitation purpose. A clinical trial targeting chronic stroke is about to start with the aim of helping patients to rewire movements through exploitation of the natural afferent feedback provided by BMI systems. Another possibility is represented by neurofeedback studies targeting Parkinson's (PD) patients implanted with Deep Brain Stimulation (DBS). Our group is currently carrying out the first home-based electrocorticographic (ECoG) neurofeedback study that exploits DBS electrodes to record cortical activity and train patients to modulate it. Preliminary results on three PD patients show that they could gain control over β-power activity with practice.

The second line of research tackles mental health and aims at providing alternative treatment to pharmacotherapy which presents side effects and shows unsatisfying mixed results. This innovative treatment program exploits BMI technology to develop system-based closed-loop therapy to gain insights into the underlying physiology of a variety of mental disorders and to investigate the anxiolytic effect reported for stimulation of specific loci.

The protocol consists of an engaging free-choice probabilistic reward task during which task difficulty is modulated to induce emotional stress in macaques and simulate pathological conditions. The protocol is divided into three blocks, namely regular, stress and stress with stimulation. Preliminary results show that the stress level, assessed through heart rate and pupil dilatation, can be modulated through stimulation. Importantly, we have been able to accomplish an additional step by closing the control loop and stimulate the animal only when the recorded variables revealed a stressed emotional state.

The third line of research addresses the lack of implantable, life-lasting, untethered neural interface systems. In this framework, while radio frequency attenuates very quickly with distance in tissue, meaning that communicating with devices deep in the body would be difficult without using potentially damaging high-intensity radiation, leveraging ultrasonic transmission provides us with the potential of shrinking down the size of the sensors to 10s of micrometers.

To this end, over the last few years, our group has been working with Michel Maharbiz's group on the development of ultrasonic neural dust [7] which allows wireless recording in the peripheral nervous system and uses ultrasound both to power and read out the measurements. The system contains a piezoelectric crystal that converts ultrasound vibrations from outside the body into electricity to power a tiny transistor that is in contact with a nerve (or muscle fiber). A voltage spike in the fiber alters the crystal vibration, which changes the echo detected by the ultrasound receiver. While the experiments so far have involved the peripheral nervous system and muscles [8], our group is currently working with the Maharbiz group to miniaturize the device further and shrink down the sensors to the 50-micron target size, which we would need for the brain and central nervous system.

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Conclusions

The field of neuroprosthetics and rehabilitation has always served great human need. In the recent years, the collaboration between biomedical and robotic engineers and neuroscientists led to quick advances in rehabilitation technologies and brain and neural interfaces aiming for effective clinical applications for people with disabilities.

In this framework, over the last years, a plethora of options for rehabilitation and function restoration have been developed. The common fact of these different solutions is the symbiotic relationship between neural interface technology and neuroplasticity, namely the brain's ability to reorganize itself by forming new neural connections. Indeed, it has been shown that this interaction results in improved functional recovery of the lost or impaired function.

Technologies for rehabilitation and function restoration can stimulate and/or record from different parts of the nervous system. Indeed, while the most popular approaches probably interface with the brain, other successful and promising methods target spinal cord, especially for restoring locomotion, and peripheral nerves, which allow to gain access into the neural signals coding for the intended movement.

Rehabilitation technologies can be classified into noninvasive and invasive approaches. For the first category, transcranial Direct Current Stimulation (tDCS) and Transcranial Magnetic Stimulation (TMS) are the most popular techniques and their importance is due to the ability of regulating cortical areas, thus inducing plastic changes. Concerning invasive approaches, their advance is strictly related to the development of a new generation of small-dimension and high-density implantable technologies characterized by long-term reliability and biocompatibility, with the twofold aim of recording and stimulating the nervous system.

Although the main goal of these technologies is rehabilitation and restoration of the lost or impaired function, in most of the cases, they can also be used to investigate the nervous system and to gain insights into the mechanisms underlying pathologies. Leveraging both invasive and noninvasive techniques to improve our understanding of the nervous system is a crucial point to properly design and refine currently available solutions.

Finally, even though most of the work has addressed the restoration of motor and sensory function in neurological patients and amputees, a number of these technologies can be used to address mental disorders. Indeed, current neuromodulatory techniques adopted in psychiatry include invasive interventions, such as deep brain stimulation, and noninvasive approaches, such as TMS and tDCS.

To conclude, scientists have provided proof of concept, in animal and human experiments, showing the potential of targeting the nervous system, both at the central and peripheral levels, to restore motor, sensory, and cognitive impairments. In the future years, persistent research, technological advance and refinement, and extended experimental and clinical trials will be crucial for the realization of effective clinical applications for people with disabilities.

In the recent years, the collaboration among biomedical and robotic engineers and neuroscientists led to quick advances in rehabilitation technologies and brain and neural interfaces aiming for effective clinical applications for people with disabilities.

The successful, highly inspiring Forum "New technologies to treat neurodisorders: neuroprosthetics" brought together experts from all over the world to discuss the current understanding of the mechanisms underlying motor and cognitive dysfunctions in neurodisorders and to present the state of the art of technologies that interface with both the central and peripheral nervous system to restore and enhance the lost or impaired functions.