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Advanced neurotechnologies for the restoration of motor function

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Abstract:	Stroke affects million people worldwide each year and is one of the leading causes of long-term disability. Recent studies report an increase in its prevalence, a trend likely to continue because of increasing life expectancy, aging of the "baby boom" generation, and improved medical treatment that increase stroke survivability. The possibility of increasing the efficacy of stroke rehabilitation by exploiting the potentialities of new therapies based on advanced technological solutions is becoming more and more popular around the world. Technology-based neuro-rehabilitation has completed its first initial phase showing that it can be used in clinical trials with interesting results. However, it is also clear that a discontinuity has to be provided to develop new approaches, which can significantly improve the clinical outcome with respect to traditional therapies. We believe that this “evolutionary” change can happen only by understanding in greater detail the basic mechanisms of natural and technology-promoted neurorehabilitation. In this review, we first describe the results achieved by existing neurotechnologies, highlighting also their current limitations. In parallel, we summarize the data available on the mechanisms of recovery using electrophysiological, behavioural and anatomical studies in humans and rodent models. Finally, we are going to discuss the possible next steps for a more effective use of neurotechnologies for the restoration of motor functions in stroke survivors but also for other neurological disorders.
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ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Geneva, January 27, 2019

Dear Dr. Dobie,

please find attached the final version of the review paper:

Advanced neurotechnologies for the restoration of motor function

for publication in Neuron. We modified the manuscript taking into account all the suggestions.

Thank you for this opportunity to publish in your journal.

All the best,

Silvestro Micera

Advanced neurotechnologies for the restoration of motor function

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Abstract – Stroke is one of the leading causes of long-term disability. Advanced technological solutions (“neurotechnologies”) exploiting robotic systems and electrodes that stimulate the nervous system can increase the efficacy of stroke rehabilitation. Recent studies on these approaches have shown promising results. However, a paradigm shift in the development of new approaches must be made to significantly improve the clinical outcomes of neurotechnologies compared with those of traditional therapies. An “evolutionary” change can occur only by understanding in great detail the basic mechanisms of natural stroke recovery and technology-assisted neurorehabilitation. In this review, we first describe the results achieved by existing neurotechnologies and highlight their current limitations. In parallel, we summarize the data available on the mechanisms of recovery from electrophysiological, behavioral, and anatomical studies in humans and rodent models. Finally, we propose new approaches for the effective use of neurotechnologies in stroke survivors, as well as people with other neurological disorders.

In brief, the use of advanced technological solutions (“neurotechnologies”) can improve the clinical outcomes of neurorehabilitation after stroke. Here, Micera et al. propose a paradigm shift that is based on a deep understanding of the basic mechanisms of natural stroke recovery and technology-assisted neurorehabilitation to improve the clinical effectiveness of neurotechnology.

I. Introduction

Stroke is the leading cause of adult long-term disability in Western countries and the second leading cause of death worldwide. The most recent global burden report indicated that stroke is the epidemy of the 21st century (Feigin et al., 2016) and that the incidence of stroke is expected to increase by 1.5-2-fold. In Europe, more than 3.7 million patients suffer from chronic stroke-related symptoms, and more than 1.5 million patients suffer a stroke every year. Only a small portion of patients recover the ability to resume their normal life. Stroke lesions frequently result in motor impairment contralateral to the affected brain hemisphere (hemiparesis); more than 80% of individuals with stroke have acute impairment, and more than 50% have chronic impairment. Notably, the main predictor of an individual resuming a normal professional and personal life is upper extremity function.

Related to stroke motor deficits, other neurological disorders, such as Parkinson's disease (PD) or multiple sclerosis (MS), as well as traumatic injuries affecting the nervous system, such as spinal cord injury (SCI) or traumatic brain injury (TBI), generate sensory-motor deficits, which significantly reduce the independence and quality of life of patients.

For example, an estimated 2.5 million people worldwide live with SCI, with more than 130,000 new injuries reported each year (see International Campaign for Cures of Spinal Cord Injury Paralysis, (Jazayeri et al., 2015)). SCIs are primarily caused by car accidents, although the incidence of sports-related accidents and weapon-related injuries is nonnegligible. Nontraumatic SCI can also occur as a result of ischemia, inflammatory demyelination or cervical myelopathy. SCI principally affects young male adults. Approximately 53% of SCIs occur in individuals between the ages of 16 and 30.

Overall, neurological disorders with motor deficits frequently occur, strongly affect the quality of an individual's personal and professional life, and have a large impact on socioeconomic and health care systems. The overall impact will increase in the next few years because of the aging of the populations since neurological disorders are often more common in elderly people.

In the recent past, several advanced technological approaches ("neurotechnologies") have been developed to restore motor functions in people with neurologically related motor deficits (Borton et al., 2013, Coscia et al., 2019). These solutions were designed based on the idea that appropriately delivering specific stimuli to the central and peripheral nervous systems of individuals can promote plasticity, functional reorganization and motor recovery. Recently, these innovative neurotechnologies have shown promising results regarding improvements in impaired functions and the quality of life of disabled people. Currently, there is a specific focus on the combined use of these methodologies to leverage their synergistic effects and further increase the clinical efficacy (Coscia et al., 2019). However, recent studies have also shown that additional important steps remain to be completed for the clinical exploitation of these technologies; for example, there is a need for better optimization, personalization, and adaptation to the course of the disorder. These next steps require a detailed understanding of the underlying mechanisms by which the used neurotechnologies influence the restoration of functions and recovery, both in preclinical and clinical studies, and the development of biomarkers that are able to stratify patients and predict their responsiveness to neurotechnological treatments.

In this review, we will briefly describe the recent clinical results of neurotechnologies (Section II), as well as highlight the limitations of the current approaches and the need for a paradigm shift. Then, advancements related to the understanding of the basic mechanisms of stroke recovery and neurotechnology used in animal models and in patients will be described (Section III). Finally, we will discuss the next steps in the field that are necessary for the development of new, integrative, knowledge-based, personalized neurotechnological solutions. Overall, we advocate a paradigm shift in the field towards precision medicine by promoting the development of new personalized, knowledge-based approaches based on a deep understanding of the mechanisms related to stroke recovery and technology-based neurorehabilitation (see **Figure 1**). In particular, we believe that artificial intelligence (AI) and machine learning are very important for several reasons: (i) the process of neuroplasticity is very complex, is only partially understood and can be captured by multimodal data (neuroimaging, EEG, functional outcomes, clinical outcomes, etc.); (ii) the variability across patients is very large, both in the size and location of brain damage and in the brain properties prior to the lesion occurring; (iii) there are many possible alternative treatments to be proposed and combined, and AI can help identify the most useful ones. We need to start sharing secure databases of patient data (multimodal) so that all these data can be combined and machine learning techniques can be applied to map patient characteristics and treatments with the best outcome. These approaches are, however, so sensitive and complex that standard black-box AI is not the best solution; on the contrary, explainable AI, i.e., the gray box approach, may be the best solution.

In this review, we will focus on neurotechnologies designed and used for upper limb motor function in stroke survivors, but in the last section, specific considerations on the overall usability of this approach (and existing neurotechnologies) for individuals with other neurologically related motor deficits will also be provided.

Figure 1 about here

II. Current neurotechnologies developed for the restoration of upper limb motor function after stroke

Many research studies have been carried out to characterize the changes in reaching and grasping movements that occur due to a stroke lesion. These studies show that the affected limb typically exhibits paresis, a lack of mobility between structures at the shoulder girdle, deficits in the angular trajectories of the elbow (Micera et al., 2005), muscle and stereotypic movement patterns or synergies (Cheung et al., 2012), spasticity (Bourbonnais and Vanden, 1989), incorrect timing of components within a movement pattern (Archambault et al., 1999, Shepherd, 2001), a loss of fine skilled movements, and a loss of interjoint functional coordination (Levin, 1996), eventually resulting in different complex patterns of impairment of gross and fine motor control. These changes in coordination seem to be the causes of the segmented nature of stroke patients' arm movements (Levin, 1996). Moreover, the stereotyped movement patterns, which are mainly caused by abnormal cortical control leading to muscle coactivation and high antagonist muscle activity, result in a reduced range of motion against gravity (Levin, 1996) and thus a limited workspace for reaching movements (Sukal et al., 2007, Ellis et al., 2008). All these deficits result in reaching movements that are characterized by low and insufficient force production, low movement amplitudes, long movement times, and segmented, inaccurate trajectories (Levin, 1996).

Patients with stroke often develop a compensatory strategy on the nonparetic side, on the proximal paretic side, or in the trunk to perform daily tasks and compensate for motor impairment (Takeuchi and Izumi, 2012; Levin et al., 2009). However, neural plasticity concerning compensatory movements, activated ipsilateral motor projections and competitive interactions after stroke can contribute to maladaptive plasticity, which may prevent the affected side from relearning normal motor patterns (Hummel and Cohen, 2006). Moreover, the long-term neural and behavioral consequences may ultimately limit the final functional outcome.

In the next sections, different neurotechnologies developed for the restoration of upper limb motor function are briefly summarized together with the most recent clinical outcomes achieved with these technologies.

A. Cortical modulation

The use of cortical modulation to treat neuropsychiatric disorders has been a vision; it was previously described by Claudius Galen (AD 50) during the Roman Empire and has reappeared consistently in ancient medicine. However, until 20-30 years ago, there were no technologies available to apply neuromodulation in a focal, noninvasive, safe, repeatable and well-controlled way, but transcranial magnetic stimulation (TMS, Peri et al., 2017) and transcranial electrical stimulation (tES) are now available. These technologies have been used with the main goal of enhancing adaptive brain plasticity and reorganization in combination with neurorehabilitative training by locally modifying cortical excitability, enhancing focal and remote neuroplastic properties and/or correcting maladaptive brain plasticity induced by a stroke (for review Hummel and Cohen, 2005; Wessel et al., 2015). Brain stimulation-based approaches for enhancing functional recovery after stroke were developed mainly based on the finding that an interhemispheric disbalance, in which a maladaptive influence of the intact hemisphere on the lesioned hemisphere with a respective functional impact on the impaired limb, exists (Murase et al., 2004). Noninvasive brain stimulation (NIBS) was first applied in 2005 with the goal of addressing this imbalance and enhancing residual motor function in stroke patients (Fregni et al., 2005; Hummel et al., 2005; Khedr et al., 2005). In recent years, several proof-of-principle studies and small clinical trials have been performed and have demonstrated promising but heterogeneous results, showing both responders and non-responders to the intervention. Within this review, we will not provide a meta-analytical view; instead, we will present exemplary recent studies to summarize the current status of the field.

In a recent study, (Guan et al., 2017) n=52 patients received either high frequency rTMS (repetitive TMS) of the ipsilesional M1 area or sham rTMS combined with rehabilitative training in the acute stage for 10 days. The active intervention led to more motor improvement in the first month than the sham intervention, but this difference was no longer apparent after 3 months. However, compared to the control intervention, high frequency rTMS led to a functional advantage in single upper limb functions in the long-term evaluation (up to 12 months). Based on the abovementioned concept of a maladaptive interhemispheric influence of the intact hemisphere towards the lesioned hemisphere in stroke patients, one of the largest trials in the field (NICHE trial, Harvey et al., 2018) was performed and recently published. The NICHE trial addressed the combination of rehabilitative training with neuronavigated (inhibitory) rTMS to the intact hemisphere for 6 weeks in n=167 patients with a sham-controlled 2:1 design. Both groups showed functional improvement. In contrast to the hypothesis of the study, the authors did not find any additional beneficial effects of rTMS. Recent neuroimaging evidence has suggested that the intact hemisphere might also support functional recovery, depending on the patient's characteristics, such as the phase of the recovery process, degree of functional impairment or lesion size and location. Thus, the assumption of a purely maladaptive, inhibitory influence of the intact hemisphere on the lesioned hemisphere appears to be over simplified (Grefkes and Fink, 2014a; Hummel et al., 2008; Morishita and Hummel, 2017), and this view is supported by the results of this large clinical trial. One explanation for the lack of an additional rTMS effect in the NICHE trial might be that the applied rTMS protocol did not (in all patients) induce an inhibitory effect, or a more likely explanation is that only in some (not all) patients the intact hemisphere has a maladaptive role. None of these postulations have been tested or monitored in a clinical study. Taken together, the recent evidence points to the need for a revision of the concept of maladaptive interhemispheric interactions with stroke impairment and a differential evaluation of this concept in relation to patient characteristics (phase of recovery, degree of impairment, lesion size/location). It is highly likely that in patients with subcortical, chronic, and rather mild impairment, this concept holds true; however, in patients in the acute and subacute phase and in severely impaired patients with large cortical-subcortical lesions, the intact hemisphere might instead have an adaptive, supportive role than a maladaptive role (Hummel et al., 2008; Morishita and Hummel, 2017). Thus, these patients will not benefit from 'classic' inhibitory neuromodulation of the intact motor cortex.

Although meta-analyses (Elsner et al., 2017a; Kang et al., 2016; O'Brien et al., 2018; Xiang et al., 2019) have demonstrated that neuromodulation is promising, the results are not satisfactory; there are modest effect sizes and heterogeneity in the responses of the patients, ranging from responders to non-responders, and the intervention protocols need be further developed and optimized. From our point of view, the developments that are needed follow three main directions, i.e., the targeting of novel areas within the motor network, the personalization of the intervention to the characteristics of the individual patient and the development of state-dependent/closed-loop stimulation paradigms. To date, neuromodulatory interventions have mainly been focused on the primary motor cortex, although it is obvious that a much larger network of primary and secondary motor areas, including the premotor cortex, supplementary motor areas and the cerebellum, is involved in the functional recovery processes after stroke (Grefkes and Fink, 2014b, Koch and Hummel, 2017, Quandt et al., 2019). Thus, in a recent clinical trial, noninvasive brain stimulation was applied to the cerebellum as a novel target to reduce gait deficits in chronic stroke patients (n=36). Koch *et al.* (2019) demonstrated a significant reduction in gait deficits by a combination of cerebellar TMS theta-burst stimulation and gait training compared to the combination of gait training with placebo stimulation (Koch et al., 2019). The targeting of secondary motor areas for neuromodulation might be especially promising when this technique is combined with personalized precision medicine approaches (Kuo et al., 2018, Elsner et al., 2017b, Kang et al., 2016). Patient-specific stroke characteristics, such as the lesion site and size, connectivity and/or dysconnectivity properties, might determine the best target for neuromodulatory interventions, e.g., the ventral premotor cortex or the cerebellum (Koch et al., 2018, Wessel and Hummel, 2018) (please see also **Figure 2),** and will allow to predict a patient's responsiveness to the intervention.

Figure 2 about here

For developments towards the use of brain stimulation as a 'neuroprosthesis' to interfere directly with motor processing and motor control, important aspects, such as the electrical and functional status of the brain during stimulation, have to be considered, analyzed and used to determine stimulation parameters and timing in a state-dependent/closed-loop fashion. NIBS techniques provide the advantage of high temporal resolution. In addition, recently, EEG combined with TMS has provided a new direction towards "closed-loop NIBS" (Kraus et al., 2016; Raco et al., 2016), which offers a novel and exciting method of neuromodulation to restore impaired functions. Treatment innovations based on these closed-loop concepts have been recently demonstrated to be successful regarding motor impairment after SCI (Wagner et al., 2018).

Taken together, neuromodulation by brain stimulation is still a promising intervention; however, based on the recent evidence, the underlying concepts need to be further clarified, and NIBS-based approaches, such as personalized, multifocal or closed-loop-based NIBS, need to be further developed. The underlying mechanisms of the NIBS modulation of macro-/microcircuit activity and connectivity in target networks and its contributions to plasticity-based reorganization and functional recovery need to be understood before new techniques can be developed.

Clearly, transcranial stimulation is only one component in the field of neuromodulation that is used to improve motor impairment after stroke. Non-focal approaches, such as pharmacological neuromodulation to enhance functional recovery after stroke, have also been evaluated in the last 20-30 years. These studies revealed rather heterogeneous and inconsistent evidence. The most prominent agent, fluoxetine, was demonstrated to be effective in the FLAME trial (Chollet et al., 2011). However, a recent large clinical trial did not show comparable results (Dennis et al., 2019). Additionally, for other promising agents in the field, such as L-dopa or amphetamine, no homogenous evidence is currently available (Cramer, 2015; Goldstein et al., 2018; Scheidtmann et al., 2001; Viale et al., 2018).

B. Peripheral stimulation

The idea for rehabilitation treatments based on peripheral training began by focusing on the motor symptoms of poststroke disability, but as we have gained more knowledge about neuroplasticity, peripheral functional training has assumed a central role in the remapping of functions in the brain. From this specific perspective, we focus our review on some technologies explicitly studied for their impact on brain plasticity: neuromuscular electrical stimulation (NMES) and robotics.

NMES was proposed more than thirty years ago and was introduced to the field as a neurorehabilitative technology for patients suffering from hemiparesis. In recent clinical trials, the method has been enriched; it has been combined with complex, multi-muscle, coordinated tasks (such as NMES-based cycling) and physiological 'controllers', such as control based on muscular activities (electromyography, EMG) and brain-computer interfaces (BCIs), to strengthen the convergence of the brain motor commands with the peripheral effectors' afferent signals. Further state-dependent stimulation protocols have been developed, e.g., protocols for the detection and stimulation of motor synergies to restore physiological patterns of muscle activation (Laffont et al., 2014; Ferrante et al., 2016; Ambrosini et al., 2011; Crema et al., 2018). In most of the current approaches, NMES is used to trigger muscle activity; however, in a few trials, peripheral electric stimulation was used solely as an afferent input to the brain (Wilson et al., 2016). The use of multielectrode systems is becoming increasingly common to address all the issues related to the positioning of the electrodes, which are very relevant for fine and complex movements of the hand (**Figure 3**).

The use of hardware and software filters to extract the volitional components of muscular activity during stimulation has allowed the combination of residual volitional control and stimulation to be performed, allowing the advancement of the EMG-controlled paradigm, which has been demonstrated to have a large positive effect on recovery (Figure 3, panel E and F). A large meta-analysis (n=782 patients) evaluating the effects of EMG-triggered/control NMES on upper extremity function in stroke patients revealed that EMG-NMES has significant benefits in the body structure and function domain for all poststroke populations and in the activity domain only for the subgroup of patients with chronic impairment. No significant benefit in favor of EMG-NMES was observed for the participation domain. However, almost all of the valid studies (20) reported outcomes in the body structure and function domain as well as in the activity domain (19), but only 6 studies considered the participation domain, so the level of evidence is much weaker in the participation domain (Monte-Silva et al., 2019).

Promising approaches used in recent clinical trials include the combination of NMES with other interventions, such as mirror therapy, goal-oriented imagery or BCI-based motor training (Biasiucci et al., 2018; Carda et al., 2017; Mrachacz-Kersting et al., 2019; Schick et al., 2017). This finding provides important evidence for the assumption that the afferent and peripheral efferent dromic and antidromic effects of NMES and the residual (efferent) motor commands are the most crucial aspects for successful neurorehabilitation (Rushton, 2003). Whether certain variations of NMES, such as EMG-triggered, myo-controlled, switch-triggered or afferent sensory stimulation, are more advantageous than others or than cyclic NMES (i.e., NMES is activated without any connection to the task execution phase) cannot be clearly determined. A longitudinal brain functional activation study (Gandolla et al 2016) on a small number of patients suggests that NMES carryover mechanism is based on the ability of a patient to plan a movement and to perceive the stimulation as a part of his/her own control loop. Additional large clinical studies must address this open question by possibly studying brain correlates to reveal the underlying mechanisms of neuroplasticity and possibly provide indications for personalization. Identifying predictive biomarkers to select the best therapy solution for each patient depending on motor disability and brain lesion site and size is of paramount importance both for the personal outcome as well as for the societal sustainability (see Section III).

Taken together, NMES is a promising intervention for the enhancement of upper extremity function. However, the effect sizes of the intervention are still not satisfactory, and there is a lack of knowledge on how to apply NMES in a personalized fashion to potentially increase effect sizes. Regardless, the translation of task-specific training for the relearning of overall limb use for daily actions is challenging, especially when the training task is focused on single muscles, as in most of the available studies.

Figure 3 about here

The goal of robotic therapy is to design and control robotic devices for rehabilitation exercise so that the selected exercises that are performed by the participant provoke motor plasticity and therefore improve motor recovery not only at the peripheral level but also at the global level. Robotic therapy is usually administered by a physiotherapist who programs a mechatronic device to assist a patient in performing a specified motor task. Robotic-based rehabilitation is becoming increasingly popular worldwide because it can easily provide an intensive and highly repeatable “dosage” of therapy. Moreover, it allows a quantitative, frequent and objective evaluation of the outcome for each patient.

For the design of neurotechnological approaches, such as robot-supported interventions to enhance functional relearning, it is important to consider general neurophysiological considerations of neurorehabilitation, e.g., high-intensity treatment, motivating feedback, the involvement of the patient’s residual capability, and the personalized adaptation of the difficulty of the task. For instance, a regular treatment session with a therapist involves approximately 30 movement repetitions of the upper paretic extremity, and a robot-assisted treatment session involves as many as 1000 repetitions. Furthermore, severely affected patients might benefit from active training when gravity support is provided; in many cases, this is the only way a patient can perform active training. In general, there are exoskeletons that assist limb movements and end-effector devices that support the mobilization of a limb, providing rehabilitative training in the form or simple passive mobilization, assist-as-needed training, resistance training and error-augmentation (Marchal-Crespo and Reinkensmeyer, 2009).

Despite these promising results, two large clinical trials with n=127 patients (Lo et al., 2010) and n=770 patients (Rodgers et al., 2019) compared robot-assisted upper limb therapy with usual care or intensive classic therapy, and the studies did not reveal significant differences between robot-assisted training and intensive conventional therapy. In the RCT conducted by Lo et al. (Lo et al., 2010), the robot-assisted therapy was fixed, administered in four predefined 3-week blocks and was not personalized, while the conventional intensive therapy was selected specifically for each patient by the therapist from a multitude of possible treatments. Because chronic stroke survivors are very different, predefining the sequence of treatment involving robotic assistance could have limited the training results. Personalization remains a key feature for any type of rehabilitation training. The RATULS trial (Rodgers et al., 2019) highlighted that robotic training using the MIT-Manus robot (Lo et al., 2010) led to a reduction in upper limb impairment compared with usual care (the body structure and function domains) but not in upper limb function or activities of daily living (ADLs). Compared with usual care, enhanced upper limb therapy (EULT), a type of training specifically focused on daily activities and functional tasks, led to improvements at the end of the intervention period (at 3 months) for both the body structure and activity domains. Recent meta-analyses and a Cochrane review revealed a small and heterogeneous but significant effect of robot-assisted rehabilitative interventions on motor functions and upper extremity recovery, with an unclear clinical impact due to the relatively small effect size (Ferreira et al., 2018; Mehrholz et al., 2018; Veerbeek et al., 2017). Figure 4 provides a simple schematic of the evolution of the field over the past 25-30 years.

Figure 4 about here

A very recent review paper (Duret et al., 2019) proposed a long-standing view that in clinical settings, robotic therapy should focus on impairment training, as well as therapist transition-to-task training, to achieve functional gains. Personalization along with focus on daily activities and functional tasks are emerging as prominent factors for facilitation of the training benefits to real-world applications.

In all the studies reviewed, no clear documentation was provided on whether (or how much) robot-assisted training was considered passive mobilization or active training with user participation. Studies on healthy subjects have demonstrated that the combination of volitional contributions from the subject and movement assistance provided by the robotic device (i.e., active robot-assisted modality) is able to induce early brain activation (i.e., earlier Event-Related Desynchronization (ERD)) associated with strong proprioceptive feedback (i.e., longer ERD, Tacchino et al., 2017). The percentage of active versus passive robotic assistance in the control scheme should be studied in future trials to better understand the benefit of robotic assistance.

To that end, EMG-triggered and myo-controlled robotic devices, as well as assist-as-needed control paradigms, that integrate sensors to monitor the continuous contribution of the user, regardless of the user's capability, have been introduced. The use of mirroring and bimanual tasks has been proposed as a tool to ensure subject participation in the task and to promote coordination recovery based on the premise that movements of the nonparetic upper limb support movements of the paretic limb when they are performed simultaneously in a symmetric or an asymmetric manner. A systematic review published in 2016 (Hatem et al., 2016) concluded that there is a sufficient amount of evidence indicating the nonsuperiority of bilateral training. This nonsuperiority was also confirmed by the more recent review conducted by Duret et al. (Duret et al., 2019).

With a focus on motor relearning, new technologies for peripheral stimulation, such as NMES and robotics, should ensure personalized treatment, training on daily tasks (ADL), assistance in complex coordinated tasks, and volitional participation of the patient in task execution, while avoiding training of pure passive mobilization. A hybrid system for upper limb rehabilitation that integrates volitional contributions from the subject, EMG-controlled NMES, an antigravity exoskeleton and an NMES hand module has been recently designed

(RETRAINER project, **Figure 5**, Ambrosini et al., 2019). Subjects are trained to perform arm reaching and grasping tasks with interactive objects in a real, not virtual, environment, RFID tags are used to monitor the target reaching tasks, and a GUI guides the patient through the sequence of complex daily tasks. The stimulation is activated by EMG signals only when the volitional muscular activation signals are coherent with the targets to be reached. Furthermore, positive visual feedback is provided to the patient by using specific filters to extract the volitional activation components during FES if volitional activation remains active during the whole motion(Ambrosini et al., 2014). Two multicenter randomized controlled trials have been registered: one for the arm system and one for the hand system (ClinicalTrials. gov # NCT03171649; NCT03199833).

Figure 5 about here

The combination of cortical stimulation by tDCS with robotic-assisted training with robotic support has also been proposed and investigated by various research groups. A recent literature review (Simonetti et al., 2017) found that tDCS (unilateral anodal or cathodal or bilateral) coupled with robotic training did not result in larger improvements than robotic therapy alone in patients in either the subacute or chronic phase (Hesse et al., 2011; Ochi et al., 2013; Triccas et al., 2015; Straudi et al., 2016), even though subacute subjects tend to show larger improvements than chronic stroke patients (Triccas et al., 2015). Furthermore, delivering anodal tDCS during and after robotic therapy did not increase performance in patients with chronic stroke (Giacobbe et al., 2013). Chronic stroke subjects treated with tDCS at the end of peripheral nerve stimulation followed by robotic therapy did not show improved motor function (Powell et al., 2016). Eventually, administering tDCS before the motion imagery-brain computer interface intervention with robotic feedback did not enhance motor functions (assessed by FMS) in chronic stroke patients compared with MI-BCI treatment alone (Ang et al., 2015). However, all of these studies included a limited number of subjects (max 32) and nonstandard therapies, and they used various tDCS treatments, different target populations (chronic and subacute stroke; with both cortical and subcortical lesions) and different types of robotic assistance. Overall, there is a lack of a clear reason for selecting tDCS solutions, which results in an excessive number of possible combinations of treatments that do not have a clear theoretical basis and eventually result in confusing clinical validation outcomes.

A deep understanding of the underlying neurophysiological mechanisms of brain plasticity and biomarker research conducted with advanced neuroimaging and transcranial magnetic stimulation are becoming essential tools for stratifying patients into groups with differing probabilities of upper limb recovery, targeting therapies for participants with the highest potential to respond, and monitoring stroke rehabilitation treatments in future trials. Eventually, we must highlight that on the one hand, combining multiple technologies can allow therapies to be tuned to the needs of a single patient based on multimodal pretherapy diagnoses, but, on the other hand, the lack of standardized rules to tailor the therapy severely limits the evidence-based outcomes, especially when multiple technologies are combined, which increases the number of parameters to be adjusted and possible combinations.

III. Recent advancements in related knowledge

A. Basic experiments in animals

Due to the costs and ethical considerations, rodent models represent a valuable tool for the efficient testing and validation of novel technologies for upper limb rehabilitation. Stroke and other lesions can be reproducibly induced in different cortical and white matter areas of rats and mice (Hinman et al., 2013), and the behavioral motor deficits can be accurately quantified (Corbett et al., 2015). Specific tests of spontaneous forelimb use (i.e., Schallert cylinder, gridwalk tests) and skilled reaching reveal robust postlesion impairments (Caleo, 2015). Although rats and mice do not show direct cortical projections to spinal motoneurons, reach-for-food tasks have been shown to involve similar hand control strategies in rodents and humans (Sacrey et al., 2009; Klein et al., 2012). Notably, automated kinematic analyses have been conducted for the quantitative assessment of grasping trajectories and velocity profiles in rats and mice (Lai et al., 2015; Lambercy et al., 2015). Due to the availability of opto- and chemo-genetic technologies, specific neuronal populations and/or circuits can be selectively stimulated or inactivated during the course of rehabilitation to determine their specific role in recovery (Cheng et al., 2014; Tennant et al., 2017).

Due to the failure of several rodent preclinical studies to be translated to human studies, a large effort needs to be directed towards improving stroke models, outcome measures, and the design of recovery protocols (Corbett et al., 2017). The focus of animal studies should be the identification of neurobiological plasticity mechanisms leading to both spontaneous and treatment-triggered recovery to gain a deeper understanding of the poststroke changes in neural dynamics that are linked to an enhanced functional outcome. This knowledge will enable the design of neurotechnologies that precisely target the circuit reorganizations promoting recovery. Clear examples of this approach include the findings that the re-emergence of low-frequency neural oscillations in the perilesional cortex drives spontaneous motor recovery poststroke and that the time-locked experimental stimulation of slow oscillatory activity improves motor performance in ischemic rats (Ramanathan et al., 2018). Thus, it is worth noting that recent technological advances allow the reliable assessment of oscillatory activity during noninvasive electrical brain stimulation in humans (Soekadar et al., 2013).

In the following sections, we review the available evidence on the use of stimulation/neuromodulatory approaches and mechatronic devices designed for promoting the restoration of forelimb function after CNS damage in rodents.

CNS stimulation and neuromodulation

It is widely accepted that the stimulation of neuroplasticity in perilesional areas promotes recovery after brain injuries. Spontaneous poststroke functional gains are mostly restricted to a "critical period" that spans the first few weeks after injury in rodents and the initial 3-6 months in humans(Zeiler and Krakauer, 2013). The definition of the critical period for recovery allows us to concentrate rehabilitative efforts during the phase of maximal sensitivity to environmental influences. Indeed, Biernaskie and colleagues compared the behavioral recovery of rats with ischemic injury that received focused motor training at 5, 14, or 30 days after the lesion (Biernaskie et al., 2004). Compared to delayed treatment, early initiation of the training provided enhanced restoration of forelimb function in the animals with ischemic lesions (Biernaskie et al., 2004). One important goal of future research should be the identification of experimental interventions that extend this heightened critical period of plasticity, thus allowing a protracted phase of effective rehabilitation.

NIBS techniques have also been tested as poststroke therapies during the "critical period" in animals. High-frequency (10 Hz) rTMS was delivered daily to facilitate excitability in the affected hemisphere, starting from 4 days after occlusion and reperfusion of the middle cerebral artery (MCA) in rats (Yoon et al., 2011). The data indicated a beneficial effect of rTMS at the behavioral level, with improved performance in the beam balance test (Yoon et al., 2011). The same group used anodal (i.e., excitatory) tDCS over the lesioned side to facilitate functional improvement after cerebral ischemia (Yoon et al., 2012). Similar data were obtained by Braun and colleagues, who found that both cathodal and anodal tDCS over the ischemic hemisphere had significant effects on poststroke recovery (Braun et al., 2016).

rTMS, tDCS and epidural electrical stimulation activate an entire CNS module, consisting of different neuronal subtypes as well as glial cells. To determine whether specific neuronal stimulation is also effective in promoting recovery, Steinberg and colleagues used optogenetic techniques to selectively activate pyramidal neurons in layer V of the ipsilesional primary motor cortex after MCA occlusion in mice. They found that the stimulated mice performed significantly better in the rotating beam test (a sensory-motor task), with a longer distance traveled and a faster speed (Cheng et al., 2014). These functional gains were accompanied by upregulation of neurotrophic factors (nerve growth factor, brain-derived neurotrophic factor and neurotrophin-3) and growth-associated protein of 43 kDa (GAP-43, a molecule involved in axonal sprouting) in the lesioned cortex, and these results suggest that neuronal stimulation enhances synaptic plasticity and its regulators (Cheng et al., 2014). Another experiment on the stimulation of cortical afferents after a stroke in the somatosensory area of mice was conducted (Tennant et al., 2017). Since stroke reduces the excitability of spared thalamocortical circuits, the authors hypothesized that chronic stimulation of these afferents (starting from 3 days to 6 weeks after the lesion) could facilitate recovery. They found that optogenetic stimulation favored the formation of new and stable thalamocortical synaptic boutons and enlarged the area of forelimb representation in the somatosensory cortex. At the behavioral level, the stimulated mice showed significantly more correct forelimb placements in the horizontal ladder walking tests, which is indicative of functional recovery (Tennant et al., 2017).

In summary, these data indicate that the selective activation of either corticospinal, layer V neurons or thalamocortical afferent fibers promotes neuronal plasticity and the amelioration of stroke-induced sensory-motor deficits. Additional studies should be conducted to determine whether combining neuron-specific stimulation with rehabilitation has additional, potentially synergistic effects on recovery. Relatedly, several reports have highlighted the beneficial effects of pairing rehabilitative training with vagus nerve stimulation (VNS) in rat models of brain injuries(Hays et al., 2014, Meyers et al., 2018). VNS is a neuromodulatory therapy employed in humans with pharmacoresistant epilepsy and is known to trigger the plasticity of motor maps via its effects on ascending cholinergic pathways (Hulsey et al., 2016). After stroke in adult rats, VNS paired with rehabilitative exercises yielded robust forelimb improvements that generalized to an untrained task and lasted months after VNS was terminated (Meyers et al., 2018). At the anatomical level, transneuronal retrograde tracing demonstrated enhanced connectivity from the lesioned sensory-motor cortex to the affected forepaw musculature in the animals with the paired treatment. These data demonstrate that VNS acts synergistically with rehabilitation techniques to enhance the plasticity of descending motor circuits and reduce motor dysfunction after stroke.

Robotic devices developed to train and measure forelimb function

Mechatronic devices have been used in rodents to determine the mechanisms of robot-based rehabilitation (Alia et al., 2017). A robotic platform, named ETH Pattus, is a three-degree-of-freedom manipulandum that allows rats to perform planar movements as well as pronosupination (Vigaru et al., 2013). Rats can learn distinct pulling tasks with this device (Lambercy et al., 2015), which highlights its utility for studying changes in movement patterns after brain injuries.

Other devices have been used to measure different aspects of forelimb function and determine the impact of CNS lesions (Hays et al., 2014; Becker et al., 2016). Spalletti and colleagues introduced a mechatronic apparatus for mice (Spalletti et al., 2014), the M-Platform (**Figure 6A**), which mimics one of the first robotic systems for upper limb stroke rehabilitation in humans, the Arm-Guide (Reinkensmeyer et al., 2000). The forelimb of head-fixed mice is extended by a linear actuator, and the animals perform a retraction task to receive a liquid reward. Recently, the system has been upgraded with a friction controller that sets the resistance exerted by the device during the retraction task (Pasquini et al., 2018), thus allowing customized rehabilitation based on the performance of individual mice. The M-Platform has been used in rehabilitation studies in stroke mice (Spalletti et al., 2014; Spalletti et al., 2017). The data showed progressive poststroke improvements in the parameters measured in the robotic platform (Spalletti et al., 2014) (force exerted, time to complete the task, etc.), with little generalization to untrained tasks (Spalletti et al., 2017). To potentiate the effects of rehabilitation, training on the M-Platform is currently combined with adjuvant therapies to enhance the susceptibility of spared circuits to experience-dependent modifications. One experiment on increased transcallosal inhibition from the healthy hemisphere, which develops after a focal photothrombotic stroke, was performed in the mouse forelimb motor cortex (Spalletti et al., 2017). To counteract enhanced interhemispheric inhibition, the synaptic blocker botulinum neurotoxin E (BoNT/E) was delivered to transiently switch off activity in the contralesional motor cortex. Silencing of the healthy side was paired with daily training on the M-Platform in stroke mice (**Figure 6B**). The data clearly indicated that the combined treatment, but neither therapy alone, promoted the restoration of function in the affected forelimb (**Figure 6C**). Importantly, a kinematic analysis of reaching indicated that this paired protocol restores several parameters (length of the trajectory, speed of movement, etc.) to prelesion values (**Figure 6D**). These findings are consistent with other results showing that paired therapies are more effective than single interventions in improving stroke recovery (Corbett et al., 2015).

Figure 6 about here

B. Neurological findings in patients during longitudinal studies

The challenge for clinical neuroscience is to understand the mechanism of neurological recovery: indeed, few markers that can predict and enhance recovery have been identified, and whether improvement of motor function is better explained by changes in behavioral, structural or functional connections in the CNS remains controversial (Koch and Hummel, 2017).

The introduction of new technologies in recent years has changed the approach to therapy in neurorehabilitation and provided new insights into the structural or functional reorganization of the CNS after stroke or the development of other neurological disorders.

In human stroke studies, emerging findings are originating from neuroradiology and neuromodulation techniques suitable for recording the activity of the brain, including functional magnetic resonance imaging (fMRI), positron emission tomography (PET), transcranial magnetic stimulation (TMS), electroencephalography (EEG), and magnetoencephalography (MEG) (Ward, 2017; Quandt et al., 2019; Koch and Hummel, 2017a; Auriat et al., 2015).

Structural and functional brain changes after stroke

Functional imaging provides excellent information about neurobiology at the cellular and molecular levels that occur post stroke, providing insights into spontaneous and therapy-induced recovery after stroke (Mandeville et al., 2017). Blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) and structural (T1, T2) and diffusion tensor imaging (DTI) techniques may reveal whether structural and functional plastic changes occur in stroke patients during the process(Kumar et al., 2016) and how these phenomena are linked to specific rehabilitation protocols.

In 2009, Askim et al. conducted a longitudinal fMRI study (Askim et al., 2009) to assess the early motor network changes in a group of ischemic stroke patients, and they found increased acute cerebellar and striatal activation, replaced by increased activation of the ipsilesional primary sensorimotor cortex in the chronic phase, demonstrating a reestablishment of a more lateralized cortical motor network that seems to correspond to the motor learning process. They also described increased bilateral activation of somatosensory areas and the contralesional secondary somatosensory cortex, which may represent cortical plasticity involved in successful motor recovery, as the activity of these areas correlates with improved strength and dexterity. Since then, several neuroimaging studies have revealed specific recovery-related patterns of reorganization in the sensorimotor control network after stroke, including the normalization of the overactivation of the sensorimotor cortex and the dynamic bihemispheric reorganization of motor networks; local remapping in the lesioned hemisphere, including the medial–premotor, lateral premotor, primary motor and primary somatosensory cortices; and increased reorganization in the contralateral undamaged hemisphere and the cerebellum(Rehme et al., 2015; Rehme et al., 2011). The role of the lesioned hemisphere has been confirmed in a recent meta-analysis including data from 24 different studies on stroke recovery. According to the review, a pattern of ipsilesional primary motor and medial-premotor cortical activation is associated with good motor recovery in chronic stroke patients. Furthermore, the authors described for the first time increased cerebellar vermal activity related to poor outcomes, possibly reflecting partially effective compensatory strategies that engage the fastigio-thalamo-cortical loop and the corticoreticulospinal pathway (Favre Isabelle et al., 2014).

Recently, connectivity-based methods have been used in stroke patients to demonstrate both anatomical and functional connectivity changes after stroke. DTI is a modern technique used for the analysis of such structural network alterations and is the most commonly used technique for this purpose since it provides relevant information regarding the properties of the white matter. Fractional anisotropy (FA) is a common measurement used in DTI studies and can be considered a measure of white matter integrity since it depends on myelination and axonal density (Mascalchi et al., 2005; Wen et al., 2016). Moreover, DTI data can be used for the three-dimensional mapping of white matter fibers (tractography) for the in vivo exploration of the anatomical connectivity of the human brain, which allows the functional assessment of motor recovery after stroke (Koch and Hummel, 2017). Pannek and colleagues used DTI to investigate corticospinal tract (CST) connectivity changes during the recovery period after stroke and found significant connectivity changes within the ipsilesional hemisphere. Over time, enhanced connectivity was correlated with good recovery (Pannek et al., 2009). In a recent study, for the first time, longitudinal changes in structural and functional connectivity in poststroke patients with motor impairment were assessed to determine which changes can best explain the recovery of function or their combined influence (Lin et al., 2018). The authors showed that FA changes in the CST correlate with motor deficits, even in patients without direct structural damage, and they hypothesized that indirect microstructural damage occurs due to disuse. They also demonstrated, with the improvements in FA, ipsilesional CST remodeling from 3 to 12 months post stroke, and they concluded that the structural integrity of the CST, rather than interhemispheric functional connectivity (FC), can be used in addition to early motor scores to predict motor outcomes (Lin et al., 2018).

It becomes increasingly clear that not only the structural integrity of CST determines the degree of recovery but also the structural integrity within other motor network parts, such as the cortico-cortical (Schulz et al., 2015; Schulz Robert et al., 2017), cortico-cerebellar (Schulz et al., 2017) or alternative cortico-spinal (Lindenberg et al., 2012) tracts. Interestingly, the functional roles of these different tracts are not independent of each other but are interrelated. Current studies have demonstrated that the functional role of secondary motor areas in residual motor areas depends strongly on the degree of structural integrity of the CST. Although the approaches used to date only provide a measure of stationary connectivity (i.e., averaged over the whole scanning session), new methods aiming at capturing dynamic functional connectivity (dFC) have also been developed (Preti et al., 2017), and these methods can be used for stroke recovery in the future.

In summary, structural brain imaging has substantially enhanced the understanding of stroke-related network changes and related them to motor functioning as well as recovery processes. However, to date, few longitudinal studies have addressed the temporal changes in structural connectivity related to motor recovery and compared different rehabilitation treatments.

To obtain a better understanding of the neurobiological and neurophysiological mechanisms underlying the modifications in brain activation patterns after stroke, including the precise temporal course of activations, it may be important to combine functional imaging both with high temporal resolution brain mapping techniques, such as EEG and MEG, and with TMS, to determine the causal links between brain areas and function by virtual lesion approaches (Guggisberg et al., 2019), determine changes in functional representations (Freundlieb et al., 2015) and intracortical neurotransmission (Liuzzi et al., 2014) and assess the changes in function in reorganized brain regions. Electroencephalography (EEG) is a potentially useful tool for monitoring the nonaffected, intact areas near and distant from the area showing neuroplastic changes and reorganization after stroke, and to date, EEG remains the only method that allows economical, noninvasive investigations of physiological and pathological actions in the human brain. However, the use of EEG in monitoring the reorganization and recovery of brain activity after stroke is partly limited by the amount of spatial information available. Few EEG studies focused on long-term recovery have been conducted, and the majority of investigations in this field have been concerned with the acute phase. In the acute and subacute stages, stroke patients present increased power in low frequency bands (i.e., delta and theta bandwidths) on both the lesioned and unaffected sides, as well as an increased delta/alpha ratio in the affected brain area; these patterns are also correlated with functional outcomes(Assenza et al., 2013; Sheorajpanday et al., 2011). Although there is an increasing number of studies in the literature related to motor recovery, studies with a longer follow-up period with more time points are needed to fully understand the relationship between temporal variability of the functional network and stroke recovery and to obtain further insight into the prediction of upper limb sensorimotor recovery.

Potential biomarkers of motor recovery after stroke

Stroke recovery biomarkers have been defined as "indicator[s] of a disease state that can be used clinically to reflect underlying molecular/cellular processes that may be difficult to measure directly in humans and can be used to predict recovery/treatment responses"(Bernhardt et al., 2016).

Technological devices used in rehabilitation are useful not only for understanding the phenomenon of brain plasticity, which determines the effectiveness of rehabilitation, but also for identifying supplementary and sensitive outcome measures that are useful for predicting sensory-motor outcomes in individuals with upper limb impairment (Guggisberg et al., 2017). Many biomarkers of brain structure and function have been discussed in the literature (Guggisberg et al., 2019; Koch and Hummel, 2017). There is a consensus that the presence of an upper limb motor evoked potential (MEP) in response to TMS in the first three days poststroke strongly predicts a good motor outcome (Stinear Cathy M. et al., 2017). Another promising parameter of TMS is the silent period (SP): in a recent longitudinal study in patients in the subacute phase after stroke, a reduction in the contralateral SP duration in the unaffected hemisphere was found, and this trend was related to clinical improvement in upper limb motor function (Lamola et al., 2016). Another neurophysiological parameter, short-latency intracortical inhibition (SICI), has also been studied and showed dynamic changes after a stroke event that can be used to determine the degree of recovery (Liuzzi et al., 2014). A limitation of these parameters is that they can only be evaluated if an MEP can be evoked, which is not the case in all patients, especially not in patients in the acute phase after stroke.

The integrity of the corticospinal tract and premotor-motor pathways have been identified as neurophysiological and neuroanatomical biomarkers for upper limb motor recovery by MRI (Lindenberg et al., 2012; Schulz Robert et al., 2017).

Using EEG, alterations in cortical oscillatory signals, evoked potentials or functional connectivity can potentially be identified as biomarkers of upper limb recovery after stroke. Activity in specific power bands is considered to be linked to specific brain functions and can have prognostic value (Assenza et al., 2013; Fanciullacci et al., 2017). In a recent study, Fanciullacci and colleagues (Fanciullacci et al., 2017) explored electrical brain activity differences, through quantitative EEG analysis, between stroke patients subdivided by the lesion location (cortico-subcortical vs subcortical lesions). The results of this study showed higher alpha band activity and an asymmetric distribution of delta band activity in subcortical stroke patients, in which a larger interhemispheric imbalance was related to better clinical functionality of the upper limb (see **Figure 7**). In contrast, in patients with cortical lesions, a scattered increase in low-frequency delta activity in both hemispheres was found. However, longitudinal studies are needed to correlate the neurophysiological data with the progression of recovery.

Cortico-muscular coherence (CMC) measured with EEG, MEG and EMG should be helpful in understanding the cortical control of movement and obtaining physiological and topographic information related to the mechanisms of motor recovery.

In a longitudinal study in patients with very good motor restoration, it was highlighted that dynamical changes in CMC are primarily localized in the contralateral sensorimotor cortices. In 2017, Belardinelli and colleagues studied CMC following a four-week brain-robot rehabilitative intervention in severely impaired stroke patients (Belardinelli et al., 2017). After the treatment, the behavioral improvements were found to be correlated with a significant CMC increase in the beta frequency band, which, as described above, reflects the efferent drive of the cortex to the muscles. They also presented the first evidence that nonprimary motor cortex and contralesional sources of CMC are dynamically modulated by therapeutic interventions, despite the presence of severe and persistent motor impairments in the chronic stage after stroke.

Figure 7 about here

Relatedly, the mechanisms of the stable relearning effect, called the carryover effect, that are associated with NMES therapy were studied by longitudinal fMRI with combined motion capture, in a group of chronic stroke patients who received one month of treatment of NMES drop-foot correction (Gandolla et al., 2016). It was possible to consistently differentiate patients with and without follow-up improvements on the basis of brain responses.

Responders had activations in the supplementary motor area and contralateral angular gyrus that were similar to those in healthy controls, strongly different with respect to non-responders. The authors suggest that the NMES carryover mechanism of action is based on movement prediction and sense of agency/body ownership, or the ability of a patient to plan a movement and to perceive the stimulation as a part of his/her own control loop, and that this mechanism of action is important for the carryover effect to occur, providing a possible understanding of the neurophysiological reason for the positive effect of EMG controlled NMES, where patient contribution is required.

IV. Future directions

Damage to the nervous system can significantly reduce the ability to perform movements in an effective way, reducing the quality of life of people after such an event. In the recent past, different types of neurotechnologies have been developed and used to address this very important clinical and social issue with promising but unsatisfactory and limited results. While it seems clear that these approaches can potentially provide better clinical outcomes after neurorehabilitation, the exploitation of their potential is hampered by several important issues. For example, for neurorehabilitation, robots were designed(Borton et al., 2013) to mimic the work of a therapist during the different rehabilitation phases in a repeatable way. Recent multicenter randomized clinical studies(Rodgers et al., 2019; Klamroth-Marganska et al., 2014) have shown that the clinical outcomes after robot-assisted therapy can be similar to those after "standard" intensive clinical care. These findings show that, to some extent, the goal of mimicking standard care was achieved. However, to have a larger clinical impact, robots need to be able to help therapists and clinicians perform tasks that cannot be performed in standard clinical therapy. An example of this idea is the use of the counterintuitive "error-enhancing" clinical protocols, which have provided interesting preliminary results(Tropea et al., 2013; Abdollahi et al., 2014), as well as the RETRAINER system, in which exoskeleton assistance is coupled with myocontrolled NMES (Ambrosini et al., 2019), a combination that outperforms traditional, standard therapy. To further exploit this approach and other innovative approaches, a better understanding of the mechanisms of robot-based neurorehabilitation is necessary to develop a personalized and optimized solution for each patient during the process of recovery.

Similarly, as described in the previous sections, NIBS protocols also need to involve the stimulation of more complex and different brain regions (Morishita and Hummel, 2017). This approach is only possible if we have a clear understanding of the roles of the different brain areas before and after the neurological ictal event and especially during the course of recovery. For this kind of application, the use of computational models can also be extremely useful for a better prediction of the outcomes, treatment efficacy and thus personalization of the neuromodulation approach (Antonietti et al., 2017). These kinds of models have been shown to be extremely useful for other neurotechnologies, such as deep brain stimulation, to alleviate motor deficits in Parkinson's disease(Lozano et al., 2019) patients and should be further exploited for other neurotechnologies.

The need for a paradigm shift becomes even more evident when different types of neurotechnologies are combined together. Few changes in the overall synergistic protocols can generate dramatic differences in the clinical outcome. A very good example of the potential of this combined approach is the recent clinical study led by Courtine for locomotion restoration after spinal cord injury using the synergistic effect of robotics and epidural electrical stimulation (Wagner et al., 2018). This clinical achievement is based on a deep understanding of the basic mechanisms together with the use of computational models (Formento et al., 2018; Capogrosso et al., 2013) and closed-loop control algorithms (Wenger et al., 2016; Wenger et al., 2014). Notably, in all of these different studies, intensive training for weeks to months supported by the neurotechnology was necessary to gain these behavioral improvements.

Moreover, we believe that the neurotechnologies we presented in this review can be applied in fields outside of stroke neurorehabilitation. However, how they should be used (and combined) in these new scenarios is determined by the basic knowledge that we have about the conditions and the specific needs of the patients.

Neurotechnologies can be seen as "building blocks" that cannot be used in the same way for different neurological disorders. Several years ago, Peckham and colleagues developed the FreeHand system, an NMES approach that can restore grasping in quadriplegic subjects (Peckham et al., 2001). The subjects were able to control the amount of stimulation by moving the contralateral shoulder. While this approach is effective for SCI patients, it is not acceptable for stroke survivors since they strongly rely on the contralateral (unaffected) side for activities of daily living. Therefore, neurotechnologies can be exploited for different neurological impairments only if they are personalized.

Finally, we think that brain biomarkers that enable us to obtain an understanding of the neurobiology of recovery after severe stroke should be studied in future work. These technological tools will allow us to design studies that involve homogeneous samples of patients in terms of the predictability of recovery. The use of this study design is most likely the only way to test the efficacy of standardized rehabilitative protocols, will allow us to administer customized rehabilitation treatment in the near future, and will allow us to move towards patient-tailored precision medicine in the field of neurorehabilitation.

Overall, we believe that neurotechnologies can significantly increase the efficacy of neurorehabilitation for people with neurological disorders. However, we will only be able to exploit their potential only if we are able to design and use them based on a deep understanding of the underlying mechanisms. To this eventual goal, we believe that a very important role will be played by explainable artificial intelligence, computational models and machine learning techniques which would be essential in order to put together many multimodal data (neuroimaging, EEG, functional outcomes, clinical outcomes, etc.) and support the understanding of neural plasticity processes and motor recovery pathways. To this, the first mandatory step is to start sharing secure databases of patient data (multimodal), including also detailed information on therapeutic interventions, and not just diagnostic data, so that all these data can be combined to determine biomarkers for identifying the most promising neurotechnological treatments for individual patients to achieve largest treatment effects, to deliver personalized, precision medicine, and allow patients to resume their normal personal and professional lives.

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Declaration of Interests

SM holds shares of the companies IUVO, GTX, Sensars Neurotechnologies and AGO Neurotechnologies, which are all developing neurotechnologies to restore the sensory-motor functions of disabled people. All the other authors have no conflict of interest to disclose.

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Figure 1 – From "one suits all" protocols to knowledge-based neurotechnologies for personalized treatment.

Figure 2. Novel strategies for noninvasive brain stimulation to enhance motor recovery.
(A) Patient-tailored targets based on the degree of structural damage. The cortical spinal tract (CST) is the main outflow tract from the motor system. The more damaged the CST is, the more impaired patients are (Lindenberg et al., 2010; (Peckham et al., 2001). Current evidence indicates that patients with mild CST damage respond well to NIBS applied to M1; in contrast, patients with severe CST damage do not respond to M1 stimulation (Lindenberg et al., 2012). Recent animal and human imaging work highlight the ventral premotor cortex (PMv) as one of the key areas involved in motor recovery. Further evidence suggests that the functional role of the PMv in recovery depends significantly on the degree of damage to the CST, i.e., the more damaged the CST is, the more important the PMv is (Schulz Robert et al., 2017). Based on this knowledge, the following patient-tailored selection for NIBS can be proposed: patients with mild damage of the CST do not rely on the PMv and will well respond to M1 NIBS (left), patients with severe damage of the CST will not respond on M1 NIBS, and the PMv plays a relevant role in motor recovery in these patients with severe damage of the CST; thus, these patients should receive NIBS to the PMv (right).
(B) Multifocal NIBS to enhance motor recovery. The brain relies strongly on interregional interactions for optimal implementation of behavior. Recent functional and structural imaging studies clearly demonstrated that interactions between primary and secondary motor areas are crucial for successful motor recovery. Thus, novel innovative NIBS-based treatment strategies should focus on supporting several network hubs in parallel and on enhancing the interactions between relevant network hubs to support functional recovery. Multifocal NIBS, e.g., the simultaneous stimulation of M1 and PMv, will have synergistic effects on motor recovery.

Figure 3 – A wearable multielectrode array for NMES (Crema et al., 2018).

A) Flexible electrode arrays have a paper-like texture; the thickness, which does not exceed 150 μm, can be seen in the top image. In the bottom of the same image, two rolled electrode arrays fixed with a paperclip are depicted; the array on the right has a superimposed layer of gel (AG702, AmGel Technologies ®). The overall thickness of the matrices, with the gel included, is approximately 1 mm.
B) Of the six electrode arrays connected to the central PCB, four constitute the butterfly like body for extrinsic muscle stimulation. The electrode arrays are routed to allow trimming both in width and in length. This design allows the reduction of the electrode arrays to fit subjects smaller than the maximum estimated size.
C) Details of the routing can be seen in the bottom left inset.
D) The system set up for one subject
E) Stimulation examples of two different arrays and details of sequential scans on five pins.
F) In an overlay of the hand nerve structure, the expected positioning of the L matrix and of the T matrix and their effect on muscle recruitment.

Figure 4 – A schematic of the evolution of the use of robots for stroke neurorehabilitation.

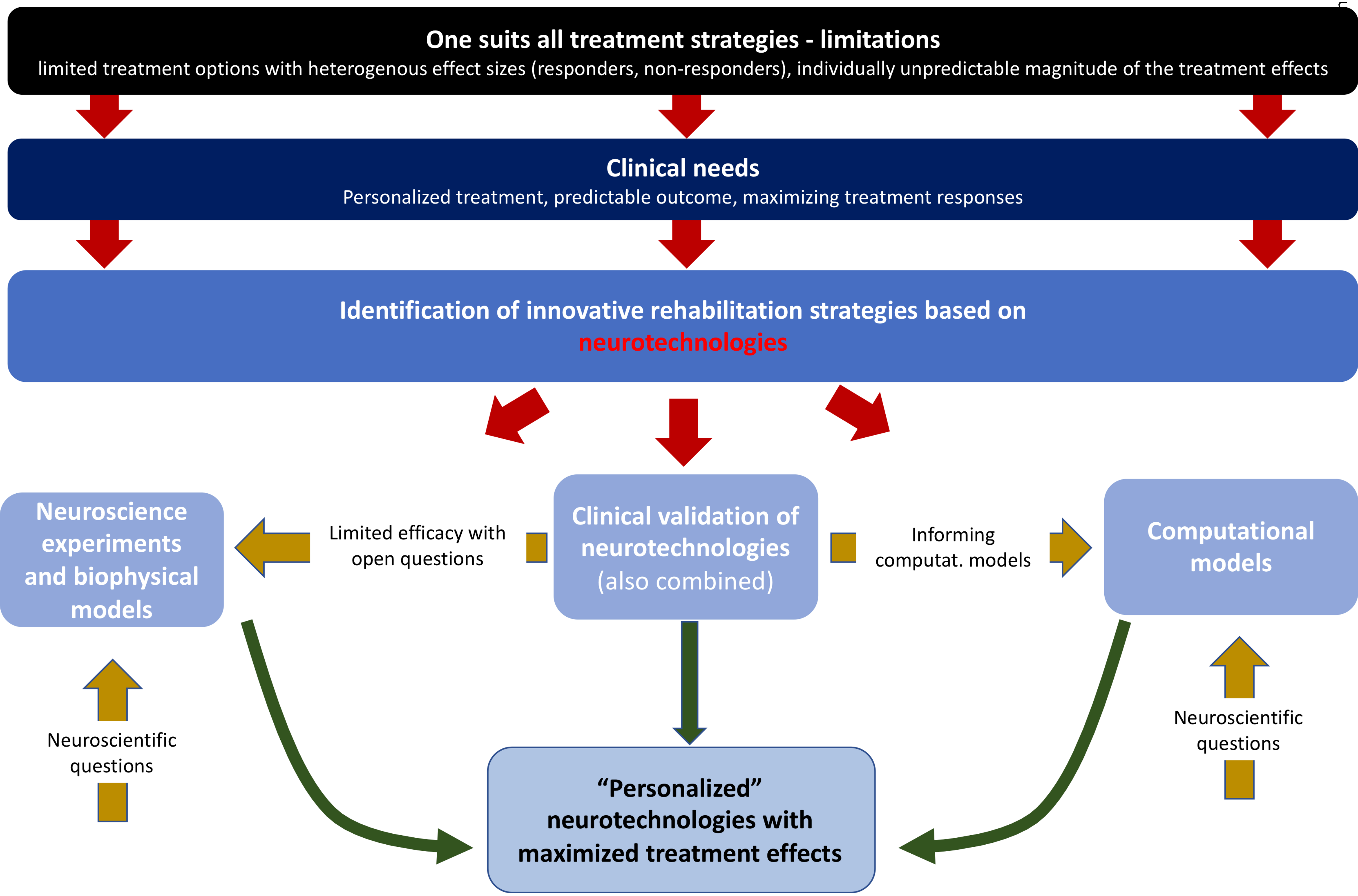
Figure 5 – RETRAINER Hybrid robotic and EMG-FES training.
A) The algorithm for estimation of the volitional EMG activity in the interpulse interval of NMES (Ambrosini et al 2014)
B) The RETRAINER system. Upper limb exercises are based on reaching targets and objects, labeled by RFID tags (interactive objects). The weight of the arm is relieved by a light passive exoskeleton. The control system allows the EMG signals of targeted muscles to be recorded and the muscles to be stimulated according to the current task. The graphical user interface informs the user of the target to be reached and the volitional contribution of the muscle during stimulation (smile).

Figure 6 - Combination of robotic training and silencing of the contralesional hemisphere to achieve forelimb recovery in stroke mice. (A) Schematic of the M-Platform, a mechatronic device for forelimb rehabilitation in mice. The animals are head-fixed, and their wrists are fastened to a handle that is connected to a load cell for force measurements. A custom-designed restrainer allows access to the brain surface for electrophysiological recordings during task execution. In each trial, the actuator extends the mouse forelimb (passive phase); then, the mouse has to voluntarily pull back the handle (active phase) to move the slide and receive a liquid reward. The resistance force of the system to the retraction movement can be varied to ensure customized rehabilitation based on the performance of each subject. Adapted from Pasquini et al., 2018. (B) Combined protocol for rehabilitation. Stroke is induced in the forelimb representation of the right hemisphere, and the synaptic blocker botulinum neurotoxin E (BoNT/E) is injected to transiently silence activity on the contralesional side. The mice undergo daily rehabilitative training in the M-Platform for one month after the injury. (C) Spontaneous forelimb use in the Schallert cylinder task 30 days after stroke. Control lesioned mice (Stroke), mice that underwent robotic rehabilitation (Robot) and mice with BoNT/E injection in the healthy cortex (BoNT/E) show an exaggerated reliance on the ipsilesional forelimb, which is indicative of persistent functional deficits in the affected forelimb. Substantial recovery is apparent in animals with the combined treatment (Robot+BoNT/E). One-way ANOVA followed by Tukey's test was performed, with $*p<0.05$ and $**p<0.01$. Adapted from Spalletti et al., 2017. (D) Kinematic analysis of reaching following the combined treatment. The total area subtended by the reaching trajectory is dramatically enhanced 2 days after stroke and then is substantially restored to prelesion values within 30 days. Two-way repeated measures ANOVA followed by Tukey's test was performed (vs baseline), with $***p<0.001$. Adapted from Spalletti et al., 2017.

Figure 7. Cortical reorganization patterns in the early phase after stroke and potential biomarkers of motor recovery.

(A) A visual representation of the power spectrum density maps of delta and alpha EEG frequency band distribution in cortical-subcortical and subcortical lesions after ischemic stroke. In the figure, the scalp distribution for the cortico-subcortical stroke patients (CS) is shown on the left, and the scalp distribution for the subcortical stroke patients (S) is shown on the right.
Delta activity is characterized by an asymmetric distribution in subcortical patients and symmetrical distribution in cortico-subcortical patients: in subcortical patients, an interhemispheric imbalance in the alpha band was found to be related to the degree of clinical impairment. Adapted from Fanciullacci et al., 2017.
(B) The silent period (SP) is a promising parameter for the prediction of the motor outcome: the figure represents the contralateral silent period (cSP) recorded by unaffected hemisphere (UH) stimulation at t0 and t1 in subcortical stroke patients.
From t0 to t1, a statistically significant reduction in the contralateral SP duration in the unaffected hemisphere in S patients is shown, and this trend is related to clinical improvement in upper limb motor function (in parallel with an increase in the Wolf Motor Function Test (WMFT) score and a decrease in the WMFT time). Adapted from Lamola et al., 2016.

Figu



One suits all treatment strategies - limitations

limited treatment options with heterogenous effect sizes (responders, non-responders), individually unpredictable magnitude of the treatment effects

Clinical needs

Personalized treatment, predictable outcome, maximizing treatment responses

Identification of innovative rehabilitation strategies based on neurotechnologies

Neuroscience experiments and biophysical models

Limited efficacy with open questions

Clinical validation of neurotechnologies (also combined)

Informing computat. models

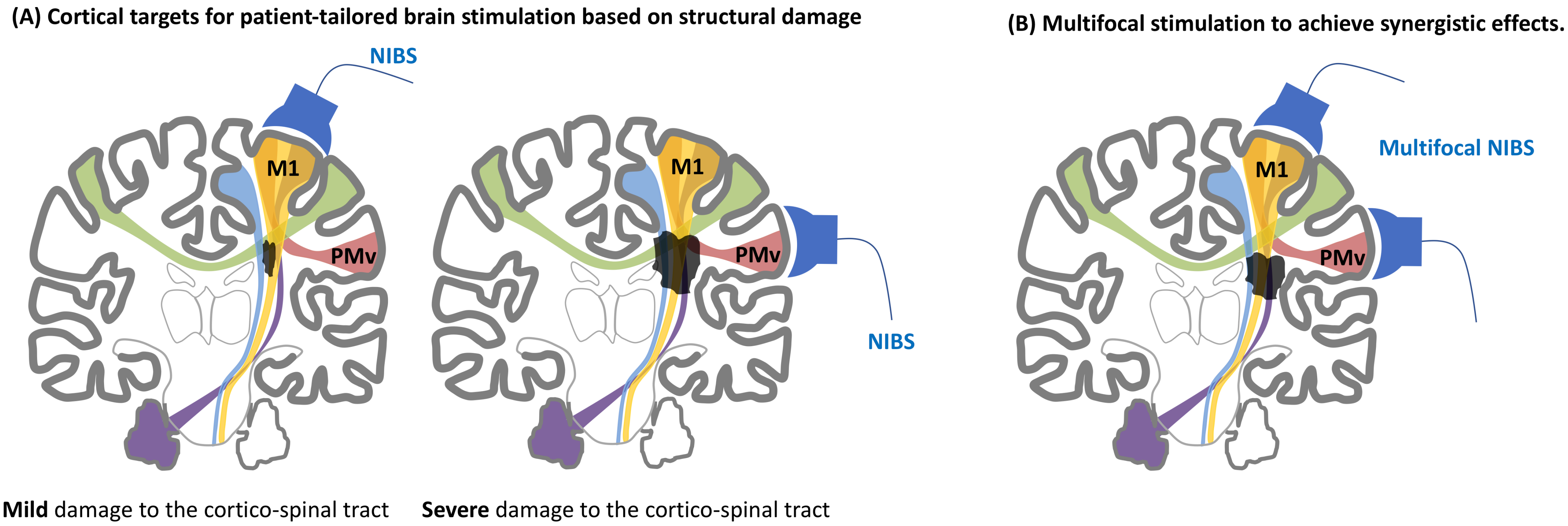
Computational models

Neuroscientific questions

Neuroscientific questions

“Personalized” neurotechnologies with maximized treatment effects

Figure2



(A) Cortical targets for patient-tailored brain stimulation based on structural damage

Mild damage to the cortico-spinal tract

Severe damage to the cortico-spinal tract

(B) Multifocal stimulation to achieve synergistic effects.

Figure3

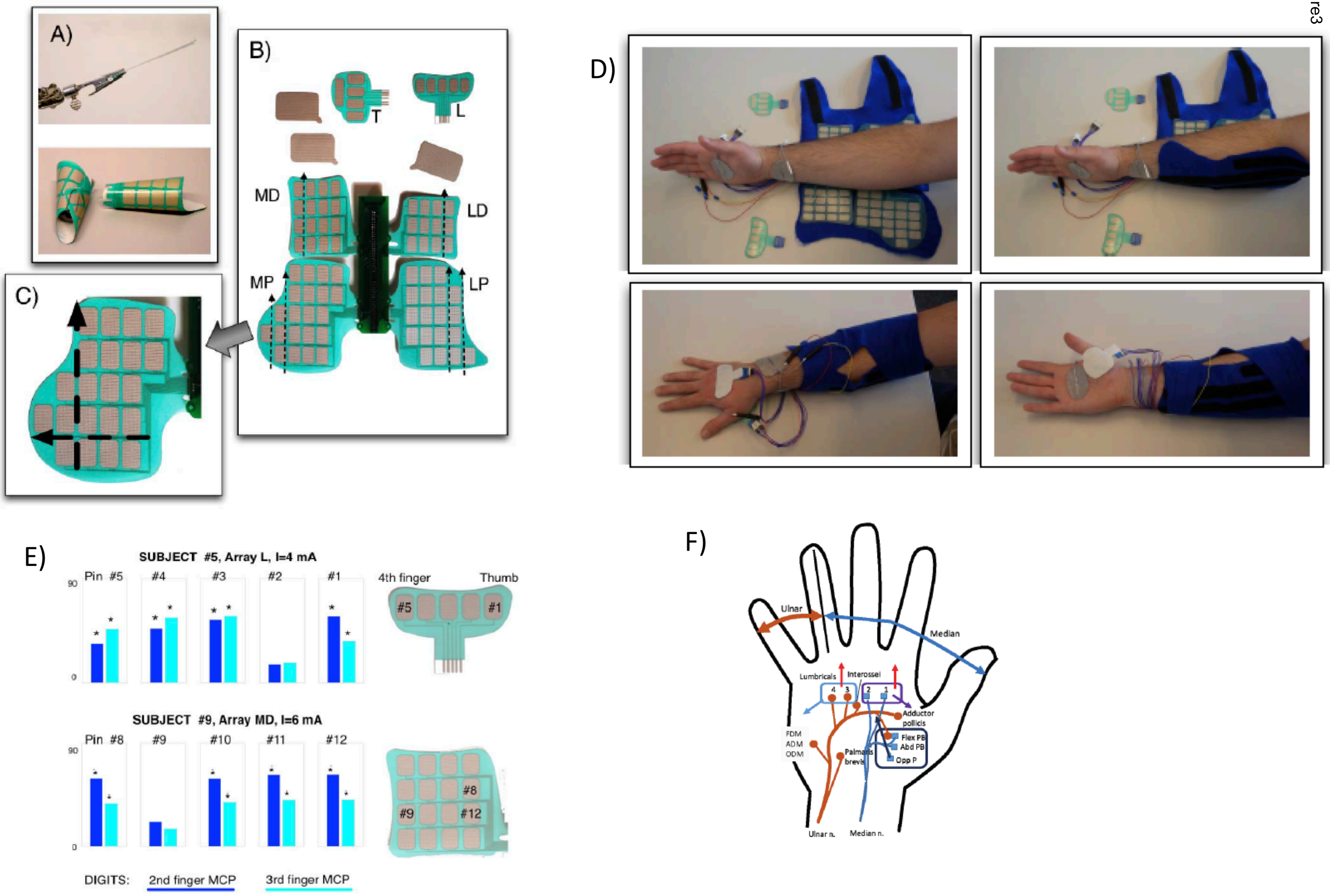

A)
B)
T
L
MD
LD
MP
LP
C)
D)
E)
SUBJECT #5, Array L, I=4 mA
Pin #5
#4
#3
#2
#1
90
0
4th finger
Thumb
#5
#1
SUBJECT #9, Array MD, I=6 mA
Pin #8
#9
#10
#11
#12
90
0
#8
#9
#12
DIGITS:
2nd finger MCP
3rd finger MCP
F)
Ulnar
Median
Lumbricals
Interossei
4
3
2
1
Adductor pollicis
FDM
ADM
ODM
Flex PB
Abd PB
Opp P
Palmaris brevis
Ulnar n.
Median n.

Figure4

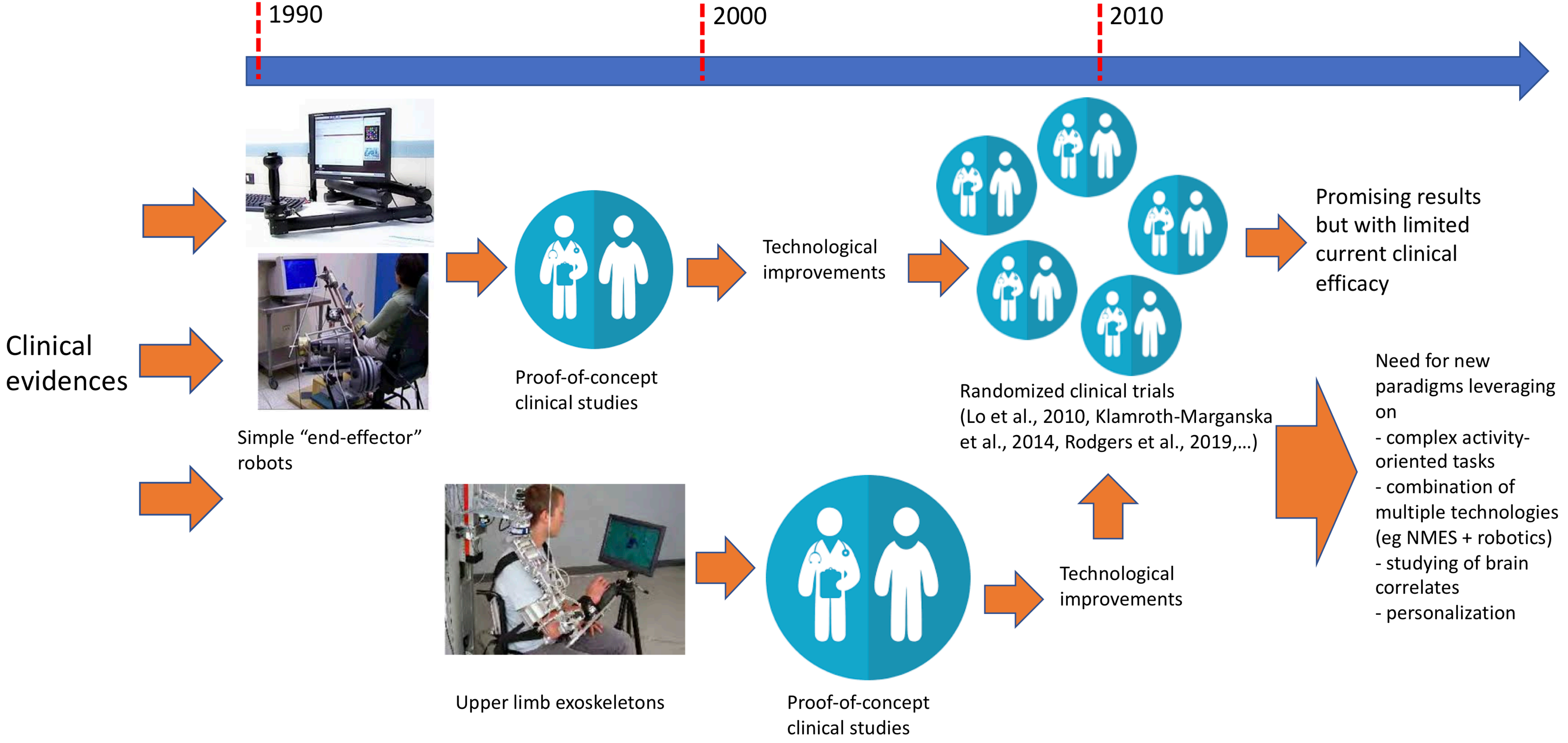
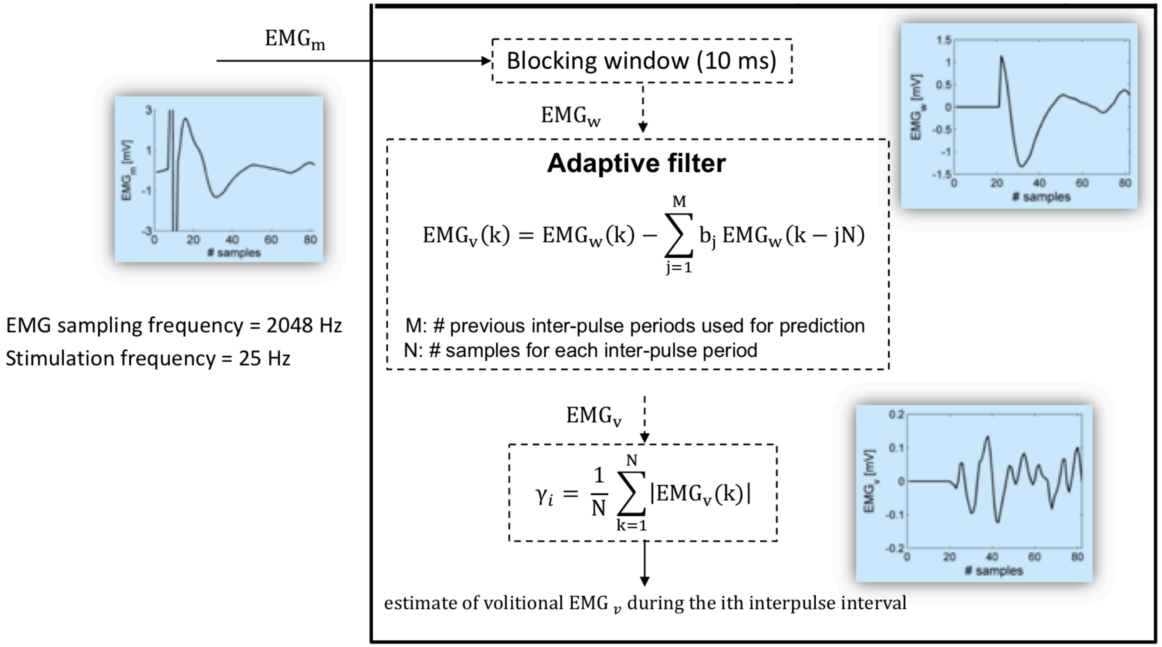

1990
2000
2010
Clinical evidences
Simple “end-effector” robots
Proof-of-concept clinical studies
Technological improvements
Randomized clinical trials (Lo et al., 2010, Klamroth-Marganska et al., 2014, Rodgers et al., 2019,…)
Promising results but with limited current clinical efficacy
Upper limb exoskeletons
Proof-of-concept clinical studies
Technological improvements
Need for new paradigms leveraging on
- complex activity-oriented tasks
- combination of multiple technologies (eg NMES + robotics)
- studying of brain correlates
- personalization

Figure5



Blocking window (10 ms)

EMG$_w$

Adaptive filter

$$\mathrm{EMG_v(k) = EMG_w(k)} - \sum_{j=1}^{M} \mathrm{b_j\,EMG_w(k-jN)}$$

M: # previous inter-pulse periods used for prediction
N: # samples for each inter-pulse period

EMG$_v$

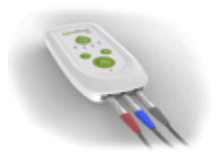
$$\gamma_i = \frac{1}{N}\sum_{k=1}^{N} |\mathrm{EMG_v(k)}|$$

estimate of volitional EMG $_v$ during the ith interpulse interval

EMG sampling frequency = 2048 Hz
Stimulation frequency = 25 Hz

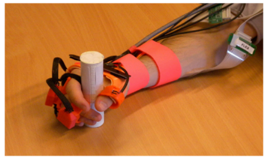
Embedded Control System

EMG + Stimulator



Exoskeleton + Arm Neuroprostheses

Hand Neuroprostheses



State Machine & Graphical User Interface (GUI)

Esercizio di spostamento di un oggetto sul piano

14:48

Andare alla posizione verde

Interactive Objects

Figure6

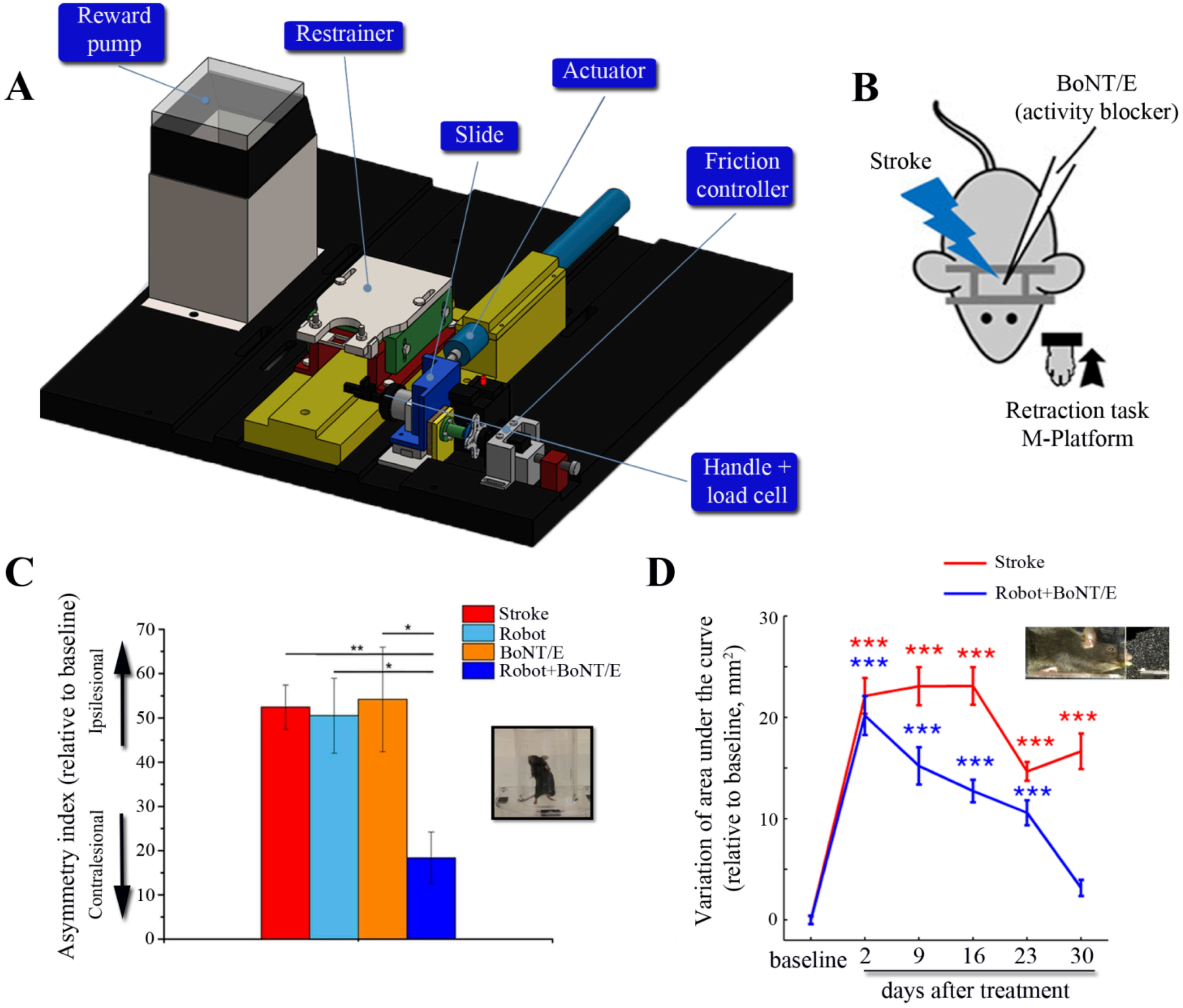
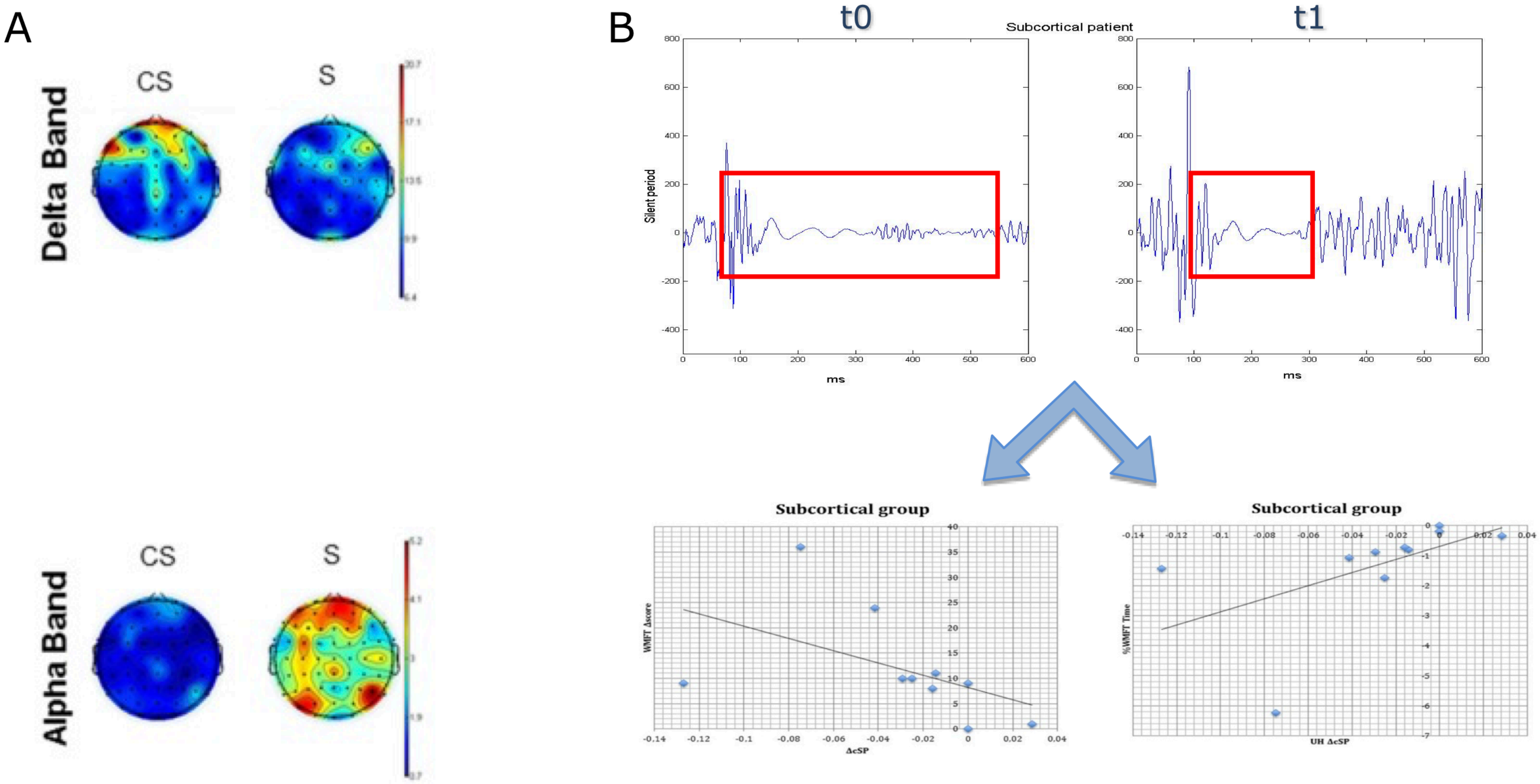

A
Reward pump
Restrainer
Slide
Actuator
Friction controller
Handle + load cell
B
BoNT/E (activity blocker)
Stroke
Retraction task M-Platform
C
Asymmetry index (relative to baseline)
Ipsilesional
Contralesional
0
10
20
30
40
50
60
70
Stroke
Robot
BoNT/E
Robot+BoNT/E
**
*
*
D
Stroke
Robot+BoNT/E
Variation of area under the curve (relative to baseline, mm²)
0
10
20
30
***
baseline
2
9
16
23
30
days after treatment

Figure7


A
Delta Band
CS
S
20.7
17.1
13.5
9.9
6.4
Alpha Band
CS
S
5.2
4.1
3
1.9
0.7
B
t0
Subcortical patient
t1
Silent period
800
600
400
200
0
-200
-400
0
100
200
300
400
500
600
ms
Subcortical group
WMFT Δscore
ΔcSP
-0.14
-0.12
-0.1
-0.08
-0.06
-0.04
-0.02
0
0.02
0.04
40
35
30
25
20
15
10
5
0
Subcortical group
%WMFT Time
UH ΔcSP
0
-1
-2
-3
-4
-5
-6
-7