A non-invasive tool for brain-plasticity-based therapy: transcranial magnetic stimulation in post-stroke rehabilitation

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Abstract—Stroke is the third most common cause of death and the commonest cause of chronic disability, and its effects can reflect in disabilities of many activities of daily life and in losses of brain functions. The mechanisms subtending post-stroke recovery are complex and operating at different levels, from molecular to synaptic and network reorganization. This reorganization largely subsums clinical recovery of motor performances and sensorimotor integration after a stroke.

Noninvasive brain stimulation modalities such as transcranial magnetic stimulation allow researchers to study human brain activity in real time, characterize balance of excitation and inhibition, and ultimately guide plastic changes. A growing body of evidence is converging on the possibility that transcranial magnetic stimulation (TMS) induces an exogenous plastic rearrangement of synaptic efficacy in the stimulated network.

Once integrated with robotic rehabilitation treatments, transcranial magnetic stimulation can be used to modulate in a targeted fashion neuronal assemblies for improving patients motor performance. A correct correlation of the data coming from the two, objective, rehabilitative/measuring systems, one at the neural level (TMS) and one at the motor level (robot) could provide rich multimodal information on patient's undergoing recovery well before it becomes apparent to a human eye and more precisely documented than with the clinical scales, and could support early corrective strategies on the robotic treatment.

The present paper presents a review of the effects of TMS on stroke recovery and suggests a possible integration of this technique with robotic rehabilitation protocols.

I. INTRODUCTION

Clinical evidence in physical medicine and rehabilitation clearly demonstrates that there is an important and increasing demand for innovative therapeutic solutions to address a wide variety of CNS injuries; for instance, patients experiencing severe stroke events have a high probability, in most cases higher than 50%, to retain severe disabilities for the rest of their lives [1].

Stroke is the third most common cause of death and the commonest cause of chronic disability; it affects many activities of daily life and brain functions, such as sensorimotor integration, movement, walking, language, vision, balance, mood, memory and sensory perception.

Recovery of function after a brain stroke is attributable to several factors, including events in the first few days (e.g. reabsorption of perilesional oedema, tissue reperfusion, diachisis) [2]. It is noteworthy that, regardless the initial stroke severity, neurological deficits typically improve in the first few weeks or months after a stroke [3]. However, such recovery can remarkably vary, even among patients with identical clinical picture and severity in the initial stages.

Our understanding of the mechanisms that promote or prevent recovery is fundamental to the design of novel medical and rehabilitation therapies for acute stroke [2]. The mechanisms subtending post-stroke recovery are extremely complex and operating at different levels, from molecular, to synaptic and to neural network reorganization of the damages areas as well as in those having with them any functional connection [5].

II. NEUROPLASTICITY IN STROKE RECOVERY

The term “neuroplasticity” encompasses all possible mechanisms of neuronal reorganization: recruitment of pathways that are functionally homologous to, but anatomically distinct from, the damaged ones (e.g. nonpyramidal corticospinal pathways); recruitment of anatomically pre-existing but functionally silent synapses as well as synaptogenesis or pruning of existing synapses; dendritic arborisation (particularly at the periphery of the damaged core) [6], [7]. Recent studies in animal models, in fact, have clearly shown improved long-term synaptic potentiation in perilesional areas, [8] fibre sprouting from surviving neurons, and the formation of new synapses have been shown to occur a few weeks after stroke [9].

The study of neural plasticity has expanded rapidly in the past decades and has shown the remarkable ability of the developing, adult, and aging brain to be shaped by environmental inputs in the healthy condition (i.e. learning new skills) and after a brain lesion.

Robust experimental evidence supports the hypothesis that neuronal aggregates adjacent to a lesion in the sensorimotor brain areas can take over progressively the function previously played by the damaged neuronal assemblies and circuits. It is also generally accepted the idea that such a reorganization modifies sensibly the interhemispheric differences in somatotopic organization (i.e. in the sensorimotor cortical relays). This reorganization largely subsumes clinical recovery of motor performances.
and sensorimotor integration after a stroke [4].

III. NON INVASIVE BRAIN STIMULATION

Noninvasive brain stimulation (NIBS) modalities such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) allow researchers to study human brain properties in real time including the dynamic balance of excitation and inhibition, as well as connectivity[10]. Moreover, different types of NIBS have been used with therapeutic purposes and there are evidences that they can ultimately drive plastic changes [11].

Transcranial magnetic stimulation (TMS) is a 25-year-old technique originally introduced to noninvasively investigate nervous propagation along the corticospinal tract, spinal roots, and peripheral nerves in humans.

The technique involves delivering a brief magnetic pulse to the scalp through a coil. This induces electric currents within the brain that produce excitation or inhibition in restricted pools of superficial cortical neurons underneath the coil. When applied on the scalp overlying the primary motor cortex (M1), single-pulse TMS allows routine evaluations of the excitability and conductivity of corticospinal motor pathways. TMS is painless and safe particularly when single-pulse stimuli are employed.

This approach has been largely applied in investigating movement physiology in the healthy, in patients with neurological disorders [12], [13] and in post-lesional follow-up studies of plastic cerebral reorganizations [2].

TMS stimulates underlying brain with electromagnetic pulses and has been used to study cortical organization by tracking motor responses to focal stimulation. It is extensively used in clinical neurophysiology, including rehabilitation and intraoperative monitoring.

Single-pulse TMS and other more recent versions (paired-pulse TMS, repetitive TMS, integration with structural and functional MRI, and neuronavigation) allow motor output to be mapped precisely to a given body motor district [14] as well as delivering electromagnetic energy (facilitatory or inhibitory) to a given brain area or injecting it within a distinct set of neuronal circuits. Moreover, different types of TMS (single-pulse, paired-pulse, repetitive) are also able to interfere with higher brain functions that require the cooperation of different brain areas and complex neuronal networks.

It also may have therapeutic effects. TMS can affect synaptic long-term potentiation and depression by modulating neurotransmitter availability and postsynaptic receptor density both in cortical neurons directly underlying the stimulus and among those connected to them [15]. Most evidence comes from studies on sensorimotor areas, but the principles are probably equally applicable to networks subserving cognition, emotion and mood regulation [16].

IV. TMS FOR STROKE RECOVERY

In particular, transcranial magnetic stimulation is a non-invasive tool that has been used to investigate the brain plasticity changes resulting from stroke and as a therapeutic modality to safely modulate neuroplastic phenomena in order to improve motor function [17]. Traversa and colleagues constructed motor maps of representative upper limb muscles with focal TMS for subacute stroke patients by recording MEPs from the abductor digiti minimi (ADM) muscle. The ADM muscle cortical maps were obtained from affected (AH) and unaffected (UH) hemispheres [18].

They described a novel procedure that allowed noninvasive investigation of the functional reorganization of hand motor areas in which the conventional analysis of MEP parameters was combined with the evaluation of interhemispheric differences between excitability as well as of the maps spatial properties of AH and UH in stroke patients [19].

Their neurophysiological findings confirm the existence in adults of a "plasticity" in the central nervous system that is still operating between 2 and 4 months from the acute ictal episode [18], [20]; the motor output is still undergoing a remarkable reorganisation characterised by the enlargement of the output area and increased MEPs amplitude from the AH and by a larger than normal contracted-MEPs amplitude from the UH, possibly reflecting increased UH excitability particularly in patients with a poor outcome [21]. This was found a negative prognostic indicator probably due to an excess of transcallosal inhibitory influences from UH towards AH contrasting to restorative processes in the latter. It is then understandable that interhemispheric balancing of contracted-MEPs amplitude is linked with a better clinical recovery [21]. The amelioration of the neurophysiological parameters was correlated with clinical improvement in disability and neurological scores [20].

TMS paired-pulse (pTMS) techniques consist of two individual stimuli of different intensity separated by a predetermined interval of time (interstimulus interval -ISI-) that can provide measures of intracortical facilitation and inhibition as well as study cortico-cortical interactions by means of a sub-threshold conditioning stimulus (S1) followed by a supra-threshold test stimulus (S2).

Cicinelli and colleagues investigated the interhemispheric asymmetries of the time course of intracortical inhibition (ICI) and facilitation (ICF) of motor cortex between the AH and UH of stroke patients in the postacute phase of recovery. In stroke patients, the ICI/ICF slopes were significantly different between the UH and AH; the intracortical inhibition was reduced in the AH and normal in the UH. Since ICI/ICF slopes are quite symmetrical on the two hemispheres of the healthy, excessive interhemispheric asymmetries of the ICI/ICF between the AH and UH could be considered a good
A neurophysiological marker of cortical plasticity implicated as a mechanism relevant for post-stroke functional recovery. Analysis of this parameter might provide a valuable neurophysiological marker in the prognosis and follow-up of patients with monohemispheric stroke [22].

Recently, a technical device has been introduced, which allows recording electroencephalographic (EEG) responses to TMS of a given scalp site. The latency, amplitude and scalp topography of such responses are considered a reflection of cortico-cortical connectivity and functional state. Paired-pulse TMS induced EEG responses whose amplitude variability was correlated with amplitude variability of MEPs [23].

EEG-pptTMS is a promising tool to better characterize the neuronal circuits underlying cortical effective connectivity as well as the mechanisms regulating the balance between inhibition and facilitation within the human cortices and the corticospinal pathway.

In the late '90s, a new generation of magnetic stimulators was introduced, able to deliver rhythmic trains of several stimuli per second, and therefore called repetitive TMS (rTMS) [16]. They were mainly utilized to create long-lasting changes in the excitability of synapses probably through LTP/LTD phenomenona, rTMS has been intensively investigated as a therapeutic tool in several neurological and psychiatric conditions and as given some promising results [24]. In fact, favorable neurologic effects have been reported after high-frequency rTMS (5-Hz range) applied in the acute stage in patients with stroke [25], [26], [27]. These studies found modest but significant improvements in grip strength, range of motion, and pegboard performance up to 1 week after rTMS and a better outcome a 3 months [26].

Since -as previously said- monohemispheric stroke is “unbalancing” the usual mutual excitatory/inhibitory control that each hemisphere is producing on the contralateral one via transcallosal fibres (Traversa et al. 1998) and because the progressive hyperexcitability of the non-affected hemisphere is deleterious on the recovery of the affected one, several attempts have been carried out in order to prevent or to temper-down such an “unbalance”. Along this line, moving from the knowledge that low-frequency rTMS (1-Hz range) decreases cortical excitability [28] this has been applied to the unaffected motor cortex to decrease hyperexcitability in chronic stroke patients as initially shown in a population of subacute subjects [29] and subsequently confirmed in other studies where 1 Hz rTMS of the unaffected motor cortex led to an increase in the excitability of the affected motor cortex with functional improvement [30], [31]. These studies suggest that decreasing inhibition in the affected M1 and perhaps other motor-related areas, such as the dorsal premotor cortex, can unmask pre-existing, functionally latent neural connections around the lesion and contribute to cortical reorganization [31].

Repetitive transcranial magnetic stimulation (rTMS) has been used to improve language skills, including naming, in stroke patients with chronic, nonfluent aphasia. Functional imaging studies with nonfluent aphasia patients have observed "over-activation" in right (R) language homologues. This may represent a maladaptive strategy; suppression may result in language improvement.

When applied slow, 1 Hz repetitive transcranial magnetic stimulation (rTMS) to an anterior portion of R Broca's homologue daily, for 10 days in four aphasia patients who were 5-11 years post-stroke a significant improvement was observed in picture naming at 2 months post-rTMS, with lasting benefit at 8 months in three patients [32].

This trial suggests that rTMS may provide a novel treatment approach for aphasia by possibly modulating the distributed, bi-hemispheric language network .

TMS can be used to temporarily facilitate or inhibit neural activity to examine intact systems, examine the presence of residual capacity in an injured system, or to accelerate natural recovery mechanisms.

V. TMS AND ROBOTIC REHABILITATION

The ability to directly assess curative brain plasticity events in terms of cortical maps’ reorganization makes TMS an interesting tool for stroke rehabilitation. One of the most promising rehabilitation approaches for functional recovery of stroke patients is based on robot therapy [33], [34]. Robotic rehabilitation devices, in fact, deliver therapy on both motor (e.g. intense, active, repetitive movements of growing speed and complexity) and cognitive (e.g. high attentive valence, planning/execution/monitoring, cognitive training) dimensions, and are thought to maximize the effects of rehabilitation on brain plasticity, by promoting and facilitating re-learning processes.

Together with the rehabilitation therapies, robotic machines are inherently able to provide accurate quantitative measurements of patient motor performance during any tasks execution. This information has been recently proposed for rigorous and objective assessment of the therapeutic approach [2], [35]. Once coupled with TMS, robotic rehabilitative machines could provide an incredibly accurate, precise, and sensitive tool for assessing the effectiveness of stroke rehabilitation, well beyond the capability of a human observer and to better tailor rehabilitation plans to individual cases.

In a previously published work, TMS was used to demonstrate the effects on cortical reorganization due to the therapeutic use of a robotic hand prosthesis by an amputee patient [36]. As with all the current robotic rehabilitation approaches, the robotic prosthesis was used to provide both enhanced motor control (the patient was asked to “think” the movement he wished to perform, but the actual motor control was left to the robot) and coherent real-time
feedback (by providing both the view of the robotic hand performing in real-time the patient’s intentions and by electrical intra-neural stimulation to simulate the tactile feedback from the missing hand) [37]. The patient could use the robotic hand for one month, during which he learned to control four different hand movements just by thinking about them, and could feel several different sensations coming from his missing hand. What was experienced by the robotic system as an increment of performance of the patient in properly controlling the movements required to fulfill his rehabilitative tasks, was fully coupled with an important cortical reorganization. In particular, the patient’s motor cortex underwent plastic changes which brought it back to its healthy configuration, that is, very close to present the same TMS maps of the unaffected hemisphere (the one connected to the existing hand). To check for interhemispheric differences, Motor Evoked Potentials were recorded from proximal muscles of both limbs (biceps and deltoide) during separate mapping of right and left hemispheres. Interhemispheric differences in the cortical representation of a given muscle have been demonstrated to remain stable in time in control populations, while they can be significantly modified by plastic reorganization following a monohemispheric lesion or a limb amputation [2], [38].

Even if these results do not directly apply to stroke patients, they show how TMS maps can be used to identify the neural correlates of the patient’s motor performance changes recorded, monitored, and identified by robotic rehabilitative systems. A correct correlation of the data coming from the two, objective, measuring systems, one at the neural level (TMS) and one at the motor level (robot) could provide rich multimodal information on patient’s undergoing recovery well before it becomes apparent to a human eye and more precisely documented than with the clinical scales, and could support early corrective strategies on the robotic treatment.

VI. CONCLUSIONS

TMS is a promising therapeutic tool to minimize motor, speech, cognitive, and mood deficits. A growing body of evidence is converging on the possibility that TMS can produce an exogenous modulation of plastic rearrangement of synaptic efficacy in the stimulated network.

The ability of TMS to map the cortical reorganization following the administration of rehabilitation therapies to stroke patients could provide a particularly efficient tool to the development of novel robotic rehabilitation approaches aimed at quantitative and real-time evaluation of patients’ healing process. Rehabilitation robots can already provide the first automatic evaluation on patients’ motor performance recovery. TMS could provide information on the underneath cortical reorganization, which could support early corrective strategies on the robotic treatment.

REFERENCES


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