Strength and Weakness of NIBS-RAR Coupled Intervention

Robot-aided rehabilitation (RAR) and non-invasive brain stimulation (NIBS) are the two main interventions for post-stroke rehabilitation. The importance of coupling these interventions, which both enhance brain plasticity to promote recovery, lies in augmenting the rehabilitation potential to constrain the limitation in daily living activities and the quality of life following stroke.

1. Introduction

Multiple strategies have been developed to enhance the post-stroke spontaneous recovery mechanisms. These include early reperfusion therapies (i.e., intravenous thrombolysis and mechanical thrombectomy) aimed at limiting damage and preventing further cell death to contain lesion size and disability [1]. Furthermore, traditional (neurofacilitation or functional retraining through either shaping or task practice) and advanced rehabilitation protocols, including pharmacological manipulation to increase sprouting and anatomical plasticity, non-invasive brain stimulation (NIBS) to modulate the activity of targeted brain areas, and robot-aided rehabilitation (RAR) to perform an intensive, repetitive, assisted-as-needed, and task-oriented motor practice, are available in any phase of the post-stroke recovery process [2][3][4][5][6][7][8][9]. These rehabilitation strategies aim to increase the adaptive plasticity processes (mainly experience-dependent plasticity mechanisms) that develop in lesional and perilesional tissues [10][11][12].

To date, NIBS and RAR represent two cornerstones of the modern post-stroke rehabilitation era. Both strategies have been employed singularly concerning post-stroke rehabilitation with valuable positive results [2][3][4][5][6][7][8][9]. Both strategies aim at potentiating neuroplasticity mechanisms supporting functional recovery via bottom-up (RAR) and top-down (NIBS) mechanisms [13][14][15]. Bottom-up approaches mainly act at the physical level and attempt to bring about changes at the level of the central neural system, whereas top-down approaches (comprising serious exergames, virtual reality, robots, brain–computer interfaces, rhythmic music, and biofeedback) attempt to stimulate the brain more directly to elicit plasticity-mediated motor relearning [14]. Therefore, RAR and NIBS act indirectly and directly, respectively, on the spontaneous recovery mechanisms occurring after a brain injury (including stroke), which are aimed at substituting a part of the brain for the function of another (according to the theory of vicariation) [10]. In particular, directly modifying the spontaneous recovery mechanisms is postulated to: (i) favor remote structures' reconnection to the site of injury following the diaschisis period (i.e., a temporary period of depressed metabolism and blood flow), including the perilesional cortex, spared areas in the injured hemisphere, and contralateral homologous and non-homologous areas; (ii) favor the learning of new, compensatory joint and muscle kinematic patterns; and (iii) avoid a maladaptive plasticity process potentially occurring during spontaneous local and sometimes distant rewiring of neural networks (through long-term potentiation, long-term depression, unmasking, synaptogenesis, dendritogenesis, and functional map plasticity) [10][16][17]. These effects occur through targeting the lesioned circuit to foster adaptive connections and minimize faulty connections by providing sensorimotor inputs to the lesioned network designed to specifically foster connections in keeping with Hebbian learning mechanisms (bottom-up approaches).

RAR, including exoskeletons and end-effector devices, may boost neural plasticity and functional recovery by providing patients with intensive, repetitive, assisted-as-needed, and task-oriented motor practice, which achieves functional motor relearning through the repetitive practice of all different phases of gait and movements of upper limbs related to functional tasks. This effect on neural plasticity is in common with conventional physiotherapy approaches. Actually, training the same movement repetitively enables the nervous system to develop circuits for better communication between the motor center and sensory pathways, which promotes motor function recovery [15][18]. Treatment by RAR compared with conventional treatment presents several advantages, including training duration, more reproducible symmetrical gait

patterns, operation by a single therapist, and a reduction in the energy expenditure imposed upon the therapists [18][19][20].In particular, RAR produces benefits similar, but not significantly superior, to those from usual care for improving upper limb functioning and disability in patients diagnosed with stroke within six months. Conversely, recent research revealed that RAR results in a more symmetrical muscle activity pattern in paretic patients compared with conventional treatment, an improvement in activities of daily living, and in lower limb functions and muscle strength, and gait performance [15][18][19][20].

NIBS, including transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS), can potentiate the neuroplasticity mechanisms entrained by rehabilitative training through associative plasticity mechanisms. At the same time, NIBS can serve as a primer to make the neuroplasticity mechanisms ready to be boosted by rehabilitative training.

2. Strength and Weakness of NIBS-RAR Coupled Intervention

Consistent with the cardinal issue that neuroplasticity is the key process in motor function relearning, targeting specific brain areas with NIBS during RAR can further improve brain metabolism and neural–synaptic activity. In line with this principle, TMS and tDCS are aimed at stimulating an appropriate brain area by depolarizing neurons and activating excitatory action potentials, which inhibits/excites cortical neurons [21]. This principle is corroborated by the clinical practice that NIBS can magnify RAR aftereffects in post-stroke patients. The NIBS-added improvement likely depends on the capability of NIBS to focus on the brain plasticity strengthening induced by sustained motor practice using RAR, thus further fostering motor function recovery.

However, the exact mechanism by which TMS works is still partially unclear. Three levels of action can be considered: molecular, cellular, and network. The levels' functionality depends on several factors related to the individual neurobiology (including an individual's excitability threshold) and the stimulation setup (including intensity, dose, and stimulation location), whose standardization is crucial across experiments [22]. In particular, magnetic pulses influence the ongoing activity of those neurons located horizontally in a surface parallel to the TMS coil [23]. The rapid change in the magnetic field induces circular electric currents; thus, the current flow is parallel to the coil and to the scalp on which the coil is placed flat, leading to axonal depolarization and the activation of cortical pathways, up to some subcortical structures, including the thalamus and the basal ganglia [24]. Motor cortex activation by TMS causes different descending volleys in the corticospinal tracts (including the earliest D-wave by direct stimulation of the neurons of the pyramidal pathway, and the I-wave by trans-synaptic stimulation of the pyramidal pathway) [25], whose motor unit recruitment follows the principle of size, from the smallest to the largest one [26]. Repeatedly stimulating the cortex leads to functional changes in synapses, mainly long-term potentiation and long-term depression, at both presynaptic and postsynaptic level [27]. These mechanisms, variably shaped, exert neurorestorative effects, leading to structural neuronal and network changes [17][28][29], with a relevant role of BDNF [30][31][32].

The neurobiological effects of tDCS are similarly partially known. tDCS consists of applying a low-intensity current (1–2 mA) between two or multiple small electrodes applied over the scalp [33]. The effects are mainly, but not only, influenced by the electrode polarity, with consequent modification of the resting membrane potential. Usually, anodal stimulation induces depolarization and increases cortical excitability, whereas cathodal stimulation produces hyperpolarization and decreases cortical excitability [34][35][36][37]. Both stimulations can be applied simultaneously on opposite targets, according to the interhemispheric inhibitory competition model [38][39][40], producing an interhemispheric rebalancing effect [41].

Consistent with these premises, coupled NIBS-RAR intervention may help in a post-stroke rehabilitation setting, although it must be acknowledged that all patients were also treated with conventional physiotherapy, which may have contributed to the recovery. Actually, conventional physiotherapy acts similar to RAR as a bottom-up approach, although robot-assisted repetition can improve gait performance and upper limb movement precision and reproducibility more than conventional physiotherapy. Notwithstanding this, it has been shown by Cochrane reviews [19][20] that RAR and conventional physiotherapy are not significantly different concerning daily life activities and arm functions, despite the greatest effects being appreciable within 3 months post-stroke. Concerning gait recovery, RAR increases the chance of independent walking (but not walking velocity and capacity) at the end of the treatment but not at the follow-up, regardless of the stroke stage, the pre-stroke status, and the type of the device employed.

One could argue that NIBS could also have positive effects when coupled with conventional therapy. Actually, several works assessed NIBS coupled with conventional physiotherapy as compared to stand-alone for either upper or lower limbs, showing the coupled intervention as an effective strategy to improve motor function recovery in post-stroke patients [2][42]. No studies directly compared RAR, NIBS, and conventional physiotherapy. However, it can be argued that RAR allows a better standardization of the rehabilitation exercises concerning, above all, the timing of execution. This is critical

if NIBS stimuli work in the temporal path of milliseconds is considered , thus being basilar regarding associative plasticity mechanisms, which are critical concerning synaptic plasticity strengthening and motor relearning; therefore, it can be speculated that RAR is more suitable for NIBS compared to conventional physiotherapy concerning plasticity mechanisms' triggering. This justifies the growing interest of the scientific community in the evaluation of the effects of RAR coupled with NIBS in stroke [43], and some preliminary, convincing data suggest a solid rationale for its implementation in advanced rehabilitation settings. NIBS can strengthen the deficitary brain network within the lesion site and inhibit the overactive brain networks neighboring the brain lesion. This NIBS-dependent bihemispheric effect was originally proven in experimental models employing intracortical microstimulation, achieving a rapid cortical reorganization of motor representation [44]. In addition, there is robust evidence that cortical stimulation can modulate cortical excitability and the motor responses evoked from the stimulated cortex, increase the dendritic density in the stimulated cortex, favor the reorganization of representational maps in the stimulated cortex, and lead to the synchronization and spreading of the perilesional neuronal activity supporting a major rewiring of far-to-distant connections, including transcallosal loops [16][45][46][47][48][49][50][51][52].

Although promising, conjugating NIBS with RAR, as well as the single implementation of such tools, requires device and instrument availability, personnel trained in the use of robots and NIBS, and time, space, and human resources [53]. In addition to these factors, a higher degree of patient compliance is mandatory to afford NIBS and/or RAR. Furthermore, no neurophysiological assessment with TMS was performed to assess cortical excitability and brain connectivity before and after treatments (with a few exceptions) [54][55]. Finally, the magnitude and duration of NIBS-RAR aftereffects depend on many variables related to instrumentation and the stimulation paradigm, and the setting and patient subjectivity to NIBS. Notwithstanding this, NIBS was safe in post-stroke settings [3][9][56][57].

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