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Literature review/Revue de la littérature

Non-invasive brain stimulation (NIBS) and motor recovery after stroke

Neuromodulation corticale non invasive (NIBS) et récupération motrice post-AVC

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Abstract

Recovery of motor function after stroke occurs largely on the basis of a sustained capacity of the adult brain for plastic changes. This brain plasticity has been validated by functional imaging and electrophysiological studies. Various concepts of how to enhance beneficial plasticity and in turn improve functional recovery are emerging based on the concept of functional interhemispheric balance between the two motor cortices. Besides conventional rehabilitation interventions and the most recent neuropharmacological approaches, non-invasive brain stimulation (NIBS) has recently been proposed as an add-on method to promote motor function recovery after stroke. Several methods can be used based either on transcranial magnetic stimulation (repetitive mode: rTMS, TBS) via a coil, or small electric current via larges electrodes placed on the scalp, (transcranial direct current stimulation tDCS). Depending on the different electrophysiological parameters of stimulation used, NIBS can induce a transient modulation of the excitability of the stimulated motor cortex (facilitation or inhibition) via a probable LTP-LTD-like mechanism. Several small studies have shown feasible and positive treatment effects for most of these strategies and their potential clinical relevance to help restoring the disruption of interhemispheric imbalance after stroke. Results of these studies are encouraging but many questions remain unsolved: what are the optimal stimulation parameters? What is the best NIBS intervention? Which cortex, injured or intact, should be stimulated? What is the best window of intervention? Is there a special subgroup of stroke patients who could strongly benefit from these interventions? Finally is it possible to boost NIBS treatment effect by motor training of the paretic hand or by additional neuropharmacological interventions? There is clearly a need for large-scale, controlled, multicenter trials to answer these questions before proposing their routine use in the management of stroke patients.

Keywords: Stroke; Motor recovery; rTMS; TBS; tDCS; PAS; Brain plasticity

Résumé

Le cerveau d'un patient victime d'un accident vasculaire cérébral (AVC) a les capacités de reconfigurer son activité dans les suites de l'infarctus. Cette plasticité cérébrale spontanée, substrat de la récupération fonctionnelle, a fait l'objet de nombreux travaux de recherche en imagerie fonctionnelle et en électrophysiologie aboutissant au concept de balance interhémisphérique et au développement de techniques de neuromodulation corticale, visant à faciliter les processus naturels de plasticité corticale. Ces méthodes non invasives utilisent soit, l'application sur le scalp à travers un coil d'un courant magnétique en mode répétitif, (stimulation magnétique transcrânienne répétitive rTMS, TBS), soit l'application d'un courant électrique continu de faible intensité à travers deux larges électrodes placées sur le scalp, (stimulation électrique directe transcrânienne, tDCS). Elles permettent d'induire une modulation de l'excitabilité du cortex moteur sous-jacent transitoire et focale, (facilitation ou inhibition en fonction des paramètres de stimulation), par un mécanisme de type LTP/LTD. Ces méthodes visent principalement à restaurer l'équilibre de la balance interhémisphérique entre le cortex moteur du côté lésé et du côté sain. Plusieurs études ont souligné leur intérêt potentiel dans la récupération motrice post-AVC en montrant des améliorations sensibles des performances motrices de la main parétique comparativement à des stimulations placebo, ainsi que leur bonne tolérance. Cependant, de nombreuses questions demeurent encore en suspens avant de pouvoir les utiliser en routine, concernant les paramètres de stimulation optimaux, les cibles potentielles, le choix des techniques, la meilleure période de leur

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application (phase aiguë, chronique), les critères de sélection des patients susceptibles d'en bénéficier et finalement leur place par rapport aux techniques conventionnelles de rééducation et les approches neuropharmacologiques.

Mots clés : AVC ; Récupération motrice ; rTMS ; TBS ; tDCS ; PAS ; Plasticité cérébrale

1. English version

1.1. Brain plasticity and cortical reorganization mechanisms after stroke

The brain has the ability to reconfigure its activity in the aftermath of an ischemic stroke thanks to its natural plasticity. The latter expresses itself via the basic brain metabolism, changes in cortical mapping (overactivation of the damaged cortices, changes in motor and sensitive somatotopies [1,2]), and recruitment of brain areas at a distance from the lesion which will be involved in functional recovery [3]. During the motor recovery phase, functional imaging studies (PET scan and functional MRI) have underlined the involvement of areas adjacent to the lesion [4] and the recruitment of areas in the healthy hemisphere [5,6]. It has been largely validated that adequate motor recovery of the paretic hand in stroke patients is correlated to a reorganization of the brain activity within the injured hemisphere [7–9]. If at first, the recovery relies on neuronal networks involving at the same time ipsilesional and contralesional secondary sensorimotor areas, the return to a more classic network would promote a quality recovery [10,11]. In fact the greater the asymmetry between both hemispheres is, the worse the recovery will be [12,13]. Longitudinal studies have validated the existence of dynamic changes in the balance of activation between the healthy and injured hemispheres (interhemispheric balance) during recovery, with an initial hyperactivity of the healthy hemisphere during a movement of the paretic hand [4,11,14]. In the dynamic evolution of recovery, it seems that patients exhibiting a poor recovery will continue to show an activation of the contralesional hemisphere [7,15]. However, imaging studies cannot refine if this bilateral activation is the consequence of poor motor performances of the paretic hand (epiphenomenon), or the indication of a disruption in the interhemispheric balance interfering secondarily with motor performances. This is why electrophysiology studies are relevant. Results from the study by Werhahn et al. [16] suggest that the role of the contralesional motor cortex in the recovery of performances of the paretic hand would be minor during the chronic phase since the reaction time of finger movements of the paretic hand is only disrupted by the application of interferential TMS on the ispilesional motor cortex but not by TMS applied on the contralesional motor cortex. However, a more recent study [17] showed that the application of interferential TMS on contralesional motor areas disrupts more the simple reaction time of a finger movement performed with the paretic hand when patients exhibit a poor recovery, thus suggesting on the contrary, a functional role of contralesional motor areas in recovery, even more so when patients have severe impairments. Conversely, Lotze et al. [18,19] showed that inhibitory rTMS applied on the contralesional motor cortex of chronic stroke patients with a good recovery induces disruptions in movement precision when performing a complex sequencing gesture with the paretic hand, thus suggesting that the hyperactivity or recruiting of contralesional motor areas during complex motor tasks could have a beneficial effect on the performances of the paretic hand. To sum up, these results underline the difficulties in apprehending the exact role played by the contralateral hemisphere in motor recovery after stroke. It most certainly relies on several factors including time elapsed since stroke (acute or chronic phase), importance and site of the lesion and complexity of the motor task to be performed.

1.2. Modulation of intra- and interhemispheric cortical excitability after stroke

TMS has enabled teams to study the changes in the excitability of the primary motor cortices of the injured and healthy hemispheres during the recovery phase as well as the modulation of interhemispheric inhibition at rest and when planning and executing a voluntary movement. The first studies in this field reported results in favor of an hyperactivity of the healthy hemisphere during motor recovery of the paretic hand [20,21], which tends to decrease over time, especially in patients with a satisfactory recovery [22]. With double-shock TMS [23], authors reported a decrease in the mechanisms of the GABAergic inhibitory interneurons (GABA-A, short intracortical inhibition [SICI]) of the motor networks for the injured and healthy hemispheres, during the acute or subacute phase [24–27]. This SICI modulation might reflect a recovery strategy promoting the use of the usual or compensatory motor areas, but its measurement only seems reliable after 3 months of recovery [28].

Each motor cortex exerts a mutual influence on its opposite counterpart via glutamatergic transcallosal fibers projecting onto the GABAergic inhibitory interneurons of the opposite motor cortex [29–31]. These interhemispheric connections (interhemispheric inhibition [IHI]) can be indirectly studied via double-shock TMS [29,30]. These interhemispheric interactions are useful in the voluntary control of unimanual and bimanual movements [32]. According to the concept of interhemispheric balance, after brain damage (M1, language areas, parietal areas), there is a decreased excitability of the ispilesional motor cortex and a hyperexcitability of the contralesional motor cortex. After an ischemic stroke, we can observe an increased IHI from the contralesional M1, exerting an action on the ispilesional M1, when preparing for a voluntary movement, which would be inversely correlated with a good