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Editorial

Human Cerebral Cortex Metaplasticity and Stroke Recovery

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Recovery after stroke is often slow and incomplete; indeed, together with its high incidence, this makes stroke the main cause of permanent disability in industrialized nations.

Several attempts have been made to improve stroke recovery, probably paying not enough attention to all the biological phenomena underlying functional restoration, some of the fondant principles of brain plasticity and learning. It is time to go back to biology and reconsider recovery at a cellular level.

Learning is mostly based on the induction of Long Term Potentiating (LTP), the activity-dependent strengthening of synaptic transmission, thus interventions that facilitate LTP and increase the ability to learn should consequently improve recovery. The induction of LTP-like plasticity is also the mechanism of action of non-invasive neuromodulation, which is mainly applied to stroke recovery within the system neuroscience framework of the interhemispheric competition model [1]. Because of the lesion, the inhibition of the Affected Hemisphere (aH) over the Unaffected Hemisphere (uH) decreases, and the resulting increased activity of the uH, in turn, over-inhibits the primarily affected side. Along this line, neuromodulation has been used, so far, to facilitate the aH and inhibit the uH. Although many clinical trials gave optimistic results, a number of good clinical studies missed the expected outcomes, suggesting that not fully-understood agents may act in this domain and the need to test novel alternative strategies.

Indeed, all the attempts to improve stroke recovery made so far by targeting the mere increase of plasticity, either by pharmacological interventions or brain stimulation, were not able to achieve consistent results beyond the recovery achievable by the physical rehabilitation alone (i.e. constrained induced movement therapy [2]). This raises the intriguing possibility that stroke recovery is not simply a matter of how much the brain is plastic, but it is rather dependent on how this ongoing plasticity is dynamically modulated and harnessed toward functional improvements.

Moving back from system to cellular neuroscience, synaptic plasticity is about the strengthening or weakening of the post-synaptic response in reaction of changes of incoming information. However, synapses own also the ability to dynamically tune their sensitivity to the incoming signals in order to re-set the threshold of activity required to undergo LTP or LTD; it can be considered as the plasticity of plasticity or, in one word, the metaplasticity [3]. Thanks to this mechanism, synaptic plasticity is very sensitive to novel stimuli, while robust against repetitive worthless inputs. It has been firstly theorized in the visual cortex, but it has been widely demonstrated quite everywhere, for instance in hippocampus and sensorimotor cortices of animals and humans.

Metaplasticity takes place either homosynaptically (confined to the primed synapses) or heterosynaptically, through postsynaptic changes of excitability and up-regulation of protein synthesis. The former, acting on specific connections between cells, selectively highlights their encoded contents [4]. The latter can favor a general permissive state of the whole cell that becomes more prone to learn also tasks different from the one responsible of the priming: this can be the base to transfer the effect of training toward non-trained tasks [5].

Thus, to induce metaplasticity it is required that a priming event, either artificial as in the case of non-invasive brain stimulation (i.e. tDCS or rTMS), or behavioral as a motor or cognitive task [6], precedes the conditioning stimulus. Whatever it is, every stimulus acting on neurons may, in theory, prime synapses by changing their "history", make metaplasticity and change the effect induced by further incoming information.

However, what is metaplasticity responsible for and what is its relationship to stroke recovery? Firstly, it has a close link with learning because it can extend the time window during which associated events can generate long term plasticity [7]. Even more important, metaplasticity has a safety regulatory function, in so far, by keeping the whole synaptic activity within physiological dynamic ranges, it allows the synapsis to be always able to react to input changes. On the other hand, this mechanism also avoids maladaptive excesses of LTP, which could lead to saturation or excitotoxicity, and of LTD, that can impair the learning process. In this it lays the homeostatic function of metaplasticity, firstly modeled by Bienenstock, Cooper, and Munro [8]: the threshold for inducing plasticity is dependent on the previous history of synaptic activity: the lower it was, the easier it is the induction of LTP and vice versa. This makes the induction of both LTP and LTD always possible, whatever it is the trend of activity. Looking at the brain in excitability domain, interventions traditionally meant to increase/decrease excitability become able to produce opposite effects [9].

The failing of these safety constrains, due to an ineffective or to an aberrant metaplasticity, has been implicated is several pathologies

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and among them the writer cramp can be considered a paradigmatic model of unregulated plasticity.

Stroke interferes with metaplasticity from a double perspective: first, the acute dramatic event is able to prime the brain per se, second the stroked brain is wholly dysfunctional and the mechanisms of plasticity are impaired, both in the aH and in the controlateral uH. Indeed, beyond the widely-accepted hypoexcitability of the aH and the hyperexcitability of the uH, stroke results in an abnormal predisposition of plasticity with a weaker propensity of the aH to undergo LTP-like plasticity and of the controlateral uH to undergo LTD-like plasticity [10]. In this light, exploiting metaplasticity may be then the key to enhance the efficacy of non-invasive neuromodulatory interventions aimed at prompting stroke recovery.

As it happens for traditional LTP/LTD inducing protocols, interventions can target either the aH or the uH. Hitherto, few studies have tested neuromodulatory protocols based on metaplasticity approach with the aim to suppress the uH hyperexcitability by using rTMS protocols capable of enhancing the excitability of this hemisphere [11-13] or physical therapy [14] both followed by inhibitory stimulation.These studies have been able to prove the safety of the techniques and the decrease of uH hyperexcitability, despite it has been reported only a weak mixed behavioral improvements.

However, in our opinion, by directly applying metaplasticity-targeting neuromodulatory protocols to the aH several advantages can be achieved. For instance, thinking about stroke recovery in terms of protection against excitoxicity, it is worth noticing that most of the mechanisms and molecules targeted for neuroprotection are also involved in metaplasticity [4]. Thus, compared with the commonly employed excitatory protocols, by modulating metaplasticity of the aH we would have the chances to spare further excitatory-induced loss of neural tissue with a reduced risk to induce epileptic seizure.

Accordingly, we recently conducted a double blinded semi-randomised sham-controlled trial to assess the safety and efficacy of a metaplasticity-based neuromodulatory approach on the aH by priming a standardized physiotherapy protocol with continuous Theta Burst Stimulation (cTBS), a robust inhibitory rTMS protocol, of the lesioned hemisphere. None of the patients reported side effects, while all of them improved on the ARAT scores, but only patients receiving real cTBS significantly improved on the Jebsen–Taylor Test, score that seems to be more sensitive to learning processes [15]. Although these enthusiastic results require to be confirmed by future studies on wider patients' sample size, the harnessing of metaplasticity for neuromodulatory attempts to improve stroke recovery is already a solid and intriguing possibility, which promises optimistic expectations. Several factors still deserve to be better elucidated, among them the more appropriate priming and the time-interval between priming and conditioning interventions.

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