● **PERSPECTIVE**

Combining motor learning and brain stimulation to enhance post-stroke neurorehabilitation

Worldwide, stroke is a leading cause of life-long disability resulting in dramatic restrictions in patient's independence and in a growing economic burden for the community. The majority of stroke survivors suffers from chronic sequels among which hemiparesis is one of the most debilitating. Despite quick progresses over the last 20 years, the impact of neurorehabilitation on post-stroke recovery remains unsatisfactory. Developing new ways to enhance neurorehabilitation could thus benefit to millions of patients. A better insight into the physiology of the normal motor system and the mechanisms driving post-stroke recovery and neural plasticity should permit to develop a new science of neurorehabilitation.

Motor recovery and motor learning after stroke: The recovery of motor function after stroke builds upon several partly overlapping processes: oedema reduction, inflammatory changes, dynamical modulation of the excitability in the perilesional zone with connectivity modulations throughout the brain, use-dependent selection of the residual motor pathways, plastic reorganisation of the (pre-)motor areas with functional and structural remodelling, development of compensatory strategies,…(Nudo, 2013). Over the last 20 years, brain imaging studies – especially those using functional magnetic resonance imaging (fMRI) – started to unveil post-stroke neuroplasticity *i.e.*, how the brain reorganizes itself after a stroke. However, the main conclusion is desperately self-evident: the more the reorganised patterns tend towards those observed in healthy individuals, the better the recovery. Nevertheless, the "abnormal" activations found in the perilesional zone or in remote areas of the damaged and/or undamaged hemispheres may reflect the adaptive recruitment of spared neural resources, *i.e.*, compensatory neuroplasticity. The precise involvement of the undamaged hemisphere in the recovery process is still debated (Grefkes and Ward 2014).

Beyond force training, spasticity reduction or repeating movements, the recovery of some level of skilled aptitudes and the development of alternative motor strategies are likely acquired through experience-dependent training and retained through residual motor learning aptitudes. In other words, without the involvement of (some forms of) motor learning, neurorehabilitation programs could not lead to long-term gains in stroke patients (Zeiler et al., 2013). Therefore, any intervention improving motor learning potential of stroke patients should enhance the impact of neurorehabilitation.

Dual-transcranial direct current stimulation (tDCS) enhances motor learning and retention: Non-invasive brain stimulations (NIBS) transiently modulate cortical excitability and behavioural performance in healthy individuals and stroke patients (Stagg and Nitsche, 2011; Orban and Shadmehr, 2014). Transcranial direct current stimulation (tDCS, a promising form of NIBS) can enhance motor skill learning in healthy individuals and the impact of neurorehabilitation after stroke (Reis et al., 2009; Madhavan and Shah, 2012). The mechanisms of tDCS are still not fully elucidated but entail a transient modulation of the resting membrane potential of cortical neurones leading to hyperpolarisation (cathode)/depolarisation (anode), reducing/increasing in turns the responsiveness of the target neurones to the on-going afferent brain activity. This allows longer-lasting changes in strength/coupling of GABAergic (γ-aminobutyric acid) and glutamatergic synapses, which could be the basis for the after-effects that last up to 1 hour (Stagg and Nitsche, 2011; Orban and Shadmehr, 2014).

After a stroke, the balance between interhemispheric interactions can be deregulated, leading to excessive inhibitory drive from the undamaged towards the damaged hemisphere, which can impede the recovery potential of the damaged hemisphere (Murase et al., 2004). To correct this deregulated interhemispheric interactions, three neuro-modulation strategies based on NIBS can be applied: (1) "up-regulating" the excitability of the damaged hemisphere, (2) "down-regulating" the excitability of the non-damaged hemisphere or (3) doing both simultaneously *e.g.*, with dual-tDCS (that is tDCS applied over both hemisphere with the "up-regulating" anode over the primary motor cortex of the damaged hemisphere ($M1_{damH}$) and the "down-regulating" cathode over the undamaged M1 ($M1_{undamH}$).

In a first sham-controlled, randomized double-blind study, 18 chronic hemiparetic stroke patients received dual-tDCS/sham tDCS in a cross-over fashion while they learned with their paretic upper limb a complex motor skill involving a speed/accuracy trade-off (SAT) (Lefebvre et al., 2012). This skill consisted in moving a cursor controlled by a mouse computer through a complex circuit, completing as many laps as possible in 30 seconds (speed) while keeping the cursor within the track (accuracy). Online motor skill learning during dual-tDCS was dramatically enhanced; 1 week later the retention of the SAT skill was largely superior after dual-tDCS (44 ± 24%, mean ± SD) compared to sham (4 ± 25%). Moreover, dual-tDCS combined with motor skill learning resulted in a transfer of performance enhancement. First, after the retention test of the skill learned 1 week before, the stroke patients performed a new circuit of similar difficultly. Motor performance on this new circuit was superior 1 week after dual-tDCS compared to sham, suggesting a generalization of motor enhancement towards a similar task. Second, dual-tDCS improved the dexterity of the paretic hand, quantified with the Purdue Pegboard Test (PPT), suggesting a transfer of motor enhancement towards a different, untrained task.

Combined dual-tDCS and motor skill learning "normalise" fMRI activation in chronic stroke: Nineteen new chronic hemiparetic stroke patients were enrolled in a study with the same design except that (i) the learning sessions were performed in the supine position and (ii) the retention sessions were performed during fMRI acquisition (Lefebvre et al., 2015) (**Figure 1**). The behavioural results were similar to those of the first study: the retention of the SAT skill was superior 1 week after dual-tDCS (52 ± 29%) compared to sham (12 ± 20%).

"Classically", a bilateral and widespread fMRI activation is seen in many chronic stroke patients; it is supposed to reflect a plastic recruitment of additional areas in both hemispheres. Bilateral activation is also observed in healthy volunteers performing difficult tasks, likely reflecting the recruitment of additional neural resources needed to face increased difficulty.

In our study, poorer retention of the skill 1 week after sham was associated with diffuse fMRI activation in both hemispheres. In contrast, the fMRI pattern associated with better motor skill retention 1 week after dual-tDCS tended towards normalisation, *i.e.*, a focusing of activation within the motor-premotor areas of the damaged hemisphere, especially in the dorsal premotor cortex (PMd_{damH}). We hypothesize that the retention might be enhanced becausecombined motor skill learning and dual-tDCS reinforced/selected an efficient motor network – mostly in the damaged hemisphere – which resulted in a better use of neural resources (as suggested by the normalisation trend) and thus in a superior retention. In other words, combined motor skill learning and dual-tDCS optimised the efficiency of the residual motor network.

Furthermore, both a behavioural and a neurophysiological (fMRI) transfers were observed. First, dual-tDCS combined with motor skill learning resulted in a lasting improvement on an untrained dexterity task (the PPT) with the paretic hand. Previously, behavioural transfer of motor aptitudes after combining NIBS with neurorehabilitation in stroke patients has been associated with increased fMRI activation in the damaged hemisphere (Lindenberg et al., 2010). From a neurorehabilitation point of view, such a transfer of performance improvement could be very useful. That is to say, one might imagine applying the combined intervention once a week and building upon the lasting behavioural transfer to enhance other motor functions/skills through "classical" neurorehabilitation sessions.

Second, a neurophysiological form of transfer was observed. During the fMRI retention sessions, the stroke patients also performed a simple motor task without speed/ accuracy constraints: moving the cursor back and forth between two large targets at a comfortable speed. There was no difference in behavioural performance for this easy task between the retention sessions after dual-tDCS and sham. Strikingly, the fMRI activation patterns were very similar to those observed during the performance of the learned skill: more widespread and intense activation 1 week after sham versus more focused activation 1 week after dual-tDCS. We propose two hypotheses to interpret this observation. The first (optimistic) hypothesis is that the combined intervention was so efficient that the fMRI activation pattern remained more focused up to 1 week later, even for simple movements of the paretic upper limb. This would suggest a prolonged shaping of neural efficiency in the motor network, if one admits that a more focused fMRI activation pattern reflects a more efficient recruitment of the residual neural resources. The second (more conservative) hypothesis is that performing the motor skill learned under dual-tDCS primed the motor system and (re-)activated the best possible residual network selected 1 week before, resulting in a more focused activation pattern even for untrained movements. This would suggest that re-performing the skill acquired previously with dual-tDCS facilitation could enhance the current efficiency of the motor network. Because the easy task was interleaved with the learned skill performance during the fMRI sessions, it is not possible to determine which hypothesis is true. Both hypotheses entail promising but different implications for neurorehabilitation (see "Perspectives").

Finally, during continued learning (*i.e.*, considering the fMRI retention session as a second – shorter - learning session), fMRI activation was widespread 1 week after sham and the correlation with performance was distributed in the bilateral M1 and posterior parietal areas, and in the primary somatosensory cortex of the damaged hemisphere. By contrast, the fMRI activation during continued learning 1 week after dual-tDCS was restricted to the damaged hemisphere ($M1_{damH}$, the supplementary motor area and PMd_{damH}) and the contralesional cerebellum; and a correlation with performance was found exclusively in PMd_{damH}. This suggests that continued motor skill learning 1 week after dual-tDCS was more efficient since it required a more restricted motor network compared to the disseminated activation found after sham.

Perspectives: Overall, these observations combined with those from previous studies (Lindenberg et al., 2010; Madhavan and Shah, 2012; Nudo 2013; Orban and Shadmehr, 2014) are encouraging for the implementation of tDCS as a tool to enhance neurorehabilitation-driven gains: (i) tDCS (transiently) enhances the function of the paretic upper limb, (ii) tDCS enhances and maintains at least for a few days/weeks the functional gains obtained through "classical" neurorehabilitation and modifies plastically the fMRI activation, (iii) tDCS enhances the learning and retention of a complex motor skill with the paretic upper limb, (iv) these enhancements are not restricted to the learned motor skill but generalize to untrained motor activities, (v) 1 week after combined dual-tDCS and motor skill learning the fMRI activation tends towards a "more normal" pattern suggesting a more efficient recruitment of the residual neural resources. Depending on the fact that the optimal recruitment of the motor network endures at least 1 week ("prolonged shaping" hypothesis) or is re-activated when re-performing the motor skill learned with dual-tDCS facilitation ("priming" hypothesis), the implementation in neurorehabilitation would be different. If the "prolonged shaping" hypothesis is true, the rehabilitation team could apply the combined intervention on Monday and the stroke patients would benefit from a lasting enhancement during the subsequent neurorehabilitation sessions during the rest of the week. In contrast, if the "priming" hypothesis is true, the stroke patients should re-perform the skill learned under dual-tDCS facilitation at the beginning of each neurorehabilitation session, which would re-activate the "near-normal" motor network selected by the combined intervention.

Applying tDCS to stroke patients while they perform motor skill learning or a challenging task that engages their motor, attentional and cognitive resources is likely to be one of the key issues to boost the beneficial effects driven by neurorehabilitation. As the knowledge about motor control and motor learning is refined in animal models, healthy individuals and stroke patients, better hypotheses could be formulated and tested to develop a new science of neurorehabilitation. Several milestones have to be achieved before applying tDCS and motor learning principles in routine neurorehabilitation: confirming the current results, refining the knowledge about residual motor learning aptitudes after stroke, demonstrating that repeated sessions lead to cumulative functional gains, testing larger samplesin international multi-centre randomized clinical trials, assessing and understanding the large inter-subject variability (López-Alonso et al., 2014). Finally, most tDCS studies focused on chronic stroke, and studies on (sub) acute stroke provided mixed results. Therefore, the best "target" population has still to be defined.

Many methods are currently investigated to boost neurorehabilitation: NIBS, motor learning theories, behavioural interventions, robot-assisted rehabilitation, pharmacological agents, and neural engineering. It is likely that the optimal combination of these different approaches shall modify the science of neurorehabilitation in the future.
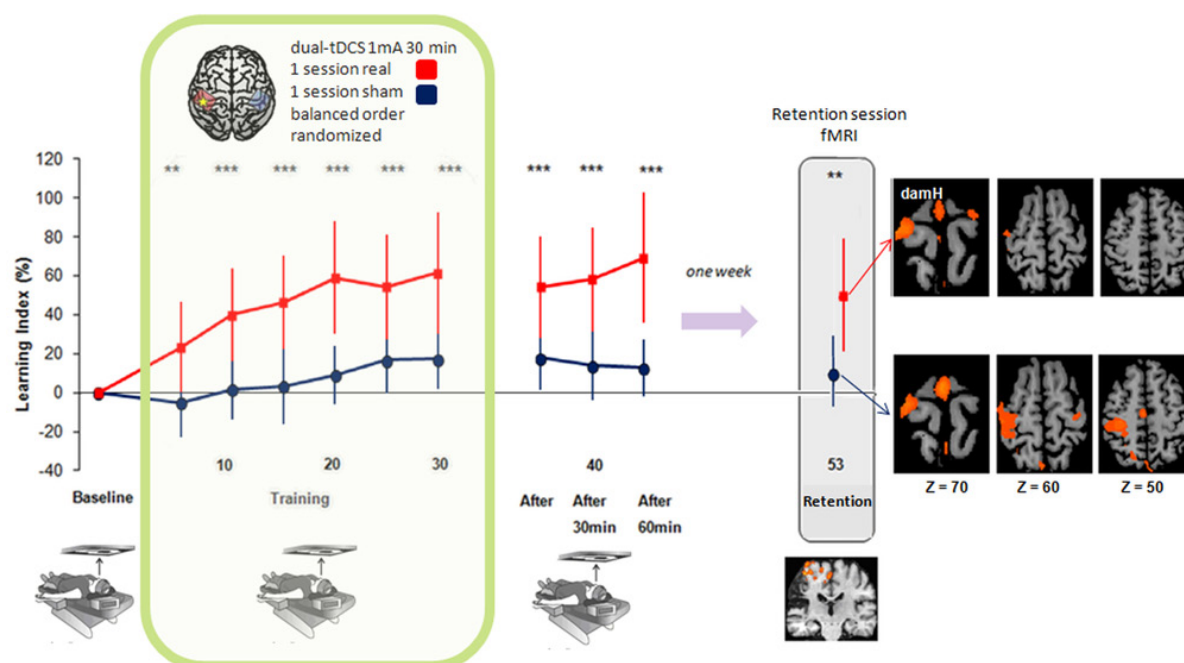
Figure 1 Dual transcranial direct current stimulation (tDCS) enhances motor skill retention and functional magnetic resonance imaging (fMRI) activation in stroke patients

In two different series, the 19 chronic stroke patients learned with the paretic hand two different circuits of equal length and difficulty, once under sham and once under real dual-tDCS (1mA, 30 minutes, anode over $M1_{damH}$ and cathode over $M1_{undamH}$). The study was performed with a randomized, double-blind, sham-controlled, cross-over design. They learned the complex motor skill (the circuit) in the supine position, to match their position in the MRI scanner 1 week later (retention session). Motor skill learning was faster and more efficient under dual-tDCS compared to sham, this effect was maintained up to 1 hour after the end of learning/stimulation. The retention of the motor skill was much better 1 week after dual-tDCS compared to sham (+52% *versus* +12%). fMRI activation was bilateral and widespread 1 week after sham. In contrast, 1 week after dual-tDCS, the fMRI activation predominated in the motor-premotor areas of the damaged hemisphere (damH) where it appeared more focused, suggesting increased neural efficiency.

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