Novel Non-invasive Brain Stimulation Techniques to Modify Brain Networks After Stroke

Ulf Ziemann

Abstract Improving motor function after stroke is an in an important area of research in neurorehabilitation. Clinical trials using non-invasive brain stimulation (NIBS) to improve rehabilitation outcome after stroke showed modest effect sizes or even lack of efficacy [1–3]. One important reason for this limited therapeutic success may be too simplistic "one hat fits it all" strategies, e.g. aiming at increasing excitability in the ipsilesional primary motor cortex [4] that disregard high interindividual variability in responses to NIBS protocols, even in healthy subjects [5]. Several strategies that have been recently developed to improve therapeutic effect size of NIBS during stroke neurorehabilitation will be detailed in this presentation.

1 Novel NIBS Techniques to Modify Brain Networks After Stroke

(1) *Modelling of the NIBS induced electrical field in the individual brain.* This is important as a stroke lesion can dramatically distort the electrical properties of the stimulated brain, e.g. by steep variations of conductivity at the border of a lesion filled with cerebrospinal fluid and adjacent normal brain tissue [6].
(2) *Navigated NIBS*. Several studies demonstrated that navigated NIBS as compared to conventional non-navigated NIBS has significant advantages with respect to stability of coil placement and magnitude of induced effects such as changes in excitability and motor performance [7].
(3) *Multiple-site stimulation* compared to conventional mono-site stimulation may increase significantly effect size. A study in chronic stroke patients demonstrated that combination of anodal transcranial direct current stimulation of the ipsilesional motor cortex with high-frequency peripheral nerve stimulation of

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the affected hand facilitated motor learning of the paretic hand compared to any of the two interventions separately [8].

(4) *Analysis of effective connectivity in the residual motor network*. In stroke patients, the ipsilesional motor cortex is inhibited to an exaggerated extent by the motor cortex in the contralesional hemisphere [9]. Targeting the contralesional motor cortex with an excitability decreasing low-frequency 1 Hz repetitive TMS protocol resulted in normalization of this exaggerated interhemispheric inhibition and this was associated with an improvement of paretic hand motor function [10].

(5) *Combination of NIBS or motor practice with neuropharmacology*. Agonists of neuromodulating neurotransmission, such as dopamine receptor agonists or levodopa enhance motor learning in healthy subjects and chronic stroke patients [11] and may be utilized to enhance rehabilitation success in stroke.

(6) *Combination of NIBS with motor practice*. NIBS may enhance motor learning but the temporal order of NIBS and motor practice is important [12]. In chronic stroke patients, NIBS (1 Hz repetitive TMS of the contralesional motor cortex) was most effective in improving paretic hand motor function, if applied prior rather than after motor practice [13].

(7) *Brain state-dependent stimulation*. The instantaneous state of activity and excitability of the stimulated cortex is highly relevant for the effects of NIBS. For example, repeated TMS during periods of event related desynchronization of beta-power in sensorimotor cortex caused by motor imagery in healthy subjects caused an LTP-like increase in corticospinal excitability while the same stimulation uncoupled of neuronal activity in motor cortex resulted in excitability depression [14].

2 Conclusions

NIBS can change activity and excitability of the stimulated brain networks and these effects may have potential in supporting stroke rehabilitation, but the effect size with current stimulation protocols is rather limited. Several strategies such as modelling of induced electrical fields in the stroke brain, navigated TMS, dual-(multi)-site stimulation, network stimulation, pharmacology, pairing with motor practice, and brain-state dependent stimulation may result in larger effect sizes. However, efficacy of these strategies remains to be proven in large-scale controlled clinical trials.

References

1. A.J. Butler, M. Shuster, E. O'Hara, K. Hurley, D. Middlebrooks, K. Guilkey, A meta-analysis of the efficacy of anodal transcranial direct current stimulation for upper limb motor recovery in stroke survivors. J. Hand Ther.: Official J. Am. Soc. Hand Therapists **26**, 162–170 (2013). quiz 71
2. W.Y. Hsu, C.H. Cheng, K.K. Liao, I.H. Lee, Y.Y. Lin, Effects of repetitive transcranial magnetic stimulation on motor functions in patients with stroke: a meta-analysis. Stroke; J. Cereb. Circ. **43**, 1849–1857 (2012)
3. J.P. Lefaucheur, N. Andre-Obadia, A. Antal et al., Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin. Neurophysiol. **125**, 2150–2206 (2014)
4. N.S. Ward, L.G. Cohen, Mechanisms underlying recovery of motor function after stroke. Arch. Neurol. **61**, 1844–1848 (2004)
5. M. Hamada, N. Murase, A. Hasan, M. Balaratnam, J.C. Rothwell, the role of interneuron networks in driving human motor cortical plasticity. Cereb. Cortex **23**, 1593–1605 (2013)
6. T. Wagner, F. Fregni, U. Eden et al., Transcranial magnetic stimulation and stroke: a computer-based human model study. NeuroImage. **30**, 857–870 (2006)
7. S. Bashir, D. Edwards, A. Pascual-Leone, Neuronavigation increases the physiologic and behavioral effects of low-frequency rTMS of primary motor cortex in healthy subjects. Brain Topogr. **24**, 54–64 (2011)
8. P. Celnik, N.J. Paik, Y. Vandermeeren, M. Dimyan, L.G. Cohen, Effects of combined peripheral nerve stimulation and brain polarization on performance of a motor sequence task after chronic stroke. Stroke J. Cereb. Circ. **40**, 1764–1771 (2009)
9. C. Grefkes, D.A. Nowak, S.B. Eickhoff et al., Cortical connectivity after subcortical stroke assessed with functional magnetic resonance imaging. Ann. Neurology. **63**, 236–246 (2008)
10. C. Grefkes, D.A. Nowak, L.E. Wang, M. Dafotakis, S.B. Eickhoff, G.R. Fink, Modulating cortical connectivity in stroke patients by rTMS assessed with fMRI and dynamic causal modelling. NeuroImage **50**, 234–243 (2010)
11. A. Flöel, F. Hummel, C. Breitenstein, S. Knecht, L.G. Cohen, Dopaminergic effects on encoding of a motor memory in chronic stroke. Neurology **65**, 472–474 (2005)
12. P. Jung, U. Ziemann, Homeostatic and non-homeostatic modulation of learning in human motor cortex. J. Neurosci. **29**, 5597–5604 (2009)
13. A. Avenanti, M. Coccia, E. Ladavas, L. Provinciali, M.G. Ceravolo, Low-frequency rTMS promotes use-dependent motor plasticity in chronic stroke: a randomized trial. Neurology **78**, 256–264 (2012)
14. A. Gharabaghi, D. Kraus, M.T. Leao et al., Coupling brain-machine interfaces with cortical stimulation for brain-state dependent stimulation: enhancing motor cortex excitability for neurorehabilitation. Front. Hum. Neurosci. **8**, 122 (2014)

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