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P 2. Modeling the active neurodynamic behavior of rTMS in the prefrontal cortex of a realistic human head—N. De Geeter, G. Crevecoeur, L. Dupré (Ghent University, Department Electrical Energy, Systems and Automation, Ghent, Belgium)

Question: Transcranial magnetic stimulation (TMS) is an established tool for non-invasive brain stimulation. It acts via a time dependent magnetic field, generated by an external coil, inducing an electric field in the brain, which can interact with the neural system. Repetitive TMS (rTMS) to the left dorsolateral prefrontal cortex (DLPFC) is clinically used for the treatment of medication-resistant depression. Although this technique is widely used, the underlying neurophysiological mechanism remains unclear. Moreover, optimal parameters such as frequency of stimulation, intensity and duration are still unknown.

Methods: Therefore, we modulate the rTMS response in the prefrontal cortex of a realistic human brain. This head model is constructed from T1-weighted magnetic resonance images (MRI) and segmented into scalp, skull, cerebrospinal fluid, grey and white matter. The anisotropic material properties are obtained from the 4-Cole–Cole model (Cole and Cole, 1941). To

track the realistic oriented pathways of nerve fibers located in the stimulated target, namely the left DLPFC, we applied MR tractography (Leemans et al., 2009) based on diffusion tensor images (DTI). These fibers are considered as one myelinated nerve bundle (Fig. 1).

The 20 mm figure-of-eight TMS coil (MagStim, UK) is positioned above the left DLPFC, perpendicular to the skull. We modeled the neurophysiological response of a sinusoidal stimulation (pulse width 450 μ s) at different intensities on the Rapid² stimulator.

The induced electric field is calculated using the recently developed independent impedance method (De Geeter et al., 2012). Studies have shown that nerves are primarily activated by the gradient of the component of the electric field along the nerves, the so-called activating function (Roth and Basser, 1990). This affects the membrane potential of the nerve bundle and can cause a generation and propagation of action potentials (AP). To describe this neurodynamic behavior along the nerve bundle we use the active cable equation (Wesseling et al., 1999), discretized by the Crank–Nicholson method.

Results: When applying one biphasic stimulation pulse at an intensity just below activation threshold, no AP is generated (Fig. 2a). Repetitive stimulation at the same intensity generated a single spike (Fig. 2b). As the intensity of rTMS increases, a second AP is initiated (Fig. 2c). For an even higher intensity of the sustained stimulation a train of spikes at a fixed frequency is rendered. Remark how this spiking frequency first increases with increasing stimulation intensity, but then decreases again (Fig. 2d–f).

Conclusions: These results point out the advantage of repetitive stimulation in comparison to a single pulse stimulation. More important, they indicate the existence of an optimal stimulation intensity for a specific TMS set-up and target, whereby a train of spikes at a maximum spiking frequency is generated. This study highlights the importance of numerical modeling in TMS, either in the determination of the underlying neurophysiological mechanism or the effect of different stimulation parameters. In future research, we aim to simulate the propagation of TMS effects in depression through anatomical connections to deeper limbic regions and to optimize this non-invasive brain stimulation technique.

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P 3. Dose-dependence of changes in cortical protein expression induced by theta burst stimulation in the rat—L.J. Volz^{a,b,c}, A. Mix^c, A. Benali^c, K. Funke^c (^aMax-Planck Institute for Neurological Research, Neuromodulation & Neurorehabilitation, Köln, Germany, ^bUniversity Hospital, Neurology, Cologne, Germany, ^cRuhr-University Bochum, Neurophysiology, Bochum, Germany)

Introduction: Theta Burst stimulation (TBS) applied via transcranial magnetic stimulation (TMS) is an effective tool to modulate human neocortical excitability (Huang et al., 2005). Repeated application of the same TBS protocol or variation of the number of stimuli has been shown to alter the strength and direction of changes in cortical excitability compared to the standard TBS protocols (Gentner et al., 2008; Gamboa et al., 2010). TBS applied to rat cortex affected the expression of activity-dependent proteins related to the cortical inhibitory systems, suggesting altered cortical inhibition contributing to the TBS after-effects (Benali et al., 2011; Funke and Benali, 2011).

Objectives: Our aim was to investigate the impact of varying numbers of TBS-stimuli applied as multiple blocks of intermittent TBS (iTBS) or continuous TBS (cTBS) on cortical protein expression in the rat, to further our insights in physiological mechanisms underlying TBS-induced changes in cortical excitability.

Materials and methods: Nine groups of anesthetized rats (male Sprague Dawley, 400–600 g) received TMS. Eight groups received a different number of iTBS/cTBS-blocks summing up to either 600, 1200, 1800, or 2400 stimuli, applied with breaks of 15 min between blocks of 600 stimuli. Sham stimulation (coil more distant to the head) was applied to a control group. Rats were sacrificed for immunohistochemical analysis or western blotting focussing on frontal, motor, sensory and visual cortex.

Results: In general, quite similar effects for iTBS and cTBS were observed. The expression of the 65-kDa isoform of glutamic acid decarboxylase (GAD65) increased, while that of the 67-kDa isoform (GAD67) and that of the calcium-binding proteins Parvalbumin (PV) and Calbindin (CB) progressively decreased. Also the expression of the immediate early gene c-Fos decreased with an increasing number of blocks. A more detailed analysis, however, revealed that the sensitivity of distinct proteins to stimulation varied with the number of stimuli and type of stimulation.

Conclusion: Our findings show that both iTBS and cTBS affect the activity of inhibitory interneurons and indicate that repeated TBS elicits no simple accumulative dose-dependent effect for all activ-

ity-markers but distinct profiles with threshold characteristics and a waxing-and-waning effect especially for two markers of inhibitory activity, CB and GAD67. Thus, our data do not suggest fundamentally different modulation of the cortical inhibitory systems by iTBS and cTBS. Subtle differences in stimulation after-effects on different neuronal subsystems might contribute to the opposite impact on cortical excitability following iTBS and cTBS and the switching sign of effect with repeated stimulation.

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P 4. Cerebral blood flow modulation by transcutaneous cranial electrical stimulation with Limoge's current—D. Gense de Beaufort^a, M. Sesay^a, L. Stinus^b, R. Thiebaut^{c,d}, M. Auriacombe^d, V. Doussset^{a,e} (^aHopital Pellegrin, Neuroradiology, Bordeaux, France, ^bCNRS UMR-5541, Bordeaux, France, ^cINSERM, U897, Bordeaux, France, ^dEA4139,INSERM IFR99, University Bordeaux 2, Bordeaux, France, ^eUniversity Bordeaux 2, Bordeaux, France)

Objectives: TCES delivers a high-frequency (166 kHz) pulsed biphasic balanced current with a pulse repetition frequency of 100 Hz with 40% duty cycle through a negative electrode and two positive electrodes over the skull.

TCES has a proven ability to potentiate anesthesia and analgesia, although the physiological mechanisms of this effect remain unclear. We hypothesized that the mechanism is a modulation of CBF in the central endogenous opioid system. This study aimed at determining the effects of TCES on CBF to elucidate its physiological mechanism.

Methods: Thirty-six healthy volunteers were randomly assigned to active or placebo TCES, and all assessments were double blind. TCES was performed using the Anesthelec™ device. In the stimulated group, an active cable was used, and in the control group (sham), the cable was inactive. CBF was measured by XeCT™ before and after two hours of TCES.

Results: Globally, CBF was unchanged by TCES. However, locally, TCES induced a significant CBF decrease in the brainstem and thalamus, which are structures involved in pain and anxiety (TCES and control CBF decrease were 18.5 and 11.9 mL/100 g brain tissue/min, respectively).

Conclusion: TCES can modulate local CBF but it has no effect on overall CBF.

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P 5. Motor cortical excitability in psychiatric disorders probed by transcranial magnetic stimulation: A systematic review—T. Bunsen^a, W. Strube^a, T. Wobrock^b, F. Padberg^a, P. Falkai^a, A. Hasan^a (^aLudwig Maximilian Universität Munich, Department of Psychiatry and Psychotherapy, Munich, Germany, ^bDarmstadt-Dieburg Clinics, Centre of Mental Health, Darmstadt, Germany)