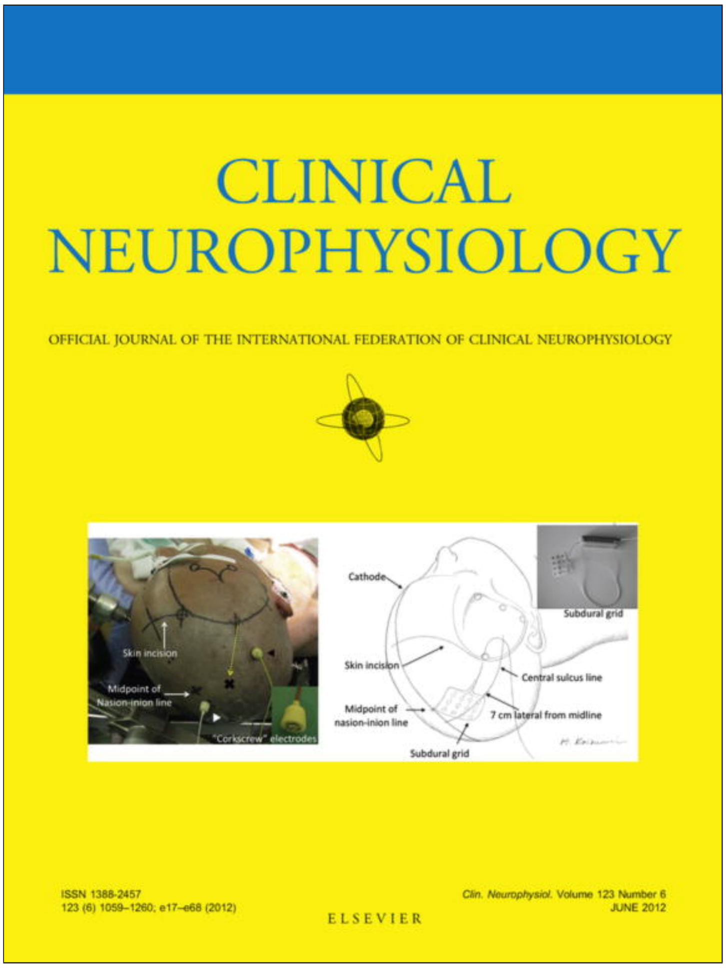
CLINICAL NEUROPHYSIOLOGY
OFFICIAL JOURNAL OF THE INTERNATIONAL FEDERATION OF CLINICAL NEUROPHYSIOLOGY
Skin incision
Midpoint of Nasion-inion line
"Corkscrew" electrodes
Cathode
Subdural grid
Skin incision
Central sulcus line
Midpoint of nasion-inion line
7 cm lateral from midline
Subdural grid
ISSN 1388-2457
123 (6) 1059–1260; e17–e68 (2012)
ELSEVIER
Clin. Neurophysiol. Volume 123 Number 6
JUNE 2012

Clinical Neurophysiology 123 (2012) 1063–1064

Contents lists available at SciVerse ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Editorial

Choosing to improve or to impair

See Article, pages 1226–1233

What for a long time appeared as a dream, has now become routine: the targeted and specific modulation of brain activity from outside, effortless without training or attention. Transcranial magnetic stimulation (TMS) alters human behavior and perception through magnetic pulses that induce currents in the brain. When single magnetic pulses are applied from outside the skull over a selected brain region, neurons within this area become transiently suppressed, resulting in what has been called a "virtual lesion" (Pascual-Leone et al., 1999), and this allows studying in an intact brain the contribution of a particular brain region to a particular behavior. In contrast, when magnetic pulses are repetitively applied, modulations of brain activity result that outlast the period of stimulation (Siebner and Rothwell, 2003), and resemble learning processes (Tegenthoff et al., 2005). In fact, many lines of evidence suggest that repetitive transcranial magnetic stimulation (rTMS) causes forms of synaptic plasticity, and many groups now use rTMS as a tool to study learning processes in human individuals.

Cellular studies have focused on long-term potentiation (LTP) and long-term depression (LTD) of synapses in the hippocampus and cortical areas to understand the requirements for persistent changes in the connection strength between neurons (Bliss and Lomo 1973; Malenka and Bear, 2004). LTP at groups of synapses can be induced reliably through intermittent high-frequency tetanic stimulation, while application of lower frequencies induces LTD (Dudek and Bear, 1992). Furthermore, animal studies showed that patterned stimulation at the theta frequency (EEG band between 4 and 8 Hz) might be optimal for induction of long-term potentiation (Larson et al., 1986). It was speculated that, when stimulation patterns resemble spike discharge patterns of hippocampal neurons in animals during exploratory situations, the conditions are particularly effective in inducing LTP. Because of the ubiquitous efficacy of these stimulation protocols in inducing learning, there is agreement that they represent fundamental mechanisms enabling persistent changes in neural networks.

In humans, however, it is difficult to study the outcome of synaptic modifications on behavioral changes induced by stimuli that drive LTP- or LTD-like processes. Therefore, adapting such protocols to TMS stimulation offers ways to study their impact on human perception and behavior. So-called TBS ("theta burst stimulation") protocols, which consist of 3 pulses at 50 Hz, repeated every 200 ms, have been adapted to human TMS to modulate motor cortex excitability, and the initial experiments contrasted different forms of TBS: a so-called intermittent form (iTBS) using a 2 s train of TBS that is repeated every 10 s, and a continuous theta burst stimulation paradigm (cTBS) using a 40 s train of uninterrupted, continuous TBS. iTBS enhanced, but cTBS reduced motor cortex excitability. Remarkably, the alterations in motor cortex physiology can be generated within a very short period such as a few minutes only, but last 30–60 min (Huang et al., 2005).

Much of this type of research has been undertaken in the motor domain (Gerloff et al., 1997; Muellbacher et al., 2000; Huang et al., 2005, for review; Di Lazzaro et al., 2010), and comparatively little is known about effects of various TMS protocols in the tactile system (Knecht et al., 2003; Satow et al., 2003; Tegenthoff et al., 2005; Ragert et al., 2004, 2008; Katayama and Rothwell, 2007; Katayama et al., 2010). In this issue of Clinical Neurophysiology, Rai and colleagues report that application of continuous theta burst rTMS over the hand representation of primary somatosensory cortex (SI) impairs tactile perception of the hand (Rai et al., 2012).

Some years ago, Ragert and colleagues had applied iTBS over the hand representation over SI using the same timing of iTBS stimulation as described for motor cortex, and this resulted in an improvement in spatial tactile discrimination abilities and in a parallel reduction of paired pulse suppression indicative of increased SI excitability (Ragert et al., 2008). In contrast, in this issue paper Rai and colleagues for the first time use the suppressive, continuous form of TBS in SI to explore effects on temporal and spatial aspects of tactile performance by measuring temporal discrimination thresholds (TDT) and spatial amplitude discrimination thresholds (SDT). They report that following cTBS both temporal and spatial thresholds were increased indicative of impaired tactile performance. Remarkably but in line with earlier reports about the brief period required to induce TBS effects, 40 s of cTBS using a 600 pulse protocol were sufficient to impair tactile perception for up to 18 min.

On the one hand TMS offers a unique window for basic human neuroscience research to obtain insight into the relation between brain physiology and behavior, on the other hand, TMS can be used in clinical applications as new forms of treatment (Miniussi and Rossini, 2011; Najib et al., 2011). The data of Rai and colleagues are of substantial relevance for both areas: through the simultaneous assessment of temporal and spatial discrimination thresholds they can demonstrate that temporal and spatial aspects of tactile behavior are not independent: when the cortical network mediating tactile perception is modulated in its activity, there are parallel alterations in spatial and temporal acuity thresholds. This is truly a non-trivial observation, which almost certainly will foster our understanding of the processes that mediate the diverse percepts of the sense of touch.

doi:10.1016/j.clinph.2011.10.011

Clinically, straightforward prerequisites for possible applications for clinical populations are protocols that have the potential to improve function. Therefore, approaches such as highfrequency TMS or repetitive sensory stimulation are widely used as intervention. However, there are conditions of hypersensitivity or hyperactivity, where individuals would benefit from protocols that diminish performance. As mentioned by Rai and colleagues, cerebral palsy is associated with hyper-responsiveness to tactile stimuli, and this is also true for autism, while patients with prefrontal damage have difficulty inhibiting task-irrelevant information (Rai et al., 2012). Also, forms of chronic pain such as typically seen in patients with complex regional pain syndrome might benefit from procedures that rather have a suppressive than enhancing effect. It should be noted, however, that further studies are needed to clarify whether such subgroups show a similar pattern of response to TMS protocols as described for healthy participants.

Research over the last few years has demonstrated many different ways to interact with brain activity through sensory and magnetic stimulation protocols, which either exert facilitatory or suppressive action, and which therefore allow a targeted improvement or impairment of human behavior. This poses a novel, yet difficult problem, namely to choose the most appropriate protocol for intervention. In many cases such as in dystonia patients it is not a priori clear whether to further enhance or to suppress cortical excitability in order to mediate beneficial behavioral effects, and this holds true for many other examples.

Data from the motor and the sensory domains provide converging evidence that rTMS modulates perception, behaviour and cognition. However, to be efficient, stimulation must conform to requirements described for protocols specifically altering synaptic transmission and synaptic efficacy. The persistence of changes, the ease of application and the wide range of effects make such approaches ideal tools for targeted brain intervention. Given that the use of TMS is a rather recent development, we may be only at the beginning of an era, in which targeted brain manipulation will offer completely new scenarios of learning and intervention, with implications that cannot yet be foreseen.

Acknowledgement

Related research and the drafting of this article was funded by grants from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) SFB grant 874, and the German Federal Ministry of Education and Research (BMBF) Bernstein Focus Neural Mechanisms of Learning.

References

Bliss TVP, Lomo T. Long-lasting potentiation of synaptic transmission in the dentate area of the anesthetized rabbit following stimulation of the perforant path. J Physiol 1973;232:331–56.

Di Lazzaro V, Profice P, Pilato F, Dileone M, Oliviero A, Ziemann U. The effects of motor cortex rTMS on corticospinal descending activity. Clin Neurophysiol 2010;121:464–73.

Dudek SM, Bear MF. Homosynaptic long-term depression in area CA1 of hippocampus and effects of *N*-methyl-D-aspartate receptor blockade. Proc Natl Acad Sci USA 1992;89:4363–7.

Gerloff C, Corwell B, Chen R, Hallett M, Cohen LG. Stimulation over the human supplementary motor area interferes with the organization of future elements in complex motor sequences. Brain 1997;120:1587–602.

Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005;45:201–6.

Katayama T, Rothwell JC. Modulation of somatosensory evoked potentials using transcranial magnetic intermittent theta burst stimulation. Clin Neurophysiol 2007;118:2506–11.

Katayama T, Suppa A, Rothwell JC. Somatosensory evoked potentials and high frequency oscillations are differently modulated by theta burst stimulation over primary somatosensory cortex in humans. Clin Neurophysiol 2010;121:2097–103.

Knecht S, Ellger T, Breitenstein C, Bernd Ringelstein E, Henningsen H. Changing cortical excitability with low-frequency transcranial magnetic stimulation can induce sustained disruption of tactile perception. Biol Psychiatry 2003;53:175–9.

Larson J, Wong D, Lynch G. Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation. Brain Res Bull 1986;368:347–50.

Malenka RC, Bear MF. LTP and LTD: an embarrassment of riches. Neuron 2004;30:5–21.

Miniussi C, Rossini PM. Transcranial magnetic stimulation in cognitive rehabilitation. Neuropsychol Rehabil 2011;30:1–23.

Muellbacher W, Ziemann U, Boroojerdi B, Hallett M. Effects of low-frequency transcranial magnetic stimulation on motor excitability and basic motor behavior. Clin Neurophysiol 2000;111:1002–7.

Najib U, Bashir S, Edwards D, Rotenberg A, Pascual-Leone A. Transcranial brain stimulation: clinical applications and future directions. Neurosurg Clin N Am 2011;22:233–51.

Pascual-Leone A, Bartres-Faz D, Keenan JP. Transcranial magnetic stimulation: studying the brain–behaviour relationship by induction of 'virtual lesions'. Philos Trans R Soc Lond B Biol Sci 1999;354:1229–38.

Ragert P, Becker M, Tegenthoff M, Pleger B, Dinse HR. Sustained increase of somatosensory cortex (SI) excitability by 5Hz repetitive transcranial magnetic stimulation (rTMS) studied by paired median nerve stimulation. Neurosci Lett 2004;356:91–4.

Ragert P, Franzkowiak S, Schwenkreis P, Tegenthoff M, Dinse HR. Improvement of tactile perception and enhancement of cortical excitability through intermitted theta burst rTMS over primary somatosensory cortex in humans. Exp Brain Res 2008;184:1–11.

Rai N, Premji A, Tommerdahl M, Nelson AJ. Continuous theta-burst rTMS over primary somatosensory cortex modulates tactile perception on the hand. Clin Neurophysiol 2012;123:1226–33.

Satow T, Mima T, Yamamoto J, Oga T, Begum T, Aso T, et al. Short-lasting impairment of tactile perception by 0.9 Hz-rTMS of the sensorimotor cortex. Neurology 2003;60:1045–7.

Siebner HR, Rothwell J. Transcranial magnetic stimulation: new insights into representational cortical plasticity. Exp Brain Res 2003;148:1–16.

Tegenthoff M, Ragert P, Pleger B, Schwenkreis P, Förster AF, Nicolas V, et al. Persistent improvement of tactile discrimination performance, enlargement of cortical somatosensory maps after 5 Hz rTMS. PloS Biol 2005;3:e362.

Hubert R. Dinse
Neural Plasticity Lab, Institut fur Neuroinformatik, Ruhr-University Bochum, Bochum, Germany
Tel.: +49 234 3225565.
E-mail addresses: hubert.dinse@rub.de, hubert.dinse@ruhr-uni-bochum.de
URL: http://www.neuralplasticitylab.de

Available online 17 November 2011