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Invited review

Non-invasive brain stimulation in neurological diseases

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ABSTRACT

Non-invasive brain stimulation has shown its potential to modulate brain plasticity in humans. Endeavour has been made to utilize brain stimulation in neurological diseases to enhance adaptive processes and prevent potential maladaptive ones. In stroke for instance both sensorimotor and higher cognitive impairment, such as aphasia and neglect, has been addressed to facilitate functional recovery. In Parkinson's disease, brain stimulation has been evaluated to improve motor and non-motor symptoms. In the present review we provide an update of the field of transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) as non-invasive brain stimulation techniques to improve motor and higher cognitive functions in patients suffering from stroke and Parkinson's disease. Rather than attempting to be comprehensive in regard of the reviewed scientific field, this article may be considered as a present day's framework of the application of non-invasive brain stimulation on selected examples of common neurological diseases. At the end we will briefly discuss open controversies and future directions of the field which has to be addressed in upcoming studies.

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1. Introduction

Widely explored during the past few decades, transcranial magnetic stimulation (TMS) and transcranial electric stimulation (such as transcranial direct current stimulation [tDCS]) have proven their potential to modulate brain activity in a non-invasive manner. Depending on the stimulation parameters it is possible to facilitate or to suppress brain activity with variable behavioural effects. Subsequent changes in cortical excitability have been shown to outlast the duration of the stimulation itself (Hummel and Cohen, 2005). Considerable efforts have been made to explore their potential in diagnostics and therapy of neurological diseases. Ideally non-invasive brain stimulation (NIBS) would serve as a complementary therapeutic modality. In stroke for instance the ultimate goal for it, in combination with intensive training, would be to promote adaptive processes and to prevent maladaptive ones in order to enhance recovery (Hummel and Cohen, 2006). In Parkinson's disease for instance, NIBS would ideally complement and even enhance standard medical management utilizing mechanisms of brain plasticity to promote changes in neural circuitry.

2. Non-invasive brain stimulation

TMS uses short-lasting, strong electric currents delivered trough a copper wire coil to generate a rapidly changing high-intensity magnetic field. Holding the coil over the subject's skull this magnetic field on its part induces perpendicular currents in the brain which are strong enough to directly depolarize neuronal elements and influence cortical excitability. Single pulses can evoke electromyographic responses providing an opportunity to quantify changes in cortical activation (for details, see Hallett, 2007). Repetitive TMS (rTMS) can either enhance (5–20 Hz, high-frequency stimulation) or suppress (approximately 0.2–1 Hz, low-frequency stimulation) cortical activity and modulate excitability beyond the duration of the applied trains (Chen et al., 1997; Fregni and Pascual-Leone, 2007; Hummel and Cohen, 2005). More recently, "theta-burst stimulation" (TBS) has been introduced as a novel TMS paradigm. Typically three short trains of repetitive high-frequency rTMS (50–100 Hz) in theta-frequency (5 Hz) are used. The stimulation pattern can be regulated to either enhance (via intermittent theta-bursts, iTBS) or suppress brain activity (via continuous theta-bursts, cTBS) (Di Lazzaro et al., 2005; Huang et al., 2005).

While rTMS can generate strong currents capable to depolarize neurons, tDCS changes cortical activity by rather weak electric currents. Suggested a purely neuromodulating approach, tDCS alters brain activity rather by influencing ion channels and gradients and hence the resting membrane potential (Fregni and

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Pascual-Leone, 2007; Nitsche et al., 2008). Briefly, prolonged weak currents (1–2 mA) are delivered into brain tissue transcranially via two large electrodes. The length of the stimulation, strength and polarity determine the duration and direction of the excitability change. Anodal tDCS leads to brain depolarization (excitation) whereas cathodal tDCS results in brain hyperpolarization (inhibition) (Nitsche and Paulus, 2000). Like rTMS, tDCS effects seem to be mainly mediated by changes of excitability of inhibiting or facilitating interneuronal circuits. The outlasting effect of neural excitability shift is thought to be longer than with rTMS (Paulus, 2003). tDCS is low priced, portable and easy to use, in particular simultaneously with multimodal behavioural tasks. Moreover, short-lasting tingling sensations at the beginning of the stimulation fading away shortly after are used for a reliable sham/placebo condition, important for double-blinded controlled clinical trials (Gandiga et al., 2006; Nitsche et al., 2008).

Besides tingling, most commonly reported adverse effects in tDCS have been itching, headache and burning sensation. Infrequent and mostly mild adverse effects in TMS have been headache and neck pain. While the most serious complication associated with tDCS is heat-induced skin lesion, with rTMS it is the induction of seizures, however a quite rare adverse effect (risk estimate of 1.4% in epileptic patients, less than 1% in healthy subjects) (Rossi et al., 2009). Recent consensus guidelines ensure safety and tolerability for both techniques (Brunoni et al., 2011a; Rossi et al., 2009) giving safety parameters for stimulation paradigms as well as appropriate monitoring methods. They also recommend careful consideration of patient characteristics that may influence the seizure threshold, such as pro-epileptogenic medication, age or sleep deprivation.

Just recently the repertoire of non-invasive brain stimulation techniques has been expanded by transcranial alternating current stimulation (Antal et al., 2008) transcranial random noise stimulation (Terney et al., 2008) and others (e.g. based on ultrasound, weak magnetic stimulation; for review please see Edelmuth et al., 2010). For example with random noise stimulation a spectrum of random electrical oscillations applied to the motor cortex results in consistent excitability increases, with some spatial advantages compared to tDCS. The effects on physiological measures of these novel approaches are tested at the moment in healthy subjects, but have not yet been applied in larger series of patients with neurological diseases.

While there is good knowledge about changes in brain excitability in motor areas, much less is known about NIBS effects in non-motor areas. The same also applies to the long-term effects which are mechanistically still poorly understood. Activating stimulation is generally thought to be mediated by an enhancement of excitability. An improvement of temporal input–output coupling of neuronal firing rates was suggested to promote synaptic plasticity, as comprehensively reviewed recently (Nowak et al., 2009). Driven by glutamate it could be considered as analogous to long term potentiation/depression (LTP/LTD) as seen in hippocampal slices after repeated activation of synaptic pathways (Hallett, 2007). In fact post-tDCS effects of anodal and cathodal stimulation could be decreased by a NMDA-antagonist (Liebetanz et al., 2002). Accordingly, a partial NMDA-agonist selectively potentiated the duration of motor cortical excitability modulation by anodal tDCS (Nitsche et al., 2004) suggesting a considerable influence of glutamatergic neurotransmission in tDCS. Recent MR spectroscopy studies revealed new insights into alteration of neurotransmission under tDCS. Anodal tDCS decreases GABAergic transmission while cathodal tDCS shows similar effects on glutamate concentrations (Stagg et al., 2009). In TMS, studies in animals (Tokay et al., 2009) and humans (Luborzewski et al., 2007) provide evidence that glutamate might be a key neurotransmitter. Hereby NIBS does not only activate the cortical stimulation areas itself but also modulates neurotransmission within or towards remote brain areas (Bestmann et al., 2003; Denslow et al., 2005; Stagg et al., 2011). It also affects neuronal gene expression (Hausmann et al., 2000). For instance longer rTMS protocols significantly enhanced Brain-derived neurotrophic factor (BDNF) mRNA in the hippocampus, parietal and piriform cortices (Müller et al., 2000). BDNF is thought to play an important role in synaptogenesis and synaptic plasticity underlying learning and memory. Interestingly, knockout experiments found that BDNF also mediated tDCS induced LTP-like effects (Fritsch et al., 2010). In summary, the understanding of the underlying mechanisms of brain stimulation has been growing in the last years. However most of the data has been acquired indirectly by pharmacological interventions, neuroimaging or electrophysiological approaches. Animal and brain slice models are further needed to directly investigate the mechanisms of NIBS.

3. NIBS to support functional regeneration after stroke: motor and higher-order cognitive functions

Stroke is the leading cause for acquired severe long-term disability in western industrialized countries (Kolominsky-Rabas et al., 2001). The impairment of both motor and higher cognitive functions is of considerable clinical importance and influences the process of rehabilitation and general outcome after stroke. 55–75% of the patients suffer from deficits in the upper limb (Lai et al., 2002). 20% show significant language impairment (Carod-Artal and Egido, 2009; Lai et al., 2002). Up to 30% of all stroke patients are seriously affected by neglect (Pedersen et al., 1997). Main predictors for re-entering normal professional and private life are impairment of hand function and aphasia. Despite of recent improvements in acute and chronic stroke therapy there is still a large need for enhancement of functional regeneration to bring a larger part of patients back to their normal life.

Human motor function is the result of a precisely modulated interplay between different brain areas distributed in both hemispheres. Not only the coordinative bimanual use of both hands depends from well-tuned interhemispheric dynamics (Swinnen, 2002). Also unimanual movements and the independent use of a single hand, particularly at increasing complexity, require considerable interhemispheric interplay (Gerloff et al., 1998; Hummel et al., 2003; Manganotti et al., 1998).

Neuroimaging studies have provided insights into the patterns how the brain adapts to an acute focal lesion, such as after a stroke, which might disturb this interhemispheric network. In the motor system for instance, an initial depression of activity in the affected hemisphere is regularly followed by a period of largely non-specific activation in brain regions close and remote to the lesion on both hemispheres. Moving the paretic hand bilaterally activates primary motor (M1) and premotor cortices (Gerloff et al., 2006; Ward et al., 2003a,b). A subsequent reactivation of lateralized motor control correlates with good recovery while a persistent overactivation of the contralesional M1 correlates with poorer outcome (Calautti et al., 2001; Cicinelli et al., 2003; Feydy et al., 2002; Johansen-Berg et al., 2002; Ward et al., 2003a,b). However, since it was also shown that a prolonged contralesional activity was beneficial for more complex, occasionally fine motor functions in well recovered patients (Gerloff et al., 2006; Lotze et al., 2006; Riecker et al., 2010; Schaechter and Perdue, 2008), there is controversial discussion about the functional role of contralesional activity (Hummel et al., 2008). Apart from the affected hemisphere, the extent of the infarction, whether subcortical or cortical, also the complexity of the task and the level of effort may be relevant.

Nevertheless, it has been proposed that an upregulated contralesional motor cortex in the acute and subacute stage after stroke