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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

might further decrease the activity of the ipsilesional M1 by an abnormally high interhemispheric inhibition, an effect more pronounced in patients with higher motor impairment (Duque et al., 2005; Murase et al., 2004; Shimizu et al., 2002). Such a competitive, interhemispheric dynamic has also been reported for attention (Corbetta et al., 2005; Kerkhoff, 2001; Kinsbourne, 1977; Rushmore et al., 2006) and language impairment after stroke (Barwood et al., 2011; Weiduschat et al., 2011; You et al., 2011).

Given the model of this interhemispheric competition of both hemispheres after a stroke, the hypothesis has been raised that purposeful modulation of brain excitability, that is suppressing the activity in the unaffected or increasing the activity in the affected hemisphere, might promote functional improvement (Hummel and Cohen, 2006; Kapur, 1996). As discussed in the following sections NIBS might serve as an innovative tool to rebalance the interhemispheric dynamics and support further recovery. Particularly simultaneously applied in combination with training and learning paradigms, NIBS might further the functional gains even in the chronic phase of recovery (Zimerman et al., in press).

3.1. Motor function

After activating electric stimulation to the ipsilesional M1 showed functional benefit in animals (Plautz et al., 2003), various proof-of-principle studies followed in stroke patients. Both activating high-frequency rTMS/iTBS (Emara et al., 2010; Kim et al., 2006) and anodal tDCS administered to the affected hemisphere (Boggio et al., 2007; Fregni et al., 2005b; Hummel et al., 2006) demonstrated their potential to promote motor recovery. Also low-frequency rTMS/cTBS (Fregni et al., 2006a; Mansur et al., 2005; Takeuchi et al., 2005, 2008) and cathodal DCS (Boggio et al., 2007; Kim et al., 2010; Nair et al., 2011) were found to suppress the contralesional overactivity, rebalance the interhemispheric dynamics and hence improve motor performance mostly in the chronic stage of stroke recovery.

Just a few studies focussed on the earlier stage after stroke. Khedr et al. (2005) investigated 52 patients within the first 2 weeks after stroke. High-frequency rTMS over the affected hemisphere showed functional improvement outlasting at least 10 days after stimulation. Other studies reported variable functional gains without serious adverse effects in the acute and subacute stage (<6 months after stroke) utilizing both activating (Chang et al., 2010) and inhibiting rTMS (Conforto et al., 2011; Liepert et al., 2007) as well as tDCS (Kim et al., 2010). More recently, variable long-term effects outlasting one to three months were also reported for both activating (Chang et al., 2010) and inhibiting (Avenanti et al., 2012; Conforto et al., 2011) rTMS when combined with motor training in early and even late phases of recovery.

Assuming that a bilateral stimulation might lead to additive and even supraadditive effects, just recently this bihemispheric approach has been investigated by a couple of studies. Simultaneous anodal and cathodal tDCS in combination with occupational therapy (Lindenberg et al., 2010) or constraint-induced movement training (Bolognini et al., 2011) resulted in additional therapeutic gains ranging from 16% after 1 week to 29% after 1 month compared to motor therapy alone. Also bilateral rTMS showed beneficial effects compared to contralesional stimulation which persisted 1 week (Takeuchi et al., 2009). However, due to the lack of sufficient control conditions it remains unclear whether this approach is superior compared to unilateral stimulation. Future studies are needed to investigate this further.

In summary there is evidence that rTMS and tDCS might help to promote functional recovery in patients with mild to severe motor impairment and subcortical strokes. However, less is known about the effectiveness of brain stimulation when the cortex itself is affected. Combining tDCS and robot assisted arm training, Hesse et al. (2011) did not find additional improvement in patients with severe paresis and extensive lesions in the subacute stage after stroke. More recently, anodal tDCS applied to the lesioned hemisphere in severely affected patients did not describe positive effects also in the acute phase after stroke (Rossi et al., 2012). These results further support two important points: it is of great importance (1) that NIBS has to be applied concurrent with specific (upper extremity) neurorehabilitative training to enhance training effects (Zimerman et al., in press) and subsequent functional recovery and (2) to determine where and assure that NIBS was applied at the targeted region, especially in the view of extensive cortical lesions. Also rTMS resulted only in a limited additional benefit in this subgroup of patients when tested against constraint-induced movement training (Yozbatiran et al., 2009). Another study which investigated the effect of rTMS to the lesioned hemisphere even reported a mild deterioration of hand function in patients presenting cortical strokes compared to patients with subcortical lesions. Hereby fMRI analysis revealed a positive correlation of ipsilesional M1 activity with rTMS response indicating that neural activity in ipsilesional M1 may serve as a surrogate marker for the effectiveness of facilitatory rTMS and should be considered when aiming to create an individually tailored treatment protocol (Ameli et al., 2009).

The concept of the relevance of interhemispheric competition is discussed controversially. Lotze et al. (2006) found that not only M1 but also the dorsal premotor cortex (PMd) and the posterior parietal cortex of the unaffected hemisphere might influence effectively recovered complex motor functions in well-recovered patients. Herewith the functional recruitment of contralesional motor areas and their facilitatory influence on the ipsilesional M1 seems to be greater in more impaired patients (Johansen-Berg et al., 2002; Ward et al., 2007). However, data is inconsistent given a number of studies arguing for (Ackerley et al., 2010; Takeuchi et al., 2007) and against the functional relevance of contralesional premotor areas in motor stroke recovery (Fridman et al., 2004). The underlying mechanisms of the interaction between contralesional premotor and motor cortices at different temporal stages in the stroke patient are still poorly understood. Further studies are necessary to sort out whether the modulation of distinct premotor areas contralesionally (up- and downregulation) could provide tailored additional approaches for further stroke recovery; particularly as neuronavigated rTMS becomes more and more available (Diekhoff et al., 2010). Hence, modestly and severely, poorly and well recovered stroke patients might considerably differ in their patterns of motor recovery. Longitudinal studies are necessary to investigate this further.

3.2. Language

Language impairment is one of the important predictors whether stroke patients come back in their normal professional and private life (Wozniak and Kittner, 2002). Despite intensive speech and language therapy recovery is often incomplete (Pedersen et al., 2004). The neural mechanisms of recovery are poorly understood. Two different paths for recovery might be targeted by neurostimulation to enhance language functions after stroke. First, in patients with smaller left-hemispheric lesions, the recruitment predominantly affects perilesional brain areas with involvement of right-hemispheric language structures to a variable degree. In patients with larger left-sided frontotemporal lesions predominantly homologous language networks in the right hemisphere are recruited (for a comprehensive review see Schlaug et al., 2011). Hence both the affected and unaffected language networks might serve as targets for brain stimulation. First, as far as parts of the perilesional language regions are preserved, activating left-hemispheric neurostimulation might improve their recruitment

for language recovery. Indeed increased perilesional activation was found to be associated with better naming performance (Fridriksson et al., 2010). Second, homologous right-sided language regions might be potential targets in two different aspects. Based on the aforementioned model of the interhemispheric competition, a downregulation might help to suppress an abnormal strong interhemispheric inhibition from right-sided regions to perilesional left-sided language areas. Conversely, in patients with extensive left-hemispheric lesions covering language-relevant regions, rather an activation of contralesional regions might support their recruitment and enhance recovery after stroke. However, the functional importance of right-sided language areas is still under debate (Schlaug et al., 2011).

Only a few controlled studies evaluated the potential of brain stimulation for language recovery. Baker et al. (2010) and Fridriksson et al. (2011) applied anodal tDCS to the affected hemisphere over several days and reported positive effects persisting one to three weeks after stimulation. Strength of the former study was the broad clinical spectrum of language impairment including both fluent and non-fluent aphasia. The authors also used functional imaging to localize the stimulation sites for neuronavigation, knowing well the spatial limitations of tDCS, particularly in the presence of a stroke lesion. Admittedly, as the areas stimulated were quite frontal their functional role remains questionable (Fridriksson et al., 2010). Another report has not found any benefit for anodal but for cathodal tDCS applied to the left Broca area (Monti et al., 2008). However, language improvements by anodal tDCS to the dominant left hemisphere were similarly observed in healthy subjects (Cattaneo et al., 2011).

Inhibiting rTMS (Barwood et al., 2011; Weiduschat et al., 2011) and tDCS (You et al., 2011) administered to the unaffected hemisphere also showed significant benefits. For example, speech therapy and cathodal tDCS to the right Wernicke area improved auditory verbal comprehension in the subacute stage after stroke (You et al., 2011). Improvements in naming performance under inhibiting rTMS for instance persisted even 2 months after stimulation in the chronic phase of recovery (Barwood et al., 2011).

Aiming to re-balance interhemispheric dynamics after stroke, this approach is limited in patients with extensive left-hemispheric lesions. In these cases contralesional language areas were suggested to play a crucial role in language recovery and should not be downregulated via NIBS. Indeed anodal tDCS applied to the non-language dominant unaffected hemisphere led to variable language improvement persisting up to 2 weeks after stimulation (Flöel et al., 2011; Vines et al., 2011). Of interest, it could be shown that also slowly growing left-sided brain tumours lead to considerable functional importance of right-sided unaffected language areas as they leave time for plastic reorganizational processes in those homologue regions to occur. Conversely, rapidly growing tumours which might parallel strokes did not show significant right-hemispheric compensation indicating that time might be a critical factor for compensation and recovery (Thiel et al., 2006; Schlaug et al., 2011).

As most outcome measures were naming tasks, the clinical relevance of these proof-of-principle studies has to be addressed in more detail. Future studies need to account for the lesion size and site that may influence the effects of anodal and cathodal ipsi- and contralesional stimulation. Further studies need to demonstrate that this promising approach will enhance language functions to a level which is clinically relevant for the patients.

3.3. Neglect

Neglect is a relevant disability influencing rehabilitation and overall outcome after stroke. It is mostly seen in right hemispheric, parietotemporal strokes. Unilateral neglect is defined as a failure to report, respond or orient to contralateral stimuli not caused by an elemental sensorimotor deficit (Heilman et al., 2000). There are two possible underlying neural mechanisms serving as potential targets for NIBS.

First, the loss of ipsilesional, mostly right-sided cortical activation is suggested to impair the attention towards the contralateral, mostly left side (Miniussi et al., 2008). Indeed, activating neurostimulation by means of anodal tDCS to the right, lesioned, posterior parietal cortex (PPC) has shown some benefit for functional recovery (Ko et al., 2008; Sparing et al., 2009).

Second, the other mechanism refers again to stroke-related changes in interhemispheric interactions. An overactivity of the unaffected contralesional parietal cortex might impair proper recovery of the attentional system after a stroke (Corbetta et al., 2005; Kinsbourne, 1977; Rushmore et al., 2006) and could be targeted by inhibiting NIBS with outlasting benefits on stroke-induced left-sided extinction (Brighina et al., 2003; Oliveri et al., 1999, 2001; Rushmore et al., 2006). For instance, inhibiting rTMS to the contralesional left-sided PPC over two weeks improved visuospatial performance in three patients up to 15 days after stimulation (Brighina et al., 2003) with similar benefits in subsequent studies (Lim et al., 2010; Song et al., 2009). rTMS thereby reduced not only the activity of the left PPC, but also the excitability of left PPC-M1 circuits. An enhanced level of excitability of this connection was found in neglect patients and positively correlated with behavioural measures (Koch et al., 2008). In fact inhibitory cTBS to the contralesional PPC in a single-session or over two weeks also showed positive effects outlasting up to 1 month (Nyffeler et al., 2009; Koch et al., 2012).

NIBS for the treatment of neglect has to prove the promises of these first proof-of-principle studies in translating such approaches into clinical relevant effects. Brain stimulation might have to be combined with specific training paradigms to induce persisting clinically relevant improvements of neglect symptoms. Therefore larger controlled, prospective, randomized and blinded studies are needed.

4. Non-invasive brain stimulation in Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disease characterized by the progressive loss of dopaminergic neurons in the substantia nigra resulting in functional dopamine depletion in the striatum. Over time it not only leads to deafferentation of cortical targets but also changes cortical excitability (Lefaucheur, 2005), activation and plasticity (Grafton, 2004). Aside from characteristic motor symptoms such as rigour, tremor, bradykinesia and gait instability, patients also suffer from non-motor symptoms like mood and sleep disturbances and attentional problems. Current therapeutic strategies include medication and deep brain stimulation (DBS) which are capable to target these symptoms and improve the daily life of the patients. Despite remarkable progress in therapy efficiency, safety and tolerability, there are limitations. Long-term dopaminergic medication as an important pillar of current medical management often leads to challenging motor fluctuations. Also the increasing prevalence of dopamine-resistant motor and neuropsychiatric symptoms poses therapeutic problems and influences disability in PD (Weintraub et al., 2004). Finally, despite its beneficial effects on medication-induced motor fluctuations, also the application of DBS is limited due to possible neuropsychiatric side effects, apart from the procedural risk as a neurosurgical intervention (Skidmore et al., 2006). For these reasons there has been a growing interest in the application of NIBS as additional therapeutic options (for a comprehensive review see also Wu et al., 2008).

As the cortex is densely connected with basal ganglia areas, NIBS is not only capable to target cortical but also subcortical structures remote from the stimulation site. Indeed in healthy subjects stimulation of M1 resulted in dopamine release in distinct subcortical areas (Strafella et al., 2001). However, the knowledge about stimulation-induced dopamine release in PD is still limited. The published findings revealed inconsistent results because uncontrolled studies reported stimulation-induced dopamine release (Strafella et al., 2005) while similar effects were seen under sham stimulation (Strafella et al., 2006). Controlled studies are needed to investigate this in more detail (Wu et al., 2008).

The ideal effect of NIBS would not only normalize the pathological subcortical-cortical circuitries but also the activation patterns and excitability levels of the cortical motor areas. Indeed in early stages of PD mesial motor areas such as the supplemental motor area (SMA) regularly show decreased activity whereas hyperactivity is found in more lateral regions such as the primary motor cortex (M1) in more advanced stages of the disease (Haslinger et al., 2001; Sabatini et al., 2000). Changes of the activational states in the course of PD were suggested to parallel motor symptoms such as early bradykinesia and later medication-induced dyskinesia that might be targeted by facilitating or inhibiting stimulation, respectively. Finally, ideally neurostimulation should provide the option to modulate rather network loops that are specifically involved in a subset of symptoms and not subcortical hubs where variable circuits converge as suggested by Wu et al. (2008).

A number of controlled studies have investigated the potential of activating brain stimulation applied to M1. rTMS in single- (Lefaucheur et al., 2004; Siebner et al., 2000) and multisession designs (Khedr et al., 2003, 2006) as well as anodal tDCS (Fregni et al., 2006b) showed variable functional improvement. 10 Hz rTMS daily over 10 days in 36 PD patients for instance improved UPDRS motor subscales and walking speed for 1 month after stimulation (Khedr et al., 2003). 25 Hz rTMS was able to further improve effects in UPDRS, gait and tapping speed (Khedr et al., 2006). Of note, more recently even 50 Hz rTMS has passed a safety study in PD patients (Benninger et al., 2009). Comparative studies based on larger cohorts are needed to investigate these different protocols.

Hence, for motor symptoms in PD the underlying cortico-subcortical circuitries might be efficiently targeted by M1 stimulation. In contrast, the dorsolateral prefrontal cortex (DLPFC) is suggested to be an “entry port” to modulate prefrontal loops (Wu et al., 2008) which are supposed to be relevant for non-motor symptoms such as mood and attentional disturbances. In depressed patients, high-frequency rTMS over the left DLPFC over 10 days improved both depression and UPDRS motor scales in an open label study (Epstein et al., 2007). The antidepressant effect, outlasting up to 8 weeks after stimulation, could be recently confirmed in controlled randomized trials whereas the beneficial effect on the motor symptoms only showed a trend for significance compared to sham stimulation (Fregni et al., 2004; Pal et al., 2010). Except for some improvement in working memory (Boggio et al., 2006), non-depressed patients do not seem to benefit in major motor function, neither from activating rTMS (del Olmo et al., 2007) nor tDCS applied to the DLPFC (Fregni et al., 2006a).

Whether the simultaneous neurostimulation to M1 and DLPFC would be beneficial has been addressed applying 25 Hz rTMS to M1 and DLPFC bilaterally over a prolonged period of 4 weeks. Improvements in bradykinesia and gait persisted 1 month after the end of the stimulation (Lomarev et al., 2006). Improved bradykinesia, notably outlasting longer than 3 months, was also reported combining tDCS to M1 and DLPFC. This approach however failed to show positive effects on the more general UPDRS motor subscale (Benninger et al., 2010). The simultaneous modulation of different neuronal circuits might provide beneficial and particularly long-term effects. However, considering homeostatic plasticity (Ziemann and Siebner, 2008), simultaneous stimulation could also limit the potential synergistic effects. So far, this approach has not been tested in depressive patients.

Whereas hypoactivity in M1 and SMA is a common finding in bradykinesia, imaging studies revealed an association of hyperactivity and dyskinesia which poses considerable therapeutic challenges in more advanced PD (Brooks et al., 2000; Rascol et al., 1998). Indeed, low-frequency rTMS to SMA (Brusa et al., 2006; Koch et al., 2005) and M1 (Filipovic et al., 2009; Wagle-Shukla et al., 2007) temporarily improved drug-induced dyskinesia. Recently down-regulation of the cerebellum was also found to improve peak-dose medication-induced dyskinesia for up to 4 weeks after (Koch et al., 2009).

In summary, on a proof-of-principle basis there is some evidence that NIBS might be a complementary tool to improve motor and non-motor symptoms in PD. Realistically we are still far away from being therapeutically relevant compared to DBS in the clinical setting, with its dramatic effects on motor symptoms. If future studies succeed to demonstrate the efficacy of NIBS in PD, it will certainly get its value in a multimodal treatment approach due to its non-invasive, safe and tolerable nature.

5. Outlook and further conclusions

In summary the available research suggests that NIBS by means of TMS and tDCS could serve as a potential complementary therapeutic tool in neurological diseases such as stroke and Parkinson’s disease with motor and higher cognitive impairment. There is good evidence for the safety and feasibility of the application. Admittedly, as the available knowledge is mainly based on studies applying single or few sessions, caution is advised when aiming to generalize the safety to prolonged daily NIBS sessions as suggested by a meta-analysis assessing adverse effects in tDCS (Brunoni et al., 2011b). Particularly in the context of possible adverse effects NIBS has to consider continuously ethical issues and limitations in basic sciences and clinical settings (see e.g. Horvath et al., 2010 for further reading). Just recently, a meta-analysis in brain stimulation in chronic pain has illustrated how difficult it is to draw clinically relevant conclusions from proof-of-principle studies (O’Connell et al., 2011). Research will have to address similar challenges in stroke recovery and Parkinson’s disease. A recent meta-analysis found at least a trend for functional improvement under anodal tDCS (Bastani and Jaberzadeh, 2011). In Parkinson’s disease two meta-analyses already demonstrated significant TMS effects on bradykinetic features particularly for high-frequency rTMS (Elahi and Chen, 2009; Fregni et al., 2005a). Present proceedings have not only contributed to the understanding of neurostimulation and its potential in stroke recovery and Parkinson’s disease for instance, they also accentuate the need for further investigations. A selection of open questions and possible future directions of research is presented in the following section.

First, the optimal time point of stimulation merits further investigations. Applied in the earlier stages after stroke, in which considerable reorganization takes place and the brain might be well-prone for standardized behavioural and cognitive treatment, NIBS might amplify neuroplasticity and functional regeneration. Also in PD, comparative trials over a broad range covering early and advanced stages of the disease might help to determine the best time for brain stimulation to unveil its full impact. Particularly in stroke, NIBS should not only consider the individual activation patterns that change over time from early contralesional to later ipsilesional activation. It should also take account for the individual level of impairment since the preferred recovery might follow different ways in different patients.

Second, as multifocal brain stimulation has become available, future developments will also have to concern simultaneous stimulation to different cortical areas. In PD future studies targeting both medial, lateral motor areas and the cerebellum will have to clarify the impact of these areas and the connected neuronal loops on the specific subsets of motor (bradykinesia, dyskinesia) and non-motor (depression) symptoms. Hence, possible interferences, additive and supra-additive effects might be further elucidated, especially in the view of homeostatic plasticity mechanisms (Ziemann and Siebner, 2008). The same also applies to stroke recovery: As there is growing evidence that the interplay of distinct motor areas of both hemispheres might impact reorganization and functional regeneration after stroke (Grefkes et al., 2008; Rehme et al., 2011), combined multifocal NIBS protocols concurrent with physical training have to be developed. Subgroups of patients might share specific pattern of interareal interactions that might serve as predictors for treatment response, possibly the key to further regeneration (Ward, 2006).

Third, concerning motor recovery after stroke, there is ongoing controversy which side to stimulate. While there is good recovery when the ipsilesional hemisphere is reactivated this is not the case in highly impaired patients. The latter would suggest that in this case, stimulation of the unaffected hemisphere might be the better access to the bilaterally working motor system in the damaged brain (Hummel et al., 2008). The question whether contralesional stimulation would be superior to ipsilesional stimulation cannot be answered by a single study (Khedr et al., 2009). As the time might also impact the effects of brain stimulation, longitudinal studies are needed for further investigations. Supporters of the concept of inhibiting stimulation of the contralesional hemisphere point out that the brain stimulation wouldn't retrieve the disadvantages of stimulating a lesioned tissue, affecting its susceptibility to seizures for instance. However, the main changes of excitability to the intact hemisphere appear in the lesioned hemisphere. Thus the risk of inducing seizures should not be different from direct stimulation, especially in the view of recent results suggesting that the effects are even more pronounced remote from the stimulated interconnected areas (Bestmann et al., 2010).

Fourth, most stimulation parameters have been deduced from healthy young subjects (Wassermann and Lisanby, 2001). Recent work suggested that elderly subjects eventually do not respond the same way (Tecchio et al., 2008). In stroke patients for instance, response patterns might also depend on the phase after stroke, as there are periods of enhanced baseline excitability alternated by phases with reduced or normal excitability levels. These questions have to be addressed in future studies to optimize the stimulation parameters (frequency, duration, amplitude) for best application, ideally individualized to the needs of each single patient. The paradigms should probably contain longer periods of combined treatment to drive the adaptive plastic changes.

Fifth, further research is needed on severely impaired stroke patients with cortical affection which might show considerable differences in both motor and higher cognitive recovery compared to patients with mild impairment. Neurostimulation in more severely impaired patients with low-level hand function who are not able to voluntarily extend the fingers and open the hand is more difficult. Particularly in these patients rehabilitation of upper extremity function remains extremely problematic and the functional outcome is mostly dissatisfying (Carter, 2008). Moreover, these patients need possibly novel interventional strategies, such as intensive home-based orthosis supported training (Farrell et al., 2007). As this therapy is long and requires highly motivated patients, an interventional approach based on brain stimulation combined with this training to enhance its effects is worthwhile to study.

To bring brain stimulation from bench to bedside multi-centre trials in larger numbers of patients are required. Recently, the first multicenter longitudinal trial was set up to investigate the role of anodal tDCS combined with standardized behavioural training for motor recovery (Neuroregeneration Enhanced by Transcranial Direct Current Stimulation (tDCS) in Stroke [NETS]). Besides the evaluation of the functional effects of NIBS, this trial will hopefully contribute to the understanding of the temporal development of motor plasticity and regeneration. Therewith it could elucidate different recovery patterns which might help to predict the effectiveness of brain stimulation using a multimodal approach (TMS, fMRI, EEG, MEG and DTI).

Disclosure/Conflict-of-interest

None.

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