

Review Article

Non-invasive brain stimulation for Parkinson's disease: Current concepts and outlook 2015

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Abstract.

BACKGROUND AND PURPOSE: In advanced Parkinson's disease (PD), the emergence of symptoms refractory to conventional therapy poses a therapeutic challenge. The success of deep brain stimulation (DBS) and advances in the understanding of the pathophysiology of PD have raised interest in non-invasive brain stimulation as an alternative therapeutic tool. The rationale for its use draws from the concept that reversing abnormalities in brain activity and physiology thought to cause the clinical deficits may restore normal functioning. Currently the best evidence in support of this concept comes from DBS, which improves motor deficits, and modulates brain activity and motor cortex physiology, though whether a causal interaction exists remains largely undetermined.

CONCLUSION: Most trials of non-invasive brain stimulation in PD have applied repetitive transcranial magnetic stimulation (rTMS) targeting the primary motor cortex and cortical areas of the motor circuit. Published studies suggest a possible therapeutic potential of rTMS and transcranial direct current stimulation (tDCS), but clinical effects so far have been small and negligible regarding functional independence and quality of life. Approaches to potentiate the efficacy of rTMS, including increasing stimulation intensity and novel stimulation parameters, derive their rationale from studies of brain physiology. These novel parameters simulate normal firing patterns or act on the hypothesized role of oscillatory activity in the motor cortex and basal ganglia in motor control. There may also be diagnostic potential of TMS in characterizing individual traits for personalized medicine.

Keywords: Non-invasive brain stimulation, therapeutic study, Parkinson's disease, repetitive transcranial magnetic stimulation (rTMS), transcranial Direct Current Stimulation (tDCS), plasticity, neurophysiology

1. Background

Parkinson's disease (PD) is prevalent in over 1% of the elderly population. As the second most common

neurodegenerative disease after Alzheimer's dementia (de Lau & Breteler, 2006), PD is a major socio-economic burden that is increasing with the "aging" of our society. In the early stages of PD, substitutive dopaminergic therapy improves motor symptoms, but the disease progression poses challenges. The therapeutic response gradually diminishes and other motor deficits emerge from the progressive degeneration which involves other non-dopaminergic neuronal

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circuits (Braak et al., 2003). Such deficits eventually become refractory to conventional dopaminergic therapy.

Motor fluctuations, dyskinesias and refractory tremor in PD can be successfully treated by deep brain stimulation (DBS) and lesional interventions, which have become the ultimate therapeutic options when conventional therapy fails. However, DBS and lesional interventions are available to a limited patient population and carry the risk of serious complications and neuropsychiatric side effects. Postural instability and gait difficulties, particularly freezing of gait, remain largely refractory to these interventions further raising the need for therapeutic alternatives. The therapeutic success of DBS and our advances in the understanding of the pathophysiology of PD have raised interest in non-invasive brain stimulation (NIBS) as an alternative therapeutic tool.

This review summarizes the current state of knowledge of the therapeutic potential of NIBS for the treatment of PD with particular focus on current concepts and an outlook for future applications.

2. Rationale for non-invasive brain stimulation

The rationale for non-invasive brain stimulation is that if abnormalities in brain activity and physiology thought to cause clinical deficits are reversed, normal functioning should be restored. Currently the best evidence in support of this concept comes from deep brain stimulation (DBS). DBS in Parkinson's disease (PD) improves motor deficits, and modulates brain activity (Ceballos-Baumann et al., 1999; Eusebio et al., 2011; Limousin et al., 1997) and motor cortex physiology (R. Chen, Garg, Lozano, & Lang, 2001; Cunic et al., 2002), suggesting causality. Although this has yet to be proven, these studies point to widespread effects of DBS which may be mediated trans-synaptically across the motor circuit that connects motor cortex, basal ganglia and thalamus. This raises hope that stimulating elsewhere within this circuit could achieve similar effects. Particular interest lies in the motor cortex due to its accessibility by NIBS. Functional imaging in transcranial direct current (tDCS) supports the concept of a cortico-subcortical connectivity that would allow for widespread activation of the motor circuit by stimulation of the primary motor cortex (M1) (Baudewig, Nitsche, Paulus, & Frahm, 2001; Lang et al., 2005). The concept of brain-enhancement offers a promising rationale in potentiating efficacy of

rehabilitative interventions by combining them with brain stimulation.

Parkinson's disease may offer a unique model to investigate whether NIBS can improve symptoms and reverse functional changes in the motor cortex and motor circuit secondary to brainstem pathology. The motor system lends itself ideally for cause-effect exploration.

3. Pathophysiology of Parkinson's disease

The primary pathophysiology of motor symptoms in PD is thought to arise from a progressive nigro-striatal dopamine deficiency. Neurophysiological investigations and imaging studies indicate functional and possibly structural changes in the primary and secondary motor areas and in the motor circuit that connects the motor cortex, basal ganglia and thalamus (Alexander, Crutcher, & De Long, 1990). The current disease model suggests that dysfunction of the cortico-striato-thalamo-cortical circuit leading to a deficient thalamo-cortical drive to the cortex causes motor symptoms (see for a review (Mink, 1996; Wichmann, DeLong, Guridi, & Obeso, 2011)). This model is a simplification of admittedly a much more complex pathophysiology. Thus, it remains largely hypothetical whether these changes in pathophysiology reflect compensatory processes or maladaptive plasticity. Some of this ambiguity stems from the divergence in findings between neurophysiological and imaging studies, which are a result of differing methodologies and populations studied.

Neurophysiology and imaging studies suggest functional integrity of motor neurons in the primary motor cortex (M1) and their direct cortico-spinal projections in PD. Changes in cortical excitability indicate abnormalities in the interaction of inhibitory and excitatory circuits whose converging influences modulate the activity and firing pattern of motor neurons and, therefore, their susceptibility to stimulation (see for references (Cantello, Tarletti, & Civardi, 2002; Lefaucheur, 2005)). These changes depend on the state of activation, whether tested at rest or during voluntary or involuntary motor activity. Cortical excitability is increased during rest and decreased during voluntary activity corresponding to reduced facilitation (Cantello et al., 1991; Valls-Sole et al., 1994). This concept is inferred from the motor evoked potential (MEP), which is subject to methodological limitations such as phase cancellation (Magistris, Rosler,

Truffert, & Myers, 1998). The recent development of TMS combined with EEG measures TMS-evoked potentials directly from cortical activity. This opens up a new approach to evaluate changes in brain excitability and plasticity with non-invasive brain stimulation.

Activation of the motor cortex is impaired preceding voluntary activity in early PD which may represent a neurophysiological correlate of bradykinesia (R. Chen, Kumar, Garg, & Lang, 2001). The impaired facilitation likely results from a deficient thalamo-cortical drive, while the increased activity during rest may be compensatory (Berardelli, Rothwell, Thompson, & Hallett, 2001). The connectivity of the primary motor cortex with secondary motor, somato-sensory and other cortical areas also appears to be compromised, but can be restored by dopaminergic substitution (Buhmann et al., 2004; Mir et al., 2005).

The persistence of stimulation effects implies functional and structural changes in synaptic strength, which constitutes the basic mechanism in plasticity. Various stimulation paradigms including 1 Hz- repetitive transcranial magnetic stimulation (rTMS) (Buhmann et al., 2004), 5 Hz-rTMS (Mir et al., 2005), continuous Theta-Burst stimulation (cTBS) (Koch et al., 2009) and paired-associative-stimulation (PAS) (Morgante, Espay, Gunraj, Lang, & Chen, 2006) demonstrate preserved plasticity in PD, which may be maladaptive in the pathogenesis of dyskinesias (Morgante et al., 2006). The efficacy of transcranial stimulation is contingent on its ability to induce persistent effects with intermittent applications in direct contrast to the chronic stimulation used in DBS. The process of plasticity in brain stimulation becomes also evident with the sequential re-emergence of tremor, bradykinesia and rigidity, and axial signs after cessation of DBS; pointing to their distinct pathogeneses (Temperli et al., 2003). The mechanisms of plasticity which are activated by brain stimulation are not well understood. Pharmacological blocking of N-methyl-D-aspartate (NMDA) receptors prevents long-lasting effects on cortical excitability from being induced by tDCS (Liebetanz, Nitsche, Tergau, & Paulus, 2002; Nitsche, Fricke, et al., 2003) suggesting tDCS may act on NMDA receptor-dependent plasticity. This plasticity is thought to depend on dopamine (Nitsche et al., 2006). This is demonstrated by the effects observed following 5 Hz rTMS (Gilio et al., 2002; Mir et al., 2005), 1 Hz rTMS (Buhmann et al., 2004) and paired-associative stimulation (PAS) (Bagnato, Agostino, Modugno, Quartarone, & Berardelli, 2006; Morgante et al., 2006; Ueki et al., 2006) only when PD

patients are on medication, but not when they are off dopaminergic therapy.

Functional imaging complements neurophysiology by delineating activity within larger networks contributing to our understanding of the pathogenesis of PD. There are numerous imaging studies with various findings, but most agree on the presence of diffuse activity changes within the motor circuit. There is an impaired activation in the supplementary motor area (SMA) and dorso-lateral prefrontal cortex (DLPFC) during voluntary motor activity which may arise from deficient stimulatory input of the basal ganglia-thalamo-cortical projections. This deficiency could be the primary dysfunction, while the increased activity in the lateral pre-motor and parietal cortices may be compensatory (Brooks, 1999; Sabatini et al., 2000). The hypoactive DLPFC may compromise motor activity which reacts to external cues (Jahanshahi et al., 1995). The difficulty in self-initiated motor activity may arise from the impaired activity in the SMA and mesial-frontal areas (Jahanshahi et al., 1995; Playford et al., 1992) as hypo-activity in the SMA correlates with a reduced early component of the Bereitschaftspotential (Dick et al., 1989; Ikeda et al., 1997; Jahanshahi et al., 1995). Clinical improvement with dopaminergic substitution parallels the increase in SMA activity (Jenkins et al., 1992; Rascol et al., 1992), while the hyperactivity in the lateral pre-motor and motor cortex diminishes (Haslinger et al., 2001). DBS of the sub-thalamic nucleus (STN) increases movement-related activation in the SMA and in the pre-motor cortex (Ceballos-Baumann et al., 1999; Limousin et al., 1997) correlating with clinical improvement.

These studies provide the rationale for the cortical targets and the polarity of non-invasive brain stimulation, which can induce widespread and sustained activity changes across the motor circuit (Baudewig et al., 2001; Lang et al., 2005). Whether PD-related functional changes are reversed, remains undetermined. The clinico-physiological correlations of bradykinesia, rigidity, tremor, dyskinesias, fluctuations, postural instability and gait disorder in PD remain largely unknown. A recent study combining functional imaging and direct testing by rTMS suggests a reduced inhibitory control mediated by the inferior frontal cortex to be involved in the generation of dyskinesias (Cerasa et al., 2015), but, whether cause or compensatory reaction remains to be determined.

The scarcity of correlative studies precludes firmer statements on the significance of the observed abnormalities and their clinical correlations. Thus,

insufficient evidence prevents substantiating a hypothesis-driven approach in therapeutic studies. Neurophysiological explorations and imaging are limited by the intricate concurrence of the various motor signs of presumably different pathophysiologies, the heterogeneous phenotype, and the progressive neuro-degeneration beyond dopaminergic neurons which remains difficult to define *in-vivo*.

4. Therapeutic studies of non-invasive brain stimulation in Parkinson's disease

Several methods of non-invasive brain stimulation have been tested in PD. The principal techniques are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). rTMS modulates cortical excitability, with high-frequency (≥ 5 Hz) rTMS being facilitatory (Pascual-Leone, Valls-Sole, Wassermann, & Hallett, 1994) and low-frequency (≤ 1 Hz) rTMS being inhibitory (R. Chen et al., 1997). tDCS delivers a continuous current that modulates membrane excitability and induces shifts in cortical excitability, with the polarity defining the effects. Anodal stimulation increases excitability and firing of active neurons (Nitsche & Paulus, 2000), but depolarization is not sufficiently rapid to produce an action potential (Nitsche & Paulus, 2000; Priori, Berardelli, Rona, Accornero, & Manfredi, 1998). The weak direct current of tDCS is barely perceived while pulsed high-voltage transcranial electric stimulation (TES) causes intense pain limiting its use. Novel promising transcranial current stimulation protocols such as alternating current (tACS), random noise (tRNS) and pulsed current stimulation (tPCS) remain yet to be tested in PD. In a pilot trial, tACS of the motor cortex presumed to interact with the rest tremor rhythm reduced the amplitude and could provide a closed-loop tremor-suppression therapy (Brittain, Probert-Smith, Aziz, & Brown, 2013). Direct motor cortex stimulation by epi-/subdural electrodes is invasive and will not be discussed here (see for a review (Canavero & Bonicalzi, 2007)), but may provide further insights into the mechanism of transcranial stimulation. Implanted electrodes offer the possibility of chronic cortical stimulation, which could become a therapeutic option, and trans-cranial stimulation may help to define eligibility by identifying responders before surgery.

Most therapeutic studies in PD have applied rTMS with promising results. Three meta-analyses concluded modest therapeutic efficacy in improving motor

performance (Elahi, Elahi, & Chen, 2009; Fregni, Simon, Wu, & Pascual-Leone, 2005; Zhu et al., 2015). The number of clinical trials is rapidly increasing, but few follow current standards of randomized, controlled trials (RCT; see for a recent Consolidated Standards of Reporting Trials [CONSORT] Statement (Schulz, Altman, & Moher, 2010). Cross-over studies risk un-blinding because of the nature of the intervention and potential carry-over effects. The best current evidence comes from parallel-designed RCTs, which have recently been reviewed by an international consortium for level of evidence and therapeutic recommendations (Lefaucheur et al., 2014). There is a substantial heterogeneity in selection criteria and stimulation characteristics between these trials which limits their comparability (see (Benninger, 2013) for a detailed discussion). There are fewer tDCS trials, which, for lack of a current consensus, will be reviewed here.

The key target of most therapeutic rTMS studies is the primary motor cortex (M1) alone or in combination with stimulation of the dorso-lateral prefrontal cortex (DLPFC). The international consortium concluded a possible anti-parkinsonian effect of high-frequency (5–25 Hz) rTMS of bilateral M1 (Level C). Despite evidence of a superior efficacy of intermittent Theta-Burst stimulation (iTBS) over conventional rTMS protocols (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005), a RCT of repeated iTBS of both M1 and DLPFC found no beneficial effects except for mood (Benninger et al., 2011). A RCT of repeated 50 Hz rTMS of both M1 did not show efficacy either (Benninger et al., 2012). The consortium concluded no evidence for therapeutic efficacy of low-frequency or unilateral high-frequency rTMS of M1 representation of the hand (Lefaucheur et al., 2014), but a more recent meta-analysis may suggest otherwise (Zhu et al., 2015).

The supplementary motor area (SMA) is another cortical target. The rationale for SMA-stimulation arises from its role in self-initiated movements which are impaired in PD (Dick et al., 1989; Ikeda et al., 1997; Jahanshahi et al., 1995). Based on the current studies, there is no evidence for therapeutic efficacy of low- or high-frequency rTMS of the SMA or the dorsal pre-motor cortex (dPMC) (Lefaucheur et al., 2014).

The DLPFC is part of the prefrontal cortico-subcortical circuit involved in cognitive processing (Alexander et al., 1990) and is active during self-initiated and externally-cued motor activity (Jahanshahi et al., 1995). The DLPFC is the prime target of high-frequency rTMS for the treatment of refractory

depression and currently the only FDA-approved therapeutic application of rTMS in clinical practice. The repeated stimulation of the DLPFC improves mood (Benninger et al., 2011; Pal, Nagy, Aschermann, Balazs, & Kovacs, 2010) comparable to antidepressants (Fregni et al., 2004) in PD. The international consortium concluded a probable antidepressant effect of high-frequency-rTMS of the left DLPFC in Parkinson's disease (Level B) (Lefaucheur et al., 2014).

Currently, a few RCT have targeted the cerebellum. There has been increasing interest in the contribution of the cerebellum in the pathophysiology of PD, whether pathological or compensatory, particularly in bradykinesia, rigidity, tremor, dyskinesias, and gait disturbances (see for a review (T. Wu & Hallett, 2013)). Repeated sessions of inhibitory continuous TBS (cTBS) over the lateral cerebellum reduce peak-dose dyskinesias for up to 4 weeks (Kishore et al., 2014; Koch et al., 2009). The rationale for cerebellar stimulation arises from the possibility to modulate intra-cortical inhibition of M1 (Koch et al., 2008). An alternative approach to reduce dyskinesias may be inhibitory 1 Hz rTMS of the SMA (Koch et al., 2005), M1 (Filipovic, Rothwell, van de Warrenburg, & Bhatia, 2009) or inferior frontal cortex (Cerasa et al., 2015), but the evidence remains weak to suggest efficacy of inhibitory intervention. This precludes a recommendation for low- or high-frequency rTMS of SMA, M1, or DLPFC or for cTBS of the cerebellum in levodopa-induced dyskinesia of PD patients (Lefaucheur et al., 2014).

5. Transcranial direct current stimulation

Although most NIBS studies on PD have employed TMS, tDCS remains a prospective therapeutic tool. Anodal tDCS is thought to restore reduced activity in motor and prefrontal cortices in PD (Fregni et al., 2006; M. Lomarev, Gurtchin, & Kirsanova, 1991). In a RCT, anodal tDCS applied to the motor and prefrontal cortices in 8 sessions over 2.5 weeks improved bradykinesia for 3 months and exerted beneficial effects on gait, but had no effects on the UPDRS, reaction time, physical and mental well-being, and self-assessed mobility (Benninger et al., 2010). The observed effect on bradykinesia was small, and needs to be confirmed in a larger study. TDCS promotes motor learning and consolidation, and may enhance long-term retention (Nitsche, Schauenburg, et al., 2003; Reis et al., 2009). This provides the rationale for combining tDCS with a

rehabilitative intervention, and has been shown to promote motor recovery in chronic stroke (Hummel et al., 2005). In a cross-over RCT, 5 sessions of anodal tDCS of M1 in 10 patients had a beneficial effect on gait, freezing of gait (FOG) and motor performance, and these effects lasted for the observation period of 1 month (Valentino et al., 2014).

Cognitive impairment is prevalent in advanced PD and a major cause of disability; fronto-executive dysfunction may manifest early. In a cross-over study, anodal tDCS with 2 mA of the left dorsolateral prefrontal cortex (DLPFC), but not of the primary motor cortex (M1) with either 1 or 2 mA, improved a working memory task performance (Boggio et al., 2006). In another cross-over study, anodal tDCS to left DLPFC more than of the left temporo-parietal cortex (TPC) improved verbal fluency which could result from tDCS-induced changes in large scale functional networks (Pereira et al., 2013).

The concept of priming offers a promising approach in potentiating efficacy of brain stimulation. Therapeutic stimulation protocols act on plasticity to induce persistent effects. This process of plasticity depends on the pre-existing neuronal activity and is referred to as homeostatic plasticity (Abraham & Tate, 1997; Bienenstock, Cooper, & Munro, 1982; Turrigiano & Nelson, 2004) which provides the rationale for a combined intervention. Thus, tDCS may prime the brain for a subsequent rTMS protocol in order to enhance its efficacy. Cathodal tDCS lowers cortical excitability and reverses the inhibition of LF rTMS into facilitation (Siebner et al., 2004); anodal tDCS, by increasing the cortical excitability, turns facilitatory HF rTMS into inhibition (Lang, Siebner, et al., 2004).

Priming by tDCS (1 mA for 10 min) modifies efficacy of subsequent LF rTMS (1 Hz, 900 pulses, 80–90% of resting motor threshold) of the M1. Cathodal tDCS interferes with beneficial effects of 1 Hz rTMS in finger tapping and pointing movements (Gruner et al., 2010), but anodal stimulation does not. Grasping cannot be modulated by tDCS-primed 1 Hz rTMS (Eggers, Gruner, Ameli, Sarfeld, & Nowak, 2012), and anodal tDCS, but not cathodal stimulation, with subsequent 1 Hz rTMS improves gait (von Papen, Fisse, Sarfeld, Fink, & Nowak, 2014). This combined approach of tDCS-priming with a subsequent rTMS protocol remains to be tested in a therapeutic trial in PD. Dopamine may also prime the brain reverting facilitation of anodal tDCS into inhibition and prolonging inhibition induced by cathodal tDCS (Kuo, Paulus, & Nitsche, 2008) which remains to be tested in PD.

6. Physiological effects of non-invasive brain stimulation in Parkinson's disease

The effects of transcranial stimulation on normal brain physiology have been widely published. In PD, few neurophysiological measures have been investigated and none has so far been proven as a reliable marker of bradykinesia, rigidity, tremor, or of overall clinical improvement. Of all measures, the cortical silent period (CSP) has most consistently correlated with dopaminergic deficiency (Cantello et al., 2002; R. Chen, Garg, et al., 2001; Siebner, Mentschel, Auer, Lehner, & Conrad, 2000; A. D. Wu, Petzinger, Lin, Kung, & Fisher, 2007). The CSP is thought to reflect excitability of the motor cortex possibly involved in inhibitory circuits (Cantello et al., 2002). In PD, the CSP is shortened in the "off"-state, normalized on medication, and lengthened during the dyskinetic state (R. Chen, Garg, et al., 2001). CSP is reported to correlate with the UPDRS motor score (A. D. Wu et al., 2007). DBS (R. Chen, Garg, et al., 2001; Dauper et al., 2002), high-frequency (up to 50 Hz) rTMS (Benninger et al., 2012; Gilio et al., 2002; Lefaucheur et al., 2004; Siebner et al., 2000), and low-frequency rTMS (Lefaucheur et al., 2004), modulate the CSP which suggests activation of common mechanisms. Yet, the functional significance of the CSP remains unknown, and the CSP may ultimately not correlate with motor function (Benninger et al., 2011; Benninger et al., 2012; Berardelli, Rona, Inghilleri, & Manfredi, 1996; Ridding, Inzelberg, & Rothwell, 1995) or other neurophysiological measures (Lefaucheur et al., 2004).

Neurophysiology of the dorsal pre-motor cortex stimulation has also been investigated in PD. High-frequency rTMS facilitated MEP on medication, but not in the "off"-state (Mir et al., 2005) and low-frequency rTMS restored short intra-cortical inhibition (SICI) (Buhmann et al., 2004).

rTMS of the prefrontal and motor cortex releases dopamine in the caudate and putamen corresponding to their cortico-striatal projections (A. P. Strafella, Paus, Barrett, & Dagher, 2001; A. P. Strafella, Paus, Fraraccio, & Dagher, 2003). This suggests a trans-synaptic mediation of cortical stimulation which may propagate across the motor cortex-basal ganglia-thalamo-cortical circuit. This release of dopamine is preserved in moderate PD (A. Strafella, Ko, & Monchi, 2006; A. P. Strafella, Ko, Grant, Fraraccio, & Monchi, 2005) and could contribute to the acute effects of transcranial stimulation. Yet, even sham rTMS releases dopamine (A. Strafella et al., 2006) which suggests the

contribution of an intrinsic reward mechanism associated with expectation on effects of stimulation. This could be a mechanism underlying the Placebo-effect, thus providing an alternative explanation to the trans-synaptic effect of stimulation.

Whether tDCS induces a release of dopamine is not known. Anodal tDCS causes widespread activation (Lang et al., 2005) that may trigger similar effects. Dopamine release could be the mechanism of acute improvement in tDCS (Fregni et al., 2006). Further support for an involvement of dopamine in tDCS effects comes from the observation that anodal tDCS of M1 prolongs CSP (Lang, Nitsche, Paulus, Rothwell, & Lemon, 2004), which is thought to reflect dopaminergic action in PD (R. Chen, Garg, et al., 2001; A. D. Wu et al., 2007).

The mechanism and the function of striatal dopamine release in rTMS and tDCS have yet to be further explored.

7. Current concepts of non-invasive brain stimulation in Parkinson's disease

None of these therapeutic trials have had a major effect. Repeated 25 Hz rTMS of M1 (Khedr, Rothwell, Shawky, Ahmed, & Hamdy, 2006) and combined M1 and DLPFC (M. P. Lomarev et al., 2006), supra-threshold 5 Hz rTMS (120% RMT, 10 sessions) of M1 (Khedr, Farweez, & Islam, 2003) and of SMA (at 110% AMT) (Hamada, Ugawa, Tsuji, & Effectiveness of rTms on Parkinson's Disease Study Group, 2008), and anodal tDCS of motor and prefrontal cortices (Benninger et al., 2010), have shown the strongest therapeutic efficacy. In contrast, iTBS of M1 and DLPFC (Benninger et al., 2011), and 0.2 Hz rTMS (110% RMT) (Okabe, Ugawa, Kanazawa, & Group, 2003) and 50 Hz rTMS (80% AMT) (Benninger et al., 2012) of M1, all failed to improve motor symptoms. Differences in stimulation parameters (target, rate, intensity, duration etc, and coil design and orientation), may help to explain some of the heterogeneity in the effects, and needs to be further investigated. The cumulative effects across multiple sessions (Khedr et al., 2003; Khedr et al., 2006; M. P. Lomarev et al., 2006) point to the superiority of multiple over a single session (Baumer et al., 2003), but the optimal number of interventions and their periodicity for maintaining efficacy remains unknown.

All positive studies report improvement of bradykinesia, but diverge in their efficacy to treat other cardinal

signs of PD. RTMS improved gait in several (Khedr et al., 2006; M. P. Lomarev et al., 2006) but not all studies (Benninger et al., 2011; Benninger et al., 2012; Rektorova, Sedlackova, Telecka, Hlubocky, & Rektor, 2007). TDCS has been suggested by some to improve gait (Benninger et al., 2010; M. Lomarev et al., 1991), while others have found no benefit (Fregni et al., 2006). In PD, gait is disturbed in various domains which arise from different pathophysiological mechanisms and therefore might differ in their response to tDCS and rTMS. Support for a therapeutic potential comes from DBS of the pedunculo-pontine nucleus (PPN) (Plaha & Gill, 2005; Stefani et al., 2007) which is reported to improve gait disturbances refractory to conventional therapy. The PPN connects with the cortico-striato-thalamo-cortical circuit and its activity could, theoretically, be modulated by cortical stimulation. Inhibitory cTBS of the cerebellum might offer an alternative to DBS for a temporary relief from peak-dose dyskinesias (Koch et al., 2009). The effects of tDCS and rTMS on rigidity are variable, but often not reported and difficult to assess, in part due to limitations in scoring and lack of reliable methods for quantifying small changes. A cross-over study demonstrates reduction of rigidity by both high- and low-frequency rTMS of M1 exerting opposite effects on cortical excitability (Lefaucheur et al., 2004) which needs further investigation.

Tremor poses a therapeutic challenge. Rest and action tremor are thought to arise from distinct mechanisms, and variable responsiveness to dopamine points to a non-dopaminergic pathogenesis. DBS of the thalamic ventral intermediate nucleus (VIM) (Benabid et al., 1991; Caparros-Lefebvre et al., 1993; Koller et al., 1997; Lenz et al., 1994; Limousin, Speelman, Gielen, Janssens, & study, 1999) has proven efficacious in treatment of refractory tremor and suggests a cerebellar or a cerebello-thalamic generator (Mure et al., 2011; Stein & Aziz, 1999) which may interact with the striato-thalamo-cortical circuit (Deuschl et al., 2000). Neurophysiology (Timmermann et al., 2003), functional (Antonini, Moeller, Dhawan, & Eidelberg, 1998; Deiber et al., 1993; Fukuda et al., 2004) and structural imaging (Benninger, Thees, Kollias, Bassetti, & Waldvogel, 2009; Kassubek, Juengling, Hellwig, Spreer, & Lucking, 2002) provide further evidence for an involvement of the cerebellum in the pathogenesis of rest tremor, but the nature of the functional disturbance remains yet to be determined. So far, no study has reported efficacy of rTMS or tDCS on tremor. The “re-setting” paradigm, which refers to the shifting of

tremor activity by TMS, has been proposed as a method for testing whether a stimulated brain area is involved in the generation or the transmission of tremor (Pascual-Leone, Valls-Sole, Toro, Wassermann, & Hallett, 1994) and may ultimately provide a therapeutic approach. Rest tremor in PD was re-set by stimulating M1 (Ni, Pinto, Lang, & Chen, 2010), while re-settability of a postulated cerebellar generator may require a stronger stimulation (Hallett & Deuschl, 2010). This needs to be clarified in further research.

The significance of non-motor features of PD is being increasingly recognized. Depression is the most prominent neuropsychiatric feature of PD and repeated high-frequency rTMS of the left dorsolateral prefrontal cortex (DLPFC) may offer a therapeutic option in PD (Lefaucheur et al., 2014), which is FDA-approved for refractory major depression.

There are changes in performance and scores which are not related to the intervention and best assessed in the sham condition. These changes can be attributed to a number of factors that include the Placebo effect, familiarization with the task, learning effects, and intrinsic variability in performance and response. These factors need to be controlled for.

The placebo effect may arise from the expectation of improvement alone that has been shown to cause a release of dopamine which may possibly be mediating the effect (A. Strafella et al., 2006). The placebo effect is thought to validate the sham intervention, and its absence suggests various possibilities including “un-masking” about the type of intervention. Blinding is required for a rigorous study methodology which depends on different factors, and is challenging with brain stimulation. In tDCS, blinding appears reliable (Benninger et al., 2010; Gandiga, Hummel, & Cohen, 2006); short-lasting and short-circuited tDCS over the forehead remains focal and causes the same “tingling” sensation that goes often unnoticed even during real tDCS. TMS and particularly rTMS pose a greater challenge and require an “active” sham-stimulation that resembles the real “set-up” and can imitate acoustic and vibratory sensation as well as effects of facial and scalp nerve stimulation. Supra-threshold rTMS of M1 poses a particular challenge because of MEPs. There are different methods of sham-stimulation that include positioning the discharging coil perpendicularly to the skull, using sham designed coils, using a sham coil with integrated bipolar electrical stimulator (Rossi et al., 2007), or using direct electrical skin stimulation (Okabe et al., 2003), but these different methods do not seem to influence outcomes in

rTMS studies and placebo responses in a meta-analysis (Elahi et al., 2009). These constraints compromise the reliability of blinding in cross-over studies as suggested by observed order effects. Prior exposure to TMS remains problematic.

Familiarization with a task and learning effects from repetitive practice contribute to the improvement in performance, which cannot be differentiated from effects related to the intervention without a control condition. Learning effects can vary, but are present even when practice is limited to a minimum. Both tDCS (Benninger et al., 2010; Nitsche, Schauenburg, et al., 2003) and rTMS (Ackerley, Stinear, Barber, & Byblow, 2010) enhance learning effects through repetitive practice, and combining brain stimulation and behavioral intervention may offer a greater therapeutic benefit.

The variability of responses to similar sham stimulation in different studies is intriguing. The absence of any changes in the sham group raises questions about possible explanations. In these studies, the absence or minimal changes in the sham group may constitute the difference that reaches statistical significance. In some studies, the sham group worsens over time compared to a stable or improving real intervention group which would suggest a possible disease-modifying effect of NIBS. In chronic stimulation with DBS, various mechanisms acting on plasticity, on the release of neuro-transmitters, and on the expression of trophic and other factors which might modify disease progression, have been claimed, but never proven (Harnack & Kupsch, 2010). This may not be the case with intermittent stimulation of tDCS and rTMS.

8. Outlook on non-invasive brain stimulation for the treatment in Parkinson's disease

The rationale for non-invasive brain stimulation in clinical practice is to provide additional benefit beyond conventional therapy, to offer an alternative approach for patients at risk or that are excluded from surgical interventions, and/or to treat refractory symptoms. The current studies suggest a possible therapeutic potential, but clinical effects so far have been small and negligible regarding functional independence and quality of life.

There might be several possibilities to potentiate the efficacy of rTMS. The conventional stimulation rationale aims to deliver more power, i.e. rate of energy transfer, though the precise mechanism of action

remains unknown. The current state of knowledge favors increasing stimulation frequency (Khedr et al., 2006) rather than intensity (Khedr et al., 2003) for reasons of safety defined by the risk of seizures (Rossi, Hallett, Rossini, & Pascual-Leone, 2009; Wassermann, 1998). Further studies need to explore stimulation parameters in regard to efficacy and safety, and also to identify neurophysiological correlates of clinical outcome measures which will allow for the determination of superior stimulation patterns and therapeutic strategies for the improvement of PD and other disorders.

Alternative NIBS approaches derive their rationale from studies in brain physiology. A novel and promising stimulation pattern, TBS, is thought to simulate normal firing patterns in the hippocampus by coupling gamma-frequency bursts (50 Hz) with theta-rhythm (5 Hz). This concept is supported by the induction of long-term potentiation (LTP) and depression (LTD) which constitute mechanisms of plasticity in an animal model (Huang et al., 2005). In PD, iTBS induces LTP-like plasticity (Zamir, Gunraj, Ni, Mazzella, & Chen, 2012), but does not improve motor symptoms (Benninger et al., 2011). The difference between cortical and cerebellar stimulation which reduces dyskinesias (Koch et al., 2009) remains unknown.

Another concept arises from the hypothesized role of oscillatory activity in the motor cortex and basal ganglia in motor control and in the pathogenesis of motor disorders. There is speculation about the possibility to modulate this activity ("entrainment") that may have therapeutic potential. In PD patients in the off-condition, pathological oscillatory activity in the beta-frequency range (10–30 Hz) predominates (Brown, 2007). This beta-activity decreases in response to dopamine (Kuhn, Kupsch, Schneider, & Brown, 2006) and high-frequency (130 Hz) DBS (Kuhn et al., 2008), while gamma activity (>30 Hz) emerges along with clinical improvement (Brown et al., 2001). Further support comes from beta-frequency (20 Hz) stimulation of the subthalamic nucleus which enhances bradykinesia (C. C. Chen et al., 2007) indicating a potential contribution of beta-activity to bradykinesia and rigidity in PD (Brown, 2007). This shift in power of beta- to gamma-activity might underlie the effects of dopamine and DBS (Garcia, D'Alessandro, Bioulac, & Hammond, 2005). RTMS might entrain oscillatory activity (Thut & Miniussi, 2009) and thus, 50 Hz rTMS might induce the hypothesized "pro-kinetic" gamma-frequency while suppressing the "akinetik" beta-frequency (Brown,

2007). Further research needs to confirm these observations. Short-lasting 50 Hz rTMS can be safely applied in patients with PD (Benninger, Lomarev, et al., 2009) though exceeding current safety limits (Rossi et al., 2009; Wassermann, 1998). In a single RCT, repeated 50 Hz-rTMS-interventions increased cortical excitability, but caused no clinical improvement (Benninger et al., 2012). Safety and technical limitations prevented longer stimulation which may be more efficacious.

Another approach is chronic stimulation which is requisite for the efficacy of DBS and may apply to all methods of brain stimulation. In direct cortex stimulation, epi-/subdural electrodes offer this possibility. Continuous stimulation by rTMS and tDCS is not now possible, but recent advances are promising. Prolonged transcranial alternating current stimulation (tACS) can now be done, and is actually approved for clinical use in the treatment of recurrent glioblastoma (Tumor Treating Field Therapy). Novel stimulation protocols besides tACS such as random noise (tRNS) and pulsed current stimulation (tPCS) offer opportunities for prolonged stimulation, while electrochemical effects may limit chronic use of tDCS.

Non-invasive brain stimulation studies will enhance our understanding of PD-pathophysiology and might provide evidence of potential therapeutic applications which could be realized by implanting electrodes for longer treatment periods. In a pre-surgical evaluation, non-invasive brain stimulation could explore potential effects before an intervention and contribute to identifying suitable candidates. Besides the therapeutic potential, neuromodulation by tDCS and rTMS allows for exploration of plasticity which may contribute to future clinical investigations.

New approaches in brain stimulation may respond more specifically to on-going demand. There is a particular interest in targeting episodic phenomena including freezing of gait, start hesitation, festination, (unpredictable) akinesia and motor fluctuations by intermittent stimulation that is adapted to the underlying pathophysiology. DBS and tDCS allow self-triggering and application, and this also may become possible for rTMS with a portable device. Such an application has been approved for preventing migraine attacks by applying single TMS (sTMS) pulses to the occipital cortex during the visual aura. The rationale is to interrupt cortical spreading depression, presumably underlying the aura, and, in a controlled study, sTMS maintained pain freedom more than sham-stimulation (Lipton et al., 2010).

A next step is a closed-loop stimulation system, in which feedback stimulation is given to a specific biological signal. The prediction of episodic events requires a far more in-depth understanding of their pathophysiology and of the optimal stimulation pattern. Such a closed-loop system requires real-time processing of incoming signals and a specific stimulation algorithm. This could be implemented by implanted recording and stimulating electrodes, and potentially also by an external system such as a portable rTMS combined with surface electrodes. A first proof-of-concept will probably come from a closed-loop stimulation system being developed in refractory epilepsy. This could allow customizing the stimulation paradigm to the particular activity.

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Conflict of interest

No relevant disclosures.

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