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Non-Invasive Neuromodulation Therapies for Parkinson's Disease

Milton C. Biagioni, Kush Sharma,
Hamzeh A. Migdadi and Alberto Cucca

Additional information is available at the end of the chapter

Abstract

Noninvasive brain stimulation (NIBS) technologies have been applied to study brain physiology and, more recently, have been recognized for their therapeutic potential as an adjunctive treatment for various neurologic and psychiatric disorders. Transcranial magnetic stimulation (TMS) and transcranial electric stimulation (tES) are two of the most studied NIBS modalities in Parkinson's disease. They are non-systemic and relatively safe. Most therapeutic trials have been conducted to ameliorate motor symptoms of Parkinson's disease (PD) with overall positive results using various stimulation modalities and methods. Notwithstanding significant results, evidence has not yet been compelling mainly due to small-size studies, lack of standardization of methodologies and other study design limitations. NIBS hold promise for treatment of PD symptoms and PD related complications. Large, well designed clinical trials are needed to corroborate these positive findings and inform its durability and the overall clinical relevance for the treatment of PD.

Keywords: neuromodulation, brain stimulation, electric stimulation, TMS, direct current, therapy, Parkinson's disease

1. Introduction

Parkinson's disease (PD) affects as many as 1.5 million people in the United States, with about 60,000 additional patients newly diagnosed each year. PD is a chronic, progressive syndrome in which a large number of dopaminergic neurons located within the basal ganglia circuitry degenerate. This dopamine depletion contributes to clinical motor symptomatology, including bradykinesia, tremor, rigidity, postural instability and gait dysfunction. Despite currently

available treatments, PD symptoms progress along with cortical dysfunction, leading to cumulative disability. The pharmacotherapy of PD is based on the restoration of dopamine levels through the administration of its precursor, levodopa (L-DOPA). Less powerful therapeutic strategies involve the direct stimulation of post-synaptic dopaminergic receptors through dopamine-agonist compounds or the inhibition of dopamine breakdown through catabolic inhibitors. A good control of symptoms is commonly obtained, leading to a good functional recovery, as well as to a general betterment of quality of life. Nonetheless, the results are maintained for a limited period, and, after a few years, certain complications related to the medication may arise, thus limiting the tolerability and the effectiveness of the treatment. At this point, doses are often limited by side-effects such as drowsiness, orthostasis, nausea, confusion, hallucinations, and the emergence of motor complications like fluctuations and dyskinesias. Furthermore, some symptoms known to be poorly responsive to available medications, such as freezing of gait, balance impairment and postural abnormalities, tend to emerge as the disease progresses. In the last decade, different therapeutic strategies have been developed in the effort to address the advanced stage of the disease, typically characterized by a progressive functional decline and decrease in quality of life with an unsatisfactory response to conventional pharmacological treatments. These "advanced strategies" show a variable profile of effectiveness and invasiveness. A recently introduced therapy is the duodenal administration of a gel formulation of L-DOPA (Duodopa), which is continuously released though a duodenal tube connected to a portable pump through a percutaneous endoscopic gastrostomy. This device permits a continuous delivery of the drug, with a stable kinetics, resulting in a significant reduction of the OFF-time and a marked simplification of the oral therapy. There are also more invasive surgical options that could offer symptomatic benefits. Deep brain stimulation (DBS) is the most commonly performed surgical treatment for Parkinson's, but it is not recommended for all patients. DBS has been demonstrated to be effective in remodulating the pathological activity of the basal ganglia motor circuit by acting on specific nuclei, including the subthalamic nucleus, the *globus pallidus* interna and the thalamus. This technique involves the implantation of pacing devices providing a continuous high frequency stimulation of the targeted area. DBS can ease some PD symptoms and motor fluctuations, but it does not change the underlying course of disease. Currently, there are no disease-modifying therapies available. Disease progression and disability eventually require a multidisciplinary approach involving physical therapy, social/occupational therapy, psychotherapy, etc. Alternative treatments able to maintain or reconsolidate function and quality of life are needed. Non-invasive brain stimulation (NIBS) techniques are potential adjunct therapies for PD. NIBS techniques do not require surgical intervention and are performed in outpatient settings. The practicality and safety of NIBS result in an important alternative therapy to maintain physical and/or cognitive function or promote functional recovery in PD patients.

NIBS is an area of rapid growth in neuroscience. The term "non-invasive brain stimulation" encompasses different modalities of intervention involving the administration of energy to modify the bioelectrical state of neuronal cells and influence brain regional activity. There is some controversy surrounding the name; some have suggested that the term "non-invasive" misrepresents both the possibility of side effects from the stimulation, and the longer-term effects (both adverse and desirable) that may result from brain stimulation [1]. The "non-invasive" denomination, as used in this review, is derived from the fact that the intervention does not require the insertion of instruments through the skin or into a body cavity.

The different sub-modalities of NIBS are named based upon how energy is physically delivered to the brain. In transcranial magnetic stimulation (TMS), transient rapid changing magnetic fields are utilized to induce secondary electric currents in the underlying cortical surface, which, in turn, trigger neuronal action potentials [2]. By contrast, in transcranial electric stimulation (tES), a weak electrical current is directly applied to the scalp to modulate neuronal membrane potentials without directly inducing synchronized neuronal discharge [3]. These different modalities of NIBS have shown a clear capacity to modify cortical excitability and potentially harness neuroplasticity for therapeutic applications, and they will be revised separately. The substantially safe, reproducible and non-invasive nature of NIBS makes these techniques of appealing interest for the study and treatment of various neurological and psychiatric disorders including PD. NIBS has proven efficacy in depression and chronic pain. NIBS in Parkinson's disease have led to numerous publications and variable results that we intend to summarize and review with a focus in research clinical trials (RCT). The chapter will be a narrative review describing the latest advancements in utilizing transcranial magnetic stimulation (TMS) and transcranial electric stimulation (tES). The proposed mechanisms of neuromodulation, its safety, therapeutic results and challenges will also be reviewed.

2. Mechanisms of action of non-invasive brain stimulation

The biological effects of NIBS are essentially determined by two types of factors: extrinsic (related to the intervention) and intrinsic (related to the stimulated subject). On one hand, extrinsic factors are related to the amount of energy and to the pattern of current flow delivered to the brain. These include specific parameters that can be actively controlled by the operator, such as current intensity, stimulation frequency, number of pulses, number of sessions, coil design, electrode montage, etc. However, for the same dose of energy delivered, different intrinsic factors inherent to the stimulated subject contribute to the individual's biological outcome. For instance, the subject's pharmacological profile can affect the brain's activation state and connectivity by modulating neuronal propensity to fire and undergo plastic phenomena. In patients with Parkinson's disease (PD), this is particularly noteworthy, as changes in cortical excitability and neuroplasticity are critically influenced by dopamine bioavailability, and the institution of a dopaminergic therapy can influence the subsequent neurophysiologic and behavioral effects of stimulation [4].

2.1. Motor cortex transcranial magnetic stimulation (TMS)

TMS is a focal modality of NIBS where an intermittent, high intensity, electrical current of brief duration is generated through a capacitor to induce transient magnetic fields spreading from the coil to the underlying surface. TMS has an FDA cleared indication for the treatment of medication refractory depression. As described by Michael Faraday's electromagnetic principle, the temporal variation of such magnetic fields—namely their exchange rate—is associated with the induction of secondary electrical currents. These currents are capable of triggering neuronal action potentials; the volume of the stimulated area roughly falls into that of a golf ball, and the transfer of energy is maximal with parallel orientation of conductors. Due to the

anatomical structure of the cortical layers, most of the neurons whose firing can be manipulated through TMS are parallel to the scalp and, as such, are mainly represented by interneurons. These cells can trans-synaptically modify the activity of interconnected pyramidal cells through indirect descendent volleys known as "I-waves" [5]. Descending volleys originating from the motor cortex (M1) can be recorded with electrodes from the peripheral muscle and the recordings are regarded as motor evoked potentials (MEPs). When TMS is delivered repetitively in trains of sufficient intensity and duration (e.g. 10–30 minutes), it is able to exert modulatory effects as evidenced by changes in MEPs amplitude, with an effect that outlasts each stimulation train. Therefore, the neurophysiological effects of trains of repetitive TMS (rTMS) can be quantified in light of some indirect neurophysiologic parameters, which are regarded as markers of cortical excitability. In healthy subjects, different stimulation frequencies are associated with opposite changes in local cortical excitability. More specifically, repetitive TMS (rTMS) at a frequency of one pulse/second (1 Hz) is associated with "inhibition-like" effects over the stimulated area, while higher frequencies of five or more Hz are associated with "excitatory-like" phenomena [6]. Newer TMS paradigms have been developed that are able to modify cortical excitability in significantly less time (20–190 seconds) [7]. Of those, one of the most popular is the theta burst stimulation, where high frequency pulses (3 pulses at 50 Hz) are applied repeatedly at intervals of 200 ms, delivered as a continuous (cTBS) or intermittent (iTBS) train. The former protocol is characterized as being "inhibitory" and the latter being "excitatory," according to the changes produced in MEPs size (**Figure 1**). This is admittedly an oversimplification, as there is a wide heterogeneity of response between subjects. The final biological effect of TMS is determined by the vector summation of all changes in the excitability of cortical interneurons, the status of the neurons prior to stimulation, the intrinsic properties and geometrical orientation of fibers within the cortical region, pharmacotherapy interactions, etc.

2.2. TMS proposed mechanisms of action for therapy

While a single session of TMS induces rather short-term effects (minutes up to hours) [9], the application of rTMS over time (several days/weeks) generates significantly longer lasting biological outcomes (in the order of weeks or a few months) [10]. The evidence of clinical changes that persist well beyond the time of stimulation is the foundations of therapeutic and rehabilitative perspectives. Two types of TMS-induced effects are essentially recognized: short-term and medium-term. Although the molecular mechanisms underlying these changes are not yet conclusive, several theories have been postulated. Short-term effects appear to be related to immediate changes in neuronal ionic conductivity induced by electrolysis phenomena resulting from propagating electromagnetic currents [11]. An additional proposed mechanism behind short-term effects is the release of neurotransmitters. It has been demonstrated that high-frequency rTMS applied over the left dorsolateral prefrontal cortex is associated with a tonic release of dopamine in the ipsilateral caudate and orbitofrontal cortex [12]. Meanwhile, medium-term effects of TMS are believed to be mediated by neuroplastic phenomena. The term "neuroplasticity" defines the ability of the CNS to respond to a broad spectrum of extrinsic and intrinsic stimuli through a functional, dynamic reorganization of its structures and connections. The epicenter of neuroplastic phenomena is the synapse. Increased synaptic strength, synaptogenesis and enhanced selectivity in the recruitment of neural pathways are
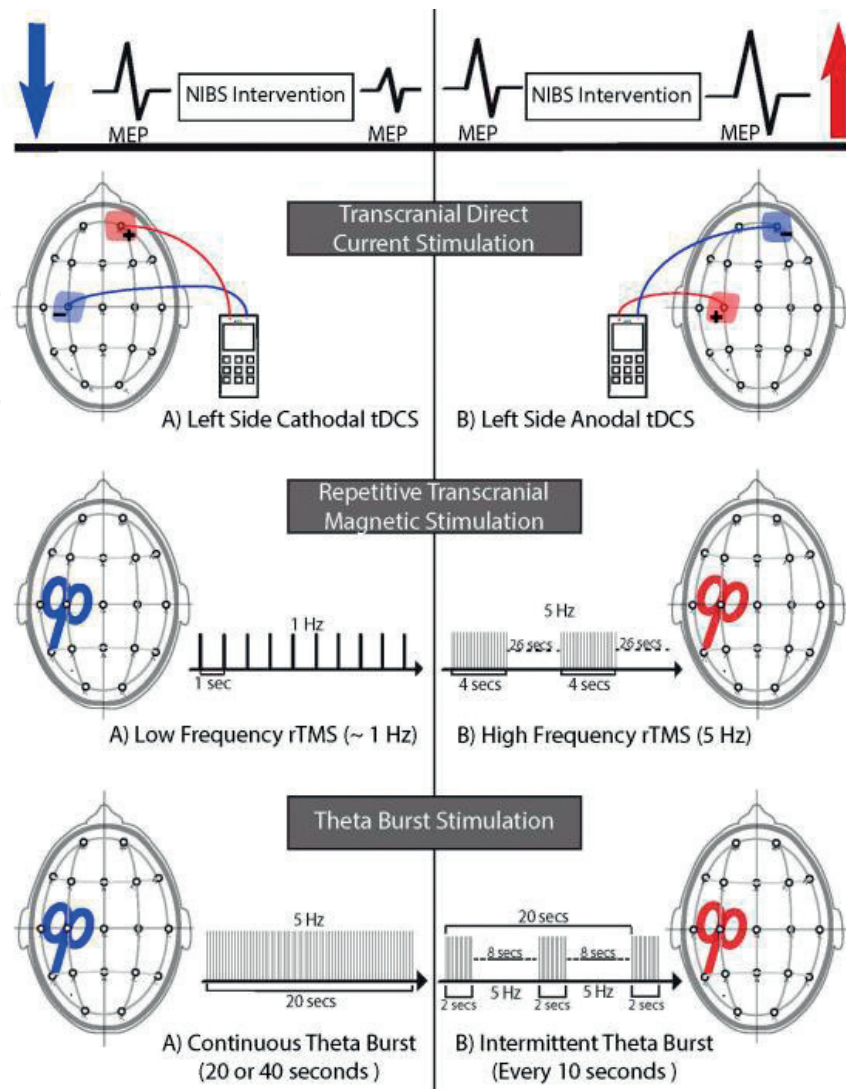
Figure 1. Illustration of motor evoked potential (MEP) changes induced by different types of NIBS over motor cortex. Blue colored arrow (left side) represents inhibitory and red colored arrow (right side) excitatory effects on MEPs.

some of the main mechanisms involved in neuroplasticity (**Figure 2**). It is believed that TMS can harness plastic phenomena by modulating long-term potentiation (LTP) and long-term depression (LTD) like phenomena. The molecular bases of such phenomena are likely to be found in the activation of the postsynaptic N-methyl-D-aspartate (NMDA) receptor [2, 8]. The calcium-mediated signal moderated by this receptor involves the activation of a complex subcellular pathway leading to downstream changes in protein synthesis and, consequently, to functional and structural changes in synaptic efficiency.

Finally, changes in gene expression of neurotrophic molecules as well as increased neurotrophic signaling are considered to be involved in the induction of more sustained effects of TMS. The knowledge concerning these effects at the molecular and cellular level is still very limited. Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophic family that has been demonstrated to exert neurotrophic and neuroprotective effects both *in vitro* and *in vivo*. In animal models, a significant increase in BDNF mRNA levels has been found in the hippocampal areas, parietal and piriform cortex following high frequency rTMS paradigms [13]. It has also
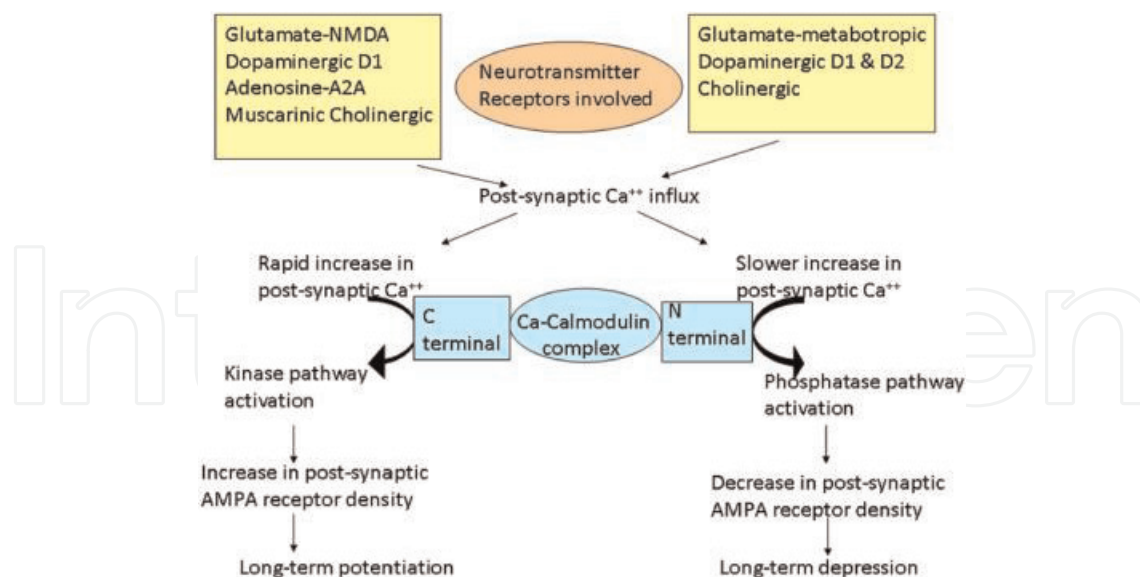
Figure 2. Schematic representation of the cascades of events involved in long-term potentiation (LTP) and depression (LTD). Reproduced with permission from Udupa and Chen [8].

been posed that rTMS could increase BDNF tropomyosin receptor kinase B (TrkB) signaling in rats and humans by increasing the affinity of BDNF for its receptor TrkB [14]. These evidences support a potential role of rTMS in providing long-term neuroprotective effects, although the exact neurochemical mechanisms underlying these properties remain to be fully elucidated.

2.3. Transcranial electric stimulation

Transcranial electric stimulation (tES) includes different NIBS techniques increasingly used for modulation of CNS excitability in humans. The principal mechanism of action of tES is a sub-threshold modulation of neuronal membrane potentials, which alters cortical excitability depending on the current flow direction through the target neurons [15]. For these reasons, tES techniques are more properly regarded as "neuromodulation" techniques, as, instead of inducing an activity in resting neuronal networks, they modulate spontaneous neuronal activity depending on the previous physiological state of target cells. Among different tES techniques, transcranial direct current stimulation (tDCS) is the best characterized and most widely used in both clinical and research settings. tDCS involves the application of a low amplitude direct current (DC) via surface electrodes on the head for a predetermined time in a painless, safe manner (**Figure 3**) [3]. tDCS offers many advantages over other NIBS devices due to a favorable non-invasive, safe profile, portability, tolerability, and cost effectiveness. Several studies have shown that tDCS modulates cortical excitability in the human motor [16, 17] and visual cortex [18]. Studies in young-adult, healthy controls showed that 13 minutes of motor cortex tDCS modifies the ampli-tude of motor evoked potential (MEP) for the subsequent 90 minutes [16]. Furthermore, pharma-cological blocking of N-methyl-D-aspartate (NMDA) receptors prevents long lasting effects of tDCS on cortical excitability, suggesting tDCS may recruit NMDA receptor-dependent plasticity. However, in animal models of tDCS, stimulation intensities comparable to those modeled in humans are not directly associated to LTP phenomena [19]. It is believed that tDCS alone produce

Figure 3. Example of transcranial direct current stimulator (tDCS) setup; mini-clinical trials (mini-CT) Unit, Soterix Medical[©].

only a subliminal neural hyperpolarization (under the cathode) or depolarization (under the anode), reducing/increasing in turns the responsiveness of the target neurons to the on-going afferent brain activity. Importantly, when combined with a second input, tDCS could results in powerful induction of LTP or LTD like phenomena. The mechanisms underlying this potential synergistic effect are not fully known, but they may rely on associative plasticity. It is known that task-specific training can induce task-specific neuronal changes based on use-dependent plasticity phenomena [20]. Therefore, the combination of behavioral tasks and tDCS may offer significant chances to achieve neuroplastic changes. The task-dependency of tDCS may influence the inter-individual variability of behavioral or neurophysiologic outcome observed after stimulation [21].

Many strategies are currently under investigation with the aim of boosting neurorehabilitation: NIBS, motor learning theories, behavioral interventions, robot-assisted rehabilitation, pharmacological agents, and neural engineering. It is likely that the optimal combination of these different approaches shall modify the science of neurorehabilitation in the future.

3. Safety of non-invasive brain stimulation

Since there are several methodological and technological differences between the different NIBS types, the tolerability, adverse effects and safety are addressed separately.

3.1. Transcranial magnetic stimulation general safety

Different side effects resulting from the application of TMS have been reported in the literature. The international safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research [6] have listed them according to their respective frequency. Common side effects include transient headache, local pain, neck pain, toothache, and paresthesia. Pain duration is usually limited, lasting up to few hours after the session, and it can be commonly relieved with acetaminophen or other over-the-counter medications. Less common adverse effects include transient hearing changes, transient cognitive/neuropsychological changes, syncope (as epiphenomenon and not related to a direct brain effect), and transient acute hypomania (after left prefrontal rTMS). Rare adverse effects reported include changes in blood levels of thyroid stimulating hormone and lactate, and seizures. Seizure activity has been reported mostly with high-frequency (HF) rTMS. TMS-induced seizures are self-limited and are not reported to have permanent sequelae. High frequency TMS has 1.4% crude risk estimate of inducing seizures in epileptic patients and less than 1% in non-epileptic subjects [22]. There is a theoretical risk of inducing currents in electrical circuits when TMS is delivered in close proximity of electric devices (e.g., pacemakers, brain stimulators, pumps, intra-cardiac lines, cochlear implants) which can cause malfunction of these devices.

3.2. Transcranial magnetic stimulation safety in Parkinson's disease population

From 211 studies published in PubMed regarding the use of TMS in Parkinson's disease patients from 1993 to October 2017, the most common adverse events (AEs) were scalp pain and headache. Most of these happened during high frequency rTMS sessions. Other less commonly reported AEs in PD include neck pain, tinnitus, and facial twitching. One study reported subclinical worsening of complex and preparatory movement as measured by spiral drawing impairment in patients after rTMS and worsening of resting tremor in one patient [41]. Rare AEs possibly related to TMS reported were transient fatigue, mild transient visual hallucinations, and transient hypotension [28]. One study reported a subject who experienced worsening in pre-existing lower back pain (**Table 1**) [37]. In our neurostimulation lab, we had one report of mild transient low mood [23] and one serious AE represented by an ischemic stroke. The ischemic stroke event was due to carotid disease (atherosclerosis) and was deemed unrelated to the study, though [26]. As an important note, to date, there are no reports of seizures induced by TMS among Parkinson's disease patients.

3.3. Safety concerns regarding "Novel" stimulation protocols

3.3.1. Deep repetitive transcranial magnetic stimulation

This technique utilizes deep TMS coils (called H-coils), which, due to a much slower decay of the electric field as a function of distance, allows for the stimulation of deeper brain regions. One study of deep rTMS [29] found that mild transient dyskinesias following stimulation to be a relatively frequent side-effect (15% of PD patients in that study). Dyskinesias happened

Study	TMS parameters	N	Adverse events (AEs)
ExerTMS (2017) [23]	HF rTMS	8	Scalp pain (n = 2), neck pain (n = 2), low mood (n = 1)
LocoTMS (2017) [24]	HF rTMS	5	Neck pain (n = 1)
Chang et al. (2017) [25]	HF rTMS ± tDCS	32	Headache (n = 1)
Brys et al. (2016) [26]	HF rTMS	61	Headache and neck pain (n = 34), ischemic stroke (n = 1)
Shin et al. (2016) [27]	HF rTMS	18	Facial twitch (n = 1), headache (n = 1)
Cohen et al. (2016) [28]	HF rDTMS	19	Scalp discomfort (n = 9), transient fatigue (n = 3), transient visual hallucinations (n = 1)
Spagnolo et al. (2014) [29]	HF rDTMS	27	Transient hypotension (n = 1), headache (n = 1), mild dyskinesia affecting only with LID (n = 4)
Shirota et al. (2013) [30]	LF rTMS	106	Tinnitus (n = 1), headache (n = 1)
Murdoch et al. (2012) [31]	HF rTMS	20	Headache (n = 2)
Benninger et al. (2011) [32]	iTBS	13	Transient tinnitus (n = 1), local scalp pain (n =?)
Pal et al. (2010) [33]	HF rTMS	12	Headache (n = 2)
Benninger et al. (2009) [34]	spTMS	10	Ipsilateral CN VII stimulation
Rothkegel et al. (2009) [35]	LF/HF rTMS	22	Headache (n = 2), nausea(n = 1)
Cardoso et al. (2008) [36]	HF rTMS	11	Headache (n =?)
Hamada et al. (2008) [37]	HF rTMS	55	Increased lower back pain (n = 1)
Khedr et al. (2006) [38]	HF rTMS	55	Headache (n =?)
Lomarev et al. (2006) [39]	HF rTMS	18	Intolerable scalp pain (n = 1)
Dragasevic et al. (2002) [40]	LF rTMS	10	Burning sensation in the scalp(n = 4), headache(n = 3)
Boylan et al. (2001) [41]	spTMS HF rTMS	10	Worsening of tremor (n = 1), scalp discomfort(n = 3), subclinical worsening of complex and preparatory movement (n = 5)

HF: high frequency; iTBS: intermittent theta burst stimulation; LF: low frequency; LID: levodopa induced dyskinesia; rDTMS: repetitive deep TMS; spTMS: single pulse TMS; rTMS: repetitive TMS; tDCS: transcranial direct current stimulation.

Table 1. Reported adverse events in studies involving TMS use in Parkinson's disease patients.

while the patients were OFF-medication and only in patients suffering from levodopa-induced dyskinesias (LID) prior to the stimulation. The same study also reported headache and one case of transient hypotension [29]. In another study, common effects reported included scalp discomfort and transient fatigue, with one episode of mild visual hallucinations [28].

3.3.2. Theta burst stimulation

To date, 19 studies have applied different patterned theta burst TMS to patients with PD. Among these studies, there is only one report of transient tinnitus (<5 minutes) and local pain during stimulation [32]. Overall, these findings seem to indicate that TBS does not carry additional risks with respect to conventional TMS protocols in PD.

3.3.3. Repetitive TMS preconditioned by tDCS

Both high frequency and low frequency rTMS preconditioned by tDCS have been used in PD. From these studies [25, 42, 43], only one occurrence of mild headache has been reported [25].

3.3.4. TMS in PD patients with implanted deep brain stimulators

Eighteen studies have been conducted in DBS-implanted PD patients with no reported AEs. Of note, electroconvulsive therapy, which uses much higher current than TMS, has also been performed in DBS patients without adverse effects. There is currently no evidence supporting the risk of heating or displacing DBS leads, but TMS has demonstrated induction of secondary currents in a DBS wire if closely applied to it [44, 45]. The main factors in determining the risk of inducing eddy currents in the DBS device seem to be the distance between the TMS coil and the DBS lead, as well as the number of loops of the wire over the DBS lead [46, 47]. Additional safety studies should be conducted to evaluate the magnitude of induced voltages and induced currents generated by TMS in implanted stimulator systems like DBS and cortical stimulation with epidural electrodes. According to current international safety guidelines [6], TMS should only be done in patients with implanted stimulators if there are scientifically or medically compelling reasons justifying it.

3.3.5. High frequency rTMS beyond 25 Hz

Rossi and colleagues seminal paper in 2009 had shown safety consideration with HF rTMS only up to 25 Hz [6]. Benninger et al. performed 50 Hz sub-threshold rTMS over the motor cortex for up to 2 seconds in 10 PD patients with only one withdrawal due to uncomfortable facial muscle stimulation [34]. A second study was then carried out with 6-second train duration where 13 PD participants received 50 Hz rTMS. No AEs and no EMG/EEG pathological increases of cortical excitability or epileptic activity were reported [48].

3.4. Transcranial direct current stimulation general safety

The protocol of stimulation (therapeutic or experimental) constitutes a critical determinant of safety, as well as the inclusion/exclusion criteria and protocol technical execution. Bikson et al. reported that from aggregated data of 33,000 sessions over 1000 subjects receiving repeated tDCS sessions, no evidence for irreversible brain injury was produced by conventional tDCS protocols within a wide range of stimulation parameters (≤40 minutes, ≤4 mA, ≤7.2 Coulombs). This includes a wide variety of subjects, including persons from potentially vulnerable populations [49]. In contrast to TMS, tDCS does not trigger neuronal depolarization; this might account for the unlikelihood of tDCS causing seizures. Although one seizure was reported in an epileptic, 4-year-old boy with cerebral palsy while receiving tDCS [50], this has been, to date, the only possibly tDCS-associated seizure reported. Other plausible causes of his seizure, such as reduced antiepileptic medication at the time and possible interactions with serotonergic medication, were considered.

Commonly reported AEs appear to be of mild intensity and transient duration. In their meta-analysis, Brunoni and colleagues characterized the incidence of AEs in 209 studies published

from 1998 until August 2010 [51]. Of these 209 studies, 117 were compared for active tDCS vs. 82 sham tDCS studies and showed side effects of tingling (22 vs. 18%), headache (15 vs. 16.2%), burning sensation (9 vs. 10%), itching (39 vs. 33%), and discomfort (10 vs. 13%) [51]. Results suggested that some AEs, such as itching and tingling, were more frequent in the tDCS active group, although this was not statistically significant. The authors disclosed a selective reporting bias for reporting, assessing, and publishing AEs of tDCS that hinders further conclusions. The authors raised awareness of the need to improve systematic reporting of tDCS-related AEs.

The local effects of tDCS on the skin are not believed to be necessarily linked to the hazards involving the underlying brain tissue. Several causative factors for skin lesions have been proposed, including electrode position (the front side of scalp due to curvature and lack of hair), skin conditions, allergic predisposition, skin preparations, high skin impedances, high electrical currents, duration of stimulation, repeated sessions, small electrodes (high current density), electrode shape, dry electrodes, inadequate fixation of electrodes, non-uniform contact pressure of electrodes to skin, extensive skin heating, solution salinity of electrode sponges, sponge shape, and deterioration of the sponges [52]. Other notable, non-skin AEs that have been reported are nausea, dizziness, and sleepiness [53, 54]. Several studies conducting tDCS over DLPFC reported hypomania or mania in unipolar and bipolar depression treatment trials, but these AEs cannot be fully attributed to tDCS [55–57]. The risk of hypomania or mania in depressed subjects receiving tDCS might not be generalizable to a different population or different brain location; however, it could be a risk if a study does not exclude depressed participants.

3.5. Remotely supervised transcranial direct current stimulation

Recent trials have developed tDCS as a 'telemedicine protocol.' This paradigm utilizes computer videoconferencing for real-time monitoring between the study subject and a study technician [58]. This innovative approach is intended to increase compliance and facilitate research participation by allowing patients to receive therapy in the comfort of their homes. While traveling to clinic or research labs for a tDCS session can present an obstacle to subjects and their caregivers, with modified devices and headgear, tDCS can be administered remotely under clinical supervision, potentially enhancing recruitment due to convenience, while still maintaining clinical trial and safety standards [59]. Perhaps the most promising and tested paradigm is remotely supervised tDCS (RS-tDCS). RS-tDCS has been proven to be safe, feasible, and acceptable for patients with multiple sclerosis [60–62].

3.6. Transcranial direct current stimulation safety in Parkinson's disease population

Current published studies utilizing tDCS in PD patients have shown mostly mild and expected adverse events [63], with only one reported event of skin burn (similar to first degree burn) [63]. The skin burn was deemed due to mal-positioned electrodes and resolved without sequela in 3 days. There is no specific provision or precautions for tDCS in PD. However, as previously pointed out by Brunoni et al., as almost half of studies do not report presence/ absence of AEs, it is indispensable that clinical research document and report AEs in an active,

systematic fashion in order to guarantee that tDCS is indeed a safe technique [51]. Our neurostimulation lab is currently conducting clinical trials with RS-tDCS for PD. Our experience has been very positive with regard to feasibility, safety, and acceptability of RS-tDCS in PD [64, 65]. Further trials of RS-tDCS need to be conducted to corroborate the feasibility and safety of remote videoconferencing tDCS sessions. At-home, tele-monitored tDCS therapy (e.g., RS-tDCS) could become crucial to ease the development of multicenter initiatives with longer period of stimulation and minimizing participant's burden.

In summary, the safety and tolerability of tDCS can be maximized by following standard procedures, defining optimal stimulation parameters, and following good clinical and good research practice implying adequately trained personnel, constant checking of stimulation settings, careful selection of subjects, prompt and systematic reporting of AEs, and regular supervision of tDCS equipment. The international safety guidelines for tDCS neuromodulation [19] emphasizes the importance of adequately trained personnel in delivering the stimulation and overseeing all related procedures (i.e., for RS-tDCS). Overall, tDCS is a generally safe technique when used within standardized protocols in a research or clinical setting. However, generalization of safety beyond these settings into different clinical contexts or do-it-yourself (DIY) should be avoided [66]. RS-tDCS standardized framework for safety, tolerability, and reproducibility, once established, will allow for translation of tDCS clinical trials to a greater size and range of patient populations.

4. Potential applications and therapeutic effects of NIBS in PD

There has been cumulative evidence supporting beneficial effects of TMS and tDCS in PD. However, several limitations have obscured the evidence-based generalizability of these results. Main limitations are wide methodological heterogeneity in study designs (outcomes, eligibility criteria, intervention parameters, brain targets, etc.) and exploratory designs with small sample sizes in the majority of the studies. As TMS research is significantly more advanced in terms of number of studies and Class I multicenter initiatives, TMS and tDCS therapeutic evidence will be revised separately.

4.1. Effects of TMS in PD

Several systematic reviews and meta-analyses support the positive therapeutic effect of TMS in PD [67, 68]. The wide use of the Unified Parkinson's Disease Rating Scale (UPDRS) across most studies enabled results to be compared through meta-analysis [67, 69]. UPDRS is likely the most widely used assessment for PD and combines elements of four scales to produce a comprehensive and flexible tool to monitor the course of Parkinson's and the degree of disability. The cumulative score will range from 0 (no disability) to 199 (total disability). Motor UPDRS (part III) is usually administered by a healthcare professional and scores the motor performance in a series of items, including rigidity, bradykinesia, and tremor. UPDRS part II, on the other hand, is a self-evaluation of activities of daily living "during the last week." It is important to point out that the beneficial TMS effects are mostly seen in motor scores in the

UPDRS part III; as such, this might question the overall functional relevance and impact in quality-of-life. The average improvement of motor UPDRS sub-score in these clinical trials ranged from −2.7 to −6.4 points and mainly reflected improvements in bradykinesia and rigidity. The minimal clinically important change of motor UPDRS sub-score has been proposed to be between 5 and 6 points [70, 71].

Chou and colleagues conducted subgroup analysis of clinical trials and showed that the effect sizes estimated from high-frequency rTMS targeting the primary motor cortex (SMD, 0.77; 95% CI, 0.46–1.08; P < .001) and low-frequency rTMS applied over other frontal regions (SMD, 0.50; 95% CI, 0.13–0.87; P = .008) were significant. The effect sizes obtained from the other 2 combinations of rTMS frequency and rTMS site (i.e., high-frequency rTMS at other frontal regions: SMD, 0.23; 95% CI, −0.02 to 0.48, and low primary motor cortex: SMD, 0.28; 95% CI, −0.23 to 0.78) were not significant. Meta-regression revealed that a greater number of pulses per session or across sessions are associated with larger rTMS effects [69].

The two more recent multicenter randomized clinical trials of TMS for PD were not included in the referenced reviews. Shirota et al. [30] explored the efficacy and stimulation frequency effect of rTMS over the supplementary motor area (SMA) in PD. Results showed a decrease (improvement) of 6.84 points in the UPDRS part III in the 1 Hz group at the last follow up (12 weeks post-intervention). Sham stimulation and 10 Hz rTMS improved motor symptoms transiently, but their effects disappeared in the observation period. The magnitude of improvement is similar to prior HF rTMS studies; however, it was only significant at the last follow up. Interestingly, the preliminary results of a prior trial from the same group showed that HF rTMS was significantly better than LF over SMA [37]. A final interesting observation is that rTMS was applied once weekly for 8 weeks rather than daily session. These findings have not been replicated yet.

The latest large multicenter clinical trial was published in 2016 by Brys et al. [26]; the study innovated "multifocal stimulation" in PD patients suffering from comorbid depression. It compared motor cortex stimulation with dorsolateral pre-frontal cortex (DLPFC) stimulation, both alone and in combination. The results provided Class I evidence of motor beneficial effects of HF rTMS over motor cortex, but failed to prove synergistic effects when combined with DLPFC. The magnitude of the improvement (−4.9 points in the UPDRS-III), was close to a minimal clinically important change on the UPDRS-III [71] but slightly below that found in meta-analyses (−6.4 and −6.3 points) [69, 72]. It is worth mentioning that the effects were only significant at 1-month follow up and not significant in the following observations at three and 6 months distance respectively. These extended follow-up period results raise concern on the sustainability of significant improvements beyond 1 month. Despite the amount of data regarding the efficacy and safety of this technique in relieving motor symptoms of PD, rTMS has not yet been systematically assessed as a potential treatment for FoG. An initial report by Rektorova and colleagues found no significant effect on OFF-related FoG in six PD patients treated with five sessions of high-frequency rTMS over the DLPFC and primary leg motor area [73]. However, a later double-blind cross-over study on 20 patients with FoG investigating the effects of a single session high frequency rTMS did suggest efficacy [74]. As recently observed, the contribution of NIBS alone or combined with neurorehabilitation to address this highly

disabling phenomenon remains to be systematically assessed through well-powered, well-designed and reproducible studies [75].

The use of rTMS for the treatment of dyskinesias is limited to small studies showing contradictory findings, with either LF rTMS over M1 [76, 77] or LF rTMS over SMA [78, 79].

In 2014, a group of European experts in TMS were commissioned to revise all available trials to elaborate evidence-based guidelines for the therapeutic use of rTMS [80]. This included randomized controlled trials with at least 10 subjects receiving active stimulation, along with at least 2 comparable studies (same cortical target and same stimulation frequency), published by independent groups before the end of March 2014. Results concluded possible antiparkinsonian effect of HF rTMS over motor cortex delivered bilaterally. Other results were: no recommendation for dyskinesias and a probable antidepressant effect on HF rTMS over the left DLPFC in PD.

Novel paradigms of pairing TMS with other rehabilitation methods to try synergies and optimizing rehabilitation have recently been explored. Experimental protocols carried out in our neurostimulation lab have combined TMS with motor skill learning [81], physical therapy [35], aerobic exercise [23], and finally, with treadmill training [82]. Larger studies will need to be conducted to further validate these paradigms. Optimal treatment parameters remain elusive. Standardization of PD outcomes, of TMS methodologies and bigger multicenter collaborative initiatives with long follow-up periods are [12] needed to demonstrate the real therapeutic potential of TMS in PD.

4.2. Therapeutic applications of tDCS in PD

tDCS has been tested to promote motor learning in healthy adults and stroke patients [83, 84]; this technique has also been explored as a treatment of migraines, aphasia, multiple sclerosis, epilepsia, tinnitus, schizophrenia, and dystonia with unclear or insufficient beneficial evidence for recommendation [85]. According to recent evidence-based guidelines for the therapeutic use of tDCS (including studies published before the end of the bibliographic search on September 1, 2016), only some types of chronic pain, fibromyalgia, depression, and craving have shown to benefit from the neuromodulation, with possible or probable recommendation levels. tDCS for PD has no formal recommendation; however, "no recommendation" means the absence of sufficient evidence to date, but not the evidence for an absence of effect [83]. Also to be noted, studies that have not been replicated were not included for analysis in this evidence-based review. tDCS seems to induce some beneficial effects in motor symptoms in PD, but studies are needed to replicate these results [86].

A Cochrane review by Elsner et al. [87], found no evidence of effect as measured by UPDRS global change in two studies and low quality evidence on motor impairment as measured by means of UPDRS Part III when real stimulation was compared vs. sham [63, 88]. Two studies specifically investigated the impact of tDCS on quantitative gait parameters [63, 89] and showed no significant changes in walking speed. There have been no reported studies exploring the efficacy of tDCS on tremor. The reduction of OFF-time and ON-time hampered by dyskinesias was analyzed in one study conducted on 25 subjects, resulting in no significant benefit [63]. In addition, health-related quality-of-life variables on both physical and mental

domains were investigated, again with no significant effect [63]. As concluded by Elsner et al., "the methodological quality of these studies needs to be improved with particular respect to the risk of allocation concealment, blinding of personnel and intention to treat analysis" [87].

The importance of non-motor features in PD has been increasingly recognized. A particularly active area is the application of tDCS to enhance cognitive function. Cognitive impairment represents a highly disabling non-motor symptom in patients with PD, and several studies in patients with Alzheimer's disease suggest that tDCS could improve memory performance [90, 91]. A few trials have been expressly designed to investigate the therapeutic potential of tDCS on cognitive function in patients with PD with mostly (but not exclusively) using neuromodulation of DLPFC [92–94]. Furthermore, fatigue is a frequently under-recognized non-motor symptom in patients with PD. So far, tDCS over DLPFC has been demonstrated to improve fatigue in other neurological conditions, including MS [95–97]. It seems therefore plausible that analogous stimulation settings could provide similar benefits in patients with PD, although this hypothesis remains to be confirmed through appropriately designed clinical trials (ClinicalTrials.gov identifier: NCT03189472).

5. Non-invasive brain stimulation challenges

The major limiting factors to the extensive clinical application of NIBS technologies are inherent to methodological properties of trials. The body of currently available data mainly rests on small-sized studies carried out with exploratory designs. As such, these studies are known to be prone to the risk of type I and type II statistical errors. Usually, a type I error leads to establish a supposed effect or relationship when, in fact, the null hypothesis is true. Conversely, a type II error leads to erroneous acceptance of the null hypothesis when this is, in fact, false. The best way to control for these errors is to design appropriately sized studies through power calculations based on the estimated magnitude of effects. Alternatively, adaptive designs can be conducted to allow for a flexible increase of the sample along with the trial implementation. This strategy, however, can further complicate the final interpretation of data. A second order of methodological limitation is represented by unavoidable differences in stimulation parameters between trials (i.e., stimulation location, frequencies, coil geometry, number of pulses, number of sessions, specific population, follow-up time, electrode montage, sponge sizes, etc.). These differences result in a commonly limited comparability between studies. At minimum, it is imperative for all NIBS trials to exhaustively disclose the followed stimulation protocol in all its components, thus maximizing comparability and reproducibility. Further, stimulation parameters should be chosen and refined on the basis of biologically plausible hypotheses, and experimental assumptions should be modeled on the pathophysiology of the targeted phenomena. Random target stimulation and "trawl fishing" experimental designs are likely to be inconclusive or to result in poor cost/effectiveness. Negative studies should be adequately reported and acknowledged to improve publication bias and expand knowledge among the scientific community. A clear description of placebo- or sham-controlled method should always be provided and all potential limitations of blinding procedure disclosed. For example, the use of non-realistic sham coils in a cross-over design can

compromise the blinding of the study. Measures to assess adequate masking/blinding procedures should be incorporated into the trial, for example through the administration of specific questionnaires. Most of the original trials published in the literature lack double-blind controlled designs. This limitation has been conveniently weaning off over the past decade as a growing number of properly controlled NIBS trials flourished. Interestingly, newly designed coils can now allow for triple blinded designs where the subject, the investigator, and the technician are unaware whether real or sham stimulation is delivered. The use of appropriate and comprehensive clinical outcome to assess efficacy constitutes another significant challenge. A broad spectrum of symptoms could be potentially affected by NIBS. In order to capture clinically meaningful effects, quality-of-life scales and other tools exploring subjective improvements on ADLs should be incorporated to assess NIBS potential beyond the simple motor effect as quantified by UPDRS-III. Standardization of outcomes can also facilitate further meta-analysis. Finally, knowledge about NIBS and its therapeutic potential on movement disorders could be boosted by collaborations across involved laboratories and multicenter initiatives. In parallel, adequate training of personnel to refine operator's expertise and skills should be provided in a standardized fashion across academic centers [19].

6. Conclusions

To summarize, clinical effects of NIBS can be attributed to complex and likely interconnected phenomena, including the normalization of cortical excitability, the modulation of connectivity between neuronal networks and the induction of neuroplastic phenomena. The substantially safe, reproducible, and non-invasive nature of NIBS makes these techniques of appealing interest for the study and treatment of various neurological and psychiatric disorders, including PD. For TMS, the pooled evidence suggests that rTMS improves motor symptoms of PD. Overall, HF rTMS over M1 and LF rTMS over SMA appears effective. The motor improvement in large multicenter clinical trials is around the minimal clinically important change of motor UPDRS. There are controversial findings in a few small studies for dyskinesias. There is insufficient data regarding the effects of rTMS for improving health-related quality-of-life, disability and activities of daily living. These data would help to better determine the clinical relevance for motor improvements. The currently available evidence supporting the use of tDCS neuromodulation in patients with PD is limited to small, single-center studies exploring different symptoms of the disease mainly through heterogeneous experimental methodologies. There is need for appropriately designed, directly comparable and well-powered trials to better characterize the therapeutic potential of this technique in this specific population. Despite these limitations, tDCS still holds much promise for a potential therapy as it is a relatively inexpensive, portable, and easy to perform technology.

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Conflict of interest

The authors declare that they have no competing interests and report no disclosures relevant to the manuscript.

Notes/Thanks/Other declarations

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Author details

Milton C. Biagioni*, Kush Sharma, Hamzeh A. Migdadi and Alberto Cucca

*Address all correspondence to: milton.biagioni@nyumc.org

The Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders at NYU Langone Health, New York, USA

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