Journal of Neuroscience Methods 347 (2021) 108957

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

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

Non-invasive brain stimulation for Parkinson's disease: Clinical evidence, latest concepts and future goals: A systematic review

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ARTICLE INFO

Keywords:
Parkinson's disease
Non-invasive brain stimulation
rTMS
tDCS
tACS
tRNS
DBS

ABSTRACT

Parkinson's disease (PD) is becoming a major public-health issue in an aging population. Available approaches to treat advanced PD still have limitations; new therapies are needed. The non-invasive brain stimulation (NIBS) may offer a complementary approach to treat advanced PD by personalized stimulation. Although NIBS is not as effective as the gold-standard levodopa, recent randomized controlled trials show promising outcomes in the treatment of PD symptoms. Nevertheless, only a few NIBS-stimulation paradigms have shown to improve PD's symptoms. Current clinical recommendations based on the level of evidence are reported in Table 1 through Table 3. Furthermore, novel technological advances hold promise and may soon enable the non-invasive stimulation of deeper brain structures for longer periods.

Clinical evidence for the treatment of PD by means of rTMS

Level	Recommendation
	Effective
Level B	HF-rTMS of M1 for the treatment of overall motor symptoms in PD
Level B	HF-rTMS over DLPFC for the treatment of depression in PD
Level B	cTBS over cerebellum for the treatment of dyskinesia in PD
Level C	HF-rTMS over SMA for the treatment of overall motor symptoms in PD
Level C	LF-rTMS over SMA for the treatment of dyskinesia in PD
	Ineffective
Level A	HF-rTMS over SMA for the treatment of depression in PD
Level B	HF-rTMS of M1 for the treatment of gait performance in PD
Level B	HF-rTMS of M1 for the treatment of depression in PD
Level B	HF-rTMS over the DLPFC for the treatment of overall motor symptoms in PD
Level B	HF-rTMS of M1 + DLPFC for the treatment of overall motor symptoms in PD
Level B	LF-rTMS over the SMA for the treatment of overall motor symptoms in PD
Level C	LF-rTMS of M1 for the treatment of overall motor symptoms in PD
Level C	LF-rTMS of M1 for the treatment of depression in PD
Level C	LF-rTMS of M1 for the treatment of dyskinesia in PD

Clinical evidence for the treatment of PD by means of tDCS

Level	Recommendation
	Effective
Level B	Anodal tDCS over M1 for the treatment of overall motor symptoms in PD
Level B	Anodal tDCS over M1 + DLPFC for the treatment of gait performance in PD

(*continued on next column*)

(*continued*)

Clinical evidence for the treatment of PD by means of tDCS

Level	Recommendation
Level C	Anodal tDCS over M1 for the treatment of gait performance in PD
Level C	Anodal tDCS + physical therapy for the treatment of cognitive function in PD
	Ineffective
Level B	Anodal tDCS + physical therapy for the treatment of overall motor symptoms in PD
Level B	Anodal tDCS + physical therapy for the treatment of gait performance in PD
Level C	Anodal tDCS + physical therapy for the treatment of bradykinesia in PD

Clinical evidence for the treatment of PD by means of tACS

Level	Recommendation
No recommendations are possible	

1. Background

The brain adapts to internal or external demands with functional and structural changes (Sharma et al., 2013). Some changes may be adaptive, and others maladaptive, as it might be the case in Parkinson's disease (PD) (Berardelli et al., 2001; Helmich et al., 2012; Caligiore

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https://doi.org/10.1016/j.jneumeth.2020.108957
Received 19 March 2020; Received in revised form 27 August 2020; Accepted 18 September 2020
Available online 2 October 2020

et al., 2016). In this review, we closely scrutinize current non-invasive brain stimulation techniques and their clinical use to treat PD. The rationale for clinical use of brain stimulation techniques aims to selectively enhance adaptive or suppress mal-adaptive patterns of neural activity; their ultimate goal is to restore normal physiology in the affected brain networks, and, in so doing, to ameliorate symptoms' manifestation. The use of specific biomarkers further empowers this strategy. Several attempts have been made to enhance human's brain function by altering brain's electrical processes; but stimulation devices for clinical practice, and also efficacious stimulation paradigms, emerged just recently (Zago et al., 2008). In this review, we will focus on non-invasive brain stimulation (NIBS) for treating PD. We will provide an overview of PD's pathophysiology, the NIBS rationale, the current evidence supporting its therapeutic use in PD, and also possible future clinical and research applications. We put particular emphasis on the reported clinical efficacy. A comprehensive collection of tables summarizes the types of stimulation, stimulation parameters, and clinical outcomes. We conclude this review with a discussion of the principal findings we consider particularly relevant to the future clinical and research practice.

1.1. Parkinson's disease

PD has a prevalence of about 1 % in the general population and higher in the elderly, and is one of the most common neurodegenerative diseases (Lau and Breteler, 2006). With the aging of the world population, the social burden and economic impact of PD will continuously increase. This calls for the search of effective, safe and ideally inexpensive treatments, suitable for the clinical practice, based on recent insights into the pathophysiology of PD. While dopaminergic replacement therapy improves motor symptoms, the emergence of motor symptoms as the disease progresses refractory to dopamine replacement (e.g. postural instability and gait difficulties) poses a therapeutic challenge. Moreover, though the therapeutic effects endure, motor fluctuations and levodopa-induced dyskinesia emerge and complicate the conventional medical treatment. The neurodegeneration primarily affects the nigrostriatal dopaminergic system, but other non-dopaminergic neural circuits also degenerate progressively (Braak et al., 2003; Surmeier et al., 2017). This explains why these symptoms do not respond to dopaminergic therapy.

This review focuses on the most used brain stimulation techniques, which can be divided into the invasive (e.g. deep brain stimulation (DBS) or direct cortical stimulation (DCS)), and the non-invasive techniques, the most prominent being transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and transcranial alternative current stimulation (tACS) (Miniussi et al., 2012).

1.2. Invasive stimulation

Deep brain stimulation has proven its clinical efficacy to treat motor fluctuations, dyskinesia and refractory tremor, and has become an established therapeutic option for advanced PD (Sugiyama et al., 2015). This evidence provides a strong rationale for NIBS. However, this approach to treatment is available only to a limited number of patients, and bears the risk of surgical e.g. infections, hemorrhage, and neuropsychiatric complications (Fenoy and Simpson, 2014). Furthermore, axial symptoms –e.g. postural instability and gait difficulties including freezing– remain refractory to DBS and other invasive options, they underscore the need for therapeutic alternatives.

Although promising for the treatment of PD, discussing recent technological developments would go beyond the scope of this review. For a review on direct (i.e. invasive) cortical stimulation see for example (Brittain and Cagnan, 2018); for new forms of DBS see for example (Bronstein et al., 2011; Lozano et al., 2019); for a review on MR-guided high-intensity focused ultrasound see for example (Krishna et al., 2018; Schlesinger et al., 2017).

1.3. Non-invasive brain stimulation

Analogous to the therapeutic success of DBS, non-invasive approaches such as rTMS, tDCS and tACS, achieved prominence (Fig. 2). Even if the evidence for their clinical efficacy is still largely insufficient, an increasing number of randomized controlled clinical studies have revealed that these approaches might improve PD symptoms, have only mild adverse effects, and are easy to use and inexpensive (Miniussi et al., 2012). In addition, they might also act as adjuvant intervention in current treatments, a potential combination that may increase their efficacy to treat PD. These approaches to treatment have reportedly the power to modulate brain plasticity processes and to foster, for example, long-lasting effects, making their use attractive (Fritsch et al., 2010). Additionally, the lightweight of handheld tDCS and tACS devices further facilitates their use in neurorehabilitation (Carvalho et al., 2018).

2. Pathophysiology of Parkinson's disease

In PD, the neurodegeneration of the dopaminergic nigrostriatal pathway leads to widespread functional and structural changes in the motor network including the motor cortex-basal ganglia-thalamo-cerebellar circuit and associated motor cortical areas (Alexander et al., 1991). There is an extensive literature on the pathophysiology of PD but it is difficult to distinguish whether the correlation found between motor deficits and neurophysiological biomarkers indicates causality or reflects a compensatory process. Furthermore, cardinal features of PD: tremor, bradykinesia, rigidity and axial signs arise from distinct pathogeneses and their underlying pathophysiologies differ as suggested by the sequential response to DBS and their reappearance after cessation of DBS (Temperli et al., 2003; Caligiore et al., 2016; Bologna et al., 2019).

2.1. Primary motor cortex

Although the structural integrity of M1 and its corticospinal projections is preserved in PD, cortical excitability (Cantello et al., 2002; Lefaucheur, 2005) and cortical activity (Schoellmann et al., 2019) are altered. Summarizing an extensive literature on M1 cortical excitability –as assessed by motor threshold in PD– cortical excitability is increased during rest and fails to increase during action (Cantello et al., 1991; Ellaway et al., 1995; Valls-Solé et al., 1994). There appears no direct effect to either medication (Ni et al., 2013; Kačar et al., 2013) or STN-DBS (Cunic et al., 2002).

2.1.1. Motor evoked potentials

The recruitment (stimulus-response or input-output) curve plots the increase of MEP size as a function of stimulus intensity and offers another method to assess the corticospinal excitability. In PD, the recruitment curve shifts to the right as higher stimulus intensities are needed for the same responses (Valls-Solé et al., 1994), and its slope steepeness correlates with the stage of the disease (Bologna et al., 2018). Moreover, when assessed prior, during and after a voluntary movement, MEP amplitudes increase earlier and decrease later, with a slower rate of increase/decrease in comparison to healthy individuals (Chen et al., 2001b). Therefore, in PD, there is an impairment in motor cortex activation and deactivation, which may correlate with bradykinesia. Some authors conclude that the increased excitability during rest may compensate for, and the impaired activation/deactivation during a movement may arise from a deficient thalamocortical drive (Berardelli et al., 2001).

2.1.2. Short-interval, intra-cortical inhibition, facilitation and sensory afferent inhibition

Short-interval, intra-cortical inhibition also shows some anomalies in PD. When a suprathreshold test stimulus –at inter-stimulus intervals (ISI) of 1−6ms–follows a subthreshold conditioning stimulus (CI), a short-interval, intra-cortical inhibition (SICI) can be observed. In PD, the

short-interval, intra-cortical inhibition is reduced, while dopaminergic medication restores it (Ni et al., 2013). In addition, clinical improvement after DBS correlates with the restoration of SICI (Cunic et al., 2002). Furthermore, long- interval, intra-cortical inhibition (LICI) inhibits SICI in healthy subjects (i.e. triple stimulation TMS), this inhibitory effect is absent in PD, and dopaminergic medication is ineffective in restoring it (Chu et al., 2009).

When a suprathreshold test stimulus –at inter-stimulus intervals (ISI) of 6 to 100ms–follows a subthreshold conditioning stimulus (CI), a short-interval, intra-cortical facilitation (SICF) can be observed. Although some authors could not find differences between PD patients and controls in short interval facilitation (Strafella et al., 2000), others found that SICF was decreased in PD (Bares et al., 2003). Interestingly SICI and SICF form a sigmoidal curve, which amplitude is reduced in PD. This impaired interplay between inhibition and facilitation might be the key to explain the impaired sensorimotor integration of afferent inputs in PD.

When the suprathreshold test stimulus is preceded by an electric stimulation of the contralateral peripheral hand nerve, a short-interval afferent inhibition (SAI) is observed (Tokimura et al., 2000). This phenomenon is thought to represent the sensorimotor integration of afferent inputs mediated through central cholinergic activity (Martin-Rodriguez and Mir, 2020). Compared to healthy subjects, PD patients show a reduction in SAI. Furthermore, SAI severity seems to correlate with disease duration and cognitive impairment, even if it does not correlate with motor impairment (Martin-Rodriguez and Mir, 2020).

SICI and SICF have also been studied in genetic forms of PD such as LRRK2 (Ponzo et al., 2017). For example, in LRRK2 SICI seemed to be reduced ON and OFF medication, whereas SICF seemed to be increased compared to idiopathic PD and healthy subjects (Ponzo et al., 2017). Each genetic PD form may have a specific SICI/SICF signature (Ponzo et al., 2017), possibly even each different mutation type: as it is seen in the G2019S vs R1441C mutation (Dubbioso et al., 2017; Di Lorenzo et al., 2017).

Furthermore, specific SICI and SICF signatures may offer a complimentary approach to discriminate between Lewy body dementia, progressive supranuclear palsy, corticobasal syndrome, Alzheimer's disease and healthy subjects with high accuracy (Benussi et al., 2018): these findings need validation and may eventually form a future new diagnostic tool.

2.1.3. The cortical silent period (CSP)

In PD, the cortical silent period (CSP) that follows a supra-threshold TMS pulse of M1 is shortened in the off-medication or off-stimulation condition, normalized on-medication or on-stimulation, lengthened during the dyskinetic state (Chen et al., 2001b; Cantello et al., 2002), and it appears to correlate with the motor UPDRS score (Wu et al., 2007) and the dopaminergic effect (Wu et al., 2007). Furthermore, rTMS (Benninger et al., 2012; Lefaucheur et al., 2004) and tDCS (Lang et al., 2004) modulate the CSP, suggesting a potential use as a biomarker in NIBS.

GABA-A receptors mediate SICI and GABA-B receptors the CSP. Therefore, and since the inhibitory effect on SICI after the triple pulse stimulation is absent in PD, motor cortex inhibition may be impaired.

2.1.4. Synaptic plasticity

The capacity for alterations of synaptic connections between neurons inducing a lasting effect over time is referred to as synaptic plasticity (Sweatt, 2016). The persistent effects after M1 stimulation with low-frequency rTMS (Buhmann et al., 2004), high-frequency rTMS (Mir et al., 2005), theta-burst stimulation (Koch et al., 2009) and paired-associative-stimulation (Morgante et al., 2006), suggest preserved plasticity in PD. Stimulation with low-frequency rTMS (Buhmann et al., 2004), high-frequency rTMS (Gilio et al., 2002; Mir et al., 2005) and paired-associative stimulation (Morgante et al., 2006; Ueki et al., 2006) yielded effects, only during the medication ON-state. Therefore, plasticity appears to be dopamine-dependent (Nitsche et al., 2006). Also, tDCS effects are dopamine-dependent (Fresnoza et al., 2014; Monte-Silva et al., 2010; Nitsche et al., 2006), pesumably with an inverted U-shape, dose-dependent relation (Monte-Silva et al., 2010). In summary, dopamine mediates synaptic plasticity and thereby modulates the effects of NIBS. However, no dopamine dependency has been shown when taking dopamine for the first time at disease onset (Kishore et al., 2012a). Hence, probably a long-term L-DOPA intake is necessary to induce plasticity. Furthermore, plasticity may be impaired even prior onset of motor symptoms, suggesting that PD foremost deteriorates motor learning rather than direct motor execution (Kishore et al., 2012a). The NIBS directional effect and its strength are both influenced by the physiological state of the brain (Miyaguchi et al., 2013) and the disease stage (Kishore et al., 2012b). Also, the plasticity may depend on chronic stimulation. DBS restores impaired short- and long-latency afferent inhibition –which correlates with clinical improvement (Shukla et al., 2013)– after six months of chronic stimulation. It indicates a long-term plasticity process. Furthermore, levodopa and bilateral STN DBS may exert synergistic effects on plasticity as suggested by motor and gait improvement when both therapies are combined (Lubik et al., 2006).

Interestingly, in early asymetric PD, the less affected brain-hemisphere restructures its functional sensorimotor organization, probably in order to compensate for the more affected hemisphere (Kojovic et al., 2012). The less affected hemisphere shows an increased motor cortical plasticity –assessed by paired associative stimulation– compared with healthy subjects. Furthermore, the less affected hemisphere preserved the intracortical inhibition whereas the more affected side had a decreased intracortical Inhibition. The negative correlation between the severity of motor symptoms and the amount of response to PAS in the less affected hemisphere supports the idea of early adaptive rather than maladaptive changes. (Kojovic et al., 2012). During a 12 months follow-up, the heightened plasticity of the less affected side, which was present at disease onset, declined: it may reflect a failure of compensatory mechanisms, which maintained function in the preclinical state (Kojovic et al., 2015).

Furthermore, the response to the plasticity inducing protocols may not be strictly correlated to the clinical improvement induced by dopamine administration (Kishore et al., 2012a; Suppa et al., 2011).

However, many studies investigating plasticity showed heterogenous results. Although some causes for heterogeneity –such as PAS dependent plasticity versus TBS dependent plasticity, or asymmetric results in early disease stages– are identified, most of them are not yet understood (for an excellent review on the topic see Koch, 2013).

2.2. Functional connectivity

Functional connectivity is the coordinated information exchange of spatially separated brain regions in order to allow integrative and higher-order functions. Connectivity studies suggest that PD affects the activation of extensive cortical networks, which mostly normalizes with dopaminergic medication (Buhmann et al., 2004; Mir et al., 2005). The network includes the SMA, the DLPFC and the mesial frontal area, the lateral pre-motor and parietal cortices. The SMA excitability increases with contralateral basal ganglia pathology (Casarotto et al., 2019); and the activation of DLPFC, SMA and mesial frontal areas are impaired during voluntary movements (Samuel et al., 2001). The hypoactive DLPFC may compromise motor reactions to external cues (Jahanshahi et al., 1995), while the hypoactive SMA and mesial frontal area may impair intentional movements (Jahanshahi et al., 1995; Playford et al., 1992). DLPFC and SMA activity correlate positively with clinical improvement during DBS (Ceballos-Baumann et al., 1999; Limousin et al., 1997); SMA correlates positively with dopaminergic medication (Jenkins et al., 1992; Rascol et al., 1992), and negatively with the early component of the Bereitschaftspotential (Ikeda et al., 1997; Jahanshahi et al., 1995). In PD, the expanded activity in the lateral pre-motor and

parietal cortices is thought to be compensatory (Brooks, 1999) and normalizes with clinical improvement after dopaminergic medication (Haslinger et al., 2001).Thus, stimulating brain areas other than M1 or multiple cortex areas (Dagan et al., 2018; Lomarev et al., 2006; Rabey et al., 2013; Benninger et al., 2011) hold promise.

2.3. The cerebellum: a new target

The cerebellum may play an essential role in the pathophysiology of PD, levodopa-induced dyskinesia (Koch et al., 2009) and in tremor pathogenesis (Benninger et al., 2009a), and should, therefore, be further investigated (Martini et al., 2019). In PD, the cerebellum may be overactive: 1 Hz rTMS decreased tremor and combined tDCS M1/cerebellum improved motor symptoms (Ferrucci and Priori, 2018).

The primary motor cortex (M1) and the cerebellum are connected through the cerebello-thalamo-cortical circuit. When a suprathreshold test stimulus of M1 –at inter-stimulus intervals of 5−7ms– follows a conditioning stimulus over the cerebellum, a cerebellar-brain inhibition (CBI) can be observed in healthy subjects. However, in PD patients, CBI seemed to be absent OFF medication and even ON medication (Carrillo et al., 2013). Similarly, cerebellar cTBS reduced MEP amplitude and SICI in controls but not in PD patients (ON and OFF medication) (Carrillo et al., 2013). Thus, PD patients may have a deficient cerebellar-thalamocortical inhibitory drive that cannot be restored by standard dopaminergic medication.

However, another study showed reduced excitability after cTBS in healthy subjects and PD patients (Bologna et al., 2015); hence, results are still heterogeneous.

Interestingly, a specific pathology such as scans-without-evidence-of-dopaminergic-deficit (SWEDD), show a specific signature of cerebello-thalamo-cortical impairment only during rest, compared with PD and dystonic patients (Schirinzi et al., 2016).

For a detailed review on the role of the cerebellum in PD, we recommend Ferrucci et al. (2016a, 2016b) and França et al. (2018).

2.4. Dyskinesia

The pathogenesis of levodopa-induced dyskinesia (LID) remains poorly understood, yet some hypotheses have emerged. LID may be caused by maladaptive plasticity (Morgante et al., 2006), by a reduced inhibitory control of the inferior frontal cortex (Cerasa et al., 2015), by cerebellar dysfunction (Nimura et al., 2004) or by a narrow-band gamma oscillation (60−90 Hz) in the motor cortex that could be used as a biomarker (Swann et al., 2018). In particular, LID seem to correlate with the overactivation of the contralateral frontal area (M1, SMA, IFC) probably mediated through direct cortico-cortical disinhibition (Ponzo et al., 2016). Furthermore, Ponzo et al. achieved to reduce the overactive influence of the IFC on the contralateral M1 –whilst reducing LID symptoms– by applying a cTBS protocol over the IFC. Similarly, Wagle-Shukla et al. (2007) used a low-frequency rTMS protocol –stimulating the contralateral M1 area– to reduce LID Symptoms. These results may help to choose target areas for NIBS protocols.

2.5. Oscillopathy in Parkinson's disease

Recently, neural oscillatory patterns in the brain have attracted the interest for studying the pathophysiology of PD. It seems possible that specific frequency patterns could gate communication and network resonance between brain regions, or that they could prevent activity perturbations by keeping the information flow in a *status quo*. However, since macroscopic oscillations of brain activity represent the sum of an important amount of microscopic events, interpreting those oscillations confronts us with the inverse inference problem (Nunez and Srinivasan, 2006). The issue arises from the fact that multiple sources could explain the observed activity. Thus, the discrimination of epiphenomena is difficult – if not impossible – and conjectures on causality often inappropriate.

EEG, Magnetoencephalography (MEG) and Stereo-EEG (SEEG) recording Local Field Potentials (LFP) allow to differentiate oscillatory activity with presumed different significance. The activity may be classified according to its frequency range: delta (<4 Hz), theta (4−8 Hz), alpha (8−13 Hz), beta (13−30 Hz), gamma (30−100 Hz) and high-frequency oscillations (i.e. HFO, >100 Hz).

2.5.1. Theta-band

Although alpha and theta rhythms have been associated more with CNS diseases other than PD (i.e. Alzheimer), PD patients also show some anomalies in these frequency bands. In PD patients in OFF compared to ON medication, the theta power –recorded respectively by depth electrodes or EEG– increases in the subthalamic nucleus (STN) (Zavala et al., 2013) and in the medial Prefrontal Cortex (mPFC) (Cavanagh et al., 2011) during conflicting tasks. PD patients with high-frequency STN DBS become more impulsive in the Stroop Task (Cavanagh et al., 2011). The Theta-power increase is probably linked to the interruption of the first behavioral response to handle an alternative one (Ghahremani et al., 2018).

2.5.2. Alpha-band

The motor cortex excitability correlates with the corticomuscular coherence in the alpha-frequency band (Schulz et al., 2014). Furthermore, in depth electrode recordings, alpha-activity increases in the pedunculopontine nucleus and the cortex during voluntary movement and with dopaminergic medication (Androulidakis et al., 2008). In addition, PD patients with freezing of gait (FOG) show a higher alpha-sample entropy– a measure of predictability in a time series– during FOG-episodes (Syrkin-Nikolau et al., 2017).

2.5.3. Beta-band

The Beta rhythm is predominant in the somatosensory and motor cortex-basal ganglia loop. In intact motor physiology, beta activity increases (i.e. synchronizes = event-related synchronization [ERS]) during rest and isometric contractions (Brown and Marsden, 1998; Engel and Fries, 2010); decreases (Pfurtscheller and Lopes Da Silva, 1999) (i.e desynchronizes = event-related desynchronization [ERD]) before movement initiation and during isotonic movement; and increases (i.e. resynchronizes), when movement ends. Thus, increased beta activity is associated with static motor control (Jenkinson and Brown, 2011; Engel and Fries, 2010). For instance, during an isometric muscle contraction, the motor cortex beta-band activity synchronizes with muscular activity (cortico-muscular coherence) (Gross et al., 2000). When cortico-muscular coherence in the beta-frequency band increases, motor-cortex excitability decreases (Schulz et al., 2014), and the amount of synchronization with the sensory cortex reflects performance (Chakarov et al., 2009). In the motor cortex, overall beta-frequency band power negatively correlates with movement acceleration (Gilbertson et al., 2005).

In PD patients, there is an excessive beta-band activity in the motor cortex (Pollok et al., 2012; Stoffers et al., 2008) and the basal ganglia (Doyle Gaynor et al., 2008); during rest (Brown and Williams, 2005) and during movement (Devos et al., 2006; Florin et al., 2013). During off-medication, the cortex-basal ganglia loop *synchronizes* within the beta-band (Brown et al., 2001; Williams, 2002; Lofredi et al., 2019; Tinkhauser et al., 2017b); and on dopaminergic medication, it *desynchronizes* (Doyle et al., 2005; Kühn et al., 2009; Ray et al., 2008; Weinberger et al., 2006; Zaidel et al., 2010; Lofredi et al., 2019; Tinkhauser et al., 2017b). In adequacy, the beta-band increase in the cortico-basal ganglia loop appears to correlate with bradykinesia (Chen et al., 2007; Jenkinson and Brown, 2011; Weinberger et al., 2009; Tinkhauser et al., 2018) and rigidity (Brown and Williams, 2005; Kühn et al., 2009; Priori et al., 2004). Moreover, FOG has been shown to specifically depend on excessive high-beta-frequency band activity (Toledo et al., 2014).

Furthermore, DBS STN in the beta-range leads to frequency synchronization in the *globus pallidus internus* (GPi) and the STN (Brown et al., 2004), while bradykinesia and rigidity increase (Chen et al., 2011; Fogelson et al., 2005; Timmermann et al., 2004). However, therapeutic high-frequency (130−180 Hz) DBS STN stimulation reduces beta-band oscillations along with an improvement in bradykinesia and rigidity (Ray et al., 2008). Sub-threshold, single-pulse TMS stimulation of M1 and SMA induces transient beta activity suppression in PD (Doyle Gaynor et al., 2008), suggesting oscillatory STN modulation through cortico-basal ganglia networks. Since NIBS might be capable of briefly alleviating motor symptoms in PD (Zanjani et al., 2015), it possibly disrupts excessive beta-frequency in cortico-basal ganglia loops, as does STN-DBS. Thus, these results suggest an anti-kinetic effect of beta-frequency excess in the cortico-basal ganglia loops, and may point to beta activity as a biomarker for closed-loop stimulation systems.

A primate PD-model study reported that a short burst of 130 Hz DBS in the GPi – 80 ms after cortical firing– yields better symptoms' improvement than continuous stimulation (Rosin et al., 2011). Thus, intermittent stimulation may cause considerably more clinical improvement than the use of continuous stimulus delivery. Short beta activity may serve as a biomarker for brain stimulation, because this activity band appears to be intrinsic to the pyramidal and the extra-pyramidal motor systems, gating motor activity with a potential anti-kinetic effect.

2.5.4. Gamma-band

Oscillatory activity in the gamma rhythm can be recorded in several cortical areas and in depth electrodes; it is thought to facilitate synchronization and information transfer necessary for a wide range of neural processes (Vinck et al., 2013). Gamma rhythm activity occurs in the sensory-motor cortex-basal ganglia loop. In intact motor physiology, gamma rhythm activity decreases during resting (i.e. desynchronizes) and increases during movement (i.e. synchronizes) (Pfurtscheller et al., 2003). The gamma frequency range can be subdivided into a low-gamma (35−50 Hz) and a high-gamma range (75−100 Hz): both ranges show different activity patterns during movement (Crone, 1998). Increased synchronization between M1 and the sensory cortex in the high-gamma band correlates with motor performance (Tecchio et al., 2008).

In PD off-medication, the gamma band has been shown to be decreased and to increase (>70 Hz) with dopaminergic medication (Brown et al., 2001; Williams, 2002), correlating with clinical improvement (Sharott et al., 2014). Also, high-frequency (130 Hz) STN-DBS suppresses beta-band oscillations in the GPi with clinical improvement (Brown et al., 2004). Thus, gamma-rhythm activity seems to be a pro-kinetic counterpart to the akinetic beta- rhythm in the motor system, enabling movement processing.

2.5.5. High-Frequency Oscillations

High-Frequency Oscillations (HFO) behave similarly to gamma rhythm in PD, whereas they are more challenging to record. During the medication off-state, no consistent HFO (Foffani et al., 2003) or only HFO with a small peak around 250 Hz (Özkurt et al., 2011) can be recorded. However, dopamine increases the HFO power significantly around 300−350 Hz (Foffani et al., 2003; Özkurt et al., 2011). HFO from within this frequency range correlates with dopaminergic medication, voluntary movement (Foffani et al., 2003) and clinical improvement (Özkurt et al., 2011), suggesting HFO to be a *pro-kinetic* biomarker.

2.5.6. Phase-amplitude coupling (PAC) in Parkinson's disease

Normal cortical function depends on the coupling between the phase of low-frequency rhythms and the amplitude of broadband activity –within and between distinct regions of the brain– coordinating the timing of neuronal activity: this phenomenon is called phase-amplitude coupling (PAC) (Canolty and Knight, 2010; de Hemptinne et al., 2015).

Excessive phase-amplitude coupling (PAC) between the phase of beta oscillation and the amplitude of high-frequency oscillations (HFO) seems to play a crucial role in PD's pathophysiology. Three PAC types have been identified to be pathological and could serve as biomarkers in future therapeutic approaches to treatment.

In STN, the phase of beta frequency activity is coupled with HFO amplitude off-medication; on dopaminergic medication, the HFO amplitude decouples from the beta frequency activity and becomes movement-dependent (López-Azcárate et al., 2010).

The STN phase of beta frequency activity has been found to be pathologically coupled with the amplitudes of HFO and gamma oscillations in M1 (de Hemptinne et al., 2015). DBS STN decreases the STN-M1 PAC, which correlates with clinical improvement of rigidity and bradykinesia (de Hemptinne et al., 2015).

Compared to healthy subjects, in PD off-medication, the M1 beta activity phase is coupled with M1 gamma oscillations amplitude. On dopaminergic therapy, the M1-M1 PAC decreases (Swann et al., 2015). Thus, the PAC paradigm may be a promising biomarker for closed-loop stimulation therapy.

2.5.7. Natural frequency mapping

TMS-induced natural-frequency EEG is an innovative way to investigate the inherent oscillatory activity of different cortical regions (i.e. endogenous rhythms) (Rosanova et al., 2009) and their interdependency with M1 excitability. The occipital cortex may resonate in the alpha range (Herring et al., 2015), the parietal cortex in the beta range, and the frontal cortex in the beta/gamma range (Rosanova et al., 2009). The excitability of M1 correlates positively with coupled, spontaneous, ipsilateral, prefrontal beta activity, with coupled bilateral centro-parieto-occipital delta activity (Ferreri et al., 2014), and with spontaneous sensorimotor gamma activity (Zarkowski et al., 2006). Conversely, M1 excitability correlates negatively with spontaneous sensorimotor alpha activity (Sauseng et al., 2009; Zarkowski et al., 2006).

Since NIBS of these areas in the natural frequency may interfere with the M1 excitability, it would be of interest to further map pathological cortex natural frequencies in PD. Pathologically altered natural frequencies could outline the rationale for a therapeutic approach.

2.6. Tremor in Parkinson's disease

Tremor does not correlate with bradykinesia and rigidity, and arises from a distinct pathophysiology (Kühn et al., 2009; Caligiore et al., 2016). Rest tremor responds to anticholinergic drugs, which increase beta activity (Priori et al., 2004). In PD patients, a stable oscillating system underlying the tremor has been postulated (di Biase et al., 2017), but the evidence is still controversial. When investigating coherence in the cortico-basal ganglia-loops at tremor frequency, some researchers found synchronization during off-medication and partial desynchronization with dopaminergic medication (Brown et al., 2001; Lalo et al., 2008), while others failed to find desynchronization (Priori et al., 2004; Tass et al., 2010). There is good evidence to suggest a cerebello-thalamo-cortical-loop pathogenesis of PD tremor (Helmich et al., 2012; Caligiore et al., 2016); while rest and postural tremor may have different pathogeneses (Ni et al., 2010). The cerebellum appears involved and may exert a compensatory role in PD (Wu and Hallett, 2013). Also, cerebellar inhibition by 1 Hz rTMS has been shown to reduce PD rest tremor (Lefaivre et al., 2016).

3. The rationale for non-invasive brain stimulation

Considering the pathophysiology of PD, we will discuss how NIBS may interact with current PD models.

3.1. Postulating causality between brain physiology and PD symptoms

The rationale for NIBS draws from the concept that reversing

abnormalities in brain activity and physiology thought to cause the clinical deficits may restore normal functioning.There is also some evidence suggesting that NIBS could be useful as an adjuvant to conventional treatment, particularly for patients with refractory symptoms, or for those for whom surgical intervention is not possible.

3.2. Deep brain stimulation

Currently, the best evidence in support of the therapeutic potential of NIBS in PD comes from deep brain stimulation (DBS). The success of DBS paved the way for studies investigating novel approaches altering the (ab)normal neuronal circuitry: as it has been done by NIBS. In PD, DBS improves motor deficits, modulates basal ganglia activity and cortex physiology (Chen et al., 2001a; Cunic et al., 2002). Thus, DBS effects may be mediated transsynaptically through cortico-subcortical loops to distant areas within the central nervous system. It can be hypothesized that stimulating the cortex with NIBS may have widespread effects, and also would modulate the entire cortex-basal ganglia network through these cortico-subcortical loops. Those widespread effects of NIBS depend on an intact anatomical (Ruff et al., 2009) and functional connectivity (Eimeren and Siebner, 2006). Prefrontal cortical stimulation triggers dopamine release in the striatum (Kanno et al., 2004; Strafella et al., 2001) and pallidal or subthalamic nucleus stimulation causes changes in motor cortex activity (Cunic et al., 2002). Moreover, stimulating the cortex modulates neural oscillations in both the stimulated cortex and the associated structures (Fox et al., 2014; Zaghi et al., 2010). In PD, M1 is the prime target for stimulation and its stimulation leads to widespread activation of the motor circuit (Baudewig et al., 2001; Lang et al., 2005).

3.3. Repetitive transcranial magnetic stimulation

The direct stimulation effect of rTMS reaches only a depth of approximately 1.5−3 cm beneath the skull (Gomez et al., 2018), but application to the motor or prefrontal cortex modulates the release of dopamine in the caudate (Strafella et al., 2001) and putamen (Strafella et al., 2003) – their cortico-striatal projections (Cho and Strafella, 2009). This release of dopamine is preserved in PD (Strafella et al., 2006) and may explain the immediate effects of rTMS on PD symptoms. Even sham rTMS triggers the dopamine release (Strafella et al., 2006), pointing also to a placebo effect.

3.4. Transcranial direct current stimulation

Transcranial direct current stimulation also triggers widespread activation (Lang et al., 2005) and dopamine release (Fregni et al., 2006b). Moreover, when PD patients show cortical dysfunction (Lefaucheur, 2006), targeting specific cortical areas with tDCS might modify the cortico-cortical or the cortico-subcortical activity – improving PD functionally.

3.5. Oscillopathies

One of the key features of PD is the lock of neural networks in specific oscillatory patterns that reinforce synchronization and lead to motor impairment (Cagnan et al., 2015). Frequencies at which TMS (Bortoletto et al., 2015; Rosanova et al., 2009) or rTMS (Romei et al., 2016; Thut et al., 2011) can modulate transient oscillations are inherent to a specific brain network. Therefore, each functional network may have a specific natural frequency (Doyle Gaynor et al., 2008). The same mechanism probably underlies tACS but it is unclear, whether tACS drives the brain oscillation to adapt to the stimulation frequency – entrainment – or if functional networks have the same natural frequencies as the stimulation frequency and resonate –resonance. These natural frequencies may gate the information exchange (e.g. for gamma tACS (Helfrich et al., 2014a; Strüber et al., 2014).

Oscillating brain structures often switch between specific frequencies, regulating synchronization and desynchronization to communicate and to encode behavior (Cagnan et al., 2016, 2015; Womelsdorf et al., 2007). By changing patterns of coherent oscillatory activity, the brain may control the information flow among connected brain structures (Akam and Kullmann, 2010; Fries, 2005; Salinas and Sejnowski, 2001).

Though the pathological oscillating patterns appear rather stable in PD (di Biase et al., 2017), different NIBS may interact with subcortical oscillating structures through transcranial stimulation (e.g. rTMS, tDCS (Fregni and Pascual-Leone, 2007; Giovanni et al., 2017; Fox et al., 2014)). Indeed, there is evidence suggesting that specific stimulation patterns may modulate neural oscillators (Akam et al., 2012; Zlotnik et al., 2016; Witkowski et al., 2016).

3.6. Long-term plasticity

NIBS also induces medium- and long-term effects that are considered to be mediated by long-term potentiation (LTP)- and long-term depression (LTD)-like plasticity (Chervyakov et al., 2015; Hoogendam et al., 2010; Orban de Xivry and Shadmehr, 2014; Udupa and Chen, 2013). LTP- and LTD-like plasticity can be elicited in different ways: intermittent theta-burst stimulation, high-frequency rTMS or anodal tDCS of M1 increases cortical excitability, and continuous TBS, low-frequency rTMS or cathodal tDCS decreases cortical excitability (Fox et al., 2014; Huang et al., 2005; Ridding and Ziemann, 2010).

3.7. Repetitive transcranial magnetic stimulation techniques

Different stimulation coils of different geometry and size can be used for rTMS. While most of the studies used a figure-of-eight coil or a circular coil, only a few studies used a double-cone coil. To target deeper brain structures (up to 5.5 cm (Zangen et al., 2005)), as for the stimulation of the mesial prefrontal cortex (Lu and Ueno, 2017), an Hesed-coil (H-coil) has been used (Dagan et al., 2017). A ca. 100–300 μsec electric current of $>$ 1000 V and up to 10,000 A flows through an induction coil, inducing a strong magnetic field –which variation, in turn– induces an electric current in the brain (Rothwell, 1997). Since the magnetic field intensity declines exponentially with the distance to its source, only the cortex and the superficial white matter are stimulated (Rothwell, 2011). There are a number of mechanisms through which rTMS may modulate plasticity, these being: the stimulation of glutamatergic prefrontal neurons (Michael et al., 2003), changes in neuronal ionic conductivity (Chervyakov et al., 2015), increased neurotrophic factors (Brunoni et al., 2008) and synaptic connectivity (LTP; LTD) (di Lazzaro et al., 2011). New patterned forms of stimulation, which may act on other mechanisms –including theta-burst stimulation or quadripulse stimulation– have emerged, but they need further investigation (di Lazzaro et al., 2011; Huang et al., 2005).

3.8. Transcranial current stimulation techniques

Transcranial direct current stimulation consists of applying a weak (1–2 mA) electrical current between an anode and a cathode. This transcranial stimulation changes the resting cortical excitability of the underlying tissue (Nitsche and Paulus, 2000). Electrode's position, impedance, head size, scalp and skull thickness, they all influence the current flow (Thair et al., 2017). Since axonal orientation can determine the excitatory or inhibitory action of transcranial stimulation (Kabakov et al., 2012), the precise targeting through shaping of the electric/magnetic field and its polarity is essential. In tCS, increasing the number of electrodes generally allows shaping the stimulation field more precisely and, thereby, a higher target specificity (Ruffini et al., 2014). A recent high-density stimulation protocol of tDCS uses multiple ring electrodes to enhance focality (DaSilva et al., 2015).

A stimulation session usually lasts for about 20 min (Lefaucheur

et al., 2017). Anodal tDCS increases, whereas cathodal tDCS decreases the excitability of the resting brain (Molaee-Ardekani et al., 2013; Nitsche et al., 2008). While tDCS does not induce an action potential, it modulates the spontaneous activity of brain cells (Fritsch et al., 2010).

Anodal stimulation depolarizes the cell membranes, thereby increasing the neuronal firing (Nitsche et al., 2008). Anodal tDCS may reduce GABAergic activity and facilitate NMDA receptors (Liebetanz, 2002; Nitsche et al., 2004a), lead to an accumulation of myoinositol in the phospholipid membrane (Rango et al., 2008), and increase the cerebral blood flow (Merzagora et al., 2010; Takai et al., 2016).

Cathodal stimulation hyperpolarizes the cell membranes, decreasing neuronal firing (Nitsche et al., 2008). In addition, it may reduce the excitability of the glutamatergic system (Stagg et al., 2009).

MEP changes after 10 min of tDCS can last for one hour beyond stimulation (Nitsche and Paulus, 2001). The duration of longer-lasting effects depends on stimulation length and intensity (Fritsch et al., 2010). They are probably mediated by NMDA receptor-dependent processes (Nitsche et al., 2004a), by LTP- and LTD-like mechanisms (Flöel, 2014; Nitsche et al., 2003a), and by gabaergic and glutamatergic activity (Kim et al., 2014; Nitsche et al., 2004b; Stagg and Nitsche, 2011). TDCS presumably also induces changes in glial cells, microvessels and inflammatory processes (Woods et al., 2016).

The transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS) and pulsed current stimulation (PCS) are newer electrical stimulation methods (Tavakoli and Yun, 2017).

The transcranial alternating current stimulation uses biphasic and sinusoidal current and aims to entrain neuronal populations into specific oscillatory patterns. Whether extrinsic tACS rhythms entrain neurons, or whether entrainment is only possible at a specific endogenous rhythm (i.e. natural frequencies), remains yet undetermined. However, it seems that if the stimulation frequency approaches the natural frequency of neural networks, spontaneous oscillations can be more easily entrained (Guerra et al., 2016; Helfrich et al., 2014b). Since the temporal relationship between oscillation patterns of specific brain regions determines their degree of information exchange (Fries, 2005), modulating oscillation patterns by tACS seems a promising approach. The tACS effects seem to be frequency- and area-dependent (Feurra et al., 2011). Natural frequencies of the cortico-basal loop seem to lie in the beta (Pogosyan et al., 2009; Hari and Salmelin, 1997) and the gamma band (Brown, 2003). Furthermore, temporal alignment – phase-dependency – plays a decisive role in modulating the membrane's potential (Thut et al., 2017) and short- and long-term plasticity (Fries, 2005). While gamma tACS provokes local GABA-A inhibition (Nowak et al., 2017), beta tACS provokes cholinergic short-latency afferent inhibition (Guerra et al., 2016). Overall, tACS produces long-lasting plastic changes (Vossen et al., 2015).

The transcranial random noise stimulation is a method in which stimulation frequency continuously changes – ranging from 0.1 to 640 Hz –increasing cortical excitability (Terney et al., 2008).

The pulsed current stimulation consists of an unidirectional pulsating current (Jaberzadeh et al., 2015).

Although both tRNS and PCS techniques are relatively new, they have been investigated in a small number of studies in PD.

Combining NIBS with other therapies may potentiate the efficacy of rehabilitative (Benninger and Hallett, 2015; Lefaucheur et al., 2017), pharmacological (Stagg and Nitsche, 2011) or even stem cell interventions (Winkler et al., 2017) and offer a promising venue. Recently, mainly the combination of NIBS with rehabilitation therapies has been investigated. Three forms of stimulation protocols are discernible: stimulation before intervention (i.e. offline) in order to prime brain physiology (meta-plasticity), simultaneously to the intervention (i.e. online), and, rarely, after the intervention to consolidate its effects. Either NIBS method can be applied before or after a therapeutic intervention, but for practical reasons, it is easier to apply tCS than TMS simultaneously (online) to the intervention.

A single session NIBS induces a relatively short-lasting effect (i.e. hours) (Maeda et al., 2000; Nitsche et al., 2008) and repetitive sessions may induce longer-lasting effects (Rossini and Rossi, 2007). Therefore, combining NIBS and rehabilitative procedures may enhance LTP-like plasticity and clinical efficacy. There are various presumed mechanisms which may mediate the consolidation of longer-term plasticity induced by NIBS including catecholaminergic transmitters (Nitsche et al., 2004a), NMDA receptors modulation (Nitsche et al., 2004a), and brain-derived neurotrophic factor (BDNF)-dependent synaptic plasticity (Filho et al., 2016; Fritsch et al., 2010).

3.9. Parkinson's disease: a good model for neurophysiologic brain exploration

Since objective biomarkers (MEP, SICI, ect…) are available when studying the motor system, investigating how NIBS interacts with motor impairment in PD offers a unique opportunity to gain more in-depth knowledge on its pathophysiology – in order to discover new specific biomarkers that could be used for individualized NIBS, and to improve clinical symptoms refractory to conventional therapy.

4. Clinical evidence update for the treatment of Parkinson's disease by means of non-invasive brain stimulation

This review aims to update the evidence for the clinical recommandations of NIBS in PD. In this section, we will review the current literature and evaluate the evidence for the clinical use of rTMS, tDCS and tACS.

We compare our results with the established European guidelines for the clinical use of rTMS (Lefaucheur et al., 2014, 2020) and tDCS in PD (Lefaucheur et al., 2017) and apply the same methodology based on the EFNS Task Force criteria and recommendations for the preparation of research reviews (Brainin et al., 2004).

We performed a search in PubMed, Embase and Cochrane (CENTRAL). For rTMS, we used the keywords "repetitive transcranial magnetic stimulation OR theta burst stimulation AND Parkinson's disease"; for tDCS "transcranial direct current stimulation AND Parkinson's disease"; for tACS "transcranial alternating current stimulation OR transcranial pulsed current stimulation AND Parkinson's disease". We screened all references since the beginning of NIBS, without limiting the time-period. Two reviewers independently screened all references; disagreements were resolved by discussion. In a first step, all titles and abstracts were screened, and ineligible references excluded. In a second step, the full text was read to determine eligibility, and to analyze the methodological quality of the studies (see Fig. 1, Flowchart). All controlled studies were analyzed and summarized in Tables 1–3. Studies, which investigated multiple stimulation paradigms and, thus, appeared under different subsections, were highlighted in purple. To assess the level of evidence, we applied the revised Brainin criteria (Brainin et al., 2004) and included only studies, which fitted criteria for class I, II or III (controlled trials).

The outcomes of interest were derived from the main categories of PD symptoms: overall motor symptoms, bradykinesia, rigidity, tremor, gait, FOG, dyskinesia, depression and cognition. In the corresponding table, high-quality studies (Class I and II) were highlighted in green. Studies using an active sham group as a control condition, or superiority studies, were highlighted with a hash, because they were rather difficult to compare.

For each stimulation paradigm, we first extensively discuss the studies with the highest evidence class (i.e. class I and II). Thereafter, we will succinctly discuss class III studies. The tables containing all the gathered data are accessible through the Supplementary material; for simplicity, in the main document, we will only present tables containing high-quality studies.

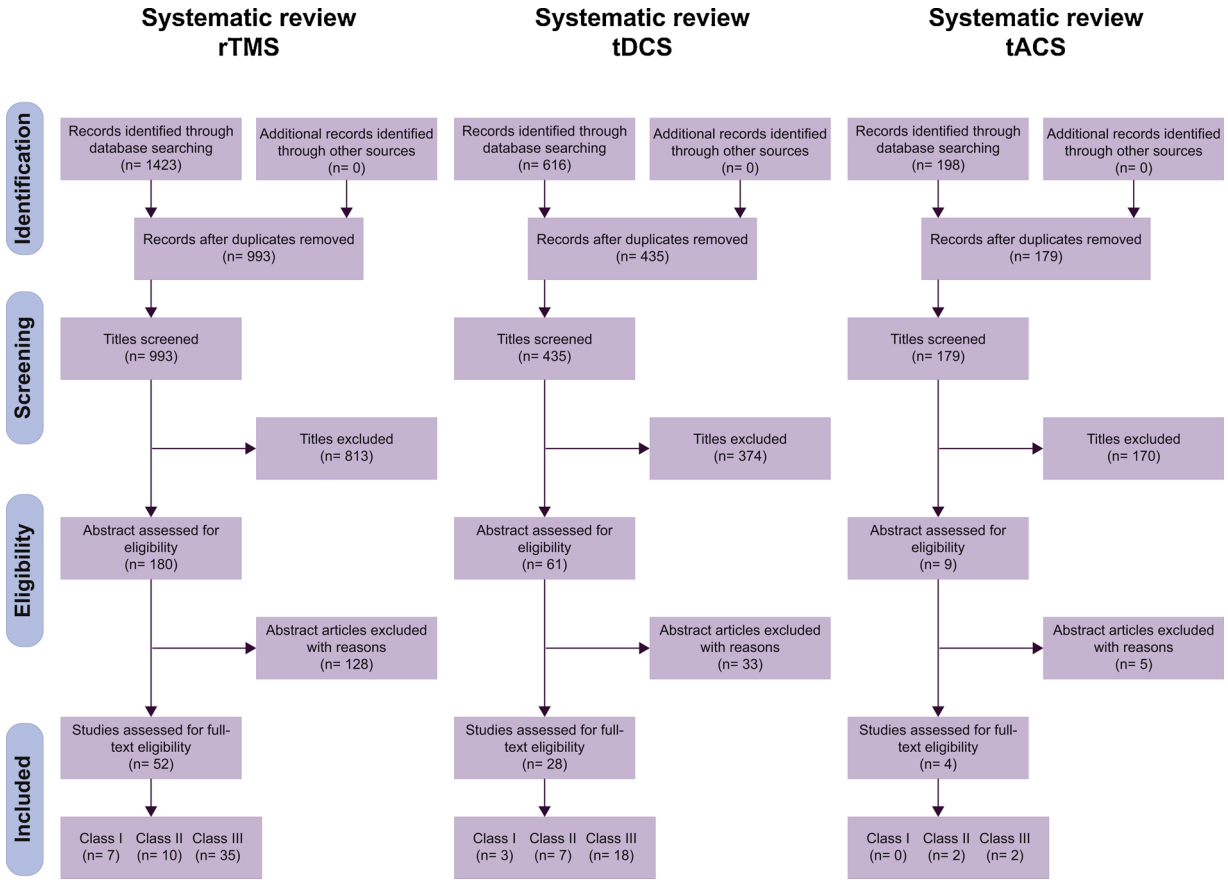

Fig. 1. Flow-chart selection adapted from Moher et al. (2009).

4.1. The EFNS task force classifies therapeutic studies as follows (Brainin et al., 2004)

4.1.1. Class I studies

A class I study has to fulfil the following criteria: 1) includes more than 25 patients in each group or is an adequately powered study 2) is prospective and controlled 3) has a parallel or a cross over design 4) is a randomized, double-blind study 5) has clearly defined primary outcome 6) has clearly defined exclusion/inclusion criteria 7) accounted adequately for dropouts and crossovers, with numbers sufficiently low to have minimal potential for biases 8) has a relevant baseline characteristic, substantially equivalent among treatment groups or appropriate statistical adjustment for differences.

4.1.2. Class II studies

A class II study included more than ten patients in each group, and only one criterion of the criteria 1–8 of a Class I study could be missed.

4.1.3. Class III studies

A class III study has to be a prospective, controlled, parallel or cross-over design study (criteria 2 and 3 of a class I study).

4.1.4. Class IV studies

Class IV studies are non-controlled, retrospective, case series or case reports.

4.2. The level of evidence

Level of evidence was defined as follow:

4.2.1. Level A

Definitely effective or ineffective:

At least two Class I or one Class I study, and at least two Class II studies.

4.2.2. Level B

Probably effective or ineffective:

One Class I study and less than two Class II studies; alternatively, at least two Class II studies; alternatively, one Class II study and at least two Class III studies.

4.2.3. Level C

Possibly effective or ineffective:

One Class II study, and less than two Class III studies; alternatively, at least two Class III studies.

Recently, the EFNS adhered to the GRADE methodology (Leone et al., 2013) – probably the currently most recognized system to perform a structured evaluation of evidence's quality, particularly when the reported results are controversial. This is often the case in studies investigating NIBS. However, GRADE 's validity has not been thoroughly tested yet (Leone et al., 2013).

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (Balshem et al., 2011; Guyatt et al., 2011; Leone et al., 2013) integrates multiple qualitative and methodological characteristics of studies and outcomes into a critical rating of the quality of the evidence. In the GRADE system, the evidence for studies' outcome is categorized as high, moderate, low, or very low, based on five quality criteria. For each quality criterium, the expert evaluates his/her confidence in the effect's estimate in order to be able to upgrade or downgrade the quality of the evidence.

The five quality criteria to be evaluated are qualitative (1−3) and

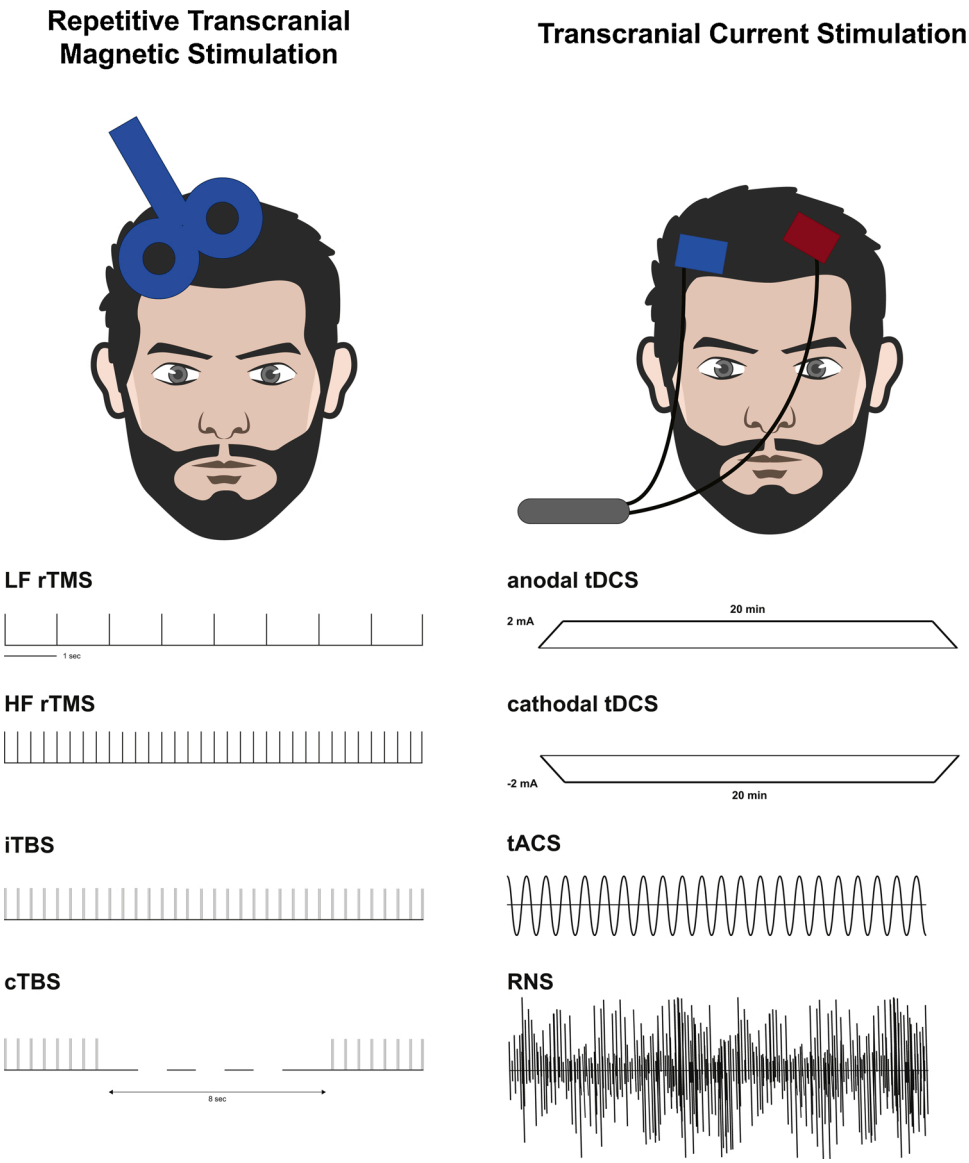

Fig. 2. Non-invasive brain stimulation techniques.

quantitative (4–5):

1) Limitations in the design and implementation (e.g. biased assessment of the intervention effect, lack of allocation concealment, lack of blinding, substantial loss to follow-up, selective reporting outcomes…); 2) indirectness (i.e. indirect comparisons differences in population definition, interventions and comparators); 3) inconsistency (i.e. heterogeneity of results across studies); 4) imprecision (i.e. small sample size, wide confidence intervals); 5) publication and selective outcome reporting bias (i.e. over-publication of positive studies or positive outcomes).

Here, we used the Brainin-EFNS criteria (Brainin et al., 2004) and took into account some of the GRADE criteria: 1) The risk of bias related to study limitations in the design and implementation was evaluated to downgrade randomized trials from Class I to Class II and III. 2) The risk of bias related to indirectness was evaluated while determining the level of evidence (i.e. A, B or C). 3) The risk of bias related to the inconsistency of results was evaluated while determining the level of evidence (i.e. A, B, C). 4) The risk of bias related to imprecision was only partially evaluated. On the one hand, the sample size contributed to building the class of evidence. On the other hand, we did not account for wide confidence intervals, since we did not do a meta-analysis. 5) The risk related to publication and selective outcome reporting bias was not taken into account, since we did not do a meta-analysis.

Meta-analysis: Due to the high heterogeneity of the study designs, we chose to perform a systematic qualitative review. Running a systematic quantitative review (meta-analysis) would be inevitably biased via unjustifiable comparisons of very different study designs. Furthermore, the most established European guidelines for the use of NIBS were systematic qualitative reviews (Lefaucheur et al., 2017, 2014, 2020). Moreover, most meta-analyses do not account for the reproducibility of results across different laboratories, and overweight large studies – even if there is only one large study. Therefore, we put strong emphasis on the replication of similar studies across independent laboratories – in qualitative analysis – to improve the reliability of research outcomes (Ioannidis, 2014).

4.3. *Approaches to treatment*

A discussion of the effectiveness of NIBS for the treatment of PD demands a differentiation of the procedures used in the stimulation protocols.

The stimulation protocols can be differentiated according to the kind

Table 1
Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham). Written in bold: primary outcomes; Written in purple: studies testing different stimulation paradigms; highlighted in green: high-quality studies class I and II; Hash: studies using an active sham or superiority studies (Kim et al., 2015; Benninger et al., 2012; Brys et al., 2016; Makkos et al., 2016; Khedr et al., 2019b; Khedr et al., 2019a). (For interpretation of the references to colour in this table legend, the reader is referred to the web version of this article.)

Study	Number HY Design	Medication state Control Group/Condition Target	Stimulation parameters	**Primary outcome** Secondary outcomes	Results at study completion (real stimulation vs. sham)	Follow-up Results	Class
rTMS on Motor Symptoms **HF rTMS over M1**							
Kim et al., 2015	17 PD HY 2.5-4 Randomized Double blinded Sham controlled Cross-over	ON during assessment and stimulation S: M1 dominant lower leg, tilted coil C1: M1 dominant leg, double corn coil	Washout: 2 weeks 10Hz, 1000 pulses, 90% RMT, 5 sessions/1 week	**Standing start 180° turn test:** **-Turning steps** **-Turning time** **-FOG-Q** TUG UPDRS-III	 **-9% vs +2%** **ns** **-13% vs +2%** ns -31% vs -6%	1 week **p** **ns** **ns** ns p	II
Benninger et al., 2012	26 PD HY 2-4 (S: 13 G1: 13) Randomized Double blinded Sham controlled Parallel	ON and OFF during assessment and ON during stimulation S: bil M1, perp coil or inactive coil G1: bil M1 (upper limbs), round coil	50 Hz, 600 pulses, 80% AMT, 8 sessions/2 weeks	**walking time (10m)** timed bradykinesia UPDRS-III SRTT UPDRS-ADL FOG-Q health survey BDI CSP	**ns** ns ns ns ns ns ns ns +	1 month **ns** ns ns ns ns ns ns ns	I
Brys et al., 2016a	61 PD HY 2-4 (S: 15 G1: 20 G2: 14 G3: 12) Randomized Double blinded Sham controlled Parallel	OFF during assessment and ON during stimulation S: M1 and DLPFC, sham coil G1: M1 and DLPFC, F8c G2: M1 and sham DLPFC, F8c G3: DLPFC and sham M1, F8c	G1: 10Hz, 2000 pulses, 100% RMT, 10 sessions/10 days G2: idem G3: idem	 **UPDRS-III** **HAM-D** Beck depression inventory II Apathy evaluation scale Clinical anxiety scale MoCA PDQ-39 UPDRS-total Clinical Global Impression	G1 / G2 / G3 **ns / -15% vs -1% / ns** **ns / ns / ns** ns / ns / ns ns / ns / ns ns / ns / ns ns / ns / ns ns / ns / ns ns / ns / ns ns / ns / ns	6 months **ns** **ns** ns ns ns ns ns ns ns	II
Makkos et al., 2016a	46 PD+ depression HY 1-4 (S: 23 G1: 23) Randomized Double blinded Sham controlled Parallel	ON during assessment and stimulation S: bil M1, tilted coil G1: bil. M1, circular coil	5 Hz, 600 pulses, 90% RMT, 10 sessions/10 days	**MADRS** **BDI** UPDRS total UPDRS-III Health related quality of life scale ESS PDSS-2 NMSS PDQ-39 MMSE MoCA Stroop test Trail test TUG	**-65% vs -20%** **-60% vs 9%** -25% vs -2% -12% vs -3% ns ns ns -65% vs -22% -25% vs +5% ns ns ns ns ns	1 month **p** **p** p p ns ns ns p p ns ns ns ns ns	II
Khedr et al., 2019[2]	52 PD (G1: 26 G2: 26) Randomized Double blinded Parallel	OFF during assessment and ON during stimulation G1: bil M1 hand area, F8c G2: bil M1 hand area, F8c	G1: 1 Hz, 1000 pulses, 100% RMT, 10 sessions/10 days G2: 20 HZ, 2000 pulses, 90% RMT, 10 sessions/10 days	 **UPDRS-III** **Instrumental activity of daily living** **Self-assessment score** RMT AMT MEP 130% RMT TCI duration	G2 vs G1 **ns** **+16% vs +12%** **ns** ns ns +23% vs -19% +12% vs -6%	1 month **ns** **p** **ns**	I#
Khedr et al., 2019a	33 PD+Dysphagia (S: 11 G1: 19) Randomized Double blinded Sham controlled Parallel	ON during assessment and stimulation S: M1, tilted coil G1: M1, F8c	20 HZ, 4000 pulses, 90% RMT, 10 sessions/2 weeks	 **Arabic-Dysphagia Handicap Index** Video fluoroscopy solid: -pharyngeal transit time -H1-H2 -Penetration aspiration -Residue Video fluoroscopy liquid UPDRS-III HY Instrumental activities of daily living Self-assessment scale	 **-40% vs -10%** -21% vs +7% -40% vs +13% ns ns ns -36% vs -6% ns ns -27% vs -5%	3 months (incl 5 boosters) **p** p ns ns ns ns p ns ns p	I

Level B Effective for the treatment of overall motor symptoms in PD
Level B Ineffective for the treatment of gait performance in PD
Level B Ineffective for the treatment of depression in PD

Short_final_rTMS: Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).
Final_rTMS: Randomized rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).

Table 2
Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham). Written in bold: primary outcomes; Written in purple: studies testing different stimulation paradigms; highlighted in green: high-quality studies class I and II; Hash: studies using an active sham or superiority studies (Li et al., 2015). (For interpretation of the references to colour in this table legend, the reader is referred to the web version of this article.)

Study	Number HY Design	Medication state Control Group/Condition Target	Stimulation parameters	**Primary outcome** Secondary outcomes	Results at study completion (real stimulation vs. sham)		Follow-up Results	Class
rTMS on Motor Symptoms **LF rTMS over DLPFC**								
Li et al., 2015a	132 PD HY 2-4 (S1: 31 S2: 34 G1: 30 G2: 37) Randomized Double blinded Sham controlled Parallel	ON during assessment S1: DLPFC, sham coil + 20 mg istradefylline S2: DLPFC, sham coil + 40 mg istradefylline G1: DLPFC, F8c + placebo medication G2: DLPFC, F8c + placebo medication	G1: 1Hz, 1000 pulses, 100% RMT, 12 weeks G2: 10 Hz, 1000 pulses, 100% RMT, 12 weeks	**UPDRS-III** Clinical global impression Daily off time	G1 **ns** ns ns	G2 **ns** ns ns	none	I#
No possible recommendation								

Short_final_rTMS: Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).
Final_rTMS: Randomized rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).

of stimulus delivery: intermittent stimulation, chronic stimulation, and stimulation concomitant to a parallel intervention. Intermittent stimulation aims to achieve long-term plasticity changes: the critical outcome is the long-term clinical benefit. In chronic stimulation, the goal is to induce immediate effects, even if they do not persist beyond the stimulation period. The critical clinical outcome is assessed during stimulation. This approach refers only to tDCS and tACS for which portable devices are available. In concomitant stimulation, NIBS is delivered simultaneously to other clinical procedure(s), as an adjuvant treatment. The critical outcome is the additional effect compared to the standard treatment alone.

The heterogeneity of NIBS studies, regarding stimulation duration, stimulation intensity, coil or electrode type, frequency of stimulation and outcome measures precludes direct comparisons; targeted areas vary. The patient populations are also heterogeneous. Moreover, while some studies used only one stimulation session, other studies used several stimulation sessions; some studies used a parallel, and some others a cross-over design. The duration of NIBS after-effects is still unknown, and the interval –wash-out period– in cross-over studies differs, ranging from 24 h to several months.

We sorted out studies according to their level of evidence and concluded according to treatment recommendations.

For each stimulation paradigm, we assess the overall effect of NIBS on motor symptoms with the UPDRS-III. Thereafter, we focus on the effects of NIBS in bradykinesia, gait, tremor, FOG, dyskinesia, depression and non-motor symptoms. Because rigidity has been poorly investigated yet, no discussion will be offered. All results we discuss were significant in comparison to a sham stimulation (i.e. placebo) group.

4.4. Repetitive transcranial magnetic stimulation (rTMS)

4.4.1. Low-frequency (LF) rTMS of M1 (for a full table see supplementary information)

No Class I or II studies for LF rTMS of M1 were found. In class III studies: only one out of eight studies improved the motor UPDRS-III. Two out of three studies reported an improvement in Bradykinesia. Two studies assessed gait, but only one reported improvement. No effects on tremor were found. Three studies investigated depression in PD but did not find any effect. Overall, LF rTMS of M1 appears to be ineffective for overall motor symptoms (Level C) and depression (Level C) in PD.

4.4.2. High-Frequency (HF) rTMS of M1 (for class I and II see Table 1; for a full table see supplementary information)

One class I study reported that 50 Hz M1 rTMS had no better effect than sham stimulation on motor symptoms (UPDRS-III), bradykinesia, gait or depression, neither at post-intervention nor at follow-ups (Benninger et al., 2012). Nevertheless, several studies reported improved motor symptoms. A class I study reported a significant reduction of the motor UPDRS-III (36 %) after ten sessions of 20 Hz stimulation. The effect persisted for at least three months. However, five boosters were given during the follow-up period (Khedr et al., 2019b). Another class II study – including ten sessions of 10 Hz rTMS – also reported a significant decrease of 15 % in the motor UPDRS-III, whereas no significant effect on depression was found (Brys et al., 2016). In contrast to the other studies, results did not persist at six months follow-up. A large class II study including 46 PD patients tested 5 Hz stimulation of M1 (Makkos et al., 2016) and reported a significant improvement (12 %) of motor UPDRS-III and depression (MADRS 65 %; BDI 60 %); all effects were maintained for at least one month. A cross-over study that tested 10 Hz stimulation of M1 during five sessions reported UPDRS-III improvement of 31 % compared to baseline, and the effect persisted for at least one week. While there was no effect on gait – number of steps during turning and especially the FOG-Q questionnaire improved by 13 % after treatment (Kim et al., 2015). Another large class I study assessed the superiority of HF rTMS over LF rTMS (Khedr et al., 2019a). This study was a superiority study and did not include a sham stimulation, precluding conlusions regarding their efficacy in comparison to other studies. The

Table 3
Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham). Written in bold: primary outcomes; Written in purple: studies testing different stimulation paradigms; highlighted in green: high-quality studies class I and II; Hash: studies using an active sham or superiority studies (Brys et al., 2016; Li et al., 2015; Pal et al., 2010). (For interpretation of the references to colour in this table legend, the reader is referred to the web version of this article.)

Study	Number HY Design	Medication state Control Group/Condition Target	Stimulation parameters	**Primary outcome** Secondary outcomes	Results at study completion (real stimulation vs. sham)			Follow-up Results	Class
rTMS on Motor Symptoms **HF rTMS over DLPFC**									
Brys et al., 2016b	61 PD HY 2-4 (S: 15 G1: 20 G2: 14 G3: 12) Randomized Double blinded Sham controlled Parallel	OFF during assessment and ON during stimulation S: M1 and DLPFC, sham coil G1: M1 and DLPFC, F8c G2: M1 and sham DLPFC, F8c G3: DLPFC and sham M1, F8c	G1: 10Hz, 2000 pulses, 100% RMT, 10 sessions/10 days G2: idem G3: idem		G1	G2	G3	6 months	
				UPDRS-III	**ns**	**-15% vs -1%**	**ns**	**ns**	
				HAM-D	**ns**	**ns**	**ns**	**ns**	
				Beck depression inventory II	ns	ns	ns	ns	
				Apathy evaluation scale	ns	ns	ns	ns	
				Clinical anxiety scale	ns	ns	ns	ns	II
				MoCA	ns	ns	ns	ns	
				PDQ-39	ns	ns	ns	ns	
				UPDRS-total	ns	ns	ns	ns	
				Clinical Global Impression	ns	ns	ns	ns	
Li et al., 2015b	132 PD HY 2-4 (S1: 31 S2: 34 G1: 30 G2: 37) Randomized Double blinded Sham controlled Parallel	ON during assessment S1: DLPFC, sham coil + 20 mg istradefylline S2: DLPFC, sham coil + 40 mg istradefylline G1: DLPFC, F8c + placebo medication G2: DLPFC, F8c + placebo medication	G1: 1Hz, 1000 pulses, 100% RMT, 12 weeks G2: 10 Hz, 1000 pulses, 100% RMT, 12 weeks		G1	G2		none	I#
				UPDRS-III	**ns**	**ns**			
				Clinical global impression	ns	ns			
				Daily off time	ns	ns			
Pal et al., 2010a	22 PD+Depression (S: 10 G1: 12) Randomized Double blinded Sham controlled Parallel	ON during assessment and stimulation S: lDLPFC, sham coil G1: lDLPFC, F8c	5Hz, 600 pulses, 90% RMT, 10 sessions/10 days					1 month	
				BDI	-44% vs -16%			p	
				MADRS	-13% vs -4%			p	
				Stroop test	15% vs 2%			p	
				TUG test	-12% vs 0%			ns	
				UPDRS-III	ns			ns	II
				TMT	ns			ns	
				MMSE	ns			ns	
				Schwab & England ADL	ns			ns	
				VAS	ns			ns	
				ESS	ns			ns	

Level B Ineffective for the treatment of overall motor symptoms in PD

Short_final_rTMS: Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).
Final_rTMS: Randomized rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).

study reported no difference between HF rTMS and LF rTMS on motor symptoms. When summarizing all class III studies, seven out of nine showed improvement in the motor UPDRS-III, all six studies improved bradykinesia and three out of six improved gait performance. Two out of nine studies couldn't show an effect of rTMS on UPDRS-III. Three out of six studies on gait and all three studies on depression, none of them were able to demonstrate any significant effects.

Overall, one class I study did not find clinical effects of 50 Hz rTMS of M1 on motor symptoms. One class I study (20 Hz), three class II studies, and several class III studies (20 Hz/10 Hz) reported a significant improvement after rTMS. Two class I studies found divergent results and preclude further conclusions; three clear class II studies remained. We conclude that 10 / 20 Hz rTMS, but not 50 Hz rTMS, of M1 is probably effective (Level B) for the treatment of motor symptoms in PD.

The evidence for the effect of HF rTMS on bradykinesia is ambiguous, 6 positive class III studies contrast with one negative class I study. The current level of evidence precludes further conclusions. HF rTMS of M1 alone seems ineffective in gait (Level B) and in depression (Level B). For the other outcome measures, the evidence is insufficient to evaluate their efficacy. However, even if the evidence for the efficacy of rTMS on motor symptoms accumulates, we emphasize that the clinical effect of rTMS on UPDRS-III remain small (12 %–36 %) compared to the clinical effect of levodopa on UPDRS-III (41 % of baseline) and the placebo effect on UPDRS-III (~16 % of baseline) (Espay et al., 2015). Nevertheless, additional effects, beyond the optimal on-medication state, suggest non-dopaminergic effects of NIBS.

4.4.3. Low frequency (LF) rTMS over DLPFC (for class I and II see Table 2; for a full table see supplementary information)

One large class I study included 132 patients and assessed the effect of LF (1 Hz) rTMS over DLPFC on motor symptoms, in comparison to the effect of istradefylline – a caffeine analogue and selective adenosine A2A receptor antagonist. There was no significant difference between groups (Li et al., 2015). As previously discussed, superiority studies are difficult to interpret. However, LF rTMS over DLPFC seems to be similarly effective as the recently FDA-approved adjuvant for motor fluctuations –istradefylline. This needs to be confirmed in further studies.

4.4.4. High frequency rTMS over DLPFC (for class I and II see Tables 3 & 10; for a full table see supplementary information)

Only one large class-I study assessed the effect of 10 Hz rTMS over DLPFC (Li et al., 2015), but this study was a superiority study comparing LF rTMS, HF rTMS and Istradefillyne combined with sham stimulation. The study reported no differences on motor symptoms between any of

these interventions. Comparison of these results with those of other studies is difficult. However, HF rTMS over DLPFC seems to be similarly effective as the recently FDA-approved adjuvant for motor fluctuations –istradefylline.

A class II study with10 Hz stimulation over the DLPFC (Brys et al., 2016) couldn't show neither an effect on motor UPDRS-III nor on depression. Another class II study stimulated the left-DLPFC at 5 Hz (Pal et al., 2010) and improved depression (BDI -44 %; MADRS -13 %), gait (TUG 12 %) and stroop-test performance (15 %); there was no effect on UPDRS-III. Except for gait (TUG), those effects persisted at one-month follow-up. To sum-up the results of the class III studies, consistent results of all seven studies neither show an effect of HF-rTMS on UPDRS-III, nor on bradykinesia (1/1), nor on gait (2/2). However, five out of six studies reported improvement of depression's symptoms.

Overall HF rTMS over DLPFC seems to be ineffective in improving motor symptoms (Level B) but effective in improving depression in PD (Level B). As shown in four studies (Boggio et al., 2005; Cardoso et al., 2008; Fregni et al., 2006a, 2004), rTMS and fluoxetine have comparable clinical efficacy on depression – a rather significant clinical relevance. No further evaluations are possible due to lack of studies or to ambiguous results. For further insights into the efficacy of HF rTMS over DLPFC on depression in PD, see the Supplementary material.

4.4.5. *Excitatory stimulation protocols: HF rTMS and iTBS of M1 and DLPFC (for class I and II see Tables 4 & 10 ; for a full table see supplementary information)*

Combining multiple stimulation targets such as M1 and DLPFC can be another approach to improve PD symptoms. The effects of iTBS of M1 + DLPFC was assessed in a class I study (Benninger et al., 2011): iTBS did not improve motor UPDRS-III, neither timed testing of bradykinesia or gait, nor FOG. However, a significant improvement on the Beck's Depression Inventory (19 %) was found, which is congruent with the approved HF rTMS DLPFC stimulation protocol for depression and this effect persisted at one-month follow-up. A small improvement in the total UPDRS (13 %) was noticed compared to sham in the off-state.

In a class II study Brys et al. did not find any effect of combined M1 + DLPFC HF rTMS on motor symptoms or bradykinesia (Brys et al., 2016). Interestingly, in the same study, the authors found an effect on motor symptoms with HF rTMS M1 stimulation alone. Thus, the lesser effects of the combined stimulation protocol compared to M1 stimulation alone may indicate an interference when combining multiple stimulation targets. A class III study reported improvements of bradykinesia, gait performance but not motor UPDRS-III. These few studies preclude further conclusions, though the class I iTBS study further strengthens the evidence for HF rTMS DLPFC stimulation in treating depression in PD, and combined HF M1 + DLPFC rTMS seems ineffective for motor symptoms (Level B).

4.4.6. *Low-Frequency rTMS over SMA (for class I and II see Table 5; for a full table see supplementary information)*

In a large class I multicenter study, Shirota and colleagues (Shirota et al., 2013) included 102 patients and investigated the effects of LF SMA- or HF SMA-stimulation compared to sham, on motor symptoms, non-motor symptoms and depression. After eight stimulation sessions, both groups showed comparable improvements to those observed in the sham group; however, at three months follow-up the improvement persisted only after LF SMA-stimulation, and only for the motor UPDRS-III and the UPDRS-total score. The remaining studies were all class III studies and failed to show any improvement compared to sham stimulation (3/3). Therefore, we conclude that LF rTMS SMA is

Table 4
Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham). Written in bold: primary outcomes; Written in purple: studies testing different stimulation paradigms; highlighted in green: high-quality studies class I and II; Hash: studies using an active sham or superiority studies. (Brys et al., 2016; Benninger et al., 2011). (For interpretation of the references to colour in this table legend, the reader is referred to the web version of this article.)

Study	Number HY Design	Medication state Control Group/Condition Target	Stimulation parameters	**Primary outcome** Secondary outcomes	Results at study completion (real stimulation vs. sham)			Follow-up Results	Class
rTMS on Motor Symptoms **HF rTMS and iTBS over M1+DLPFC**									
Brys et al., 2016 c	61 PD HY 2-4 (S: 15 G1: 20 G2: 14 G3: 12) Randomized Double blinded Sham controlled Parallel	OFF during assessment and ON during stimulation S: M1 and DLPFC, sham coil G1: M1 and DLPFC, F8c G2: M1 and sham DLPFC, F8c G3: DLPFC and sham M1, F8c	G1: 10Hz, 2000 pulses, 100% RMT, 10 sessions/10 days G2: idem G3: idem		G1	G2	G3	6 months	II
				UPDRS-III	**ns**	**-15% vs -1%**	**ns**	**ns**	
				HAM-D	**ns**	**ns**	**ns**	**ns**	
				Beck depression inventory II	ns	ns	ns	ns	
				Apathy evaluation scale	ns	ns	ns	ns	
				Clinical anxiety scale	ns	ns	ns	ns	
				MoCA	ns	ns	ns	ns	
				PDQ-39	ns	ns	ns	ns	
				UPDRS-total	ns	ns	ns	ns	
				Clinical Global Impression	ns	ns	ns	ns	
Benninger et al., 2011a	26 PD HY 2-4 (S: 13 G1:13) Randomized Double blinded Sham controlled Parallel	ON and OFF during assessment and ON during stimulation S: M1 (upper limb) + DLPFC, sham coil G1: M1 (upper limb) + DLPFC, round coil	iTBS, 2400 pulses, 80% AMT, 8 sessions/2 weeks		ON	OFF		1 month	I
				walking time (10m)	**ns**	**ns**		**ns**	
				timed bradykinesia	**ns**	**ns**		**ns**	
				UPDRS-total	ns	-13% vs -2%		ns	
				UPDRS-III	ns	ns		ns	
				UPDRS-II	ns	ns		ns	
				UPDRS freezing	ns	ns		ns	
				FAB	ns			ns	
				BDI	-19% vs 8%			ns	
				Mental health	ns			ns	
				physical health	ns			ns	
				SRTT	ns			ns	
Level B Ineffective for the treatment of overall motor symptoms in PD									

Short_final_rTMS: Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).
Final_rTMS: Randomized rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).

ineffective for improving motor symptoms in PD (Level B).

4.4.7. High-Frequency rTMS over SMA (for class I and II see Table 6; for a full table see supplementary information)

As discussed above, a class I study did not find an effect of 10 Hz rTMS SMA on motor symptoms, non-motor symptoms or depression (Shirota et al., 2013). However, in another large multicenter class I study including 98 patients, Hamada et al. reported improvement of UPDRS-III (20 %), and in the sub-item for bradykinesia (23 %) after 5 Hz rTMS SMA, which persisted at one-month follow-up, but not for depression. These two studies are high-quality studies with a similar design, yet their results are contradictory. However, in the one study, the stimulation frequency was 5 Hz (Hamada et al., 2009) and in the other, 10 Hz (Shirota et al., 2013). This difference might explain the contradiction. Surprisingly, another class II study stimulated at 10 Hz during ten sessions to show an improvement in UPDRS-III (17 %), walking time (20 %), and the self-reporting FOG-Q (18 %). These effects persisted even at the one-month follow-up (Ma et al., 2019).

Summarizing class III studies, one out of three studies showed improvement in motor UPDRS-III after stimulation. One study (1/1) did not find any effect of stimulation on gait and depression, and another study (1/1) found that bradykinesia even worsened. Although two high-quality studies show ambiguous results, class III studies support the efficacy of HF-rTMS over the SMA for treating motor symptoms in PD (Level C). All studies are consistent regarding the ineffectivity of HF-rTMS SMA for depression (Level A).

4.4.8. rTMS over the cerebellum (for class I and II see Table 7; for a full table see supplementary information)

A single class II study reported reduction of dyskinesia (CAPSIT-LID 30 %) after cTBS of both cerebellar hemispheres, but no change in motor UPDRS-III which persisted at one-month follow-up (Koch et al., 2009). Another class III study used a similar study design and found a reduction of dyskinesia, which persisted at one-month follow-up (Kishore et al., 2014). Therefore, cerebellar cTBS may be effective to reduce dyskinesia (Level B).

4.4.9. Other stimulation paradigms (for class I and II see Table 8; for a full table see supplementary information)

Few studies evaluated the efficacy of frontal cortex rTMS. A single class III study reported benefits of LF rTMS over the frontal area on motor symptoms and depression (Shimamoto et al., 2001). On the other hand, a class II study did not find any effect of LF M1 + PMd rTMS on motor symptoms, bradykinesia or tremor (Fricke et al., 2019).

4.4.10. rTMS and dyskinesia (for class I and II see Table 9; for a full table see supplementary information)

Different protocols have been tested to treat levodopa-induced dyskinesia. All studies used inhibitory stimulation protocols (i.e. LF rTMS or cTBS) targeting different brain areas, including M1, SMA, DLPFC, the inferior frontal cortex and the lateral cerebellum. One single high-quality class II study investigated the effect of cTBS over the cerebellum on dyskinesia (Koch et al., 2009) (see also the section rTMS over the cerebellum). All the other studies were class III studies. Summarizing results for each brain region, the following picture emerges: one LF-rTMS of M1 out of four studies found reduction of dyskinesia, the other three did not. All three SMA LF-rTMS studies found significant reduction of dyskinesia as did a single study performing cTBS of the right inferior frontal cortex.

Overall, LF-rTMS over SMA and cTBS over both cerebellar hemispheres may reduce dyskinesia in PD (Level C and B, respectively), whereas LF-rTMS of M1 may not have any effect on dyskinesia (Level C).

4.4.11. rTMS and non-motor symptoms (for class I and II see Table 11; for a full table see supplementary information)

Several studies assessed the effect of rTMS on different non-motor symptoms in PD. A class I study, reported a beneficial effect of 20 Hz rTMS of M1 on dysphagia (Khedr et al., 2019b). Another class I study, did not find any effect of rTMS on the non-motor symptoms questionnaire, neither after 1 Hz nor after 10 Hz SMA stimulation (Shirota et al., 2013). A class II study showed, that 25 Hz rTMS improved executive function, but only after stimulation of the right DLPFC (Srovnalova et al., 2012). However, stimulation frequencies, targeted brain areas and outcomes were all heterogeneous. The limited number of studies precludes further conclusions on the efficacy of rTMS on non-motor symptoms (please note that class III studies have been included in the supplementary tables).

Table 5
Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham). Written in bold: primary outcomes; Written in purple: studies testing different stimulation paradigms; highlighted in green: high-quality studies class I and II; Hash: studies using an active sham or superiority studies (Shirota et al., 2013). (For interpretation of the references to colour in this table legend, the reader is referred to the web version of this article.)

Study	Number HY Design	Medication state Control Group/Condition Target	Stimulation parameters	**Primary outcome** Secondary outcomes	Results at study completion (real stimulation vs. sham)		Follow-up Results		Class
					G1	G2	G1	G2	
rTMS on Motor Symptoms									
LF rTMS over SMA									
Shirota et al., 2013a	102 PD HY 2-4 (S: 34 G1: 34 G2. 34) Randomized Double blinded Sham controlled Parallel	ON during assessment and stimulation S: bil SMA, sham coil G1: bil SMA, F8c G2: bil SMA, F8c	G1: 1Hz, 1000 pulses, 110% AMT, 8 sessions/8 weeks G2: 10Hz, 1000 pulses, 110% AMT, 8 sessions/8 weeks	**UPDRS-III** UPDRS total Hamilton rating scale apathy score nonmotor symptoms questionnaire	**ns** ns ns ns ns	**ns** ns ns ns ns	3 months **p** p ns ns ns	 **ns** ns ns ns ns	I
Level B Ineffective for the treatment of overall motor symptoms in PD									

Short_final_rTMS: Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).
Final_rTMS: Randomized rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).

Table 6
Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham). Written in bold: primary outcomes; Written in purple: studies testing different stimulation paradigms; highlighted in green: high-quality studies class I and II; Hash: studies using an active sham or superiority studies (Hamada et al., 2009; Shirota et al., 2013; Ma et al., 2019). (For interpretation of the references to colour in this table legend, the reader is referred to the web version of this article.)

Study	Number HY Design	Medication state Control Group/Condition Target	Stimulation parameters	**Primary outcome** Secondary outcomes	Results at study completion (real stimulation vs. sham)	Follow-up Results	Class
rTMS on Motor Symptoms **HF rTMS over SMA**							
Hamada et al., 2009	98 PD HY 2-4 (S: 43 G1:55) Randomized Double blinded Sham controlled Parallel	ON during assessment and stimulation S: SMA, sham coil G1: SMA, F8c	5Hz, 1000 pulses, 110% AMT, 8 sessions/8 weeks	**UPDRS-III** **UPDRS-Bradykinesia** UPDRS total HRSD VAS	**-20% vs -5%** **-23% vs -2%** ns ns ns	1 month **p** **p** ns ns ns	I
Shirota et al., 2013b	102 PD HY 2-4 (S: 34 G1: 34 G2: 34) Randomized Double blinded Sham controlled Parallel	ON during assessment and stimulation S: SMA, sham coil G1: SMA, F8c G2: SMA, F8c	G1: 1Hz, 1000 pulses, 110% AMT, 8 sessions/8 weeks G2: 10Hz, 1000 pulses, 110% AMT, 8 sessions/8 weeks		G1 G2	3 months G1 G2	I
				UPDRS-III UPDRS total Hamilton rating scale apathy score nonmotor symptoms questionnaire	**ns ns** ns ns ns ns ns ns ns ns	**p ns** p ns ns ns ns ns ns ns	
Jinghong et al., 2019	28 PD-FOG (S: 10 G1:18) Randomized Double blinded Sham controlled Parallel	ON during assessment and ON during stimulation S: SMA, tilted coil G1: SMA, F8c	10 Hz, 1000 pulses, 90% RMT, 10 sessions/2 weeks	**Sequence Effect** FOG-Q UPDRS-III Gait time Gait steps Gait cadence Gait velocity	**ns** -18% vs 0% -17% vs -5% -20% vs -4% ns ns ns	1 month ns p p p p p p	II

Level C Effective for the treatment of overall motor symptoms in PD
Level A Ineffective for the treatment of depression in PD

Short_final_rTMS: Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).
Final_rTMS: Randomized rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).

4.4.12. H-coil rTMS (for class I and II see Table 12; for a full table see supplementary information)

An H-coil (Hesed-coil) is presumed to stimulate deeper (up to 5.5 cm (Zangen et al., 2005)) and less focally than other coil types, and deserves a separate discussion. A class II study including 42 patients showed a small improvement of UPDRS-III (10 %) with H-coil rTMS over M1 (1 Hz) + PFC (10 Hz). However, no effect could be found for bradykinesia, gait or depression (Cohen et al., 2018). A class III study found an improvement of UPDRS-III and less FOG in a FOG- provoking test with 10 Hz medial PFC stimulation; the regularity of gait kinematic parameters was improved. However, the study was interrupted because of pain – which may be a limiting side effect of the H-coil. The heterogeneity and low number of studies preclude further conclusions on the level of evidence as regards the efficacy of deep rTMS.

4.4.13. Meta-analyses on rTMS effects in PD

There are a few meta-analyses that investigated the effects of rTMS on PD symptoms. However, these results should be interpreted cautiously, because the studies performing stimulation at different frequencies and of different brain areas were pooled together. While some authors found an improvement of motor symptoms after LF rTMS over several brain areas (Zhu et al., 2015), others did not (Elahi et al., 2009). Furthermore, a study showed an improvement of motor symptoms after LF rTMS, but only when the stimulation occurred over brain areas other than M1 (Chou et al., 2015). When studies stimulating different brain areas were merged in the analysis, HF rTMS improved motor symptoms (Elahi et al., 2009). Moreover, studies stimulating M1 with HF rTMS improved motor symptoms the most (Chou et al., 2015; Yang et al., 2018). In addition, these studies showed that a higher number of pulses correlated with a more significant effect on motor symptoms.

When LF rTMS and HF rTMS studies were merged in the analysis, rTMS improved motor symptoms but had no effect on cognition (Goodwill et al., 2017), and rTMS of M1 had the largest effect (Zanjani et al., 2015). Some authors did not confirm the antidepressant effect of prefrontal cortex rTMS (Zhou et al., 2019). A meta-analysis merging all tDCS and rTMS studies concluded that NIBS improved the motor UPDRS-III and FOG, the most efficacious being M1 stimulation (Kim et al., 2019).

4.5. Transcranial direct current stimulation (tDCS)

4.5.1. Anodal tDCS over M1 (for class I and II see Table 13; for a full table see supplementary information)

One class I study including 60 PD patients compared the effect of 6 sessions anodal M1 tDCS alone to physical therapy combined with sham stimulation (Yotnuengnit et al., 2018). Though no difference was found in motor UPDRS-III and gait performance, the effects of tDCS are comparable to physical therapy – a well-established therapy for PD motor symptoms and gait performance (Tomlinson et al., 2012; Rutz and Benninger, 2020). A class II study found that 5 sessions of anodal M1 tDCS reduced the FOG episodes (50 %), FOG duration (75 %), the number of steps (30 %), and the time to complete a stand-walk-sit test (45 %). The improvement included the UPDRS-III, the FOG-Q, the gait and falls questionnaire and effects lasted for one month (Valentino et al.,

Table 7
Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham). Written in bold: primary outcomes; Written in purple: studies testing different stimulation paradigms; highlighted in green: high-quality studies class I and II; Hash: studies using an active sham or superiority studies (Koch et al., 2009). (For interpretation of the references to colour in this table legend, the reader is referred to the web version of this article.)

Study	Number HY Design	Medication state Control Group/Condition Target	Stimulation parameters	**Primary outcome** Secondary outcomes	Results at study completion (real stimulation vs. sham)	Follow-up Results	Class
rTMS on Motor Symptoms **rTMS over the Cerebellum**							
Koch et al., 2009a	20 PD HY 2-4 (S: 10 G1: 10) Randomized Double blinded Sham controlled Parallel	ON during assessment and stimulation S: cerebellum, sham coil G1: bil cerebellum, F8c	cTBS, 2400 pulses, 80% AMT, 10 sessions/2 weeks	**Dyskinesia (CAPSIT-LID)** Diary on with LID UPDRS-III	**-30% vs ns** -38% vs -15% ns	1 month **p** p ns	II
	10 PD HY 2-4 Randomized Double blinded Sham controlled Cross-over	ON during assessment and stimulation S: cerebellum, sham coil C1: cerebellum, F8c	Washout: 1 week cTBS, 600 pulses, 80% AMT, 1 session	**Dyskinesia (CAPSIT-LID)** UPDRS-III SICI LICI	**imp** ns reduced (3-5 ms) increased	none	II
Level B Effective for the treatment of Dyskinesia in PD							

Short_final_rTMS: Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).
Final_rTMS: Randomized rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).

Table 8
Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham). Written in bold: primary outcomes; Written in purple: studies testing different stimulation paradigms; highlighted in green: high-quality studies class I and II; Hash: studies using an active sham or superiority studies (Fricke et al., 2019). (For interpretation of the references to colour in this table legend, the reader is referred to the web version of this article.)

Study	Number HY Design	Medication state Control Group/Condition Target	Stimulation parameters	**Primary outcome** Secondary outcomes	Results at study completion (real stimulation vs. sham)	Follow-up Results	Class
rTMS on Motor Symptoms **LF rTMS over M1 + PMd**							
Fricke et al., 2019	20 PD HY 1-3 Randomized Double blinded Sham controlled Cross over	OFF during assessment and stimulation S: PMd and M1, tilted coil C1: PMd and M1, D coil	Washout:7 days 1 Hz,1000 pulses, 80% AMT, 1 session	**UPDRS-III** Finger tapping Spectral tremor power	**ns** ns ns	1 hour **ns** ns ns	II
No possible recommendation							

Short_final_rTMS: Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).
Final_rTMS: Randomized rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).

2014). However, a class II study failed to find any effect of anodal M1 tDCS on FOG-provoking test, gait performance and executive functions (Dagan et al., 2018a). Summarizing the class III studies: one study found a beneficial effect of tDCS on UPDRS-III (1/1), bradykinesia (1/3) and FOG (1/1); however, two studies (2/3) found no effect on bradykinesia, and one study none on working memory. Overall, anodal tDCS over M1 may improve motor symptoms (Level B) and possibly gait performance (Level C). Considering some contradictory results among studies, the efficacy of tDCS on gait performance reached only a level C evidence. The current studies preclude further recommendations.

4.5.2. Anodal tDCS over DLPFC (for class I and II see Table 16; for a full table see supplementary information)

While there were only class III studies investigating the effect of anodal tDCS over DLPFC on motor symptoms, two class II studies investigated the effect of tDCS on non-motor symptoms. A study including 38 demented PD patients did not find any effect of tDCS on vigilance and reaction time (Elder et al., 2017). Another study including 60 patients tested the effect of tDCS on impulsivity in PD (Benussi et al., 2017). Cathodal, but not anodal tDCS reduced the impulsivity in the Iowa Gambling Task. When summarizing the class III studies, two out of four studies improved gait, one out of two improved executive function and one study improved verbal fluency and working memory (1/1).

Table 9
Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham). Written in bold: primary outcomes; Written in purple: studies testing different stimulation paradigms; highlighted in green: high-quality studies class I and II; Hash: studies using an active sham or superiority studies (Koch et al., 2009). (For interpretation of the references to colour in this table legend, the reader is referred to the web version of this article.)

Study	Number HY Design	Medication state Control Group/Condition Target	Stimulation parameters	**Primary outcome** Secondary outcomes	Results at study completion (real stimulation vs. sham)	Follow-up Results	Class
rTMS Effect on Dyskinesia							
Koch et al., 2009b	20 PD HY 2-4 (S: 10 G1: 10) Randomized Double blinded Sham controlled Parallel	ON during assessment and stimulation S: cerebellum, sham coil G1: cerebellum, F8c	cTBS, 2400 pulses, 80% AMT, 10 sessions/2 weeks	**Dyskinesias (CAPSIT-LID)** Diary on with LID UPDRS-III	**-30% vs ns** -38% vs -15% ns	1 month **p** p ns	II
	10 PD HY 2-4 Randomized Double blinded Sham controlled Cross-over	ON during assessment and stimulation S: cerebellum, sham coil C1: cerebellum, F8c	Washout: 1 week cTBS, 600 pulses, 80% AMT, 1 session	**Dyskinesia (CAPSIT-LID)** UPDRS-III SICI LICI	**imp** ns reduced (3-5 ms) increased	none	II
Level B Effective cTBS over the cerebellum for the treatment of Dyskinesia							
Level C Effective LF-rTMS over the SMA for the treatment of Dyskinesia							
Level C Ineffective LF-rTMS over M1 for the treatment of Dyskinesia							

These heterogenous results do not allow recommending the use of anodal tDCS over the DLPFC in PD.

4.5.3. Anodal tDCS over SMA (for a full table see supplementary information)

Only two class III studies investigated the effect of anodal tDCS over SMA. One study improved UPDRS-III while the other did not improve gait, and symptoms even worsened. This contradiction in the two studies does not allow for any recommendation.

4.5.4. Anodal tDCS over M1 + DLPFC (for class I and II see Table 14; for a full table see supplementary information)

In a class II study with 25 PD patients, we investigated the effect of eigth sessions of bilateral tDCS of alternating M1 and PFC (Benninger et al., 2010). We found improvement in timed testing of bradykinesia (ON 31 % and OFF 39 %) –consisting of ten repetitive hand and arm movements– and in a 10 m walking test (23 % only in the off-condition), but no effect on motor UPDRS-III, depression or working memory. The beneficial effect on bradykinesia persisted for at least three months, and also reflected enhanced motor learning. This potential enhancement of motor learning with anodal stimulation may be beneficial to a combined physical therapy currently under investigation in a study on FOG. Another class II study reported a beneficial effect of anodal tDCS over M1 + DLPFC on FOG (FOG provoking test: 20 %), gait (TUG 21 %; speed 80 m 4.2 %) and the Stroop test (11 %). The study also showed the superiority of the combined M1 + DLPFC stimulation compared to M1 stimulation alone (Dagan et al., 2018a). Based on these two class II studies, we conclude that anodal tDCS over M1 + DLPFC seems beneficial for gait difficulties in PD (Level B).

4.5.5. Physical therapy and anodal tDCS (for class I and II see Table 15; for a full table see supplementary information)

A few studies tested whether combining tDCS with physical therapy (PT) would enhance motor learning and, thereby, potentiate the efficacy of PT (Tomlinson et al., 2012; Rutz and Benninger, 2020). One class I study of combined anodal M1 tDCS with PT failed to find a complementary effect on UPDRS-III and gait (Yotnuengnit et al., 2018). However, tDCS alone had a comparabale effect to PT + sham stimulation. This could indicate a "ceiling" effect or response saturation to either intervention without further benefit by combining them. Another class II study confirmed no additional effect of anodal stimulation on UPDRS-III, gait or bradykinesia (Costa-Ribeiro et al., 2017). However, although the improvement in the 10 m walking test and the timed-up-and-go test was similar immediately after the ten stimulation sessions, the effect tended to manifest within fewer days and persisted for longer time periods (i.e. for at least one month, in the tDCS group). Summing-up the class III studies, one out of three studies improved the UPDRS-III, one out of three improved bradykinesia, and two studies improved the cognitive outcome (2/2) (i.e. PD-CRS and correct response rate); four studies (4/4) didn't show a benefit on gait performance, and one study (1/1) failed to show any effect on depression. Overall, anodal tDCS + rehabilitation may not have an additional effect as compared to rehabilitation + sham stimulation on motor symptoms (Level B), bradykinesia (Level C) and gait performance (Level B). However, an additional effect may exist on the cognitive outcome (Level C).

4.5.6. Anodal tDCS of the medial frontal cortex (for a full table see supplementary information)

Only one class III study in 20 PD patients suffering from mild cognitive impairment reported an improvement of the cognitive outcome (i.e. attribution of intention task assessing comprehension of displayed stories) after anodal tDCS over the medial frontal cortex. This single study precludes further conclusion.

4.5.7. Anodal tDCS + cognitive training (for class I and II see Table 17; for a full table see supplementary information)

The presumed enhancement of learning by anodal tDCS provides the rationale to combine it with cognitive training. So far, there are a few studies. A class I study tested whether tDCS would enhance the effect of computerized cognitive training (Manenti et al., 2018). After ten sessions of anodal tDCS over the left-DLPFC + computerized cognitive training, the authors found an additional effect of the combined therapy on depression (BDI 25 %) compared to computerized cognitive training alone (+ sham tDCS), and this effect lasted for three months. However,

Table 10
Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham). Written in bold: primary outcomes; Written in purple: studies testing different stimulation paradigms; highlighted in green: high-quality studies class I and II; Hash: studies using an active sham or superiority studies (Pal et al., 2010; Brys et al., 2016; Benninger et al., 2011). (For interpretation of the references to colour in this table legend, the reader is referred to the web version of this article.)

Study	Number HY Design	Medication state Control Group/Condition Target	Stimulation parameters	**Primary outcome** Secondary outcomes	Results at study completion (real stimulation vs. sham)	Follow-up Results	Class
DLPFC rTMS effect on Depression in PD							
Pal et al., 2010b	22 PD+Depression (S: 10 G1: 12) Randomized Double blinded Sham controlled Parallel	ON during assessment and stimulation S: lDLPFC, sham coil G1: lDLPFC, F8c	5Hz, 600 pulses, 90% RMT, 10 sessions/10 days			1 month	II
				BDI	-44% vs -16%	p	
				MADRS	-13% vs -4%	p	
				Stroop test	15% vs 2%	p	
				TUG test	-12% vs 0%	ns	
				UPDRS-III	ns	ns	
				TMT	ns	ns	
				MMSE	ns	ns	
				Schwab & England ADL	ns	ns	
				VAS	ns	ns	
				ESS	ns	ns	
Brys et al., 2016d	61 PD HY 2-4 (S: 15 G1: 20 G2: 14 G3: 12) Randomized Double blinded Sham controlled Parallel	OFF during assessment and ON during stimulation S: M1 and DLPFC, sham coil G1: M1 and DLPFC, F8c G2: M1 and sham DLPFC, F8c G3: DLPFC and sham M1, F8c	G1: 10Hz, 2000 pulses, 100% RMT, 10 sessions/10 days G2: idem G3: idem		G1 / G2 / G3	6 months	II
				UPDRS-III	**ns / -15% vs -1% / ns**	**ns**	
				HAM-D	**ns / ns / ns**	**ns**	
				Beck depression inventory II	ns / ns / ns	ns	
				Apathy evaluation scale	ns / ns / ns	ns	
				Clinical anxiety scale	ns / ns / ns	ns	
				MoCA	ns / ns / ns	ns	
				PDQ-39	ns / ns / ns	ns	
				UPDRS-total	ns / ns / ns	ns	
				Clinical Global Impression	ns / ns / ns	ns	
Benninger et al., 2011b	26 PD HY 2-4 (S: 13 G1:13) Randomized Double blinded Sham controlled Parallel	ON and OFF during assessment and ON during stimulation S: M1 (upper limb) + DLPFC, sham coil G1: M1 (upper limb) + DLPFC, round coil	iTBS, 2400 pulses, 80% AMT, 8 sessions/2 weeks		ON / OFF	1 month	I
				walking time (10m)	**ns / ns**	**ns**	
				timed bradykinesia	**ns / ns**	**ns**	
				UPDRS-total	ns / -13% vs -2%	ns	
				UPDRS-III	ns / ns	ns	
				UPDRS-II	ns / ns	ns	
				UPDRS freezing	ns / ns	ns	
				FAB	ns	ns	
				BDI	-19% vs 8%	ns	
				Mental health	ns	ns	
				physical health	ns	ns	
				SRTT	ns	ns	

Level B Effective for the treatment of depression in PD

Short_final_rTMS: Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).
Final_rTMS: Randomized rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).

no additional effect was found for cognition, UPDRS-III, memory, language, executive functions or attention. A RCT class II study investigated the additional effect of anodal tDCS of left-DLPFC with an occupational therapy on fatigue (Forogh et al., 2017). The study reported an additional effect in the fatigue severity index (17 %), which did not persist at the three months follow-up, but none in the Epworth sleepiness scale. One class III study found an additional effect of DLPFC anodal tDCS on memory, language, attention and executive function, but none on visuospatial abilities and global cognitive functions. The inconsistency of these results, their heterogeneity and the lack of class I RCT preclude a conclusion as to whether or not tDCS provides the additional efficacy of tDCS + cognitive training.

4.5.8. Cathodal tDCS (for class I and II see Table 18; for a full table see supplementary information)

Although –in most studies– the anodal tDCS targeted the region of interest without giving importance to cathode's position, some studies investigated the effect of cathodal in comparison to anodal stimulation. One class II study reported that cathodal tDCS over the DLPFC can reduce the impulsivity of PD patients while anodal tDCS cannot (Benussi et al., 2017). Investigators of a class II study placed the anode over the ipsilateral DLPFC and the cathode over the contralateral DLPFC: they could improve the fatigue severity index (Forogh et al., 2017). Another class III study with the same experimental design neither improved gait nor cognition (Swank et al., 2016). However, in a class III study, the cathode was placed over the more affected and the anode over the less affected M1: a 50 % improvement of the UPDRS-III baseline motor score was obtained. When reversing the electrode polarity, they found no improvement (Salimpour et al., 2015). In a class III study, the more affected M1 was stimulated first with the anode and then the cathode, followed by stimulation of the less affected M1. Each corresponding electrode was placed over the contralateral orbital frontal region. The authors found that anodal stimulation of the more affected M1, and cathodal stimulation of the less affected M1 improved motor symptoms; anodal stimulation of the less affected M1, and cathodal stimulation of the more affected M1 didn't improve motor symptoms – or even worsened them (Cosentino et al., 2017). The authors interpreted these findings to result from a presumed pathological imbalance of excitability between the brain hemispheres (Cosentino et al., 2017). The rationale for the placement of the depolarizing anodal and the hyperpolarizing cathodal stimulation would be to remediate this imbalance. The heterogeneity of these studies precludes further conclusion regarding the efficacy of cathodal stimulation; but underlines the importance of electrode placement and the direction of current flow.

Table 11
Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham). Written in bold: primary outcomes; Written in purple: studies testing different stimulation paradigms; highlighted in green: high-quality studies class I and II; Hash: studies using an active sham or superiority studies (Srovnalova et al., 2012; Khedr et al., 2019b; Shirota et al., 2013). (For interpretation of the references to colour in this table legend, the reader is referred to the web version of this article.)

Study	Number HY Design	Medication state Control Group/Condition Target	Stimulation parameters	**Primary outcome** Secondary outcomes	Results at study completion (real stimulation vs. sham)		Follow-up Results		Class
				rTMS effect on Non-Motor Symptoms					
Srovnalova et al., 2012	10 PD Randomized Double blinded Sham controlled Cross-over	OFF during assessment and stimulation S1: lDLPFC, sham coil S2: rDLPFC, sham coil C1: lDLPFC, F8c C2: rDLPFC, F8c	Washout: 24h C1: 25Hz, 600 pulses, 80% RMT, 1 session C2: idem		C1	C2	none		II
				Tower of London (executive function)	**ns**	**-9% vs +2%**			
Khedr et al., 2019b	33 PD+Dysphagia (S: 11 G1: 19) Randomized Double blinded Sham controlled Parallel	ON during assessment and stimulation S: M1, tilted coil G1: M1, F8c	20 HZ, 4000 pulses, 90% RMT, 10 sessions/2 weeks				3 months (incl 5 boosters)		I
				Arabic-Dysphagia Handicap Index	**-40% vs -10%**		**p**		
				Video fluoroscopy solid:					
				-pharyngeal transit time	-21% vs +7%		p		
				-H1-H2	-40% vs +13%		ns		
				-Penetration aspiration	ns		ns		
				-Residue	ns		ns		
				Video fluoroscopy liquid	ns		ns		
				UPDRS-III	-36% vs -6%		p		
				HY	ns		ns		
				Instrumental activities of daily living	ns		ns		
				Self-assessment scale	-27% vs -5%		p		
Shirota et al., 2013b	102 PD HY 2-4 (S: 34 G1: 34 G2. 34) Randomized Double blinded Sham controlled Parallel	ON during assessment and stimulation S: bil SMA, sham coil G1: bil SMA, F8c G2: bil SMA, F8c	G1: 1Hz, 1000 pulses, 110% AMT, 8 sessions/8 weeks G2: 10Hz, 1000 pulses, 110% AMT, 8 sessions/8 weeks				3 months		I
					G1	G2	G1	G2	
				UPDRS-III	**ns**	**ns**	**p**	**ns**	
				UPDRS total	ns	ns	p	ns	
				Hamilton rating scale	ns	ns	ns	ns	
				apathy score	ns	ns	ns	ns	
				nonmotor symptoms questionnaire	ns	ns	ns	ns	

No possible recommendation

Short_final_rTMS: Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).
Final_rTMS: Randomized rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).

Table 12
Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham). Written in bold: primary outcomes; Written in purple: studies testing different stimulation paradigms; highlighted in green: high-quality studies class I and II; Hash: studies using an active sham or superiority studies (Cohen et al., 2018). (For interpretation of the references to colour in this table legend, the reader is referred to the web version of this article.)

Study	Number HY Design	Medication state Control Group/Condition Target	Stimulation parameters	**Primary outcome** Secondary outcomes	Results at study completion (real stimulation vs. sham)	Follow-up Results	Class
				H-coil rTMS			
Cohen et al., 2018	42 PD HY 2-4 (S: 21 G1: 21) Randomized Double blinded Sham controlled Parallel	ON during assessment and stimulation S: M1 + PFC, sham coil G1: M1 + PFC, H-coil	1Hz M1, 900 pulses, 110% RMT + 10 Hz PFC, 800 pulses, 100% RMT, 24 sessions/3 months	**UPDRS total**	**-10% vs -6%**	none	II
				UPDRS-III	**-10% vs -6%**		
				Timed finger and foot tapping	ns		
				TUG	ns		
				BDI	ns		
				Digit span test	ns		
				Word fluency test	ns		
				Pegboard	ns		

No possible recommendation

Short_final_rTMS: Randomized controlled studies of rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).
Final_rTMS: Randomized rTMS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).

Table 13
Randomized controlled studies of tDCS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham). Written in bold: primary outcomes; Written in purple: studies testing different stimulation paradigms; highlighted in green: high-quality studies class I and II; Hash: studies using an active sham or superiority studies (Valentino et al., 2014; Yotnuengnit et al., 2018; Dagan et al., 2018a). (For interpretation of the references to colour in this table legend, the reader is referred to the web version of this article.)

Study	Number HY Design	Medication state Control Group/Condition Target	Stimulation parameters	Online/Offline **Primary outcome** Secondary outcomes	Results at study completion (real stimulation vs. sham)		Follow-up Results		Class
tDCS on Motor Symptoms **Anodal tDCS over M1**									
Valentino et al., 2014	10 PD-FOG+ HY 2.5-4 Randomized, double blinded, Sham controlled cross-over	OFF during HY and ON during assessment C1: anode M1 (leg area); cathode cofa	Washout: 3 months C1: 20 min, 2.0 mA, 5 sessions/1 week	Offline measurement **Stand Walk Sit Test:** **-Number of FOG** **-Duration of FOG** **-Number of steps** **-Time to complete test** total UPDRS UPDRS III FOG-Q Gait and Falls Questionnaire	 **-50% vs +3%** **-75% vs -10%** **-30% vs -5%** **-45% vs -3%** imp imp imp imp		1 month **p** **p** **p** **p** p p p p		II
Yotnuengnit et al., 2018a	60 PD HY 2-3 (S: 20 G1: 20 G2: 20) Randomized Double blinded Sham controlled Parallel	ON during assessment and stimulation G1: anode M1; cathode cofa G2: anode M1 cathode cofa + PT S: sham + PT	G1: 30 min, 2 mA, 6 sessions/2 weeks G2: 30 min, 2 mA + PT, 6 sessions/2 weeks	Offline measurement **walking speed** step length step width cadence UPDRS-II UPDRS-III	 G1 **ns** ns ns ns ns ns	 G2 **ns** ns ns ns ns ns	6 weeks G1 **ns** ns ns ns ns ns	 G2 **ns** ns ns ns ns ns	I
Dagan et al., 2018a	20 PD-FOG+ HY 2-3.5 Randomized Double blinded Sham controlled Cross-over	ON during assessment C1: anode M1; cathode AF4, CP1, FC1 C2: anode M1 + left DLPFC (F3); cathode AF4, CP1, FC1, FC5	Washout: 48 h C1: 20 min, 1.5 mA, 1 session C2: idem	Offline measurement **FOG provoking test (cued and non-cued)** TUG test Speed (80 meters walk test) Stroop test	C1 **ns** ns ns ns	C2 **-29% vs 0%** -21% vs +12% +4.200% vs +4.192% +11% vs +7%	none		II
Level B **Effective for the treatment of overall motor symptoms in PD**									
Level C **Effective for the treatment of gait performance in PD**									

Short_final_tDCS: Randomized controlled studies of tDCS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).
Final_tDCS: Randomized controlled studies of tDCS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).

4.5.9. Dual stimulation: tDCS + rTMS (for class I and II see Table 19; for a full table see supplementary information)

Dual stimulation refers here to simultaneous stimulation or to priming with tDCS followed by rTMS. One class I study investigated whether anodal tDCS over the left-DLPFC would have an additional effect on PD symptoms when combined with subsequent HF M1 rTMS (Chang et al., 2017). The study showed a significant additional improvement of gait (TUG 11 %; turn steps 11 %), cognition (MoCA 6 %) and executive function (TMT-B 18 %), whereas no additional effect was found for UPDRS-III, depression or FOG. The improvement in the TMT-B persisted even at one-week follow-up. This single study precludes further conclusion.

4.5.10. Meta-analyses on tDCS effects in PD

Two meta-analyses investigated the effect of tDCS on motor symptoms, cognition and gait function in PD. When tDCS studies were merged in the analysis, tDCS improved motor symptoms but not cognition (Goodwill et al., 2017). The tDCS induced a short-lasting beneficial effect on gait function without any longer-term effect. Targeting multiple brain areas (multifocal stimulation) may also be beneficial (Lee et al., 2019a). In a meta-analysis, merging results of both rTMS and tDCS studies, NIBS improved FOG and the UPDRS-III; when targeting M1, the effect was even stronger. However, the heterogeneity of studies preclude a comparison, and merging all the data may lead to biased results, which should be interpreted cautiously.

4.6. Transcranial Alternating Current Stimulation (tACS) (for class I and II see Table 20; for a full table see supplementary information)

In a class II study with 15 PD patients and 15 healthy subjects, the investigators chose a personalized stimulation protocol based on a disease model related to the excess or deficiency in EEG-power maps. The rationale of placing the electrode targetting the brain region with the largest difference in EEG-power maps is to counterbalance the prevalent beta excess in PD (found in two thirds of their sample) with 4 Hz tACS and conversely the theta excess with 30 Hz tACS. The Random Noise Stimulation (RNS) was used in a control group of PD patients; in both conditions, stimulation was followed by physical therapy (10 sessions). The personalized tACS protocol did not cause an additional effect regarding motor symptoms, gait, depression, cognition, executive functions or language. However, there was an improvement with tACS in the Montreal cognitive assessement (MoCA) compared to RNS, which persisted at one-month follow-up. Theta stimulation reduced beta-power and increased theta-power in PD patients; the beta-power increase persisted even at one-month follow-up. No power-spectrum changes were found after 30 Hz stimulation (del Felice et al., 2019). Since they studied an active control condition and no sham stimulation, it is difficult to compare these results with those of other studies. Moreover, 4 Hz and 30 Hz are relatively low-frequency stimulations and low frequencies are increased in PD pathophysiology. Therefore, stimulating with higher frequencies appears more promising.

Table 14
Randomized controlled studies of tDCS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham). Written in bold: primary outcomes; Written in purple: studies testing different stimulation paradigms; highlighted in green: high-quality studies class I and II; Hash: studies using an active sham or superiority studies (Dagan et al., 2018; Benninger et al., 2010). (For interpretation of the references to colour in this table legend, the reader is referred to the web version of this article.)

Study	Number HY Design	Medication state Control Group/Condition Target	Stimulation parameters	Online/Offline **Primary outcome** Secondary outcomes	Results at study completion (real stimulation vs. sham)		Follow-up Results		Class
tDCS on Motor Symptoms **Anodal tDCS over M1+DLPFC**									
Dagan et al., 2018b	20 PD-FOG+ HY 2-3.5 Randomized Double blinded Sham controlled Cross-over	ON during assessment C1: anode M1; cathode AF4, CP1, FC1 C2: anode M1 + left DLPFC (F3); cathode AF4, CP1, FC1, FC5	Washout: 48 h C1: 20 min, 1.5 mA, 1 session C2: idem	Offline measurement	C1	C2	none		II
				FOG provoking test (cued and non-cued)	**ns**	**-29% vs 0%**			
				TUG test	ns	-21% vs +12%			
				Speed (80 meters walk test)	ns	+4.200% vs +4.192%			
				Stroop test	ns	+11% vs +7%			
Benninger et al., 2010	25 PD HY 2-4 (S: 12 G1:13) Randomized, double blinded, Sham controlled parallel	ON and OFF during assessment and ON during stimulation G1: anodes both M1 + PFC; cathodes mastoids	G1: 20 min, 2mA, 8 sessions/2.5 weeks	Offline measurement	ON	OFF	3 months ON	OFF	II
				walking time (10m)	**ns**	**-23% vs +3%**	**ns**	**ns**	
				timed bradykinesia	-31% vs -15%	-39% vs -23%	p	p	
				UPDRS-III	ns	ns	ns	ns	
				SRTT	ns	ns	ns	ns	
				depression score (BDI)	ns	ns	ns	ns	
				health survey	ns	ns	ns	ns	
				self-assessment	ns	ns	ns	ns	

Level B Effective for the treatment of gait performance in PD

Short_final_tDCS: Randomized controlled studies of tDCS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).
Final_tDCS: Randomized controlled studies of tDCS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).

Table 15
Randomized controlled studies of tDCS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham). Written in bold: primary outcomes; Written in purple: studies testing different stimulation paradigms; highlighted in green: high-quality studies class I and II; Hash: studies using an active sham or superiority studies (Yotnuengnit et al., 2018; Costa-Ribeiro et al., 2017). (For interpretation of the references to colour in this table legend, the reader is referred to the web version of this article.)

Study	Number HY Design	Medication state Control Group/Condition Target	Stimulation parameters	Online/Offline **Primary outcome** Secondary outcomes	Results at study completion (real stimulation vs. sham)		Follow-up Results		Class
tDCS on Motor Symptoms **Physical therapy and anodal tDCS**									
Yotnuengnit et al., 2018b	60 PD HY 2-3 (S: 20 G1: 20 G2: 20) Randomized Double blinded Sham controlled Parallel	ON during assessment and stimulation G1: anode M1; cathode cofa G2: anode M1 cathode cofa + PT S: sham + PT	G1: 30 min, 2 mA, 6 sessions/2 weeks G2: 30 min, 2 mA + PT, 6 sessions/2 weeks	Offline measurement	G1	G2	6 weeks G1	G2	I
				walking speed	**ns**	**ns**	**ns**	**ns**	
				step length	ns	ns	ns	ns	
				step width	ns	ns	ns	ns	
				cadence	ns	ns	ns	ns	
				UPDRS-II	ns	ns	ns	ns	
				UPDRS-III	ns	ns	ns	ns	
Costa-Ribeiro et al., 2017	22 PD HY 1-3 (S: 11 G1: 11) Randomized Double blinded Sham controlled Parallel	ON during assessment G1: anode SMA; cathode cofa	G1: 13 min, 2 mA, 10 sessions/ 4 weeks + cued gait training	Offline measurement			1 month		II
				10 m walk test	**ns**		**p**		
				Timed up and go test	**ns**		**p**		
				cadence	**ns**		**ns**		
				stride length	**ns**		**ns**		
				UPDRS-III	ns		ns		
				Bradykinesia	ns		ns		
				Berg Balance scale	ns		ns		
				PDQ-39	ns (faster effect in the tDCS group)		ns		

Level C Effective for the treatment of cognitive function in PD
Level B Ineffective for the treatment of overall motor symptoms in PD
Level B Ineffective for the treatment of gait performance in PD
Level C Ineffective for the treatment of bradykinesia in PD

Short_final_tDCS: Randomized controlled studies of tDCS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).
Final_tDCS: Randomized controlled studies of tDCS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).

Table 16
Randomized controlled studies of tDCS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham). Written in bold: primary outcomes; Written in purple: studies testing different stimulation paradigms; highlighted in green: high-quality studies class I and II; Hash: studies using an active sham or superiority studies (Elder et al., 2017; Benussi et al., 2017). (For interpretation of the references to colour in this table legend, the reader is referred to the web version of this article.)

Study	Number HY Design	Medication state Control Group/Condition Target	Stimulation parameters	Online/Offline **Primary outcome** Secondary outcomes	Results at study completion (real stimulation vs. sham)		Follow-up Results	Class
tDCS on Non-Motor Symptoms **Anodal tDCS over DLPFC**								
Elder et al., 2017	38 PD+Dementia Randomized Double blinded Sham controlled Cross-over	ON during assessment and stimulation C1: anode lDLPFC; cathode right deltoid muscle	Washout: 24 h C1: 20 min, 2.8 mA, 1 session	Offline measurement **choice reaction time** **digit vigilance** **attention network task** simple reaction time	**ns** **ns** **ns** ns		none	II
Benussi et al., 2017 a	60 PD (S: 20 G1: 20 G2: 20) Randomized Double blinded Sham controlled Parallel	ON during assessment and stimulation G1: anode rDLPFC; cathode cofa G2: cathode rDLPFC; anode cofa	G1: 10 min, 2 mA, 1 session G2: idem	Online measurement Iowa gambling task	G1 ns	G2 imp	none	II
No possible recommendation								

Short_final_tDCS: Randomized controlled studies of tDCS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).
Final_tDCS: Randomized controlled studies of tDCS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).

A class II tACS study found no effects on motor symptoms, depression and sleepiness after 77.5 Hz stimulation over the frontal area (Shill et al., 2011). A class III study failed to show an effect of 10 Hz tACS on diadochokinesia, fast-finger tapping, EEG-power maps and cortico-muscular coherence. However, 20 Hz stimulation paradoxically reduced beta cortico-muscular-coherence and increased fast-finger tapping regularity (Krause et al., 2014). The study assessments were done after the stimulation, i.e. offline, which may have missed the immediate effect of stimulation.

In two studies, Brittain et al. investigated the online effect of tACS on tremor. In an exploratory class III study, the investigators reported that stimulating M1 with the tremor's frequency – out of phase and in a closed-loop manner – enabled a tremor reduction of 42 % baseline value (Brittain et al., 2013). In another exploratory class IV study, they showed that stimulating the cerebellum with the tremor frequency enabled real-time tremor entrainment, with no effect on tremor amplitude (Brittain et al., 2015). This last study underscores the importance of personalized, closed-loop, real-time stimulation systems able to adapt to the underlying physiopathology. Although these tACS studies in PD patients need to be confirmed, tACS studies in healthy subjects are promising. Gamma tACS of M1 improves (Santarnecchi et al., 2017) and beta tACS impairs motor performance by presumed entrainment of the cortical circuit (Pogosyan et al., 2009). When stimulating the medial frontal cortex at the individual theta frequency, tACS modulated the frontal-midline theta-oscillation phase, disrupted the working-memory task-related frontal-midline power increase, and the working-memory performance (Chander et al., 2016). These results are promising for further investigations in PD patients.

4.7. Transcranial pulsed current stimulation (tPCS) (for a full table see supplementary information)

A single pilot, class III study compared the effects of tPCS of M1 alone, tPCS combined with treadmill walking and walking on a treadmill alone (Alon et al., 2012). The results suggested that tPCS alone had a greater impact on gait function than treadmill walking alone or combined with tPCS. However, results of a single class III study should be interpreted wih caution.

4.8. Some review limitations

Because the Brainin criteria (Brainin et al., 2004) assess the methodological value of a whole study, no distinction is made to give weight to primary and secondary outcomes during the analysis. However, differentiating between primary and secondary outcome measures protects against the multiple comparisons problem. Consequently, a new methodology for future systematical reviews is still needed and should be developed.

4.9. Conclusions

LF-rTMS of M1 appears to be ineffective for motor symptoms (Level C) and depression (Level C) in PD. HF-rTMS of M1 is probably *e*ffective to treat motor symptoms (Level B). Conversely, it seems *in*effective to treat gait (Level B) and depression (Level B) in PD. HF-rTMS over DLPFC may be *in*effective to improve motor symptoms (Level B), but *e*ffective to improve depression in PD (Level B). Combined HF M1 + DLPFC rTMS may be *in*effective to treat motor symptoms (Level B). All studies being consistent, we conclude that LF-rTMS of SMA is *in*effective for the improvement of motor symptoms in PD (Level B). HF-rTMS SMA may be *e*ffective on motor symptoms (Level C), but results are ambiguous. All studies being consistent, we conclude that HF-rTMS over SMA is *in*effective to treat depression in PD (Level A). Furthermore, LF-rTMS over SMA and cTBS over cerebellum may reduce dyskinesia (Level C and Level B, respectively), whereas LF-rTMS of M1 may not be effective for dyskinesia (Level C) (See also Table 1).

Anodal tDCS of M1 may improve motor symptoms in PD (Level B) and gait (Level C). Anodal tDCS of M1 + DLPFC may be beneficial for gait (Level B). Combined anodal tDCS + rehabilitation may not have an additional effect compared to rehabilitation (+ sham stimulation) alone on motor symptoms (Level B), bradykinesia (Level C) and gait (Level B). However, combined with a cognitive training an additional effect on

Table 17
Randomized controlled studies of tDCS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham). Written in bold: primary outcomes; Written in purple: studies testing different stimulation paradigms; highlighted in green: high-quality studies class I and II; Hash: studies using an active sham or superiority studies (Manenti et al., 2018; Forogh et al., 2017). (For interpretation of the references to colour in this table legend, the reader is referred to the web version of this article.)

Study	Number HY Design	Medication state Control Group/Condition Target	Stimulation parameters	Online/Offline **Primary outcome** Secondary outcomes	Results at study completion (real stimulation vs. sham)	Follow-up Results	Class
tDCS on Non-Motor Symptoms **Anodal tDCS + cognitive training**							
Manenti et al., 2018	22 PD (S: 11 G1: 11) Randomized Double blinded Sham controlled Parallel	ON during assessment G1: anode lDLPFC; cathode cofa	G1: 25 min, 2 mA, 10 sessions/2 weeks + computerized cognitive training	Offline measurement 1)Depression: **BDI-II** 2)Cognition: **PD-CRS score** MMP 3)Clinical scales: UPDRS-III PDQ-39 BIS-11 RBDSQ Apathy evaluation scale 4)Memory: Rey auditory Verbal learning test 5)Language: Verbal fluency Naming 6)Executive: FAB Stroop test Trail making test Digit span 7)Attentional: Go/NoGO Working memory Response flexibility	 **-25% vs 2%** **ns** ns ns ns ns ns ns ns ns ns ns ns ns ns ns ns ns	3 months **p** **ns** ns ns ns ns ns ns ns ns ns ns ns ns ns ns ns ns	I
Forogh et al., 2017a	23 PD HY 2-3 (S: 11 G1: 12) Randomized Double blinded Sham controlled Parallel	ON during assessment G1: anode lDLPFC; cathode rDLPFC	G1: 20 min, 4 mA, 8 sessions/2 weeks + occupational therapy	Offline measurement **Fatigue severity index** Epworth Sleepiness scale	 **-17% vs +9%** ns	3 months **ns** ns	II
No possible recommendation							

Final_tDCS: Randomized controlled studies of tDCS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).

cognitive outcome is possible (Level C) (See also Table 2).

Although the current data is insufficient for recommending the clinical use of tACS, the promising results call for further investigations (See also Table 3).

In total, we reviewed 92 studies (class I, II and III), but only 29 qualify as high-quality studies (class I and II).

In total, 1411 PD-patients participated in the 52 rTMS studies: six studies with less than ten, 29 studies had between 10 and 25, and 17 studies more than 25 participants. Forty trials had balanced groups in a parallel design or were cross-over studies and 12 trials had imbalanced groups in a parallel design.

In total, 616 PD-patients participated in the 28 tDCS studies: one study had less than ten, 21 studies between 10 and 25, and six studies more than 25 participants. Twenty-eight trials had balanced groups in a parallel design or were cross-over studies and none had imbalanced groups.

53 PD-patients participated in the four tACS studies: one study had less than ten, three studies between 10 and 25, and none more than 25 participants. Three trials had balanced groups in a parallel design or were cross-over studies and one had imbalanced groups.

There is a recent increase in high-quality, class I RCT to complement the current state of evidence. More multi-center, phase 3 studies are needed to confirm the efficacy of these promising stimulation protocols before they can be approved for clinical practice.

There are a number of methodological issues to resolve: the choice of whether to compare an intervention to a control sham condition or another active intervention in a superiority study. In the current state of evidence, a sham stimulation controlled study design is preferable. Another potential shortcoming of many RCT is their rather small number of participants even when assuming a substantial effect size.

A great challenge is the selection of the best stimulation protocol among a practically unlimited number of possible stimulation parameters. The choice is difficult: also for the limited comparability between the current studies considering the heterogeneity of study designs. Promising stimulation protocols of ideally class I studies could provide the evidence for larger multi-center RCT.

5. Outlook and new technologies

The current state of evidence suggests a potential efficacy of NIBS for the treatment of Parkinson symptoms, but the mostly modest effects remain to be confirmed in large multicenter RCTs. In addition, more powerful stimulation protocols are needed for clinical practice since the effect sizes are small and insufficient to considerably improve the patients' quality of life.

The current concept of NIBS stipulates three possible modes of clinical applicability: 1) given the effects persist beyond the stimulation period, the intermittent application of NIBS remains the standard approach; 2) given plasticity promoting effects, the NIBS may potentiate the efficacy of combined interventions; 3) given immediate effects

Table 18
Randomized controlled studies of tDCS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham). Written in bold: primary outcomes; Written in purple: studies testing different stimulation paradigms; highlighted in green: high-quality studies class I and II; Hash: studies using an active sham or superiority studies (Benussi et al., 2017; Forogh et al., 2017). (For interpretation of the references to colour in this table legend, the reader is referred to the web version of this article.)

Study	Number HY Design	Medication state Control Group/Condition Target	Stimulation parameters	Online/Offline **Primary outcome** Secondary outcomes	Results at study completion (real stimulation vs. sham)		Follow-up Results	Class
				Cathodal tDCS				
Benussi et al., 2017b	60 PD (S: 20 G1: 20 G2: 20) Randomized Double blinded Sham controlled Parallel	ON during assessment and stimulation G1: anode rDLPFC; cathode cofa G2: cathode rDLPFC; anode cofa	G1: 10 min, 2 mA, 1 session G2: idem	Online measurement Iowa gambling task	G1 ns	G2 imp	none	II
Forogh et al., 2017b	23 PD HY 2-3 (S: 11 G1: 12) Randomized Double blinded Sham controlled Parallel	ON during assessment G1: anode lDLPFC; cathode rDLPFC	G1: 20 min, 4 mA, 8 sessions/2 weeks + occupational therapy	Offline measurement **Fatigue severity index** Epworth Sleepiness scale	 **-17% vs +9%** ns		3 months **ns** ns	II

No possible recommendation

Short_final_tDCS: Randomized controlled studies of tDCS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).
Final_tDCS: Randomized controlled studies of tDCS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).

Table 19
Randomized controlled studies of tDCS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham). Written in bold: primary outcomes; Written in purple: studies testing different stimulation paradigms; highlighted in green: high-quality studies class I and II; Hash: studies using an active sham or superiority studies (Chang et al., 2017). (For interpretation of the references to colour in this table legend, the reader is referred to the web version of this article.)

Study	Number HY Design	Medication state Control Group/Condition Target	Stimulation parameters	Online/Offline **Primary outcome** Secondary outcomes	Results at study completion (real stimulation vs. sham)	Follow-up Results	Class
				Dual Stimulation Anodal tDCS + rTMS			
Chang et al., 2017	32 PD (S: 16 G1: 16) Randomized Double blinded Sham controlled Parallel	ON during assessment and stimulation G1: M1 rTMS & tDCS anode lDLPFC; cathode cofa S: sham tDCS + real M1 rTMS	G1: 10 Hz rTMS + tDCS, 20 min,1 mA, 5 sessions	Offline measurement **FOG-Q** Turn steps Turn time UPDRS-III TUG Digit span forward Digit span backward Trail making test part B MoCA Geriatric depression scale -RMT -AMP	 **ns** -11% vs -5% ns ns -11% vs -5% ns ns -18% vs -1% +6% vs +0.4% ns ns ns	1 week **ns** ns ns ns ns ns ns p ns ns ns ns	I

No possible recommendation

Short_final_tDCS: Randomized controlled studies of tDCS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).
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–which do not persist beyond the stimulation period– the 3rd option may be chronic stimulation as with DBS, but this is only feasible with tCS and not rTMS.

Resuming the current state of knowledge: First, the long-term improvement after stimulation seems to be rather modest. Second, the NIBS' adjuvant effect on other therapies –e.g. physiotherapy, cognitive training– may be overlaid by a ceiling effect (i.e. saturation of response). Third, the online improvement may be the most promising, but has been poorly studied so far.

Considering the risks of current invasive therapies –therefore many patients are not eligible– searching for alternative therapies seems essential: NIBS is secure, inexpensive and portable (i.e. tCS). Also –paralleling the insights into pathophysiology– stimulation techniques are becoming more personalized and precise, and some novel technological advances hold promise.

Respecting the safety guidelines and the limitations of the

Table 20
Randomized controlled studies of tACS or tPCS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham). Written in bold: primary outcomes; Written in purple: studies testing different stimulation paradigms; highlighted in green: high-quality studies class I and II; Hash: studies using an active sham or superiority studies (Del Felice et al., 2019; Shill et al., 2011). (For interpretation of the references to colour in this table legend, the reader is referred to the web version of this article.)

Study	Number HY Design	Medication state Control Group/Condition Target	Stimulation parameters	Online/Offline **Primary outcome** Secondary outcomes	Results at study completion (real stimulation vs. sham)		Follow-up Results		Class
				tACS					
Del Felice et al., 2019	15 PD HY 1-2 (G1: 10 G2: 5) Randomized, Double blinded, RNS controlled Cross-over	OFF during assessment Target individually defined based on EEG power spectra differences; reference mastoid S: RNS as active sham G1: if beta excess => 4 Hz stim G2: if theta excess => 30 Hz stim	Washout: 2 months S: RNS 0-100 Hz, 30 min, 10 sessions/2 weeks + 1 hour PT G1: 4Hz, 30 min, sinusoidal 1-2 mA, 10 sessions/2 weeks + 1 hour PT G2: 30Hz, 30 min, sinusoidal 1-2 mA, 10 sessions/2 weeks + 1 hour PT	Offline measurement	G1	G2	1 month G1	G2	II#
				Beta excess (proportion of patients)		**10/15**		**na**	
				UPDRS III	**ns**	**ns**	**ns**	**ns**	
				UPDRS-bradykinesia	ns	ns	ns	ns	
				UPDRS-tremor	ns	ns	ns	ns	
				UPDRS-axial symptoms	ns	ns	ns	ns	
				Dynamic gait index	ns	ns	ns	ns	
				BDI-II	ns	ns	ns	ns	
				GDS	ns	ns	ns	ns	
				State trait anxiety inventory	ns	ns	ns	ns	
				MoCA	ns	ns	p	p	
				Trail making test	ns	ns	ns	ns	
				phonemic fluency	ns	ns	ns	ns	
				Rey complex figure	ns	ns	ns	ns	
				Hopkins verbal learning	ns	ns	ns	ns	
				spectral power modifications	+ theta power	ns	ns	ns	
				spectral power modifications	- beta power	ns	p	ns	
Shill et al., 2011	23 PD (S: 11 G1:12) Randomized Double blinded Sham controlled Parallel	OFF during assessment S: target frontal area; reference mastoid G1: idem	G1: 77.5 Hz, 45 min, sinusoidal 15 mA, 10 sessions/2 weeks	Offline measurement			14 weeks		II
				UPDRS-III	**ns**		**ns**		
				Hamilton Anxiety scale	ns		ns		
				Geriatric depression scale	ns		ns		
				Epworth sleepiness scale	ns		ns		

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Final_tACS: Randomized controlled studies of tACS or tPCS for the treatment of Parkinson's disease (i.e. only statistically significant results of stimulation vs sham).

applicability of NIBS –in particular rTMS (see Rossi et al., 2009 for IFCN consensus paper)– NIBS techniques are considered safe (Rossini et al., 2015; Krishnan et al., 2015; Nitsche et al., 2003b; Wassermann, 1998). Although NIBS studies had only few side effects, a deep rTMS study using the H-coil over the prefrontal cortex had to be interrupted because of pain (Dagan et al., 2017). In another study, cutaneous nociception limited the intensity of tCS (Khatoun et al., 2017). Nevertheless, some strategies have emerged to counter these side effects. For instance, topical anaesthetics on the scalp (Khatoun et al., 2017) or the use of high-frequency amplitude-modulated stimulation (Witkowski et al., 2016) –which stimulates beyond the response range of cutaneous receptors– are two effective ways to make the techniques more tolerable.

Most of the clinical studies investigated the cortical excitability, using MEPs as the only parameter to assess the neurophysiological effects of NIBS. But, understanding the cortical functionality just as 'excitability improvement or impairment' is obviously too simplistic. However, new paradigms are emerging – and biomarkers uncovered – that provide a new rationale for future assessment and treatment approaches (Benninger et Hallett, 2015; Benninger et al., 2020). For this reason, the role of oscillatory activity in the cortico-basal ganglia loops in information gating, coupling, and decoupling of distant brain areas has raised interest. The search for new biomarkers that may correlate with clinical outcome is underway. New studies based on computational simulations suggest that oscillations might be modulated by enhancement of natural frequencies (i.e. resonance), entrainment to a specific external rhythm or subharmonic frequency (i.e. entrainment), or non-linear acceleration – when stimulating at high frequencies (Herrmann et al., 2016). Especially, the non-linearity of brain interactions has been poorly investigated so far, and might be a promising research focus (Syrkin-Nikolau et al., 2017).

5.1. Innovative concepts

There are innovative information-theory concepts being examined in PD.

For instance, functional connectivity –assessed through the imaginary part of cortico-cortical coherence (Nolte et al., 2004)– showed to be impaired in PD (Schoellmann et al., 2019).

Neural entropy – which quantifies the disorder in terms of patterns of neuronal activity – has also been found to be altered; being elevated in the basal ganglia, it alleviates after STN DBS in a rat (Dorval and Grill, 2014) and primate model (Dorval et al., 2008), and it inversely correlates with clinical outcome. Although neural entropy usually correlates with information transmission in the healthy brain – higher entropy enables increased information encoding – it inversely correlates with it in the Parkinsonian basal ganglia; probably encoding unusable information (Dorval and Grill, 2014). Furthermore, PD patients with FOG show a beta-band entropy excess during walking, when compared to those without FOG, and an alpha-band entropy excess during FOG episodes (Syrkin-Nikolau et al., 2017).

Another non-linear strategy the brain may use to encode information in the motor system is noise variation, also called stochastic resonance (McDonnell and Abbott, 2009). Although still little is known, the new concepts may offer new venues to understand dynamic neural signalling through non-linear processing.

Natural-frequency mapping of different cortical areas becomes feasible with simultaneous TMS/EEG recordings (Rosanova et al., 2009; Casarotto et al., 2019), enabling the development of novel and potentially more specific stimulation patterns. With this methodology, stimulation could be better targeted, and the frequency and phase of stimulation fine-tuned based on excitability and natural-frequency mapping.

The cortical silent period (CSP) seems a reliable biomarker (Benninger et al., 2012) and other new biomarkers hold promise. As previously discussed, MEP, the MEP recruitment curve, the short-interval intra-cortical inhibition, the CSP, short- and long-latency afferent inhibition, oscillatory activity (theta/alpha/beta/gamma/HFO), phase-amplitude coupling, as well as tremor and other movement measures, all are possible biomarkers. They all will improve NIBS through better targeting, personalized stimulation, closed-loop stimulation and better post-intervention effect evaluation.

5.2. Fine-tuning NIBS parameters

In NIBS, a vast number of parameters have to be be adjusted and these adjustments lead to several challenges. For obvious reasons, it would be difficult to test all possible parameters' combinations on patients. Rather than a one-design-fits-all approach, further knowledge about pathophysiology will enable to adjust the stimulation intensity, the frequency, the oscillation phase, the amplitude and the target region to specific symptoms and patients (Chung and Mak, 2016; Fröhlich, 2015).

NIBS effects seem to be more easily obtained in PD patients than in healthy controls (Krause et al., 2014). Regularly administered, long-term stimulation (several years Málly et al., 2018) may improve the clinical outcome, and may also have a disease-modifying effect.

In PD mice models, a disease-modifying treatment effect of tDCS (Lee et al., 2018, 2019b) and rTMS (Ba et al., 2019) has been shown; as for DBS in PD patients (Hacker et al., 2018), although the latter remains a topic of controversy.

5.3. Personalized targeting

Heading towards a more personalized medicine, specific symptoms of PD and the side effects of medication could be targeted more precisely (Benussi et al., 2017; Koch et al., 2009). The efficacy of NIBS in clinical trials is variable, most probably due to the heterogeneity of NIBS protocols and study populations. There may be subgroups such as akinetic-rigid PD patients (Khedr et al., 2019a), patients with severe FOG (Broeder et al., 2019), or more affected PD patients (Cohen et al., 2018) that seem to respond particularly well to NIBS treatment. Moreover, the intra-subject variability appears to be also important and needs to be considered. For instance, there has been a recent discussion on the individual asymmetry of PD, which might define which hemisphere should be excited or suppressed (Cosentino et al., 2017; Simpson and Mak, 2019). Because of the heterogeneous patients' characteristics –as regards the presence of tremor, postural instability, gait difficulties including freezing, motor fluctuations and dyskinesia, and also non-motor features such as depression and pain– a personalized approach may improve NIBS' benefits. For instance, TMS (Ferreri and Rossini, 2013) or tACS (Witkowski et al., 2016) combined with EEG/-MEG or bayesian optimization –an iterative approach to select adequatly stimulation parameters in order to maximize the personalized effect– could be used to characterize individual traits for a personalized medicine. To personalize the stimulation rhythm, the stimulation frequency could be determined by assessing bradykinesia or with EEG maps (del Felice et al., 2019). For instance, when needed, patients could trigger the stimulation as an intermittent add-on therapy adapted to the underlying pathophysiology of the particular event such as FOG. Such a self-triggered therapy has already been approved for migraine with visual aura, which is presumed to result from the spreading depression. Two single TMS pulses (within 30 s) during the aura may interrupt this processus and prevent the subsequent migraine attack (Lipton et al., 2010).

5.4. Closed-loop systems

Closed-loop systems that combine online processing of ongoing signals or other biomarkers with specific detection algorithms (Bergmann et al., 2016; Fox et al., 2014) can personalize the stimulation and enhance its potency. A closed-loop system which could consist of a high-temporal resolution recording (EEG/MEG) of cerebral activity

combined with tACS or rTMS may adjust the stimulation pattern to the specific brain state and modulate the cerebral oscillations through phase (Keil et al., 2014; Sauseng et al., 2019), frequency and amplitude (Allali et al., 2018; Thut et al., 2017). For instance, the timing of NIBS stimulation could be locked to power values such as the desynchronization of the beta band; similar attempts have been successful using DBS and LFP in a closed-loop system (Little et al., 2013; Tinkhauser et al., 2017a). NIBS could also be phase-locked to a specific frequency range in order to enhance it (in-phase) or decrease it (out-of-phase). Attempts to phase-lock NIBS to a specific frequency range have been already made using EEG/MEG signals (Helfrich et al., 2014a; Saturnino et al., 2017; Strüber et al., 2014; Thut et al., 2017; Zrenner et al., 2018).

Wearable devices such as inertial monitors (accelerometers, gyroscopes, magneto- and barometers) can detect episodic events such as FOG or the onset of resting tremor, in order to trigger or to change the stimulation protocol (Chen and Chen, 2019); or record tremor for phase-locked coupling of tACS with the tremor frequency (Brittain et al., 2013). Complex algorithms based on signal processing concepts (i.e. Fourier transformation, wavelet spectrum, entropy, and recurrence rate) enable to predict tremor recurrence (Basu et al., 2013).

5.5. NIBS as an adjuvant to other approaches to treatment

NIBS is also promising as add-on therapy. Evidence suggests that it could enhance plasticity and promote learning, which is at work in rehabilitation, treadmill training, mirror visual feedback and cognitive training. However, a ceiling effect (i.e. saturation of response) may exist.

The idea of combining virtual reality with NIBS and neuroimaging (i. e EEG; MEG) is also interesting (for a review see Teo et al., 2016).

Since the pharmacological state of patients may determine the positive or negative effect of NIBS on the outcome (McLaren et al., 2018), it will be crucial to gain more insights on the interactions between NIBS and medication (i.e. dopaminergic and other CNS-active medication). Rehabilitative interventions, NIBS and medication may interact –e. g. dopamine mediates mechanisms underlying plasticity– in complex ways not well understood yet (Ghosh, 2019).

Further promising add-on effects of NIBS have been reported after cell transplantation, where anodal tDCS has improved the integration and survival of dopaminergic cells in a rat model of PD (Winkler et al., 2017).

Combining DBS and cortical stimulation might be a novel method to explore the interaction within the network connecting the cortex and deep brain nuclei. Single-pulse STN DBS generates cortical evoked potentials at an early phase (ca. 3 ms), probably through the hyper-direct pathway (Ashby et al., 2001), and, at a later phase (ca. 23 ms), through the indirect pathway (Kuriakose et al., 2010); combined DBS-TMS with an ISI of 3 and 23 ms are facilitated at both phases (Kuriakose et al., 2010). Since DBS affects the cortical excitability, combined therapeutic DBS/NIBS has been suggested as a new approach to treatment (Fox et al., 2014; Udupa et al., 2016), with the expectation that NIBS and DBS will interact to improve the clinical outcome of DBS alone.

5.6. New technologies

Technological innovations bring a number of novel promising approaches to treatment and that will – undoubtedly – transform NIBS procedures. For instance, the availability of smaller and light-weight tCS devices (Kouzani et al., 2016) allows NIBS application outside the clinical environment (i.e. at home). Some studies have investigated the feasibility of remotely supervised tDCS and this approach appeared to be safe (Cucca et al., 2019), effective (Dobbs et al., 2018) and could enhance patients' compliance. Furthermore, remotely supervised tCS will facilitate more ambitious study designs by making study recruitment easier, by enabling longer protocols, and by facilitating specific day-time stimulation (Agarwal et al., 2018). This could prove useful, when circadian variability of cortical plasticity is considered (Dinse et al., 2017; Nader et al., 2010).

Chronic stimulation is a DBS requirement and this may also apply to direct current stimulation and NIBS in general. Although not available for the other NIBS methods yet, this kind of current stimulation could become available in the near future. Prolonged tACS, tPCS or tRNS are already possible, and even if long-term NIBS presents some disadvantages, it could precede the minimal-invasive implantation of subdural cortical stimulation electrodes.

Still other new approaches to treatment, such as combining anodal tDCS of M1 and exergaming (Harris et al., 2018) are emerging.

5.7. New stimulation patterns

New stimulation patterns are promising. Coupling different types of rhythms such as gamma and theta rhythms in TBS (Schulz et al., 2014; Huang et al., 2005), randomly varying the stimulation frequency in tRNS (Stephani et al., 2011), delivering pulsed current unidirectionally in tPCS (Alon et al., 2012), or stimulating with higher frequencies (i.e. 50 Hz and beyond) (Benninger et al., 2012, 2009b) are all promising possibilities. However, safety limits have not been explored yet beyond 50 Hz at higher intensities and for longer periods (Rossi et al., 2009). Concerns about stimulation and technological limitations include the energy supply for the maintenance of a high-frequency stimulation and coil overheating. Nevertheless, a stimulation device with multiple condensators and a liquid-helium-coil cooling system would be a possible solution.

Additionally, triangular stimulation waveforms may be stronger brain-activity modulators than sine-waves (Dowsett and Herrmann, 2016), although their seizure-inducing potential should be cautiously investigated first.

A further focus of research is the shape of the magnetic or electric field used for stimulation. Apart from conventional coils, coils such as the H-coil enable deeper stimulation (i.e. 2 cm–5.5 cm) through magnetic field shaping (Gomez et al., 2018; Zangen et al., 2005). Also, high-density tDCS improves the precision of electric fields. While the electric field magnitude lacks directly underneath the conventional rectangular electrode, it is observed underneath the ring electrode of high-density tDCS (HD-tDCS), increasing its focality and intensity (Datta et al., 2009). The 4×1 ring electrode configuration enables an individual distribution of cathode and anode over the electrodes. The design of an adequate sham has been problematic, because of the increased tingling – but the issue has been resolved by stimulating only the scalp (Garnett and den Ouden, 2015). One further advantage is the simultaneous use of EEG/MEG (Roy et al., 2014) and tDCS, which is a requirement for future closed-loop stimulation. The increased effect of HD-tDCS compared to conventional tDCS on cortical excitability has been already reported (Kuo et al., 2013).

Two new technologies hold promise to make stimulation deeper and preciser, enabling – perhaps – non-invasive deep brain stimulation in the near future. Nevertheless, these techniques have been used only in animals.

Perhaps the most innovative of both innovations is the temporal interference paradigm (Grossman et al., 2017). In this multi-focal alternating electric current stimulation, frequencies are delivered in the kHz range, far beyond frequencies stimulating pain receptors or the cortical territory. The different electrodes stimulate with slightly different frequency and intensity, so that interference patterns rise at the intersection of the electric fields. This enables selective stimulation of deep brain regions with specific frequencies (e. g. 50 Hz) and amplitudes. The technique must be combined with neuroimaging to target deeper brain regions. Even if it has only been investigated in mice, it appears also feasible in humans.

The second technique is the so-called transcranial magneto-acoustical stimulation, which consists of focused ultrasound stimulation within a static magnetic field. It enables the modulation of neural

activity in deep brain areas (Yuan et al., 2016) and has been tested in a mice model, with promising results (Wang et al., 2019).

5.8. A future outlook: enhancing physiopathological knowledge

Non-invasive brain stimulation studies will contribute to gain better insights into the pathophysiology. Combined NIBS-DBS studies will help to elucidate functional connectivity in the motor circuit. Technological progress will offer novel approaches in the stimulation protocols that could become personalized, operating within a closed-loop system. Wearable devices would define the indication to stimulation, which could be delivered via implanted electrodes –for longer stimulation periods of time– if needed.

CRediT authorship contribution statement

Julian Madrid: Conceptualization, Data curation, Formal analysis, Investigation, Resources, Methodology, Writing - original draft, Visualization. **David H. Benninger:** Conceptualization, Data curation, Investigation, Methodology, Formal analysis, Supervision, Funding acquisition, Writing - review & editing.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgement

This work was funded, in part, by a grant from the Baasch-Medicus Foundation (to D. H. Benninger).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jneumeth.2020.108957.

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