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Title

The effect of transcranial direct current stimulation on upper limb motor performance in Parkinson's disease: A systematic review

Abstract

Background and purpose: Parkinson's disease (PD) reduces independence and quality of life through deterioration of upper limb motor function. Transcranial direct current stimulation (tDCS) may offer an alternative, adjunctive therapy for PD. However, the efficacy of tDCS for upper limb motor rehabilitation in PD is unknown. In this systematic review, evidence is compiled regarding the effects of tDCS on upper limb motor function in PD.

Methods: Studies of tDCS applied to PD patients that assessed upper limb motor function, conducted between January 2000 and November 2018, were screened for inclusion via a systematic search of Medline, Cochrane, PsycINFO, EMBASE, CINAHL, and Web of Science.

Results: Ten out of 606 studies were included and their findings synthesized into five categories regarding the effects of tDCS on: (1) Unified Parkinson's disease rating scale motor section (UPDRS III), (2) upper limb motor tasks, (3) manual dexterity, (4) reaction time, and (5) neurophysiology.

Conclusions: When applied to the primary motor cortex, tDCS may improve UPDRS III and the speed and force of movement. Considerable variation was found in tDCS parameters and further study is needed to clarify the long-term effects of tDCS on both simple and complex motor tasks and to compile relevant neurophysiological evidence.

Keywords: Parkinson's disease, Upper limb, tDCS, Motor function

Contents

1. Introduction

Parkinson's disease (PD) is characterized by progressive degeneration of dopaminergic neurons in the basal ganglia, leading to motor impairments including bradykinesia, rigidity, tremor, and postural instability [1]. Reduced dopamine in the basal ganglia causes a regulatory imbalance between the direct and indirect motor circuits, giving rise to a cascade of activity changes in the basal ganglia-thalamo-cortical circuit [2,3] and interconnected areas including the cerebellum [4] and pedunculopontine nucleus [5]. Degeneration of the basal ganglia occurs asymmetrically in early PD and leads to unilateral motor impairment [6]. However, with disease progression, degeneration spreads to the bilateral basal ganglia leading to reciprocal motor impairment [6]. Dopamine replacement therapy is the primary source of symptomatic relief for PD patients. Another treatment, deep brain stimulation, uses surgically implanted electrodes to stimulate basal ganglia nuclei. Despite the efficacy of dopamine substitution, its effects are short lived and extended use can lead to secondary motor symptoms [7]. On the other hand, deep brain stimulation entails surgical risk and is only available to a small patient population [8].

Adjunctive therapies such as physical therapy [9] and non-invasive brain stimulation [10] are important strategies for ameliorating motor symptoms in line with conventional therapy. Research in these areas has largely focused on lower limb rehabilitation, whereas upper limb rehabilitation has received far less attention. In early onset PD, patients experience unilateral upper limb motor deficits, including decreased writing velocity and impaired coordination [11]. Throughout the disease, impairments progressively effect upper limb function, manifesting abnormal force generation [12], impaired fine manual dexterity [13], and poor bimanual coordination [11]. The ability to perform activities of daily living becomes compromised and patients often adopt compensatory strategies or avoid tasks entirely.

Transcranial direct current stimulation (tDCS) is a class of non-invasive brain stimulation techniques used to modulate cortical excitability. A weak electrical current is delivered at the scalp between two electrodes: one anode and one cathode. The interaction between current and neural tissue causes a shift of neural excitability [14,15]. Ordinarily, neural tissue beneath the anode is depolarized, while under the cathode it is hyperpolarized.

Excitability changes in cortical-subcortical areas may help to rectify abnormal regulatory mechanisms and improve motor function in PD [16]. When applied to PD patients, tDCS has been shown to significantly enhance gait and lower limb performance [17]. Despite its clinical utility, the effects of tDCS for upper limb rehabilitation in PD are unclear. Therefore, the aim of this review is to systematically establish the effects of tDCS on upper limb motor performance in PD patients.

2. Methods

2.1. Search strategy

Six databases were systematically searched for full text articles published in English between January 2000 and November 2018. The databases Medline (PubMed), Cochrane Library (CENTRAL), PsycINFO, EMBASE, CINAHL, and Web of Science were all searched using the following search terms: “Parkinson’s Disease” or “Parkinson Disease” or “PD” or “Parkinsonism” or “Parkinsonian”, and “Transcranial direct current stimulation” or “tDCS” or “direct current stimulation” or “non-invasive brain stimulation” (in all text). Articles with the terms “schizophrenia” and “stroke” in the title were excluded. Titles and abstracts were then scanned to identify relevant articles for full-text screening.

2.2. Selection criteria

Articles with tDCS as the primary intervention were included. The following criteria were set for article inclusion: 1) studies assessing the effects of tDCS on any aspect of upper limb performance, 2) articles including PD patients of all types and severity levels, 3) studies using a sham control protocol. Studies were excluded if other non-invasive brain stimulation techniques, such as transcranial alternating current or random noise stimulation, were used, or if combined non-invasive brain stimulation techniques, such as both tDCS and repetitive transcranial magnetic stimulation (rTMS), were used as interventions. Furthermore, review articles, articles in abstract form, and animal studies were excluded. The risk of bias for included studies was assessed using the Cochrane risk of bias tool [18].

3. Results

Ten out of 606 articles were identified through the search strategy and criteria above. Quality was largely controlled with all studies employing either double- or single-blinded designs (see Table 1). The risk of bias assessment is presented in Table 3. Seven of the included trials were deemed to have a low risk of bias [19-25].

Patient age ranged from 58 to 74 years. Disease duration and Hoehn and Yahr scores varied from 5.8 to 12.3 years and 1.6 and 2.5, respectively.

All studies applied tDCS in the clinically defined ON-medication phase, except for two studies that applied it during the OFF-medication phase [24,26]. The heterogeneous nature of the clinical and methodological data prevents pooling of the results. In the following section, we present the effects of tDCS on 1) the Unified Parkinson's Disease Rating Scale motor section (UPDRS III), 2) upper limb motor tasks, 3) manual dexterity, 4) reaction time, and 5) neurophysiology.

[Insert Table 1 here]

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3.1. UPDRS III

Seven studies measured the effect of tDCS on UPDRS III. Three out of four studies found a significant decrease of UPDRS III scores following a single session of tDCS applied over M1 [21,24,27]. These effects seem unrelated to polarity given that Cosentino et al. [21] and Fregni et al. [24] both applied anodal tDCS, whereas multiple experiments by Salimpour et al. [27] favored cathodal stimulation. Moreover, by combining five sessions of frontopolar tDCS with physical therapy, Ishikuro et al. [26] found that anodal tDCS significantly improved UPDRS III compared to sham stimulation. However, no washout period was incorporated into this study and caution is required when interpreting its results. Among the four studies, stimulation density varied. Positive effects of anodal tDCS came from densities between 0.029 and 0.057 mA/cm^2 [21,26,24], whereas the density of cathodal tDCS was much higher at 0.08 mA/cm^2 [27]. The effect of multi-session tDCS on UPDRS III is unclear as Salimpour et al. [27] found no difference in outcome between single and multi-session tDCS. The remaining studies found non-significant effects following multi-session tDCS [19,28,23]. These studies applied tDCS over M1, the premotor cortex, the dorsolateral prefrontal cortex (DLPFC), and the cerebellum [19,28,23]. Note that although Benninger et al. [19] reported no change in UPDRS III score, the bradykinesia composite score significantly improved post intervention compared to sham stimulation.

3.2. Upper limb motor tasks

Six studies measured the impact of tDCS on upper limb motor task performance. Three of the four studies that targeted the M1 with single and multi-session tDCS reported a significant effect on movement speed in a sequential task [19,21] and force production [27]. Cosentino et al. [21] found an immediate improvement in upper limb motor sequence and finger tapping performance after anodal/cathodal tDCS over the more-affected/less-affected M1, respectively. Interestingly, upper limb sequence performance significantly deteriorated after cathodal tDCS to the more-affected M1. On the other hand, Salimpour et al. [27] found an increase in force assignment to the more-affected hand after bilateral tDCS with the cathode over the more-affected, and anode over the less-affected, M1. Benninger et al. [19] noted a significant improvement in upper limb motor sequence performance after eight sessions of anodal tDCS to M1/premotor and prefrontal cortices [19]. These effects persisted at a three-month follow-up assessment, suggesting multisession tDCS may have a long-term beneficial effect on upper limb motor sequencing. Acute daily effects of multi-session tDCS were assessed in two studies [19,22]. Benninger et al. [19] showed significant improvement in upper limb motor sequence performance in the first two of eight stimulation sessions. On the other hand, Costa-Ribeiro et al. [22] observed no overall or acute effects of ten sessions of tDCS on upper limb motor sequence performance. The long-term effects of single session tDCS were not investigated. Moreover, stimulating areas beyond M1, including the supplementary motor area [22] and DLPFC [28], revealed no significant effect.

3.3. Manual dexterity

The effect of tDCS on manual dexterity was assessed in four studies using the Purdue Pegboard Test (PPT) [28,24], the “simple test for evaluating hand function” [26], shirt-buttoning [28], and writing [20]. Fregni et al. [24] noted a trend toward better Purdue pegboard task performance after anodal tDCS over M1, yet all the other studies found no effect of single or multi-session tDCS on the Purdue pegboard task, shirt buttoning, or hand function. Broeder et al. [20] applied anodal tDCS over M1 during a writing task and noted a significant increase in writing amplitude compared to sham stimulation in patients who experienced freezing.

3.4. Reaction time

Five studies measured the effect of tDCS on various reaction time measures including simple, choice, and serial reaction time [19,28,24,23,25]. One study noted an immediate effect of anodal tDCS applied to M1 on simple reaction time [24]. Yet, in the same study, anodal/cathodal tDCS applied to the DLPFC/M1 respectively had no

effect. The remaining studies reported non-significant effects of multi-session tDCS on reaction time when targeting M1, the prefrontal cortex, or the cerebellum [19,28,23,25].

3.5. Neurophysiology

The effects of tDCS on active motor threshold and motor evoked potential (MEP) were reported by three studies [21,22,24]. Polarity-specific modulation of MEP amplitude was reported in two studies when stimulating M1 whereby anodal/cathodal tDCS significantly increased/decreased MEP amplitude, respectively [24,21]. Cosentino et al. [21] noted that increased MEP amplitude was significantly associated with faster finger-tapping speed. Fregni et al. [24] also noted a trend of improved UPDRS III with increased MEP amplitude. On the other hand, both active motor threshold and MEP amplitude were unaffected by 10 sessions of anodal tDCS over the supplementary motor area in conjunction with gait training [22].

4. Discussion

The aim of this review was to establish the effects of tDCS on upper limb motor performance when applied to PD patients. When pooled together, the high heterogeneity of stimulation parameters, study designs, and outcome measures make it difficult to draw firm conclusions. Thus far, tDCS appears to improve UPDRS III and upper limb motor task performance but has a negligible effect on manual dexterity and reaction time. Below, we will discuss the effect of stimulation parameters on UPDRS III and upper limb motor tasks and on reaction time and manual dexterity, as well as the effect of tDCS on neurophysiology.

4.1. Effect of tDCS on UPDRS III and upper limb motor tasks

4.1.1. Stimulation site

Stimulating the motor cortex of PD patients is logical, as hypo-activity of this area gives rise to bradykinetic symptoms during self-initiated movement [29-31]. Stimulation of the motor cortex by tDCS has been shown to modulate cortico-striatal and thalamo-cortical connectivity [15]. An interaction between tDCS and basal ganglia nuclei may enhance striatal function and the direct motor circuit, resulting in overall motor and functional improvement. Upregulation of the direct motor circuit may further enhance projections to interconnected nuclei such as the pedunculopontine nucleus, to which deep brain stimulation has been shown to improve gait and balance [32,33].

Recent meta-analyses have shown that rTMS of the motor cortex decreases UPDRS III [32,33], but the effects of stimulating non-motor areas are less clear. M1 is a node for motor execution and modulating its depolarization

threshold may alter sensitivity to – and thus maximize – the execution of motor programs [14,34]. As in healthy adults and stroke patients [35,36], the effects of tDCS in PD appears site-specific, as stimulation of areas beyond M1 has a negligible effect on motor performance. Non-motor areas such as the DLPFC are implicated as having a role in motor processes, particularly dual-tasking [37]. However, no assessment of tDCS and upper limb function in PD has adopted a dual-task paradigm.

In addition to improved UPDRS III, stimulation of the motor cortex by tDCS appears to improve upper limb motor task performance, reflecting increased motor speed [19,21] and force production [27]. Improvements could be related to the somatotopic area of stimulation as tDCS was delivered over the hand homunculus of M1. In healthy adults, anodal tDCS of this area has been shown to significantly improve completion time of the Jebsen Taylor test [38]. On the other hand, inhibiting the M1 hand homunculus in healthy adults with low frequency rTMS has been shown to reduce maximal finger-tapping speed in healthy adults [39]. Analogously, reduced basal ganglia facilitation of the motor cortex causes hypo-activity of motor areas in PD patients. Therefore, excitation of the hand motor area may compensate for or partially reverse such abnormalities in PD patients and amplify motor performance.

4.1.2. Stimulation polarity and montage

It may be expected that opposing stimulation polarities exert opposing behavioral effects, yet anodal and cathodal tDCS both improved UPDRS III and upper limb motor task performance. Six studies applied anodal tDCS to M1, four of which reported significant motor improvement [21,24,20,19]. On the other hand, two of the three studies that applied cathodal tDCS to M1 also reported significant motor improvement [27,21]. Interestingly, only cathodal tDCS significantly deteriorated motor performance in a sequential upper limb task [21]. Similar behavioral effects resulting from opposing stimulation polarities may be explained by tDCS montage.

A range of tDCS montages targeting the left/right or more-affected/less-affected M1 with unilateral or bilateral stimulation complicate the task of understanding the effects of tDCS. For example, anodal stimulation of the more affected hemisphere increased movement speed of the more-affected hand whereas cathodal tDCS decreased movement speed [21]. Another study applied cathodal stimulation to the more-affected M1 and anodal stimulation to the less-affected M1 and observed an increase in force production [27]. Motor improvement following anodal tDCS could be explained by excitability changes of the direct motor pathway, a mechanism supported by the increased MEP amplitude following anodal tDCS in PD [21]. Asymmetric cortical

excitability has been reported in early onset PD [40], which may offset transcallosal inhibition [16]. Bilateral tDCS of the motor cortex may act to accentuate or rebalance such interhemispheric inhibition and improve motor function [27]. Using an animal model, Tanaka et al. [41] reported that cathodal tDCS significantly increased striatal dopamine, which suggests increased inhibition of the indirect pathway, which may improve basal ganglia BG facilitation of M1 and facilitate motor performance. These findings indicate that disease laterality (i.e., the more-affected or less-affected side), unilateral or bilateral stimulation, and stimulation polarity are important considerations for the use of tDCS in PD. However, very few studies have examined the effect of tDCS on cortical excitability and upper limb function in PD [21,24,22], and no studies have looked into intra-cortical or inter-hemispheric inhibition. Thus, further study is needed to understand the effects of tDCS polarity and montage on motor performance and associated neurophysiology.

4.1.3. Stimulation intensity and number of applications

Other methodological considerations include the intensity and number of stimulations to apply. Stimulation densities ranged from 0.021 to 0.080 mA/cm^2, yet the density of stimulation appeared to have no effect on motor improvement. For example, Fregni et al. [24], Cosentino et al. [21], and Salimpour et al. [27] all observed significant improvement in UPDRS III, but from densities of 0.029, 0.057, and 0.080 respectively. Due to a lack of available data, we are unable to determine the magnitude of change in each study. The majority of reviewed studies apply single session tDCS with no follow-up assessment. The effects of single-session tDCS could be short lived [42], which may limit its clinical utility. On the other hand, multi-session tDCS protocols may produce more robust effects that outlast the intervention period [43-45]. For example, in healthy adults, single-session tDCS can elevate cortical excitability for up to two hours post stimulation with cumulative increases in excitability when sessions are repeated daily [46]. In PD, single and multi-session tDCS both improved UPRDS III and upper limb motor sequence performance. Acute daily effects of tDCS reported by Benninger et al. [19] indicates a cumulative effect of tDCS on upper limb motor task performance when applied daily. Furthermore, motor improvement was retained three months post intervention, suggesting a carry-over effect of tDCS [19]. However, these effects were not replicated [22], making it difficult to discern a superior protocol from available data. Further study is needed clarify to the effects of multi-session tDCS.

4.2. Effect of tDCS on reaction time and manual dexterity

Reaction time and manual dexterity appear largely unaffected by tDCS, although an interaction between task nature and stimulation site may provide further insight. Simple reaction time decreased after anodal tDCS of the motor cortex, but not of the DLPFC [24]. Serial reaction time was, however, unaffected by motor cortex, prefrontal cortex, and cerebellar tDCS [19,23,25]. Reaction time tasks differ according to the action preparation afforded. The simple reaction time task requires the release of a single motor response, whereas several responses are possible in the serial reaction time task. Motor cortex tDCS may amplify existing motor programs to generate faster responses. However, when several motor programs are prepared for execution, tDCS may not affect cognitive facets of motor control required to suppress the release of incorrect movements (i.e. action understanding, motor affordances, and coordination) [47]. Anodal tDCS of the motor cortex also improved stroke amplitude in a writing task [20], whereas motor or prefrontal cortex tDCS had no effect on Purdue pegboard performance [24,28]. We postulate that the writing task requires less speed and accuracy than the Purdue pegboard task, which also entails a greater degree of object manipulation. Together, these findings suggest that tDCS may be more effective for simple motor tasks and may not improve complex motor processing.

4.3. Effect of stimulation on neurophysiology

Behavioral effects of tDCS are not easily predicted [48], highlighting a need to better understand the mechanism of tDCS underlying behavioral changes. Consistent with findings regarding both healthy adults and stroke patients [49,50], tDCS exhibited polarity-dependent changes on cortical excitability when applied to M1. Anodal tDCS increased, whereas cathodal tDCS decreased, MEP amplitude in PD patients [21,24]. Moreover, an increased MEP amplitude was associated with faster finger-tapping speed [21] and improved the UPDRS III score [24]. Improved PD motor symptoms from M1 excitation reiterates findings from high-frequency rTMS of M1 in PD [51]. rTMS over the supplementary motor area increased the M1 excitability threshold and improved fine motor task performance in PD patients [52]. In contrast, anodal tDCS over the supplementary motor area did not alter M1 excitability [22]. Thus far, increased M1 excitability appears to improve motor symptoms in PD. However, M1 excitability has been measured only by examining the change in MEP; no study has examined intracortical inhibition/facilitation. Further study is needed to examine the effects of tDCS on inhibitory and facilitatory neural mechanisms in PD.

5. Conclusion

This review has highlighted the disparity of tDCS effects among upper limb motor task performance in PD. Stimulation of M1 by tDCS may improve UPDRS III and amplify the speed and force of movement, yet more complex tasks seem unaffected by the direct effects of tDCS. Further study is needed to investigate the effects of tDCS on the performance of simple and complex motor tasks. Moreover, the long-term benefits of single-session and multi-session tDCS in PD are unknown and need clarification. No study has investigated the combined effects of tDCS and motor learning in PD; thus, the utility of tDCS as an adjunctive tool for motor learning and rehabilitation in PD is unknown. Lastly, tDCS montages may play a key role in determining patient-specific tDCS therapy by targeting brain areas in relation to patients' more-affected and less-affected hemispheres.

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Ethical standards

The manuscript does not contain clinical studies or patient data.

Conflicts of interest

The authors declare that they have no conflict of interest.

6. References

1. Jankovic J (2008) Parkinson’s disease: clinical features and diagnosis. Journal of Neurology, Neurosurgery & Psychiatry 79 (4):368-376
2. Albin RL, Young AB, Penney JB (1989) The functional anatomy of basal ganglia disorders. Trends in Neurosciences 12 (10):366-375
3. Obeso JA, Rodriguez-Oroz MC, Rodriguez M, Lanciego JL, Artieda J, Gonzalo N, Olanow CW (2000) Pathophysiology of the basal ganglia in Parkinson's disease. Trends in Neurosciences 23:S8-S19
4. Middleton FA, Strick PL (2000) Basal ganglia and cerebellar loops: motor and cognitive circuits. Brain Research Reviews 31 (2-3):236-250
5. Fasano A, Daniele A, Albanese A (2012) Treatment of motor and non-motor features of Parkinson's disease with deep brain stimulation. The Lancet Neurology 11 (5):429-442
6. Brooks DJ (2000) Morphological and functional imaging studies on the diagnosis and progression of Parkinson’s disease. Journal of Neurology 247 (2):II11-II18
7. Jankovic J (2005) Motor fluctuations and dyskinesias in Parkinson's disease: clinical manifestations. Movement Disorders 20 (S11):S11-S16
8. Benabid AL, Chabardes S, Mitrofanis J, Pollak P (2009) Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. The Lancet Neurology 8 (1):67-81
9. Mak MK, Wong-Yu IS, Shen X, Chung CL (2017) Long-term effects of exercise and physical therapy in people with Parkinson disease. Nature Reviews Neurology 13 (11):689
10. Fregni F, Simon D, Wu A, Pascual-Leone A (2005) Non-invasive brain stimulation for Parkinson’s disease: a systematic review and meta-analysis of the literature. Journal of Neurology, Neurosurgery & Psychiatry 76 (12):1614-1623
11. Ponsen MM, Daffertshofer A, van den Heuvel E, Wolters EC, Beek PJ, Berendse HW (2006) Bimanual coordination dysfunction in early, untreated Parkinson's disease. Parkinsonism & Related Disorders 12 (4):246-252
12. Ingvarsson PE, Gordon AM, Forssberg H (1997) Coordination of manipulative forces in Parkinson's disease. Experimental Neurology 145 (2):489-501
13. Shukla AW, Ounpraseuth S, Okun MS, Gray V, Schwankhaus J, Metzer WS (2012) Micrographia and related deficits in Parkinson's disease: a cross-sectional study. BMJ Open 2 (3):e000628
14. Nitsche MA, Paulus W (2000) Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. Journal of Physiology 527 Pt 3:633-639
15. Polanía R, Paulus W, Nitsche MA (2012) Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. Human Brain Mapping 33 (10):2499-2508
16. Spagnolo F, Coppi E, Chieffo R, Straffi L, Fichera M, Nuara A, Gonzalez-Rosa J, Martinelli V, Comi G, Volontè MA (2013) Interhemispheric balance in Parkinson's disease: a transcranial magnetic stimulation study. Brain Stimulation 6 (6):892-897
17. Broeder S, Nackaerts E, Heremans E, Vervoort G, Meesen R, Verheyden G, Nieuwboer A (2015) Transcranial direct current stimulation in Parkinson's disease: Neurophysiological mechanisms and behavioral effects. Neuroscience & Biobehavioral Reviews 57:105-117
18. Higgins J (2011) Cochrane handbook for systematic reviews of interventions. Version 5.1. 0 [updated March 2011]. The Cochrane Collaboration. www cochrane-handbook org
19. Benninger DH, Lomarev M, Lopez G, Wassermann EM, Li X, Considine E, Hallett M (2010) Transcranial direct current stimulation for the treatment of Parkinson's disease. Journal of Neurology, Neurosurgery & Psychiatry 81 (10):1105-1111
20. Broeder S, Heremans E, Pereira MP, Nackaerts E, Meesen R, Verheyden G, Nieuwboer A (2018) Does transcranial direct current stimulation during writing alleviate upper limb freezing in people with Parkinson’s disease? A pilot study. Human Movement Science

21. Cosentino G, Valentino F, Todisco M, Alfonsi E, Davì R, Savettieri G, Fierro B, D'Amelio M, Brighina F (2017) Effects of More-Affected vs. Less-Affected Motor Cortex tDCS in Parkinson's Disease. Frontiers in Human Neuroscience 11:309
22. Costa-Ribeiro A, Maux A, Bosford T, Tenório Y, Marques D, Carneiro M, Nitsche MA, Alberto Filho M, Monte-Silva K (2016) Dopamine-Independent Effects of Combining Transcranial Direct Current Stimulation with Cued Gait Training on Cortical Excitability and Functional Mobility in Parkinson's Disease. Journal of Rehabilitation Medicine 48 (9):819-823
23. Ferrucci R, Cortese F, Bianchi M, Pittera D, Turrone R, Bocci T, Borroni B, Vergari M, Cogiamanian F, Ardolino G (2016) Cerebellar and motor cortical transcranial stimulation decrease levodopa-induced dyskinesias in Parkinson's disease. The Cerebellum 15 (1):43-47
24. Fregni F, Boggio PS, Santos MC, Lima M, Vieira AL, Rigonatti SP, Silva MTA, Barbosa ER, Nitsche MA, Pascual-Leone A (2006) Noninvasive cortical stimulation with transcranial direct current stimulation in Parkinson's disease. Movement Disorders 21 (10):1693-1702
25. Schabrun SM, Lamont RM, Brauer SG (2016) Transcranial direct current stimulation to enhance dual-task gait training in Parkinson's disease: a pilot RCT. PloS One 11 (6):e0158497
26. Ishikuro K, Dougu N, Nukui T, Yamamoto M, Nakatsuji Y, Kuroda S, Matsushita I, Nishimaru H, Ferreira Pereira De Araujo M, Nishijo H (2018) Effects of transcranial Direct Current Stimulation (tDCS) over the frontal polar area on motor and executive functions in Parkinson's disease; A pilot study. Frontiers in Aging Neuroscience 10:231
27. Salimpour Y, Mari ZK, Shadmehr R (2015) Altering effort costs in Parkinson's disease with noninvasive cortical stimulation. Journal of Neuroscience 35 (35):12287-12302
28. Doruk D, Gray Z, Bravo GL, Pascual-Leone A, Fregni F (2014) Effects of tDCS on executive function in Parkinson's disease. Neuroscience Letters 582:27-31
29. Moroney R, Heida C, Geelen J (2008) Increased bradykinesia in Parkinson's disease with increased movement complexity: elbow flexion-extension movements. Journal of computational neuroscience 25 (3):501-519. doi:10.1007/s10827-008-0091-9
30. Contreras-Vidal JL, Stelmach GE (1995) A neural model of basal ganglia-thalamocortical relations in normal and parkinsonian movement. Biological Cybernetics 73 (5):467-476
31. Jahanshahi M, Jenkins IH, Brown RG, Marsden CD, Passingham RE, Brooks DJ (1995) Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. Brain 118 (Pt 4):913-933
32. Chou Y-h, Hickey PT, Sundman M, Song AW, Chen N-k (2015) Effects of repetitive transcranial magnetic stimulation on motor symptoms in Parkinson disease: a systematic review and meta-analysis. JAMA neurology 72 (4):432-440
33. Zanjani A, Zakzanis KK, Daskalakis ZJ, Chen R (2015) Repetitive transcranial magnetic stimulation of the primary motor cortex in the treatment of motor signs in Parkinson's disease: a quantitative review of the literature. Movement Disorders 30 (6):750-758
34. Nitsche MA, Paulus W (2001) Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 57 (10):1899-1901
35. Fregni F, Pascual-Leone A (2007) Technology insight: noninvasive brain stimulation in neurology—perspectives on the therapeutic potential of rTMS and tDCS. Nature Reviews Neurology 3 (7):383
36. O'Shea J, Boudrias M-H, Stagg CJ, Bachtiar V, Kischka U, Blicher JU, Johansen-Berg H (2014) Predicting behavioural response to TDCS in chronic motor stroke. Neuroimage 85:924-933
37. Wu T, Kansaku K, Hallett M (2004) How self-initiated memorized movements become automatic: a functional MRI study. Journal of Neurophysiology 91 (4):1690-1698
38. Boggio PS, Castro LO, Savagim EA, Braite R, Cruz VC, Rocha RR, Rigonatti SP, Silva MTA, Fregni F (2006) Enhancement of non-dominant hand motor function by anodal transcranial direct current stimulation. Neuroscience Letters 404 (1):232-236

39. Jäncke L, Steinmetz H, Benilow S, Ziemann U (2004) Slowing fastest finger movements of the dominant hand with low-frequency rTMS of the hand area of the primary motor cortex. Experimental Brain Research 155 (2):196-203
40. Kojovic M, Bologna M, Kassavetis P, Murase N, Palomar F, Berardelli A, Rothwell J, Edwards M, Bhatia K (2012) Functional reorganization of sensorimotor cortex in early Parkinson disease. Neurology 78 (18):1441-1448
41. Tanaka T, Takano Y, Tanaka S, Hironaka N, Kobayashi K, Hanakawa T, Watanabe K, Honda M (2013) Transcranial direct-current stimulation increases extracellular dopamine levels in the rat striatum. Frontiers in Systems Neuroscience 7:6
42. Horvath JC, Forte JD, Carter O (2015) Quantitative review finds no evidence of cognitive effects in healthy populations from single-session transcranial direct current stimulation (tDCS). Brain Stimulation 8 (3):535-550
43. Ditye T, Jacobson L, Walsh V, Lavidor M (2012) Modulating behavioral inhibition by tDCS combined with cognitive training. Experimental Brain Research 219 (3):363-368
44. Fregni F, Boggio PS, Nitsche MA, Marcolin MA, Rigonatti SP, Pascual-Leone A (2006) Treatment of major depression with transcranial direct current stimulation. Bipolar Disorders 8 (2):203-204
45. Meinzer M, Lindenberg R, Antonenko D, Flaisch T, Flöel A (2013) Anodal transcranial direct current stimulation temporarily reverses age-associated cognitive decline and functional brain activity changes. Journal of Neuroscience 33 (30):12470-12478
46. Alonzo A, Brassil J, Taylor JL, Martin D, Loo CK (2012) Daily transcranial direct current stimulation (tDCS) leads to greater increases in cortical excitability than second daily transcranial direct current stimulation. Brain Stimulation 5 (3):208-213
47. Haggard P (2005) Conscious intention and motor cognition. Trends in Sognitive Sciences 9 (6):290-295
48. Li, Uehara K, Hanakawa T (2015) The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. Frontiers Cellular Neuroscience 9:181. doi:10.3389/fncel.2015.00181
49. Bastani A, Jaberzadeh S (2012) Does anodal transcranial direct current stimulation enhance excitability of the motor cortex and motor function in healthy individuals and subjects with stroke: a systematic review and meta-analysis. Clinical Neurophysiology 123 (4):644-657
50. Lüdemann-Podubecká J, Bösl K, Rothhardt S, Verheyden G, Nowak DA (2014) Transcranial direct current stimulation for motor recovery of upper limb function after stroke. Neuroscience & Biobehavioral Reviews 47:245-259
51. Elahi B, Elahi B, Chen R (2009) Effect of transcranial magnetic stimulation on Parkinson motor function—systematic review of controlled clinical trials. Movement Disorders 24 (3):357-363
52. Randhawa BK, Farley BG, Boyd LA (2013) Repetitive transcranial magnetic stimulation improves handwriting in Parkinson's disease. Parkinson's Disease 2013

Table 1

Table 1. Literature review search results and study descriptions

Citation		Population (number, age, H&Y)	Description	Outcome Measures	Stimulation Site	Duration, Intensity, Density (mA/cm²)	ON- / OFF-Phase
Benninger et al. [19]	-	25, 63.9 yrs, 2.5	Parallel, randomised, double-blind, sham	UPDRS III, UL-MT, Serial RT	[M1 + PMC] & PFC	20m @ 2mA (0.021)	ON
Broeder et al. [20]	-	10, 63.2 yrs, 2	Crossover, single-blind, randomised, sham	FOUL & Writing Amplitude	M1	20m @ 1mA (0.029)	ON
Cosentino et al. [21]	-	14, 58.0 yrs 1.6	Crossover, double-blind, randomised, sham	UPDRS III, UL-MT, FT, MEP	M1	20m @ 2mA (0.057)	ON
Costa-Ribeiro et al. [22]	-	22, 61.6 yrs, 2.3	Parallel, randomised, single-blind, sham	UL-MT, MEP, aMT	SMA	13m @ 2mA (n.a.)	ON
Doruk et al. [27]	-	18, 61.0 yrs, n.a.	Parallel, randomized, double-blind, sham	UPDRS III, FT, PPT, Simple & Choice RT Button-up, Hand Sup/Pro	DLPFC	20m @ 2mA (0.057)	ON
Ferrucci et al. [23]	-	9, 74.0 yrs, 2.5	Crossover, randomised, double-blind, sham	UPDRS III, Serial RT	M1 & Cerebellum	20m @ 2mA (0.057)	ON
Fregni et al. [24]	Exp 1	9, 59.2 yrs, 2.4	Crossover, randomised, sham	UPDRS III, Simple RT, PPT	M1	20m @ 1mA (0.029)	OFF
	Exp2	8, 65.9 yrs, 2.3	Crossover, randomised, sham	UPDRS III, Simple RT, PPT	M1	20m @ 1mA (0.029)	OFF
	Exp3	9, 59.2 yrs, 2.4	Single session	UPDRS III, Simple RT, PPT	DLPFC	20m @ 1mA (0.029)	OFF
	Exp4	17, 61.7 yrs, 2.4	Crossover, sham	UPDRS III, Simple RT, PPT, MEP	M1	20m @ 1mA (0.029)	OFF
Ishikuro et al. [26]	-	9, 77.5 yrs, 1.8	Multi-session, crossover, randomized, sham	UPDRS III, STEF	FPA	15m @ 1mA (0.029)	OFF
Salimpour et al. [28]	Exp 2	10, 59.6 yrs, 1.75	Single session	UPDIS III, Force Assignment	M1	~25m @ 1mA (0.029)	ON
	Exp 3	10, 61.7 yrs, 1.75	Single session	UPDIS III, Force Assignment	M1	~25m @ 2mA (0.080)	ON
	Exp 4	10, 60.5 yrs, 1.85	Crossover, double-blind, sham	UPDIS III, Force Assignment	M1	~25m @ 2mA (0.080)	ON
	Exp 5	8, 59.4 yrs, 1.5	Multi-session, single-blind	UPDIS III, Force Assignment	M1	~25m @ 2mA (0.080)	ON
Schabrun et al. [25]	-	16, 67.5 yrs, 2	Randomised; double-blind; Sham	UL-MT, Serial RT	M1	20m @ 2mA (0.080)	ON

Stimulation targets:

CSA, Contralateral supraorbital area
DLPFC, Dorsolateral prefrontal cortex
M1, Primary motor cortex
PMC, Pre-motor cortex
TPC, Tempo-parietal cortex
FPA, Frontopolar area

Outcome measures:

FT, Finger tapping
MEP, Motor evoked potential
aMT, Active motor threshold
PPT, Purdue pegboard task
RT, Reaction time
Hand Sup/Pro, Supination and Pronation
UL-MT, Upper limb motor task
UPDRS III, Unified Parkinson's disease rating scales part three
FOUL, Freezing of the upper limb
STEF, Simple test for evaluating hand function
ON- / OFF-Phase, the medication status of patients when stimulated and assessed

Table 2

Table 2. Comparison of transcranial direct current stimulation parameters and effects on upper limb motor performance outcomes in patients with Parkinson's disease.

Outcome	Citation		Outcome measure	Target (An / Ca)	Duration, Intensity Density	Single- / Multi-Session	Number of Subjects	H&Y	Disease duration (yrs)
Unified Parkinson's Disease Rating Scale: Motor Section									
Positive Change	Cosentino et al. [21]	-	UPDRS III	(more) M1 / CSA	20m, 2mA (0.057)	Single	14 (8M/6F)	1.6	n.a.
	Fregni et al. [24]	Exp 1	UPDRS III	(left) M1 / CSA	20m, 1mA (0.029)	Single	17 (11M/6F)	2.4	12.3
	Ishikuro et al. [26]	-	UPDRS III	FPA / CSA	15m, 1mA (0.029)	Multiple (5)	9 (3M/6F)	1.8	5.8
	Salimpour et al. [28]	Exp 3	UPDRS III	(right) M1 / M1 (left)	~25m, 2mA (0.080)	Single	10 (8M/2F)	1.8	8.5
		Exp 4	UPDRS III	(less) M1 / M1 (more)	~25m, 2mA (0.080)	Single	10 (6M/4F)	1.9	8.3
		Exp 5	UPDRS III	(less) M1 / M1 (more)	~25m, 2mA (0.080)	Multiple (5)	8 (5M/3F)	1.5	6.9
No Change	Benninger et al. [19]*	-	UPDRS III	Bi- [M1 + PMC] or Bi- PFC / Mastoids	20m, 2mA (0.021)	Multiple (8)	25 (16M/9F)	2.5	9.9
	Doruk et al. [27]	-	UPDRS III	(left) DLPFC / CSA or (right) DLPFC / CSA	20m, 2mA (0.057)	Multiple (10)	18 (12M/6F)	n.a.	n.a.
	Ferrucci et al. [23]	-	UPDRS III	Bi- M1 / Right Deltoid or Bi- Cerebellum / Right Deltoid	20m, 2mA (0.057)	Multiple (5)	9 (5M/4F)	2.5	10.8
	Fregni et al. [24]	Exp 2	UPDRS III	CSA / M1 (dominant)	20m, 1mA (0.029)	Single	17 (11M/6F)	2.4	12.3
		Exp 3	UPDRS III	(left) DLPFC / CSA	20m, 1mA (0.029)	Single	17 (11M/6F)	2.4	12.3
	Salimpour et al. [28]	Exp 2	UPDRS III	(left) M1 / M1 (right)	~25m, 1mA (0.029)	Single	10 (6M/4F)	1.8	6.9
Upper Limb Motor Task									
Positive Change	Benninger et al. [19]	-	UL-Sequence	Bi- [M1 + PMC] or Bi- PFC / Mastoids	20m, 2mA (0.021)	Multiple (8)	25 (16M/9F)	2.5	9.9
	Cosentino et al. [21]	-	UL-Sequence & FT	(more) M1 / CSA & CSA / M1 (less)	20m, 2mA (0.057)	Single	14 (8M/6F)	1.6	n.a.
	Salimpour et al. [28]	Exp 3	Force Assignment	(right) M1 / M1 (left)	~25m, 2mA (0.080)	Single	10 (8M/2F)	1.8	8.5
		Exp 4	Force Assignment	(less) M1 / M1 (more)	~25m, 2mA (0.080)	Single	10 (6M/4F)	1.9	8.3
		Exp 5	Force Assignment	(less) M1 / M1 (more)	~25m, 2mA (0.080)	Multiple (5)	8 (5M/3F)	1.5	6.9
Negative change	Cosentino et al. [21]	-	UL-Sequence	CSA / M1 (more)	20m, 2mA (0.057)	Single	14 (8M/6F)	1.6	n.a.
No Change	Costa-Ribeiro et al. [22]	-	UL-Sequence	SMA / CSA (more)	13m, 2mA (n.a.)	Multiple (10)	22 (15M/7F)	2.3	6.2
	Doruk et al. [27]	-	Hand Sup/Pro & FT	(left) DLPFC / CSA or (right) DLPFC / CSA	20m, 2mA (0.057)	Multiple (10)	18 (12M/6F)	n.a.	n.a.
	Salimpour et al. [28]	Exp 2	Force Assignment	(left) M1 / (right) M1	~25m, 1mA (0.029)	Single	10 (6M/4F)	1.8	6.9
	Schabrun et al. [25]	-	UL-Sequence	(left) M1 / CSA	20m, 2mA (0.080)	Multiple (9)	16 (10M/6F)	2	5.8
Manual Dexterity									
Positive Change	Broeder et al. [20]	-	FOUL & Writing	(left) M1 / CSA	20m, 1mA (0.029)	Single	10 (8M/2F)	2	6.9
No Change	Doruk et al. [27]	-	PPT	(left) DLPFC / CSA or (right) DLPFC / CSA	20m, 2mA (0.057)	Multiple (10)	18 (12M/6F)	n.a.	n.a.
	Fregni et al. [24]	Exp 1	PPT	(left) M1 / CSA	20m, 1mA (0.029)	Single	17 (11M/6F)	2.4	12.3
		Exp 2	PPT	CSA / M1 (dominant)	20m, 1mA (0.029)	Single	17 (11M/6F)	2.4	12.3
		Exp 3	PPT	(left) DLPFC / CSA	20m, 1mA (0.029)	Single	17 (11M/6F)	2.4	12.3

	Ishikuro et al. [26]	-	STEF	FPA / CSA	15m, 1mA (0.029)	Multiple (5)	9 (3M/6F)	1.8	5.8
Reaction Time									
Positive Change	Fregni et al. [24]	Exp 1	Simple RT	(left) M1 / CSA	20m, 1mA (0.029)	Single	17 (11M/6F)	2.4	12.3
No Change	Benninger et al. [19]	-	Serial RT	Bi- [M1 + PMC] or Bi- PFC / Mastoids	20m, 2mA (0.021)	Multiple (8)	25 (16M/9F)	2.5	9.9
	Doruk et al. [27]	-	Simple/Choice RT	(left) DLPFC / CSA or (right) DLPFC / CSA	20m, 2mA (0.057)	Multiple (10)	18 (12M/6F)	n.a.	n.a.
	Ferrucci et al. [23]	-	Serial RT	Bi- M1 / Right Deltoid or Bi- Cerebellum / Right Deltoid	20m, 2mA (0.057)	Multiple (5)	9 (5M/4F)	2.5	10.8
	Fregni et al. [24]	Exp 2	Simple RT	CSA / M1 (dominant)	20m, 1mA (0.029)	Single	17 (11M/6F)	2.4	12.3
		Exp 3	Simple RT	(left) DLPFC / CSA	20m, 1mA (0.029)	Single	17 (11M/6F)	2.4	12.3
	Schabrun et al. [25]	-	Serial RT	(left) M1 / CSA	20m, 2mA (0.080)	Multiple (9)	16 (10M/6F)	2	5.8
Neurophysiology									
Positive change	Cosentino et al. [21]	-	MEP	(more) M1 / CSA	20m, 2mA (0.057)	Single	14 (8M/6F)	1.6	n.a.
	Fregni et al. [24]	Exp 4	MEP	(left) M1 / CSA	20m, 1mA (0.029)	Single	17 (11M/6F)	2.4	12.3
No Change	Costa-Ribeiro et al. [22]	-	MEP, aMT	SMA / CSA (more)	13m, 2mA (n.a.)	Multiple (10)	22 (15M/7F)	2.3	6.2

* Bradykinesia subcomponent of UPDRS III significantly improved compared to sham.

Outcome measures:

FT, Finger tapping
MEP, Motor evoked potential
aMT, Active motor threshold
PPT, Purdue pegboard task
RT, Reaction time
Hand Sup/Pro, Supination and Pronation
UL, Upper limb
UPDRS III, Unified Parkinson's disease rating scales part three
FOUL, Freezing of the upper limb
STEF, Simple test for evaluating hand function

Stimulation targets:

CSA, Contralateral supraorbital area
DLPFC, Dorsolateral prefrontal cortex
M1, Primary motor cortex
PMC, Pre-motor cortex
TPC, Tempo-parietal cortex
FPA, Fronto-polar area
More, The brain hemisphere contralateral to the more affected side
Less, The brain hemisphere ipsilateral to the more affected side
Bi, Bilateral

Table 3. Cochrane risk of bias for included trials.

Author	Adequate sequence generation?	Allocation concealment?	Blinding of participants and personnel?	Blinding of outcome assessment?	Incomplete data addressed?	Free from selective reporting?	Number of items fulfilled the criteria
Benninger et al. [19]	Y	Y	Y	Y	Y	Y	6
Broeder et al. [20]	Y	U	Y	N	Y	Y	4
Cosentino et al. [21]	Y	Y	Y	Y	Y	Y	6
Costa-Ribeiro et al. [22]	Y	U	Y	Y	U	Y	4
Doruk et al. [27]	Y	U	U	U	U	Y	2
Ferrucci et al. [23]	Y	U	Y	Y	U	Y	4
Fregni et al. [24]	Y	U	Y	Y	Y	Y	5
Ishikuro et al. [26]	U	U	Y	U	Y	Y	3
Salimpour et al. [28]	U	U	Y	Y	U	Y	3
Schabrun et al. [25]	Y	Y	Y	Y	Y	Y	6

Y, yes; N, no; U, unclear - Insufficient information to permit judgement.
Trials with a low risk rating of four or more are considered at low risk of bias.