Parkinsonism and Related Disorders 64 (2019) 82–89

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

Effects of non-invasive brain stimulation on freezing of gait in parkinsonism: A systematic review with meta-analysis

Yong Wook Kim[a], In-Soo Shin[b], Hyun Im Moon[c], Sang Chul Lee[a,*,1], Seo Yeon Yoon[c,**,1]

[a] Department and Research Institute of Rehabilitation Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea
[b] Department of Education, College of Education, Jeonju University, Jeonju, Republic of Korea
[c] Department of Rehabilitation Medicine, Bundang Jesaeng General Hospital, Gyeonggi-do, Republic of Korea

ARTICLE INFO

Keywords:
Non-invasive brain stimulation
Repetitive transcranial magnetic stimulation
Transcranial direct current stimulation
Freezing of gait
Parkinsonism

ABSTRACT

Introduction: To investigate the effect of non-invasive brain stimulation (NIBS), including repetitive transcranial magnetic stimulation and transcranial direct current stimulation, on freezing of gait (FOG) in parkinsonism.
Methods: The PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and Physiotherapy Evidence Database (PEDro) databases were searched up to October 2018 for articles published in English or Korean. Quality assessment was performed using the PEDro scale. Studies with random allocation and pre-intervention and post-intervention assessments for FOG were included, and the standardized mean differences for each outcome were calculated.
Results: Seven studies including 102 participants were included in the final analysis. The meta-analysis showed a significant improvement in freezing of gait questionnaire (FOG-Q) scores (SMD = 0.28; 95% CI, 0.01 to 0.55) and turning time (SMD = 0.30; 95% CI, 0.02 to 0.58). When analyzing only participants with Parkinson's disease, the effect size according to the FOG-Q score was greater (SMD = 0.57; 95% CI, 0.15 to 0.98) and the United Parkinson's disease rating scale-III score was significantly improved after NIBS (SMD = 0.43; 95% CI, 0.01 to 0.86). Both motor and frontal cortex stimulation didn't reveal significant improvement for FOG, but, the effect size of motor cortex stimulation (SMD = 0.35; 95% CI, −0.06 to 0.76) was almost double compared with that of frontal cortex stimulation (SMD = 0.19; 95% CI, −0.26 to 0.63).
Conclusion: NIBS showed a beneficial effect on FOG in parkinsonism, and the effects were more prominent in Parkinson's disease. Further studies are needed to determine the optimal protocol and elucidate effects according to the intervention and disease type.

1. Introduction

Freezing of gait (FOG) is defined as a brief, episodic absence or marked reduction in forward progression of the feet despite the intention to walk, which is one of the most disabling symptoms of Parkinson's disease (PD) [1,2]. FOG is significantly associated with longer disease duration, with its prevalence ranging from 7% in early PD to 60% in the advanced stages [3]. The phenomenon of FOG might be profound, thus, to identify whether FOG is present is difficult and people with PD sometimes do not realize whether they have FOG by themselves [4]. FOG increases the risk of falling and has a significant effect on the quality of life of person with PD [1,5]. In addition to PD, FOG is also common in atypical parkinsonism (AP), such as vascular parkinsonism (VP), progressive supranuclear palsy (PSP), and multiple system atrophy (MSA), and is observed early and frequently in the course of disease [6].

The pathophysiology of FOG is not fully understood, although several not mutually exclusive hypotheses have been postulated [7]. Recent theoretical frameworks have suggested that transient overactivation in inhibitory striatal output nuclei projecting to the motor thalamus and brainstem locomotor regions, as well as dysfunctional cortical and cerebellar projections to these subcortical and brainstem regions, may ultimately be involved in the manifestation of FOG in PD [8]. Thus, various strategies for the management of FOG have been

* Corresponding author. Department and Research Institute of Rehabilitation Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul, 03722, Republic of Korea.
** Corresponding author. Department of Rehabilitation Medicine, BundangJesaeng General Hospital, 20, Seohyeon-ro, 180beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do, Republic of Korea.
E-mail addresses: bettertomo@yuhs.ac (S.C. Lee), seoyeon0521@gmail.com (S.Y. Yoon).
[1] Sang Chul Lee and Seo Yeon Yoon contributed equally to this work.

https://doi.org/10.1016/j.parkreldis.2019.02.029
Received 14 December 2018; Received in revised form 19 February 2019; Accepted 19 February 2019
1353-8020/

attempted. The current treatment for FOG involves a multidisciplinary approach with pharmacological and surgical treatment options, as well as non-pharmacological treatment including physiotherapy and occupational therapy [8]. However, the effects of those treatment still remain inconclusive, and surgical options are, at best, partially efficacious [9,10]. The development of new and more effective treatments for FOG is important, and recently, studies on non-invasive brain stimulation (NIBS), such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), for FOG have been performed.

NIBS, including rTMS and tDCS, has been performed in various diseases such as stroke, schizophrenia, depression, and PD [11,12]. RTMS at frequencies of 5 Hz and higher can enhance motor cortex excitability, whereas frequencies of rTMS of 1 Hz and lower can transiently depress cortical excitability [13]. TDCS delivers a continuous current that modulates membrane excitability and induces shifts in cortical excitability, with the polarity defining the effects. These neuroplastic mechanisms may reflect useful therapeutic NIBS avenues. In person with PD, deep brain stimulation (DBS) has been shown to improve motor deficits and modulates brain activity and motor cortex physiology [10]. Likewise, NIBS could also be used as an another option to access the cortex, stimulating the cortico-basal ganglia-thalamo-cortical circuit, which is suggested as a part of the important pathophysiology of PD [14].

Previous studies on the effect of NIBS in PD have been conducted, and there have been several systematic reviews and meta-analyses [14–16]. These studies evaluated the effects of NIBS for various symptoms of PD including motor symptoms, dyskinesia, gait function, and mood. However, there have been few trials on NIBS, for which FOG was the focus of treatment. Recently, several clinical trials have been conducted. El-Tamaway et al. showed the beneficial effects of rTMS on the freezing of gait questionnaire (FOG-Q) and unified Parkinson's disease rating scale (UPDRS) scores in PD [17], whereas other studies revealed no significant effect on FOG or gait function in PD and AP [18,19]. Therefore, the aim of this meta-analysis was to review the existing literature to evaluate the effect of NIBS on FOG in person with parkinsonism. We additionally performed subgroup analysis to elucidate whether there are differences in the effects of NIBS according to stimulation protocols or diagnosis of the enrolled patients.

2. Methods

2.1. Study search and selection

We searched for references on the PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and Physiotherapy Evidence Database (PEDro) databases up to October 2018 without any date restriction. Database searches were limited to articles published in English or Korean. Key terms used to conduct the literature search were chosen and combined with the following English terms and their equivalents: "Non-invasive brain stimulation" AND "freezing of gait" AND "Parkinson". Search strategies per database were outlined in Appendix 1 (Online available). Studies were included if: 1) participant allocation was randomized; 2) the sample was composed of participants with parkinsonism and FOG; and 3) interventions were NIBS, such as rTMS or tDCS. Studies were excluded if NIBS was intended for the treatment of conditions other than FOG, the intervention was DBS, the trial was not conducted with a comparison group, or data on baseline score or end-point outcome were not provided sufficiently. Abstracts and conference proceedings were excluded if they lacked sufficient reporting detail. Review articles, editorials, and other nonclinical trials were also excluded.

Two reviewers independently reviewed the titles and abstracts of articles to determine eligibility for inclusion. Studies that clearly failed to meet the inclusion criteria were not reviewed further. Those that could not be excluded were retrieved, and the full text was reviewed by the two reviewers. When the confirmation of any data or additional information was needed, the authors were contacted by e-mail. In all instances, differences in opinion were resolved by discussion with a third party. Studies that met the criteria were retrieved and reviewed in detail.

2.2. Data extraction and quality assessment

The following information was extracted from included studies: first author, year of publication, patients' demographics and clinical presentations, types of interventions, intervention protocols, total sample size and sample size per arm, scales and measures used to evaluate the efficacy of interventions, and baseline and end-point outcome measurements.

The quality of evidence generated by this meta-analysis was classified using the PEDro Scale. The PEDro Scale assesses the methodological quality of a study based on important criteria (e.g., concealed allocation, intention-to-treat analysis, adequacy of follow-up). These characteristics make the PEDro Scale a useful tool for assessing the quality of rehabilitation trials [20,21]. Methodological quality was independently assessed by two researchers. When there were discrepancies between the two reviewers, we applied the scoring criteria more rigorously. Studies were scored on the PEDro Scale, which consists of eleven items. One item on the PEDro Scale (eligibility criteria) is related to external validity and is generally not used to calculate the method score, leaving a score ranging from 0 to 10.

2.3. Data synthesis and statistical analysis

The meta-analysis represents the quantitative findings of each study in the form of effect sizes, which produces a statistical standardization [22]. The calculation of effect sizes for NIBS on FOG was based on the standardized mean difference (SMD) measure suggested by Morris [23]. Effect size was calculated based on the mean pre-post change in the treatment group minus the mean pre-post change in the comparison group, divided by the pooled pretest standard deviation [23]. SMD ± standard error and 95% confidence interval between the treatment and comparison groups were calculated for each study, and the results, pooled. Analyses were conducted using RevMan 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). This software enables the calculation of a treatment effect using differing forms of summary-level data. The number of the studies included and calculations of the heterogeneity statistic I^2 showed that estimates should be based on fixed effect models [24]. The degree of heterogeneity was assessed using I^2. The I^2 statistic ranges from 0% to 100% and cutoff values of 25%, 50% and 75% indicate low, moderate, and high degrees of heterogeneity, respectively. We used two-tailed P values, and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Description of selected studies

A flowchart of the search process is shown in Fig. 1. A total of 724 studies were identified in the initial search. After duplicates were removed and abstracts screened, 16 studies remained for further assessment. After reviewing the full papers to obtain additional details and excluding studies for various reasons (non-randomized studies, no control group, no relevant outcomes reported, brief reports, and letters to editor), seven studies [17–19,25–28] including 102 participants fulfilled the inclusion criteria and were included in the final analysis (ICC 0.873).

3.2. Quality assessment

The PEDro scores of the included studies ranged from 6 to 9, with a

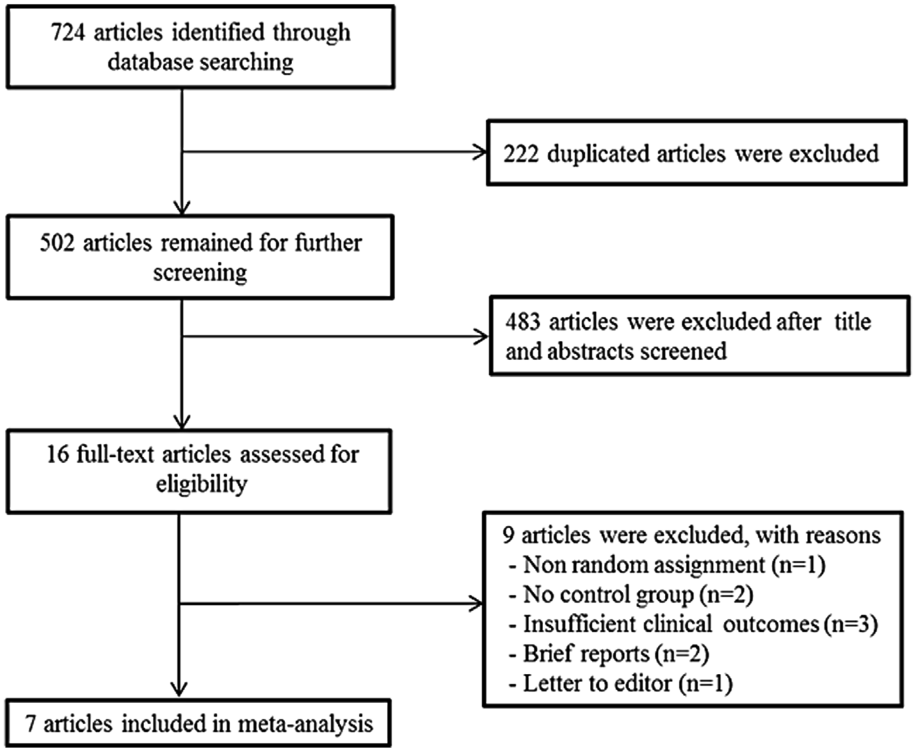

Fig. 1. Flow chart of study search and selection methods.

mean score of 7.3 indicating overall good quality (ICC 0.921). One study was of very high quality [25], and the other six were of high quality [17–19,26–28]. All of the studies performed random allocation with participant blinding. All trials reported between-group differences as well as point estimates and variability. A detailed evaluation of the methodological quality is provided in Supplementary Table 1 (Online available).

3.3. Study characteristics

The number of participants in the included studies ranged from 7 to 32. The mean age of participants ranged from 64.5 [18] to 74.6 [26] years. All studies, except for one study (no report of participant sex) [26], included participants of both sexes, but there was an overall predominance of men. The mean duration after diagnosis ranged from 4.3 [19] to 10.3 [26] months. Five studies [17,18,25,26,28] enrolled only participants with PD, and two studies [19,27] enrolled AP as well as PD. Six studies [17–19,26–28] compared the effects between real or sham rTMS, whereas one study [25] performed dual stimulation, comparing the effects of (rTMS + tDCS) and (rTMS + sham tDCS). Two studies [12,23] performed NIBS during on medication state, however, in other studies, timing of stimulation was not suggested. Stimulation site was leg motor cortex [12–14] in 3 studies, frontal cortex in 2 studies [20,21], and 2 studies [22,23] stimulated both leg motor cortex and dorsolateral prefrontal cortex. Five studies [13,14,21–23] performed high frequency stimulation, and only one study [12] performed low frequency stimulation. The duration of stimulation ranged from 6 min [23] to 25 min [21]. The intervention period ranged from a single session [27] to eight weeks [26]. The follow up period ranged from immediately after NIBS [12,22] to 6 weeks [23]. Five studies [12,13,20,21,23] conducted test for outcome variables during on medication state, whereas 2 studies [14,22] for participants with AP didn't mention about the timing of test or stimulation, because participants were resistant with medication. All studies reported FOG-Q and UPDRS scores, five studies [18,19,25,27,28] performed TUG, and four studies [18,19,25,27] examined turning ability. Two studies [25,28] performed neuropsychological assessments and two studies [26,28] performed gait analysis. Table 1 summarizes the characteristics of the included studies.

3.4. Effects of NIBS on freezing of gait and motor symptoms

All studies reported FOG-Q scores. The meta-analysis showed a significant improvement in the FOG-Q score for NIBS (SMD = 0.28; 95% CI, 0.01 to 0.55) relative to the comparison group. One study [17] reported only the UPDRS total score and did not include UPDRS-III subscores. The other six studies [18,19,25–28] included UPDRS-III scores, and there were no significant differences in the UPDRS-III scores between groups (SMD = 0.23; 95% CI, −0.04 to 0.50) (Fig. 2).

3.5. Effects of NIBS on gait function

Five studies assessed turning ability, including turning time (TT) and turning steps (TS) [18,19,25,27,28]. The meta-analysis showed a significant improvement in TT for the NIBS group (SMD = 0.30; 95% CI, 0.02 to 0.58) relative to the comparison group, whereas there was no significant difference in TS (SMD = 0.17; 95% CI, −0.11 to 0.46) between the two groups. Four studies used TUG as an outcome [18,19,25,27], and there were no significant difference in TUG (SMD = 0.25; 95% CI, −0.04 to 0.53) (Fig. 2).

3.6. Subgroup analysis

We additionally performed a meta-analysis in PD participants alone, and five studies covering 74 participants with PD were included [17,18,25,26,28]. NIBS still showed a beneficial effect on FOG-Q scores in PD patients, and the effect size was much larger (SMD = 0.57; 95% CI, 0.15 to 0.98). There was a somewhat different result for UPDRS-III in this subgroup analysis, and the meta-analysis for UPDRS-III revealed a significant improvement in PD participants (SMD = 0.43; 95% CI, 0.01 to 0.86). For other outcome variables, there was no significant difference in TS (SMD = 0.28; 95% CI, −0.19 to 0.75), TT

Table 1
Characteristics of included studies.

	Participants	Intervention Type	Procedure	Outcome measures
Chang et al. (2016) [19]	N = 8 Age (yr) = 71.9 (SD 7.8) Sex (M/F) = 6/2 Diagnosis = MSA (1), PSP (2), VP (5) Duration (yr) = 4.3 (SD 1.8)	Real or sham rTMS Double cone coil	Timing: NR Leg primary motor cortex Frequency = 10 Hz 90% RMT Total pulse = 1000 Duration = 20 m 1 daily session for 5 consecutive days	Timing: NR FOG-Q, UPDRS-III, TUG Turning ability – TT, TS
Chang et al. (2017) [25]	N = 32 Age (yr) = 63.7 (SD 7.9) Sex (M/F) = 20/12 Diagnosis = PD (32) Duration (yr) = 9.5 (SD 5.0)	(rTMS + tDCS) or (rTMS + sham tDCS) rTMS: double cone coil tDCS electrode size = 25 cm^2	Timing: NR rTMS) Leg primary motor cortex Frequency = 10 Hz 90% RMT Total pulse = 1000 Duration = 20 m 1 daily session for 5 consecutive days tDCS) Anode: left dorsolateral prefrontal cortex Cathod: right supraorbital region Current strength = 1 mA Current density = . 40A/m^2 Duration = 20 m 1 daily session for 5 consecutive days	Timing: On medication state FOG-Q, UPDRS-III, TUG Turning ability – TT, TS Neuropsychological assessments – Digit span, Trail making test, K-MoCA, GDS-SF Cortical excitability – RMT, MEP amplitude
Dagan et al. (2017) [26]	N = 7 Age (yr) = 74.6 (SD 7.1) Sex (M/F) = NR Diagnosis = PD (7) Duration (yr) = 10.3 (SD 3.8)	Real or sham rTMS H3 coil	Timing: NR Bilateral medial prefrontal cortex Frequency = 10 Hz 100% RMT Total pulse = 2100 Duration = 25 m 3 sessions/wk x 4wk +1 session/wk x 4wk	Timing: On medication state FOG-provoking test, UPDRS-III, Gait analysis
El-Tamawy et al. (2013) [17]	N = 16 Age (yr) = 67 (SD 7.3) Sex (M/F) = 11/5 Diagnosis = PD (16) Duration (yr) = NR	Real or sham rTMS Figure-of-8 coil	Timing: On medication state Leg primary motor cortex contralateral to the more affected side Frequency = 1 Hz 90% RMT Total pulse = 500 Duration = 700 s 12 sessions over 4 weeks [1,2]	Timing: On medication state Freezing episode FOG-Q, UPDRS
Kim et al. (2015) [18]	N = 17 Age (yr) = 64.5 (SD 8.4) Sex (M/F) = 12/5 Diagnosis = PD (17) Duration (yr) = 7.8 (SD 4.9)	Real or sham rTMS Double cone coil	Timing: NR Leg primary motor cortex Frequency = 10 Hz 90% RMT Total pulse = 1000 Duration = 20 m 1 daily session for 5 consecutive days	Timing: On medication state FOG-Q, UPDRS-III, TUG Turning ability – TT, TS Cortical excitability – RMT, MEP amplitude, SICI, ICF
Lee et al. (2014) [27]	N = 20 Age (yr) = 71.6 (SD8.6) Sex (M/F) = 13/7 Diagnosis = PD (7), VP (6), MSA (6), LBD (1) Duration (yr) = 4.7 (SD 2.6)	Real or sham rTMS Double cone coil: leg primary motor cortex, supplementary motor area Figure-of-8 coil: dorsolateral prefrontal cortex	Timing: NR Three different cortical regions = leg primary motor cortex, supplementary motor area, dorsolateral prefrontal cortex Frequency = 10 Hz 90% RMT Total pulse = 1000 Duration = 20 m Single session	Timing: NR FOG-Q, UPDRS-III, TUG Turning ability – TT, TS Cortical excitability – MEP amplitude
Oh et al. (2015) [28]	N = 12 Age (yr) = 71.0 (SD 6.1) Sex (M/F) = 8/4 Diagnosis = PD (12) Duration (yr) = 6.0 (SD 2.6)	Real or sham rTMS Figure-of-8 coil	Timing: On medication state Bilateral motor cortices + alternative dorsolateral prefrontal cortex Frequency = 5 Hz 110% RMT Total pulse = 1000 Duration = 6 m 5 sessions/wk x 2wk	Timing: On medication state FOG-Q UPDRS-III Turning ability – TT, TS Neuropsychological assessments – 3MS K-MMSE, K-MoCA, K-NMSS, K-PDQ39, FAB Gait analysis

M, male; F, female; MSA, multiple system atrophy; VP, vascular parkinsonism; PSP, progressive supranuclear palsy; rTMS, repetitive transcranial magnetic stimulation; RMT, resting motor threshold; FOG-Q, freezing of gait-questionnaire; UPDRS, unified Parkinson's disease rating scale; TUG, timed up and go test; TT, turn time; TS, turn step; PD, Parkinson's disease; tDCS, transcranial direct current stimulation; K-MoCA, Korean version of the Montreal Cognitive Assessment; GDS-SF, Geriatric Depression Scale Short Form; MEP, motor evoked potential; SICI, short-interval intracortical inhibition; ICF, intracortical facilitation; LBD, Lewy body disease; 3MS, Modified mini-mental state test; K-MMSE, Korean version of Mini-mental status exam; K-NMSS, Korean version of non-motor symptom scale, K-PDQ39, Korean version of 39-item Parkinson disease questionnaire, FAB, frontal assessment battery; NR, Not reported.

(SMD = 0.18; 95% CI, −0.28 to 0.65), or TUG (SMD = 0.11; 95% CI, −0.38 to 0.60) between the two groups (Fig. 3).

Subgroup analysis according to stimulation site was also performed. Both motor cortex [17–19,27] and frontal cortex [25,26,28] stimulation didn't reveal significant improvement for FOG, but, the effect size of motor cortex stimulation (SMD = 0.35; 95% CI, −0.06 to 0.76) was almost double compared with that of frontal cortex stimulation (SMD = 0.19; 95% CI, −0.26 to 0.63) (Fig. 4). Additionally, we performed subgroup analysis after excluding the study by Chang at el [25]. to elucidate the effects of rTMS on FOG, and it revealed no definite

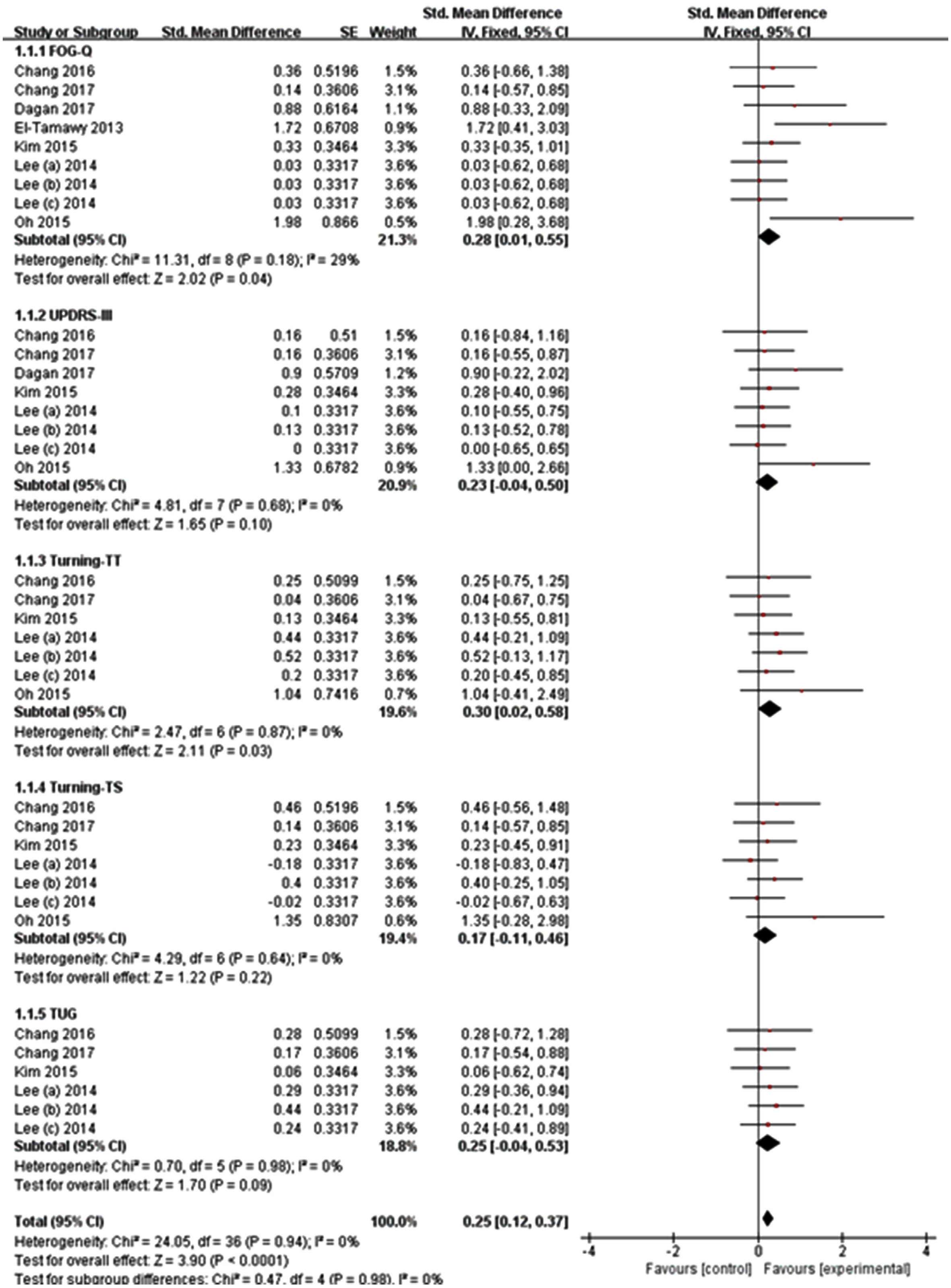

Fig. 2. Meta-analysis of non-invasive brain stimulation for freezing of gait in parkinsonism.

difference compared with the results of the meta-analysis for the effects of NIBS (Supplementary Fig. 1).

3.7. Effects of NIBS on cognitive function in participants with parkinsonism and FOG

Of the 7 included studies, two studies [25,28] evaluated cognitive function before and after NIBS, and 55 PD participants were included. One study [25] compared the effects of (rTMS + tDCS) and

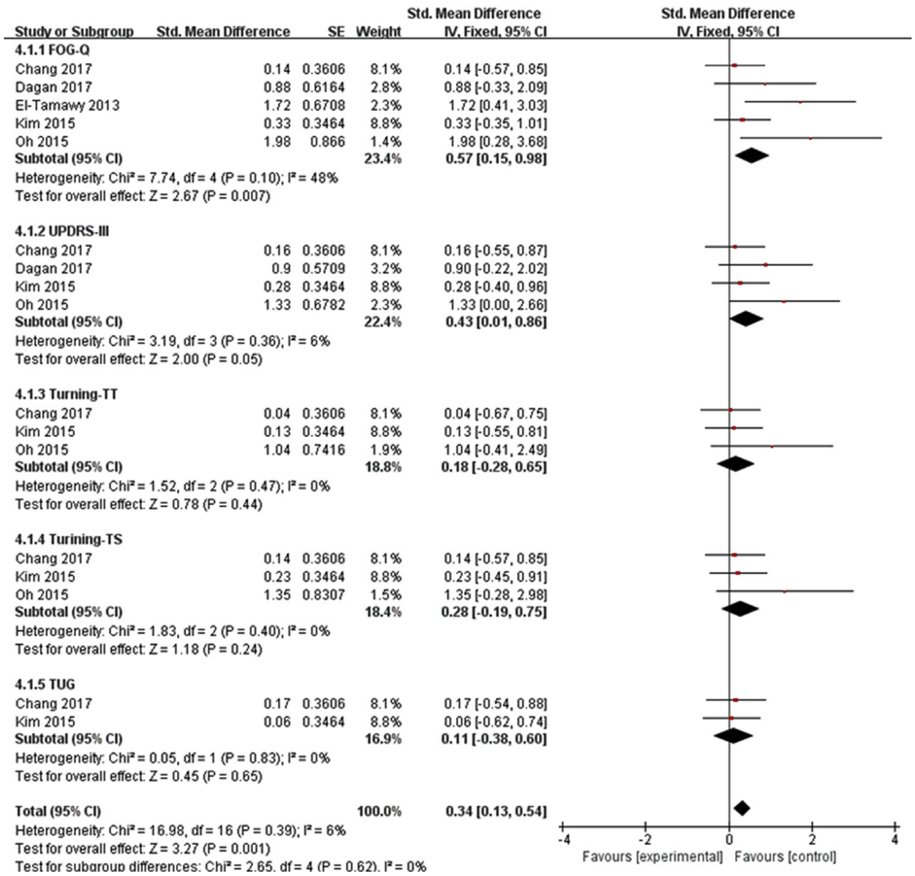

Fig. 3. Subgroup analysis of non-invasive brain stimulation for freezing of gait in Parkinson's disease.

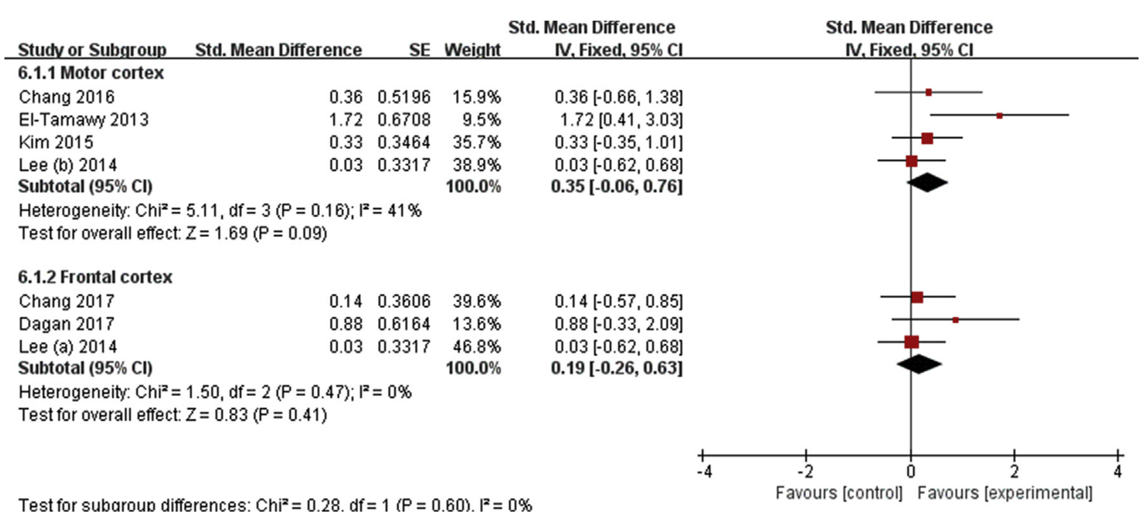

Fig. 4. Subgroup analysis of non-invasive brain stimulation according to stimulation site.

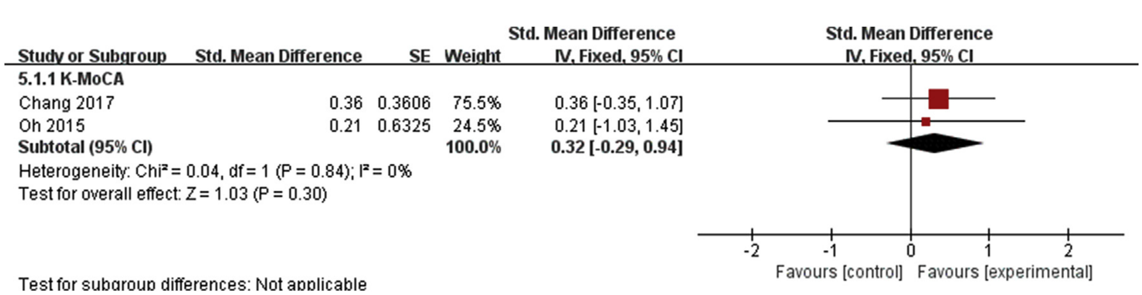

Fig. 5. Meta-analysis of non-invasive brain stimulation for cognitive function in participants with parkinsonism and FOG.

(rTMS + sham tDCS), and the stimulation site was leg primary motor cortex for rTMS and left dorsolateral prefrontal cortex for tDCS. Another study [28] evaluated the effects of rTMS, and the stimulation site were bilateral motor cortices and alternative dorsolateral prefrontal cortex. There was no significant improvement in cognitive function after NIBS (SMD = 0.32; 95% CI, −0.29 to 0.94) (Fig. 5).

3.8. Safety/adverse events

Of the 7 studies included in this review, three studies reported that there were no adverse events. Three studies [18,25,26] reported mild headache, which disappeared soon after the stimulation was discontinued. One study [26] reported unexpected elbow and shoulder movement immediately after the stimulation, and one study [27] reported transient headache and nausea, which resolved after a few hours without any serious side effects. There were no reports about safety issues during the intervention in all studies.

4. Discussion

To the best of our knowledge, this is the first meta-analysis to evaluate the effectiveness of NIBS in treating FOG in person with parkinsonism. In this study, we reviewed 7 studies including 102 participants with parkinsonism and FOG, and our meta-analysis found that NIBS was effective in improving FOG-Q scores and turning ability-related variables such as TT. In the subgroup analysis of participants with PD alone, the effect size for the change in FOG-Q score was more prominent, and UPDRS-III was significantly improved after NIBS in PD patients. Both motor cortex and frontal cortex stimulation didn't reveal significant improvement for FOG, but, the effect size of motor cortex stimulation was almost double compared with that of frontal cortex stimulation. NIBS could be considered an effective method for improving FOG in parkinsonism, especially in participants with PD.

Our meta-analysis revealed the beneficial effect of NIBS on FOG-Q score and TT. One possible mechanism is that NIBS might correct basal ganglia dysfunction through a cortico-basal ganglia–thalamo-cortical circuit. Decreased neural reserve and automaticity due to dysfunctional basal ganglia are the major pathophysiological mechanisms of FOG [29]. By directly increasing cortical excitability, NIBS increases the activity of the striatum and modulate inhibitory impulses of the globus pallidus interna, which leads to improvement of FOG [29,30]. Another hypothetical explanation could be that high-frequency rTMS might directly activate dopaminergic neurons in the striatum, supplying endogenous dopamine. A previous study by Khedr et al. reported that serum dopamine levels were significantly elevated after six daily sessions of high-frequency rTMS [31]. High-frequency rTMS on motor cortex was shown to increase endogenous dopamine release in the ipsilateral dorsal striatum in a previous study using positron emission tomography [32].

A waning levodopa response, development of additional symptoms, and more rapid progression of disease are characteristic of AP compared with PD. The effect of NIBS could be different between the two diseases, and we additionally performed a subgroup analysis. In the analysis with PD participants alone, NIBS had better effects on FOG-Q score and UPDRS-III than in the AP group. The effect size of the change in FOG-Q almost double, and the UPDRS-III, representing various motor symptoms in PD, significantly improved after NIBS only in PD patients. This is consistent with previous results in a Cochrane review from 2016, where the beneficial effects of tDCS on UPDRS-III in PD was shown [15]. The focus of that review was the effects of tDCS in PD, not for FOG in PD. AP generally don't respond to dopaminergic medications, and reveals various lesions other than basal ganglia in the brain imaging, such as pons, middle cerebellar peduncles in MSA, and brain stem atrophy in PSP. In our results, UPDRS-III was not significantly improved after NIBS in participants including both PD and AP. We thought that beneficial mechanism of NIBS, by improving basal ganglia dysfunction through a cortico-basal ganglia–thalamo-cortical circuit, would not influence AP participants due to underlying different pathophysiology compared with that of PD.

The association between FOG and mental dysfunction has long been recognized, and such mental dysfunction includes frontal executive dysfunction, inattention, and anxiety [33]. In a two-year follow-up study, the presence of FOG was considered to be a marker of early executive dysfunction [34], and dual-tasking has been suggested to influence FOG [35]. In the subgroup analyses according to stimulation site, both motor and frontal cortex stimulation didn't reveal significant improvement for FOG, but, the effect size of motor cortex stimulation was almost double compared with that of frontal cortex stimulation. Only two studies [25,28] evaluated cognitive function as an outcome parameter, and the stimulation site in those two studies were both motor cortex and dorsolateral prefontal cortex. Meta-analysis including the two studies revealed no significant improvement in cognitive function or FOG. According to our results, the improvement of FOG after NIBS might be related with modulation of motor cortex excitability, and the effect of NIBS for cognitive function to improve FOG was not significant. However, the number of studies included in this sub-group analysis was small, and the stimulation protocols were different between the studies. Thus, we thought it could not be conclusive, and future studies on the focus of stimulation site should be warranted.

The interventional protocol used in the included studies was heterogeneous. Duration of stimulation; stimulation intensity; number of stimulation sessions; follow up periods differed by each study. Thus, we could not evaluate the effects of different factors, such as optimal stimulation protocols and long-term effects. According to stimulation type, rTMS showed similar results to those of NIBS including rTMS and tDCS. Only one study evaluated the effects of dual stimulation comparing rTMS + tDCS and rTMS + sham tDCS, and we could not perform a meta-analysis for the separate effect of tDCS alone. In the regards of on or off medication state, test for outcome variables were all performed on medication state in PD participants, thus, we could not perform a subgroup analysis for the effect of NIBS according to the medication status. A previous meta-analysis about the effect of subthalamic nucleus-DBS for FOG has shown different results between on and off medication status [10]. Effects of NIBS for FOG according to medication state also should be explored in the future studies. Previous studies on the effects of NIBS for motor symptoms in PD also used various protocols. Stimulation sites included motor cortex, supplementary motor cortex, dorsolateral prefrontal cortex, and cerebellum, and different intervention protocols such as stimulation intensity, duration, coil design, and number of sessions might influence heterogeneous results. Gait function and bradykinesia were improved in some clinical trials, but there was a lack of investigation regarding the effects for rigidity or tremor [14]. Thus, even review articles on the effect of NIBS on PD have reached inconclusive results because of this heterogeneity [13–16]. Future studies on the optimal method of NIBS would be needed to increase its clinically meaningful application.

Our study has several limitations. First, the total number of included studies and participants was small. We only included studies of participants with parkinsonism and FOG. There have been studies of NIBS for motor symptoms in PD, and some studies also reported the results of FOG. We tried to figure out the effects of NIBS focusing on the FOG in PD, thus, we excluded the studies of participants with parkinsonism, but not showing FOG. Second, the diversity of the protocols used in each study may have caused variation in the results. Although, our results suggested the effect of NIBS in specific participants with parkinsonism and FOG, the small number of studies and heterogeneous stimulation protocols should be considered when interpreting results. Third, we only included studies published in English or Korean. Finally, some studies included in the meta-analysis were published by the same research center, resulting in a probability of data overlap. Further investigation is required to evaluate how the positive effects of NIBS can be sustained over time and to determine the optimal stimulation protocols including stimulation intensity, duration, and number of sessions. Further studies on the effects of NIBS on FOG according to disease type and intervention type are also warranted. We believe the value of NIBS on FOG in parkinsonism deserves special attention in future studies.

Conflicts of interest

The authors have no conflicts of interest to report.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.02.029.

References

[1] J.G. Nutt, B.R. Bloem, N. Giladi, M. Hallett, F.B. Horak, A. Nieuwboer, Freezing of gait: moving forward on a mysterious clinical phenomenon, the Lancet, Neurology 10 (8) (2011) 734–744.
[2] N. Giladi, A. Nieuwboer, Understanding and treating freezing of gait in parkinsonism, proposed working definition, and setting the stage, Mov. Disord.: Offic. J. Mov. Disord. Soc. 23 (S2) (2008) S423–S425.
[3] M. Macht, Y. Kaussner, J.C. Möller, K. Stiasny-Kolster, K.M. Eggert, H.P. Krüger, H. Ellgring, Predictors of freezing in Parkinson's disease: a survey of 6,620 patients, Mov. Disord. 22 (7) (2007) 953–956.
[4] J. Nonnekes, A.H. Snijders, J.G. Nutt, G. Deuschl, N. Giladi, B.R. Bloem, Freezing of gait: a practical approach to management, Lancet Neurol. 14 (7) (2015) 768–778.
[5] I.C. López, P.J.G. Ruiz, S.V.F. del Pozo, V.S. Bernardos, Motor complications in Parkinson's disease: ten year follow-up study, Mov. Disord. 25 (16) (2010) 2735–2739.
[6] S.A. Factor, The clinical spectrum of freezing of gait in atypical parkinsonism, Mov. Disord.: Offic. J. Mov. Disord. Soc. 23 (S2) (2008) S431–S438.
[7] A. Nieuwboer, N. Giladi, Characterizing freezing of gait in Parkinson's disease: models of an episodic phenomenon, Mov. Disord. 28 (11) (2013) 1509–1519.
[8] M. Gilat, A.L.S. de Lima, B.R. Bloem, J.M. Shine, J. Nonnekes, S.J. Lewis, Freezing of gait: promising avenues for future treatment, Park. Relat. Disord. 52 (2018) 7–16.
[9] S. Vercruysse, W. Vandenberghe, L. Münks, B. Nuttin, H. Devos, A. Nieuwboer, Effects of deep brain stimulation of the subthalamic nucleus on freezing of gait in Parkinson's disease: a prospective controlled study, J. Neurol. Neurosurg. Psychiatry 85 (8) (2014) 871–877.
[10] C. Schlenstedt, A. Shalash, M. Muthuraman, D. Falk, K. Witt, G. Deuschl, Effect of high-frequency subthalamic neurostimulation on gait and freezing of gait in Parkinson's disease: a systematic review and meta-analysis, Eur. J. Neurol. 24 (1) (2017) 18–26.
[11] A.T. O'Brien, F. Bertolucci, G. Torrealba-Acosta, R. Huerta, F. Fregni, A. Thibaut, Non-invasive brain stimulation for fine motor improvement after stroke: a meta-analysis, Eur. J. Neurol. 25 (8) (2018) 1017–1026.
[12] N.I. Kennedy, W.H. Lee, S. Frangou, Efficacy of non-invasive brain stimulation on the symptom dimensions of schizophrenia: a meta-analysis of randomized controlled trials, Eur. Psychiatry: J. Assoc. Eur. Psychiatrists 49 (2018) 69–77.
[13] G. Koch, Do studies on cortical plasticity provide a rationale for using non-invasive brain stimulation as a treatment for Parkinson's disease patients? Front. Neurol. 4 (2013) 180.
[14] D.H. Benninger, M. Hallett, Non-invasive brain stimulation for Parkinson's disease: current concepts and outlook, NeuroRehabilitation 37 (1) (2015) 11–24 2015.
[15] B. Elsner, J. Kugler, M. Pohl, J. Mehrholz, Transcranial direct current stimulation (tDCS) for idiopathic Parkinson's disease, Cochrane Database Syst. Rev. 7 (2016).
[16] R.C. Helmich, H.R. Siebner, M. Bakker, A. Münchau, B.R. Bloem, Repetitive transcranial magnetic stimulation to improve mood and motor function in Parkinson's disease, J. Neurol. Sci. 248 (1–2) (2006) 84–96.
[17] M.S. El-Tamawy, H.S. Shehata, N.M. Shalaby, A. Nawito, E.H. Esmail, Can repetitive transcranial magnetic stimulation help on-freezers with Parkinson's disease? Egypt J. Neurol. Psychiat. Neurosurg. 50 (4) (2013) 355–360.
[18] M.S. Kim, W.H. Chang, J.W. Cho, J. Youn, Y.K. Kim, S.W. Kim, Y.H. Kim, Efficacy of cumulative high-frequency rTMS on freezing of gait in Parkinson's disease, Restor. Neurol. Neurosci. 33 (4) (2015) 521–530.
[19] W.H. Chang, M.S. Kim, J.W. Cho, J. Youn, Y.K. Kim, S.W. Kim, A. Lee, Y.H. Kim, Effect of cumulative repetitive transcranial magnetic stimulation on freezing of gait in patients with atypical Parkinsonism: a pilot study, J. Rehabil. Med. 48 (9) (2016) 824–828.
[20] Y. Li, Q. Wei, W. Gou, C. He, Effects of mirror therapy on walking ability, balance and lower limb motor recovery after stroke: a systematic review and meta-analysis of randomized controlled trials, Clin. Rehabil. 32 (8) (2018) 1007–1021.
[21] M. Gomes-Neto, M.B. Saquetto, C.M. Silva, V.O. Carvalho, N. Ribeiro, C.S. Conceição, Effects of respiratory muscle training on respiratory function, respiratory muscle strength, and exercise tolerance in patients poststroke: a systematic review with meta-analysis, Arch. Phys. Med. Rehabil. 97 (11) (2016) 1994–2001.
[22] M.W. Lipsey, D.B. Wilson, Practical Meta-Analysis, Sage Publications, Inc, 2001.
[23] S.B. Morris, Estimating effect sizes from pretest-posttest-control group designs, Organ. Res. Methods 11 (2) (2008) 364–386.
[24] M. Borenstein, L.V. Hedges, J.P. Higgins, H.R. Rothstein, Introduction to Meta-Analysis, John Wiley & Sons, 2011.
[25] W.H. Chang, M.S. Kim, E. Park, J.W. Cho, J. Youn, Y.K. Kim, Y.H. Kim, Effect of dual-mode and dual-site noninvasive brain stimulation on freezing of gait in patients with Parkinson disease, Arch. Phys. Med. Rehabil. 98 (7) (2017) 1283–1290.
[26] M. Dagan, T. Herman, A. Mirelman, N. Giladi, J.M. Hausdorff, The role of the prefrontal cortex in freezing of gait in Parkinson's disease: insights from a deep repetitive transcranial magnetic stimulation exploratory study, Exp. Brain Res. 235 (8) (2017) 2463–2472.
[27] S.Y. Lee, M.S. Kim, W.H. Chang, J.W. Cho, J.Y. Youn, Y.H. Kim, Effects of repetitive transcranial magnetic stimulation on freezing of gait in patients with Parkinsonism, Restor. Neurol. Neurosci. 32 (6) (2014) 743–753.
[28] E. Oh, S. Park, J. Lim, A.Y. Lee, S.-K. Bok, H.-J. Song, High frequency repetitive transcranial magnetic stimulation for freezing of gait and nonmotor symptoms in Parkinson's disease, J. Kor. Neurol. Assoc. 33 (4) (2015) 297–305.
[29] J.M. Shine, S.L. Naismith, S.J. Lewis, The pathophysiological mechanisms underlying freezing of gait in Parkinson's Disease, J. Clin. Neurosci.: Offic. J. Neurosurg. Soc. Australas. 18 (9) (2011) 1154–1157.
[30] N. Kamble, M. Netravathi, P.K. Pal, Therapeutic applications of repetitive transcranial magnetic stimulation (rTMS) in movement disorders: a review, Park. Relat. Disord. 20 (7) (2014) 695–707.
[31] E.M. Khedr, J.C. Rothwell, O.A. Shawky, M.A. Ahmed, N. Foly K, A. Hamdy, Dopamine levels after repetitive transcranial magnetic stimulation of motor cortex in patients with Parkinson's disease: preliminary results, Mov. Disord. 22 (7) (2007) 1046–1050.
[32] A.P. Strafella, T. Paus, M. Fraraccio, A. Dagher, Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex, Brain: J. Neurol. 126 (Pt 12) (2003) 2609–2615.
[33] N. Giladi, J.M. Hausdorff, The role of mental function in the pathogenesis of freezing of gait in Parkinson's disease, J. Neurol. Sci. 248 (1–2) (2006) 173–176.
[34] M. Amboni, P. Barone, M. Picillo, A. Cozzolino, K. Longo, R. Erro, A. Iavarone, A two-year follow-up study of executive dysfunctions in parkinsonian patients with freezing of gait at on-state, Mov. Disord. 25 (6) (2010) 800–802.
[35] J. Spildooren, S. Vercruysse, K. Desloovere, W. Vandenberghe, E. Kerckhofs, A. Nieuwboer, Freezing of gait in Parkinson's disease: the impact of dual-tasking and turning, Mov. Disord. 25 (15) (2010) 2563–2570.