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Effects of Cueing Techniques on Gait, Gait-Related Mobility, and Functional Activities in Patients with Parkinson's Disease: A Systematic Review And Meta-Analysis

Assmaa Magdi [1], Asma Mohamed [1]*, Esraa Elsayed [1], Razan Ahmad [1], Senthilnathan Ramakrishnan [2] and Marian Gabor [3]

[1,3]Physiotherapy Department, Fatima College of Health Sciences, Abu Dhabi, United Arab Emirates, [2]Physiotherapy Department, Fatima College of Health Sciences, Al Ain, United Arab Emirates

*Correspondence: Asma Mohammed Sayed Ahmed. assoma1435@gmail.com

Assmaa: 0000-0001-9697-1191

Asma: 0000-0001-9999-0662

Esraa: 0000-0001-7763-6312

Razan: 0000-0001-5204-6033

Senthilnathan Ramakrishnan: 0000-0003-4557-1301

Marian Gabor: 0000-0001-5170-9771

[1] Third year physiotherapy students, interested in neurology physiotherapy.

[2] Physiotherapy instructor with an interest in neurological and educational research.

[3] Physiotherapy instructor of musculoskeletal practice with interest in educational research and development of evidence-based practice among students.

Effects of Cueing Techniques on Gait, Gait-Related Mobility, and Functional Activities in Patients with Parkinson's Disease: A Systematic Review And Meta-Analysis

Background: Parkinson's disease (PD) is a neurodegeneration of dopaminergic neurotransmitters results in disturbance in gait, balance, and impairs the functional activities. Cueing techniques which are spatial stimuli facilitating repetitive movements are used in combination with other interventions to manage these disturbances.

Objectives: To determine the effects of cueing techniques for PD patients on the outcomes of gait, balance, functional activity, and freezing of gait.

Methods: The search was conducted in Medline, CINAHL, Cochrane, OVID and PEDro databases. In addition, a manual search in Google Scholar and reference lists of the included studies was conducted. Randomized Controlled Trials (RCTs) that compare the effects of cueing techniques with other interventions on any of the previously mentioned outcomes for PD patients were included according to the eligibility criteria.

Results: A total of 8 RCTs were included (n = 239 participants); 5 used auditory cueing, 3 used visual, and 1 used proprioceptive. The results revealed a significant medium effect of non-cueing techniques on gait (MD of 0.41(95% CI, 0.14, 0.68; P=0.003), a non-significant small effect of cueing on balance (MD of -0.13 (95% CI, -0.52, 0.27; P=0.54)), and a significant effect of cueing on functional activities (MD of -0.54 (95% CI, -0.86, -0.21; P=0.001). While no quantitative outcome measures were assessing freezing of gait, a meta-analysis for it was not applicable.

Conclusions: Cueing techniques are beneficial in improving functional activities and balance. It may not provide a significant change on gait parameters when compared to non-cueing techniques unless combined with other treatment programs.

Keywords: Parkinson's disease, cueing techniques, gait, balance, functional activities

Introduction

Overview of the disease

Parkinson's disease (PD) is a multiple-system progressive neurodegenerative disease that targets mainly the dopaminergic neurotransmitters which play important roles in executive functions and motor control. This results in three cardinal motor complications which are bradykinesia (slowness of the movement), stiffness, and resting tremor [1], as well as several non-motor effects including dementia, anxiety, optical hallucination, and autonomic impairments such as urinary and sexual dysfunction [2]. As the disease progresses, motor symptoms affect the gait of patients with PD, their balance, and functional activities, therefore increases freezing of gait and fall episodes [3]. The causes of PD are still poorly understood although its first description published by James Parkinson was 200 years ago [4].

Statistics showed that PD affects approximately 1–2 per 1000 of population at any time [5], and a rising prevalence with age was determined by the global data (all per 100,000): 41 in 40 to 49 years; 107 in 50 to 59 years; 173 in 55 to 64 years; 428 in 60 to 69 years; 425 in 65 to 74 years; 1087 in 70 to 79 years; and 1903 in older than age 80 [6]. PD is considered as the second most prevalent neurodegenerative disorder globally following Alzheimer's disease [7].

The worldwide prevalence of PD varies widely. One reason for the variation in prevalence estimates could be due to the differences in survival rates across countries as well as the use of epidemiological studies using medical records could be another reason for the variation in disease frequency [8]. Another meta-analysis of the worldwide data showed some differences in prevalence by age group, which shows a rising prevalence of PD with age, geographic location that was seen in prevalence for only individuals 70 to 79 years old, with a prevalence of 1,601 in individuals from North America, Europe, and

Australia, compared with 646 in individuals from Asia. And sex is found only for individuals 50 to 59 years old, with a prevalence of 41 in females and 134 in males [6].

Disease management

PD is a degenerative condition and there is no treatment to decelerate or stop the disease progression, therefore all the available therapies are aimed at relieving symptoms (symptomatic) [9]. Effective management and maximum clinical outcomes are obtained by including a combination of pharmacological and non-pharmacological interventions in managing PD [10].

Drug therapy such as dopamine-replacement with levodopa is considered as the mainstay of the treatment of Parkinson's disease, and it has been found to have the greatest effect on PD patients compared to other drug therapy (e.g. dopamine agonists) in alleviating the symptoms and improving motor function [11,12]. On the other hand, drug therapy has shown to have several side effects such as dyskinesia, hallucinations, confusion, and sleep disorders [12].

Other than pharmacological intervention, surgeries can also be a part of the treatment of PD in patients who cannot be managed medically or those who developed drug-resistant PD [13]. Deep Brain Stimulation (DBS), which is a surgery done by implanting a device that can send electrical signals to the brain, can help reducing tremor, freezing, stiffness, and gait impairments in PD patients [14]. However, it can lead to further complications such as: stroke (1.1%), seizures (1.1%), intracranial haemorrhage (2.2%), confusion (6.6%), and infection which seems to be the most commonly reported surgical complication (7.2%) [15].

The many adverse and side effects of the drug and surgical treatments of PD, as well as the decrease in the effectiveness of drug treatments coinciding with the progression of the

disease, were among the reasons that led to the emergence of non-pharmacological and non-surgical approaches to disease management in current years to improve PD patients' quality of life [16].

One of the non-pharmacological interventions is physiotherapy. Many different physiotherapy approaches that can be combined into a rehabilitation program have been found to enhance the quality of life by maximizing physical ability and minimizing the progression of symptoms. Some of these approaches are trunk muscle strength training, postural correction exercises like stretching as well as back and neck extension exercises, standing and stepping activities, and general mobility exercises [17]. Moreover, cueing techniques are one of the most common physiotherapy interventions used in combination with other approaches to treat patients with PD in order to improve outcomes [18]. All the mentioned techniques contribute to the improvement in mobility, muscular strength, resistance, and endurance leading to indirect improvements in gait, function, and balance in patients with PD [17].

Intervention description

Cueing is described as temporal or spatial stimuli, which facilitate repetitive movement and is usually provided as an auditory cue like music, visual cue by giving colorful strips on the floor, or a somatosensory cue using a tactile stimulation [18]. Cueing has an important role in PD management by reducing the problems associated with gait such as balance disturbance and freezing of gait, and it works to enhance PD patients' quality of life [18]. Cueing has a direct effect on the brain area, especially on cerebellar and thalamocortical networks. Because these areas are involved in perceiving and producing rhythm, parallel improvement in rhythmic tasks beyond gait is expected, and therefore a reduction in balance disturbances, falling, and freezing of gait episodes [19]. Not all patients will respond to cueing strategies and this might be related to some cognitive

problems and inability to follow commands [18].

The importance of conducting this review

The fact that the cueing techniques are one of the most common interventions used for PD motor symptoms inspired us to conduct this review to evaluate the effects of cueing techniques on gait, balance, functional activities, and freezing of gait in PD patients. Additionally, the limited primary and secondary researches about this particular topic encouraged us to explore the gaps in existing research. Previously, a systematic review was published in 2018, however, it was reviewing only the effects of rhythmical auditory cueing on one outcome which is the gait [20].

A few RCTs have been published evaluating the effectiveness of cueing techniques on different PD motor symptoms, this encouraged us to explore existing information in the fields of research by including the most relevant and up to date RCTs into one systematic review in order to make it easier for readers.

Review Aims

Primary Aim

To summarize the results of trials comparing the effects of cueing techniques to alternative interventions for PD patients on the outcomes of gait, balance, functional activity, and freezing of gait.

Secondary Aims

- To describe cueing types that have been used in RCTs.
- To summarize the tools that were used to perform the different types of cues.
- To summarize the outcome measures related to PD that have been used in the RCTs.

Methods

This review was conducted according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analysis: The PRISMA statement (Appendix 2).

Selection Criteria

Inclusion Criteria

Types of Studies. The studies that were included in this systematic review were different types of RCTs that compare the effects of cueing techniques with any type of other interventions on patients with PD on the outcomes of gait, balance, functional activities and freezing of gait. These types may include randomized controlled trials (with experimental and control groups), pilot randomized controlled trials, randomized clinical trials (different experimental groups), or randomized cross-over trials.

Types of Participants. Trials with participants with the following characteristics were considered as eligible for this review: participants clinically diagnosed with PD, any disease stage (early, middle or late stage), both male and female, any duration of PD, all ages, and undergo any drug therapy. Trials were excluded if they met any of the following participant characteristics: underwent any surgery related to managing symptom/s of PD, suffering from any severe respiratory, cardiovascular, auditory, or visual diseases, diagnosed with other neurological or psychological conditions, diagnosed with dementia or cognitive deficits, or unable to follow instructions.

Types of Interventions. Included trials must involve any type of cueing techniques (e.g. auditory, visual, somatosensory, or attentional cueing) for treating PD that aim to maximize functional activities and improve quality of life. The comparison interventions

in the included studies must be any other intervention such as treadmill, conventional physiotherapy, or home walking program.

Types of Outcomes. We defined the primary outcomes for this review as gait and balance. We included any outcome measure of gait including but not limited to: Functional Gait Assessment (FGA) and timed up-and-go test (TUG). And for balance, we included outcome measures such as Berg Balance Scale (BBS), limits of stability test (LOS), and Tinetti Fall Efficacy Scale (FES).

For the secondary outcomes, we have included any of the outcome measures associated with functional activities and freezing of gait:

- Functional activities (i.e. Unified Parkinson's Disease Rating Scale (UPDRS))
- Freezing of gait (i.e. new Freezing of Gait (FOG) questionnaire)

Exclusion Criteria

Criteria for excluding papers include:

- Studies published before 2011.
- Studies not published in the English language.
- Studies with locked full text.
- Studies with <4 PEDro score.

Searching

Search Strategy

We developed our search strategy based on the key search terms which were used in the PICO (population, intervention, comparison, and outcomes) framework. We have set a few synonyms for our keywords and adapted them to fit some databases. But due to the limited results found in the databases, the search terms were modified. Also, we have

used different methods to broaden or limit the search such as truncations and Boolean operators: “OR” for broadening the results by linking the synonyms and including any of them in the result and “AND” for narrowing the results by separating the key terms and including them all in the result. To show an example of what have been done, a full search strategy for Medline is detailed below in Table 1.

Electronic Search

Searching was a process that had extended through the first 2 weeks of February 2020. We have searched in the following electronic databases without the language or publication limitations (database (inclusive dates of articles)):

- MEDLINE- EBSCO (2011-2020)
- CINAHL- EBSCO (2011-2020)
- The Cochrane Central Register of Controlled Trials (2011-2020)
- Ovid (2011-2020)
- PEDro: Physiotherapy Evidence Database (2011-2020)

Searching Other Resources

We have done a hand search by screening the reference lists in some full-text articles identified, as well as manual searching in Google Scholar for any further eligible studies.

Selection of Studies

According to the PRISMA guidelines, duplicates were removed using Mendeley after completion of the electronic and hand search. Then, screening for the title and abstract for each study was done to exclude studies that are not related to our topic. After that, the remaining studies were assessed based on our eligibility criteria identified previously in the selection criteria section. The full-text studies that met our inclusion criteria have been read fully and were added in our review. This process was the result of a group

work in which each of the four student researchers participated, and we conducted meetings for discussions and worked out solutions to the points of disagreement.

Quality Assessment of Included Studies

We have assessed the potential risk of bias that might be found in the included studies using PEDro scale quality assessment tool for RCTs, the PEDro scores for each RCts are in Table 2. The PEDro scale was developed to assess important design features that affect the influence of bias or confounders on trial outcomes. It contains 11 items, with 10 items each scored "Yes" or "No" (item 1 is not scored), where 10/10 is a trial that is very well-conducted to control for bias, while 0/10 has no obvious bias control.

Extraction of the Data

Data from each included study were extracted and listed in Table 3. This process was a teamwork completed by each of the four student researchers, and any disagreements were resolved by discussion between the four researchers. The data extracted contains the details of the patients who participated in the studies, the interventions (experimental and control interventions), and the outcome measures used to report the effectiveness of the interventions.

Data Analysis

This systematic review included a meta-analysis approach using RevMan 5.3 to develop a better understanding of the incorporated interventions. The presence and lack of heterogeneity asserted the use of either random or fixed effect meta-analysis. Otherwise, heterogeneity between the studies was assessed using I^2 statistics. Interpretation of heterogeneity was as; 0%, 25%, 75% as low, moderate, and high heterogeneity, respectively. Forest plots with 95% confidence intervals are reported. Thresholds for interpretation of effect sizes were as follows; a standard mean effect size of 0 means no effect, mean effect size of 0.2 considered a small effect, 0.5 a medium effect, and 0.8 a

large effect. For each trial the effect was plotted by the inverse of its standard error. The significance or alpha level of 0.05 was adopted.

Results

Characteristics of Included Studies

Our initial search yield includes a total of 234 studies, which on fulfilling our eligibility criteria, were reduced to eight as shown in (Appendix 1). Out of the eight included studies, six were randomized controlled trials, one was crossover randomized controlled trial, and one was pilot crossover randomized controlled trial.

Included studies

The included studies provided data on a total of 239 participants (n = 83 females/151 males). Out of the eight included studies, six incorporated mix gender patients, one incorporated only male participants, and one study did not specify the gender of the included participants. Besides, all the included studies provided the age, and the disease duration of participants as a mean value ranged from (61.4 –78.1) and from (3.7-10.5), respectively. Furthermore, Hoehn and Yahr stages of PD patients were provided in seven of the included studies as a mean value ranges from (1.93-3), while one study did not mention the patient's disease stage.

Risk of bias

To reduce the risks of bias, studies scoring ≥4 on PEDro scale were included in the review according to our eligibility criteria. The average PEDro score for the eight included studies was computed to be 6.6 out of 10, indicating good quality of the overall studies. One study scored 4, three scored 6, one scored 7, and three studies scored 8. For publication bias, the funnel plot is unlikely to detect any bias in our review; due to the smaller number of studies included in the review.

Cueing Techniques Versus Non-Cueing Techniques on Gait

Gait parameters were assessed in all the included studies with 239 participants. 1) Speed of gait was measured in 8 studies with 239 participants, 2) step length in 2 studies with 60 participants, 3) cadence in 5 studies with 124 participants, and 4) stride length in 6 studies with 205 participants. Results found a significant medium effect size favoring non-cueing techniques on the speed of gait (MD of 0.68 (95% CI, 0.13, 1.24; P=0.02)) with high heterogeneity (I^2=77%). Results of step length found non-significant small effect size favoring non-cueing techniques (MD of 0.14 (95% CI, -0.39, 0.67; P=0.60)) presented with a low heterogeneity (I^2=0%). Cadence showed non-significant medium effect size favoring non-cueing techniques (MD of 0.50 (95% CI, -0.18, 1.19; P=0.15)) with a moderate heterogeneity (I^2=72%). A significant medium effect size favoring non-cueing technique was found on the stride length (MD of 0.52 (95% CI, 0.00, 1.04; P=0.05)) presented with a moderate heterogeneity (I^2=72%). Functional gait was evaluated in 3 studies with 100 participants using two outcome measures which are TUG and FGA. Functional gait showed non-significant medium effect size favoring cueing techniques (MD of -0.32 (95% CI, -0.77, 0.13; P=0.17)) with a low heterogeneity (I^2=24%). The pooling of statistical data of the outcome of gait revealed that there was a significant medium effect size favoring non-cueing techniques illustrated in Figure 1 (MD of 0.41 (95% CI, 0.14,0.68; P=0.003)) with a moderate heterogeneity (I^2=70%).

Cueing Techniques Versus Non-Cueing Techniques on Balance

The balance was assessed in three trials with a total of 98 participants using several outcome measures: FES, BBS, and LOS. Results of balance illustrated in Figure 2 showed non-significant small effect size favoring cueing techniques (MD of -0.13 (95% CI, -0.52, 0.27; P=0.54)) presented with a low heterogeneity (I^2=0%).

Cueing Techniques Versus Non-Cueing Techniques on Functional Activities

Functional activity was analyzed among four studies with 139 participants using different sections from UPDRS. Results showed a statistically significant large effect size of cueing techniques on functional activities illustrated in Figure 3 (MD of -0.54 (95% CI, -0.86, -0.21; P=0.001)). The heterogeneity test showed an I^2 of 0% which can be interpreted as low heterogeneity.

Cueing Techniques Versus Non-Cueing Techniques on Freezing of Gait

There were no quantitative outcome measures that assessed the freezing of gait in any of the included studies. Therefore, the meta-analysis was not applicable.

Discussion

Summary of Main Findings

The primary objective of this present systematic review and meta-analysis was to develop a current state of knowledge for the effects of cueing techniques on gait, balance, functional activities, and freezing of gait in PD patients when compared to alternative treatments. The included trials compared different cueing techniques to multiple other interventions including treadmill training, conventional over-ground gait training, home walking program, conventional physiotherapy, progressive modular rebalancing system, and stepping in place. The effectiveness of cueing techniques compared to alternative interventions was assessed using clinical outcome measures such as gait parameters, FGA, TUG, BBS, LOS, FES, and UPDRS. In total, results showed a statistically significant difference between the groups in all outcomes except for balance as summarized in (Appendix 3).

The types of cueing techniques were not the same in all the studies. There were three types of cueing used. Five studies used auditory/acoustic cueing techniques applied by

music playlist, headphones, iPod, digital metronome, MP3, and GaitTrainer3 device [21,22,23,24,25]. Three studies used visual cueing provided by colored stripes, white parallel transverse lines placed on the ground, dots or photos, computerized dancing system, and Smart-EquiTest Balance Master [21,17,26]. And one study used proprioceptive cueing provided by vibratory devices [27]. For more explanation, Chaiwanichsiri 2011 has compared auditory cueing to two control interventions, while De Icco 2015 has compared auditory to visual cueing to another control intervention, that is why it was noted in the forest plot as A and B.

In our meta-analysis, the overall results revealed that non-cueing techniques have a significant effect on gait and its parameters when compared to cueing techniques. In a more detailed explanation, both the speed of gait and stride length were significantly affected by non-cueing techniques, while step length and cadence were not significantly affected. The meta-analysis of most of the gait parameters was greatly affected by the result of El-Tamawy study since it has the largest mean difference. In contrast to our gait parameters meta-analysis, a systematic review, that evaluates the effect of external cues on the gait parameters for Parkinson's disease patients, conclude that cues generally led to a statistically significant improvement in the step and stride length, speed of gait, and cadence [28]. Similar to that, another systematic review, aimed to analyze the effects of different auditory feedbacks on gait and postural performance in patients affected by Parkinson's disease, showed different results to ours. Its analysis revealed an overall positive effect on gait velocity, stride length, and a negative effect on cadence with application of auditory cueing [20]. Furthermore, a systematic review, of studies evaluating the effects of external rhythmical cueing on gait in patients with Parkinson's disease, showed strong evidence for improving walking speed with the help of auditory cues, but insufficient evidence was found for the effectiveness of visual and

somatosensory cueing [29]. The functional gait was our last and only sub-outcome that showed non-significant effect favoring cueing techniques. On the other hand, functional gait was investigated by another prospective randomized controlled trial, its results conclude similar findings to ours in the effectiveness of cueing, but it was a significant improvement [30].

Looking at the second review outcome of interest which is the balance, its pooled result appeared to have non-significant effect favoring cueing techniques when compared to non-cueing techniques. A study that compared the effects of partnered and non-partnered dance (applied with external cues) on balance and mobility, supports our result on the effectiveness of cueing techniques on balance but with a significant effect [31]. Similar results to that were reported in another study that compared the effects of tango classes with external auditory cues and exercise classes on gait and balance [32].

With regard to functional activity outcome, its results found to be significantly affected by cueing techniques when compared to non-cueing techniques. Same results were reported by a RESCUE trial that had investigated the effects of a home physiotherapy program based on rhythmical cueing on gait and gait-related activity [33]. Similar results were also interpreted by a randomized crossover trial that aimed to investigate the effects of a home cueing training program on functional walking activity in PD [34]. A systematic review, of studies investigating the effectiveness of external sensory cues in improving functional performance in individuals with Parkinson's disease, reported statistical evidence of an improvement in ADL performance in individuals with PD following the application of external sensory cues, which is a kind of similar results to ours [35].

For the freezing of gait outcome, there were no quantitative outcome measures that evaluated it in any of the included studies, however, it may have affected the measurements of gait.

To sum up, the review findings reported a small-medium effect size of cueing techniques on balance and functional activities which was supported by many pieces of evidence. While for the gait, the meta-analysis found a non-significant medium effect of non-cueing techniques which was different from most of the existing evidence. This conflicted findings may have been affected by the relatively small number of participants joined the included studies, in addition to other review limitations such as not including articles with a language other than English as well as difficulties in accessing full-text articles that may have good control of bias and a robust conclusion regarding the objectives of this review.

There were some limitations of this study. The number of studies that were included was small. This may have resulted from the difficulties in accessing full-text articles and restricting our search to English-language publications only, which suggest that there may be missing studies or indicate the possibility that the available data are biased. Moreover, supporting our results with existing evidence was difficult due to the limited number of studies that discussed the same review topic. However, to reach a high-quality research, authors tried hard to diminish these limitations through searching in Google scholar and the reference lists of the included studies, which helped in coming up with more relevant findings either to be included in the review or used to support the review’s results. Besides, authors have tried to use the locked articles' DOI where permits as another way to obtain full-text articles.

Another limitation, most of the included studies have relatively a small sample size, which may have affected the precision of the review results or led to biased outcomes. Nevertheless, this was controlled by the inverse variance weighting of studies that were used in our meta-analysis.

This review recommends conducting more studies investigating the effectiveness of cueing techniques on freezing of gait. Also, larger randomized controlled trials are required, particularly those focusing on the application of cueing techniques for improving parkinsonian motor symptoms, with big sample sizes and low risk of bias.

Conclusion

This review aimed to investigate up to date knowledge regarding the effect of cueing techniques on PD patients' gait, balance, functional activity, and freezing of gait. According to what we have found, we conclude that applying cueing techniques in clinical practice is valid for the enhancement of PD patients' functional activities and balance. On the other hand, this review did not support its effect on the gait. Therefore, to enhance the effectiveness of cueing techniques, it is preferred to be applied adjunctively to a comprehensive treatment program that may include varied interventions.

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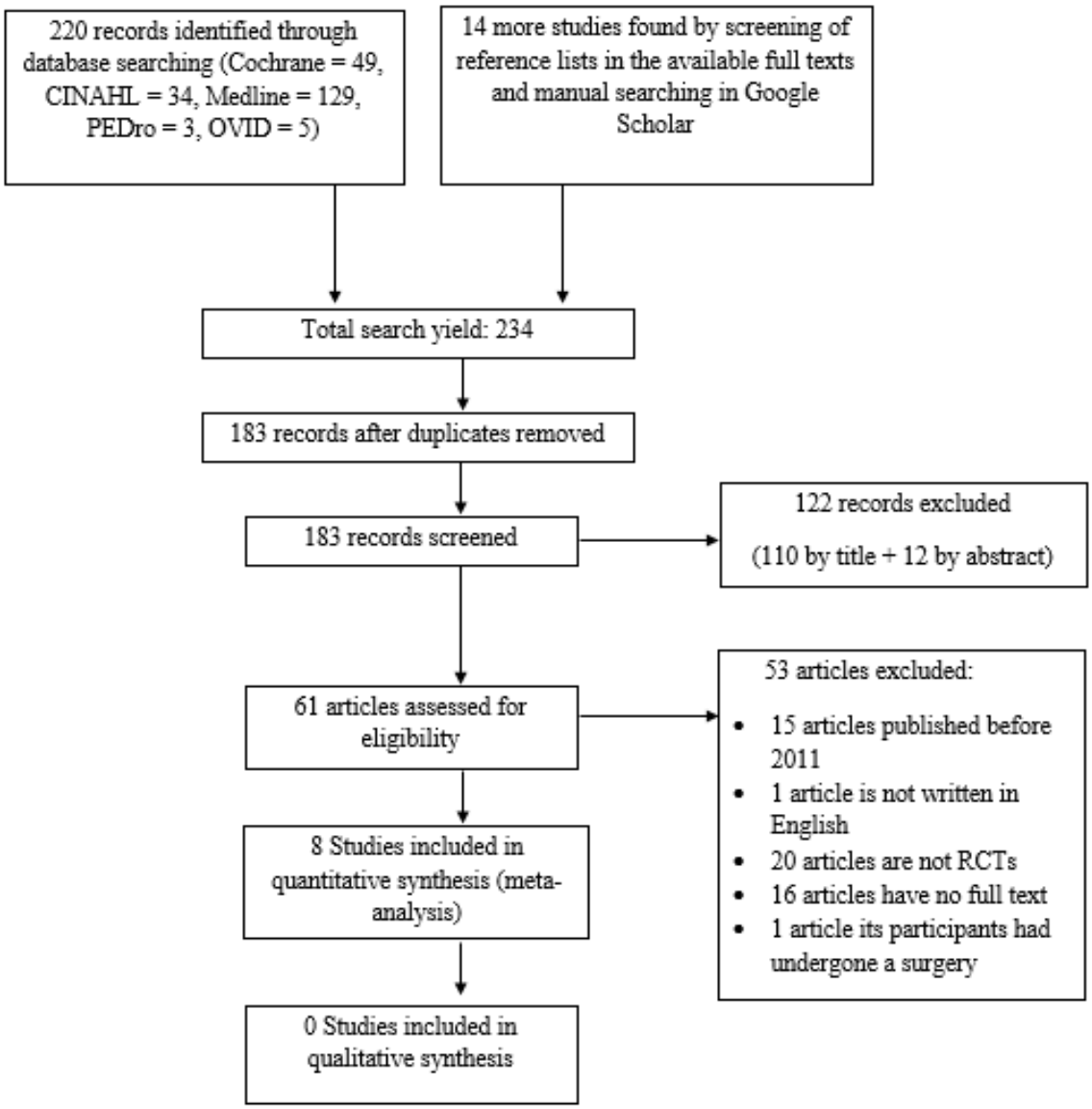
Appendices:

Appendix 1. PRISMA flow chart



Appendix 2. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			Page 1
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			Page 2
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2
INTRODUCTION			Page 3
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 6
METHODS			Page 7
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	This review was conducted towards the fulfilment of a coursework for the Research Methodology course/module. A protocol was developed for this study and reviewed by supervisors and feedback received were considered for the final review. But the protocol was not registered/unpublished.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 8
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 10

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 10
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 24
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	Page 10
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			Page 11
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 11, Page 26
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 28
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			Page 13
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 17
FUNDING			Page 17
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 17

Appendix 3. Meta-Analysis of Outcomes

Outcome/sub-outcome		No. studies	No. of participants	Statistical method	Effect estimate
Gait parameters	Speed of gait	8	239	Std. Mean difference (IV, Random, 95% CI)	MD of 0.68 (95% CI, 0.13,1.24; P=0.02)
	Step length	2	60	Std. Mean difference (IV, Random, 95% CI)	MD of 0.14 (95% CI, -0.39,0.67; P=0.60)
	Cadence	5	124	Std. Mean difference (IV, Random, 95% CI)	MD of 0.50 (95% CI, -0.18,1.19; P=0.15)
	Stride length	6	205	Std. Mean difference (IV, Random, 95% CI)	MD of 0.52 (95% CI, 0.00,1.04; P=0.05)
Functional gait		3	100	Std. Mean difference (IV, Random, 95% CI)	MD of -0.32 (95% CI, -0.77,0.13; P=0.17)
Gait (total result)		8	239	Std. Mean difference (IV, Random, 95% CI)	MD of 0.41 (95% CI, 0.14,0.68; P=0.003)
Balance		3	98	Std. Mean difference (IV, Fixed, 95% CI)	MD of -0.13 (95% CI, -0.52, 0.27; P=0.54)
Functional activities		4	139	Std. Mean difference (IV, Fixed, 95% CI)	MD of -0.54 (95% CI, -0.86, -0.21; P=0.001)

Abbreviations: Std., Standardized; IV, inverse variance; CI, confidence interval; MD, mean difference.

Tables:

Table 1. **Search Strategy Used in Medline**

S1	Parkinson's disease	113,836
S2	Shaking palsy	60,229
S3	S1 OR S2	113,845
S4	Cue*	143,574
S5	Alternative interventions	4,012
S6	Conventional physiotherapy	5,188,891
S7	Treadmill	31,816
S8	S5 OR S6 OR S7	5,215,128
S9	Gait	60,089
S10	Freezing	50,129
S11	Balanc*	11
S12	Functional activities	43,176
S13	S9 OR S10 OR S11 OR S12	151,441
S14	S3 AND S4 AND S8 AND S13	129

Table 2. Summary of Quality Assessment of Included RCTs												
Study	**Item 1[1]**	**Item 2[2]**	**Item 3[3]**	**Item 4[4]**	**Item 5[5]**	**Item 6[6]**	**Item 7[7]**	**Item 8[8]**	**Item 9[9]**	**Item 10[10]**	**Item 11[11]**	**Total score**
Calabrò 2019	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8/10
Chaiwanichsiri 2011	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6/10
Chang 2019	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7/10
De Icco 2015	Yes	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4/10
El-Tamawy 2012	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	7/10
Harro 2014	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6/10
Serrao 2019	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	8/10
Shen 2012	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8/10

[1] Eligibility criteria were specified.

[2] Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received).

[3] Allocation was concealed.

[4] The groups were similar at baseline regarding the most important prognostic indicators.

[5] There was blinding of all subjects.

[6] There was blinding of all therapists who administered the therapy.

[7] There was blinding of all assessors who measured at least one key outcome.

[8] Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups.

[9] All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analyzed by “intention to treat”.

[10] The results of between-group statistical comparisons are reported for at least one key outcome.

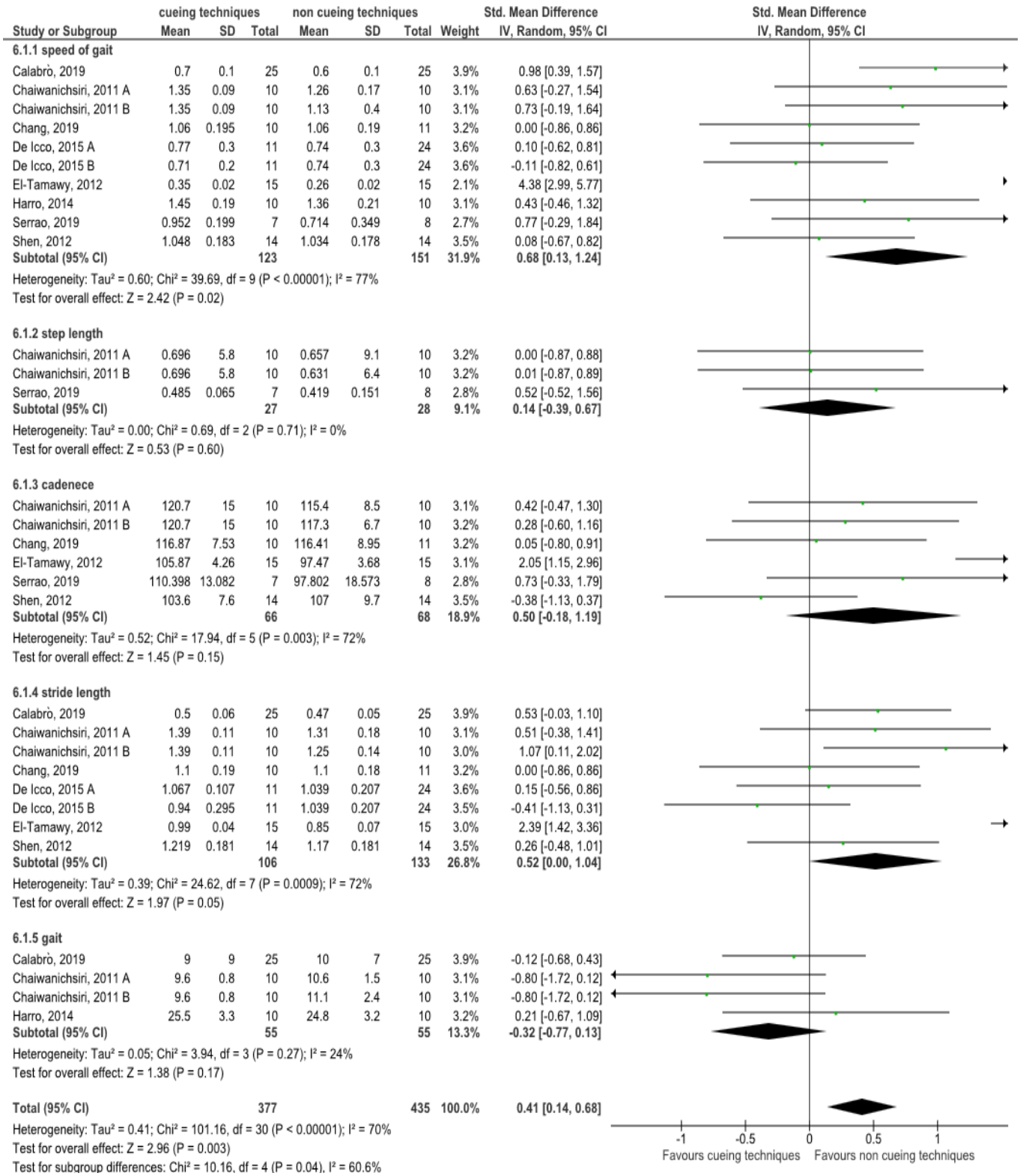
[11] The study provides both point measures and measures of variability for at least one key outcome.

Table 3. Data Extraction from Each Study

Author (Year)	Study design	Samp-le size	Age mean ± SD	Hoehn and Yahr stages of PD (range) mean ± SD	Disease duration mean ± SD	Type of cueing	Control condition	Outcome measures
Calabrò et al. (2019)	RCT (Parallel Group)	25E, 25C	70.0 ± 8.0 73.0 ± 8.0	(2-3) 3.0 ± 1.0	10.0 ± 3.0 9.3 ± 3.0	Auditory	Conventional overground gait training, speech therapy, and biomechanical training	Gait parameters, UPDRS, TUG, FES,
Chaiwani-chsiri et al. (2011) A	RCT (Single-blind)	10E, 10C	67.1 ± 4.0 67.9 ± 6.3	(2-3)	3.7 ± 4.1 7.4 ± 3.4 4.4 ± 2.3	Auditory	Treadmill training and home walking program	Gait parameters, TUG
Chaiwani-chsiri et al. (2011) B	RCT (Single-blind)	10E, 10C	67.1 ± 4.0 68.6 ± 5.2	(2-3)	3.7 ± 4.1 7.4 ± 3.4 4.4 ± 2.3	Auditory	Home walking program	Gait parameters, TUG
Chang et al. (2019)	RCT (Cross-over)	10E, 11C	63.48 ± 6.23	(1-3) 2.14 ± 0.85	7.56 ± 4.12	Auditory	Stepping in place without auditory cues	Gait parameters
De Icco et al. (2015) A	RCT	11E, 24C	78.1 ± 6.1 72.1 ± 7.3	(2-4)	10.0 ± 3.1 9.0 ± 2.4 10.5 ± 5.2	Acoustic	Gait training without cues	Gait parameters, UPDRS
De Icco et al. (2015) B	RCT	11E, 24C	73.2 ± 6.9 72.1 ± 7.3	(2-4)	10.0 ± 3.1 9.0 ± 2.4 10.5 ± 5.2	Visual	Gait training without cues	Gait parameters, UPDRS
El-Tamawy et al. (2012)	RCT (Double-blind)	15E, 15C	61.4 ± 7.28 63.2 ± 5.6	(2-3) 2.8 ± 0.5 2.6 ± 0.4	2.8 ± 0.5 2.6 ± 0.4	Proprio-ceptive	Stretching, functional and balance training	Gait parameters
Harro et al. (2014)	RCT (Single-blind)	10E, 10C	66.10 ± 10.31	(1-3) 1.93 ± 0.57	4.12 ± 2.26	Auditory	Treadmill training	Gait parameters, FGA, BBS
Serrao et al. (2019)	Pilot RCT (Cross-over)	7E, 8C	68.857 ± 8.627 71.158 ± 7.522	(1– 4) 2.9 ± 0.9 2.9 ± 1.2	8.952 ± 4.899 8.536 ± 3.508	Visual	Progressive modular rebalancing system	Gait parameters, UPDRS
Shen & Mak (2012)	RCT	14E, 14C	63.0 ± 8.5 66.5 ± 8.6	(0-5) 2.2 ± 0.5 2.3 ± 0.5	7.1 ± 3.2 5.8 ± 2.2	Visual	Lower limb strength training	Gait parameters, UPDRS-PG, LOS

Abbreviations: SD, Standard Deviation; E, Experimental; C, Control; UPDRS, unified Parkinson's disease rating scale; TUG, time up and go; FES, Tinetti Fall Efficacy Scale; FGA, functional gait assessment; BBS, berg balance scale; UPDRS-PG, unified Parkinson's disease rating scale-posture and gait; LOS, limits of stability test.

Figures:



[Figure 1]

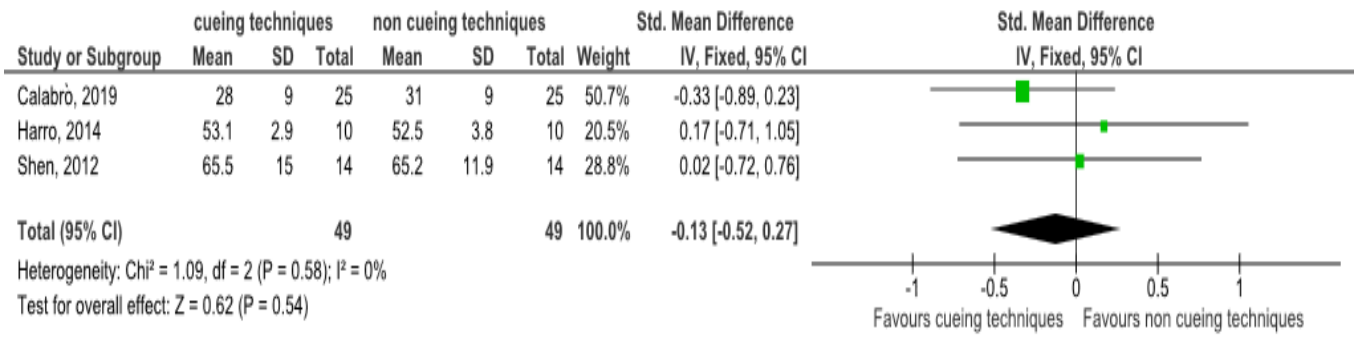


Figure 2

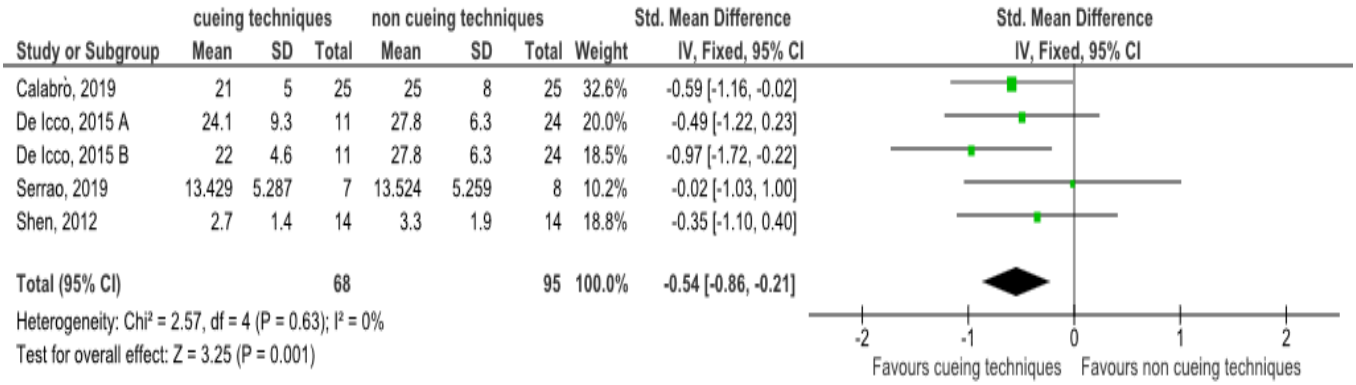


Figure 3

Figure captions:

Figure 1. Gait meta-analysis

Figure 2. Balance meta-analysis

Figure 3. Functional activities meta-analysis