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Review article

One cue does not fit all: A systematic review with meta-analysis of the effectiveness of cueing on freezing of gait in Parkinson's disease

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ABSTRACT

The difficulty in assessing FOG and the variety of existing cues, hamper to determine which cueing modality should be applied and which FOG-related aspect should be targeted to reach personalized treatments for FOG. This systematic review aimed to highlight: i) whether cues could reduce FOG and improve FOG-related gait parameters, ii) which cues are the most effective, iii) whether medication state (ON-OFF) affects cues-related results. Thirty-three repeated measure design studies assessing cueing effectiveness were included and subdivided according to gait tasks (gait initiation, walking, turning) and to the medication state. Main results reveal that: preparatory phase of gait initiation benefit from visual and auditory cues; spatio-temporal parameters (e.g., step and stride length) are improved by visual cues during walking; turning time and step time variability are reduced by applying auditory and visual cues. Some findings on the potential benefits of cueing on FOG and FOG gait-related parameters were found. Questions remain about which are the best behavioral strategies according to FOG features and PD clinical characteristics.

1. Introduction

Freezing Of Gait (FOG), described as a sudden inability to generate effective stepping that might result into falls (Giladi and Nieuwboer, 2008), is one of the most disabling symptoms in Parkinson's disease (PD) patients. FOG is a paroxysmal phenomenon, mostly triggered by motor (e.g., gait initiation) (Cucca et al., 2016), environmental (e.g., doorways) (Bloem et al., 2004), cognitive (e.g., dual-tasking, DT) (Spildooren et al., 2010), and emotional (e.g., fear) factors (Lagravinese et al., 2017; Lagravinese et al., 2017). The typical motor manifestations of FOG are shuffling forward, trembling in place, and complete akinesia (Schaafsma et al., 2003) and the gait circumstances where freezing happens more frequently are gait initiation, turning and, with disease progression, also straight walking (Schaafsma et al., 2003). Indeed, FOG has been associated to continuous gait abnormalities such as increase of cadence, especially during turning (Spildooren et al., 2010), reduction of stride

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amplitude, and increased variability (e.g., step time, stride to stride asymmetry) (Nutt et al., 2011). In addition, it is also known that FOG may be related to the medication state: "OFF-freezing" is more frequent but is not uncommon to see PD patients manifesting "ON-freezing" episodes. Therefore, beyond its definition, FOG is a complex phenomenon, and it is still unclear whether these different manifestations share the same underlying mechanisms (Martens et al., 2018; Mancini et al., 2019).

Pharmacological (e.g., increasing dopaminergic therapy) (Cui and Lewis, 2021) and surgical (e.g., Deep Brain Stimulation of the subthalamic nucleus or pedunculopontine nucleus) (Razmkon et al., 2023) options aimed at improving FOG symptoms do exist, however, it has been reported that none of these interventions is fully effective and fail over time (Cui and Lewis, 2021). Among non-pharmacological interventions, physiotherapy (PT) is crucial for managing FOG symptoms (Kwok et al., 2022). To date, even if results of emerging PT strategies, such as action observation (Pelosin et al., 2018; Agosta et al., 2017), non-invasive brain stimulation combined with gait training (Kim et al., 2019), split-belt and virtual reality treadmill training (Seuthe et al., 2020; Bekkers et al., 2020) seem promising, one of the most applied interventions in the clinical setting are behavioral strategies, such as cueing.

Cues are defined as discrete targets or references that aimed to facilitate and improving motor execution (Ginis et al., 2018). They are typically classified as follows: visual cues (e.g., stripes lines and laser flashes projected on the floor), auditory cues (e.g., metronome, rhythmic music, and verbal instructions), and somatosensory cues (e.g., vibrotactile or tactile feedback). Cueing can be applied in a variety manners, including open-loop (e.g., constant rhythmical stimuli), closed-loop (e.g., intermittent stimuli set on individual's gait pattern), and on-demand (also known as "intelligent cueing", delivered when a specific gait alteration occurs) (Ginis et al., 2018).

So far, the main neurophysiological mechanism attributed to external cueing effectiveness is that cues induce a redirection from more affected neural circuits to spared ones (Redgrave et al., 2010), which means a shift from a habitual to a goal-directed behavior. In this regard, Ginis and co-workers (Ginis et al., 2018) nicely illustrated a framework of three specific mechanisms related to cueing efficacy. The first is that cues may facilitate the focus of attention on gait (executive role), the second is that they can reduce variability and improve spatio-temporal gait parameters, thus walking is less likely to break down (stabilizing role) and the third, related to auditory cues, is that they may enable the coupling of postural control (APAs) and step initiation (preparatory role).

However, although cueing-based training has shown some improvement on FOG, the evidence produced by randomized controlled trials (RCTs) does not support conclusive results for their effectiveness (Cosentino et al., 2020). Thus, it is still challenging to determine which cueing should be used and which type of cues is best according to the patients' needs.

Moreover, the unpredictable nature of FOG makes its evaluation extremely complex, so much that a gold standard measure is still missing. Indeed, the most used tool to assess its severity, NFOGQ, beside not being sufficiently reliable or responsive to detect small effect sizes (ESs) (Hulzinga et al., 2020), does not have cut-offs able to cluster patients according to FOG severity.

Plus, it frequently happens that PD subjects, when observed in the clinical or in laboratory setting, shift their gait from automatic to goal-direct control, and thus FOG is less frequent or even absent. This leads to use FOG-related gait measurements (e.g., spatio-temporal parameters), rather than directly quantify direct FOG parameters (i.e., number of episodes and duration) to assess treatments' effectiveness.

Despite the complexity of FOG, the variety of cueing and delivery methods, and the lack of a standardized and reliable assessment, a systematic review of the studies assessing the immediate (i.e., one single session) effect of external cues provided during the gait tasks (i.e., online) on FOG could help clarify what type of strategies might be best suited to improve freezing symptoms and gait-related problems in PD. This information could be instrumental to move towards a more personalized treatment of FOG.

To this aim, the purposes of this systematic review are (i) to summarize the current evidence by providing an overview of all existing types of cueing and their immediate effectiveness on FOG symptoms and FOG-related gait parameters (i.e., proxy gait parameters), (ii) to understand if there are differences among types and modalities of cueing, and (iii) to elucidate whether medication state (ON-OFF) might affect cues-related results.

2. Methods

2.1. Protocol registration

This systematic review was conducted under the methodological guidance of The Cochrane Handbook for Systematic Reviews of Intervention (JPT and J T, 2022). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used for the manuscript reporting. The protocol was registered into the International Prospective Register of Systematic Reviews – PROSPERO and is publicly available.

(https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019144684).

2.2. Information sources and search strategy

Two independent reviewers (CC, MP) performed an extensive search in MEDLINE, Cochrane Library (CENTRAL), Web of Science, and Scopus to identify eligible studies. Grey literature (Google Scholar) and study registries (Clinicatrial.gov) were also investigated. Each information source was examined from inception to 3rd March 2023. Details of search strategies are reported in the supplementary material (S1_Search string). References of included papers were reviewed to ensure that no relevant studies, unidentified through the electronic database searches, were missing. The search was performed to find English-language articles.

2.3. Eligibility criteria

2.3.1. Inclusion criteria

Experimental studies (both randomized controlled trials and Non-Randomized Studies of therapeutic Interventions, NRSI) (JPT and J T, 2022) assessing the effectiveness of one single session of external cueing in idiopathic PD patients with FOG were eligible. Studies were selected based on the following a priori inclusion criteria: (i) reporting a baseline condition (no cueing) and at least one cueing condition; (ii) focusing on gait-related task aimed at evoking FOG episodes (e.g., turning) under single task (ST) or dual task (DT) conditions; (iii) FOG diagnosis based on widely-recognized methods (Barthel et al., 2016) (S2_FOG assessing); (iv) reporting data on cueing effectiveness on FOG (i.e., number of freezing episodes or FOG duration) and/or on gait parameters (e.g., spatio-temporal).

2.3.2. Exclusion criteria

The exclusion criteria were the following: (i) studies evaluating the effectiveness of physiotherapy or exercise training (> 1 session); (ii) data published as abstracts or conference proceedings.

2.4. Study selection process

Rayyan QCRI online software (Ouzzani et al., 2016) was used to remove duplicates and for the study selection. Two authors (CC, MP) independently screened titles, abstracts, and then full texts. Disagreements were solved by a third reviewer (SM). The selection process is reported in the PRISMA flowchart.

2.5. Data collection process

The following data from included studies were extracted by two independent reviewers (CC, MC) using a planned standardized spreadsheet: i) study aim; ii) cueing types (visual, auditory, somatosensory) and modalities (i.e., how cues are delivered; for example, stripes line or laser cane); iii) sample size; iv) Hoehn & Yahr (H&Y) stage; v) pharmacological condition of participants during the task (i.e., ON and OFF phase, end of dose); vi) likelihood of carry-over effect (i.e., baseline [no cueing] condition included in the randomization); vii) description of the task; viii) outcome measures; ix) main study results; x) gait analysis system used to collect data. In case of missing data, the authors of the studies were contacted a maximum of three times.

2.6. Critical appraisal of included studies

This review included also studies having a within participants repeated measures design. So far, there are no specific tools or checklists to assess the methodological quality of this type of study. However, to correctly interpret the results, the quality of the studies must be examined. Thus, based on the existing and validated checklists (Downs and Black, 1998; Sterne et al., 2019), we developed an ad hoc tool to evaluate both the quality of reporting and the risk of bias. The critical appraisal was conducted by two authors (CC, MC) independently, whereby discrepancies were solved by another moderator (MP). The reporting was assessed via a "YES-NO" table. Risk of Bias section consisted of 4 domains (randomization process, measurement of outcome, missing outcome data, selective reporting) deemed as "low risk of bias" (green), "high risk of bias" (red), or "unclear risk of bias" (yellow). An extensive explanation of the tool and assessment processes is provided in the supplementary materials (S3_Reporting and ROB tool).

2.7. Data synthesis and analysis

Due to the difficulty of eliciting FOG episodes in the laboratory setting, here we also reported, in addition to direct FOG measures (i.e., number of FOG episodes and its duration), FOG-related spatio-temporal parameters, classified as five independent domains (pace, rhythm, variability, asymmetry, and postural control) (Fig. 1). Then, data synthesis was structured as follows. First, the studies were subdivided into three groups (1. Gait initiation 2. Walking 3. Turning) according to the main gait task of each study. If a study assigned to a group reported data related to another group, those data were pooled in the appropriate category. Second, the articles were grouped based on patients' medication state during the experiment (i.e., ON or OFF) (Fig. 2). When at least three studies provided data of a specific outcome measure, a meta-analysis to assess the overall effect of cueing was performed. A subgroup meta-analysis was run in case of studies reporting data related to different types of cueing.

Given the study design of the included articles, several comparisons were extracted from each study (e.g., Study 1: a. No cueing vs. cueing type X; b. No cueing vs. Cueing type Y; c. No cueing vs. cueing type Z).

Due to the variety of procedures used to assess the outcome measures, the standardized mean difference (SMD; Hedges'g) was used, and the pooled effect was determined using a random-effects model. Hedges'g is a variation of Cohen's d that corrects for biases attributed to small sample sizes (Grissom et al., 2005). The ES was expressed as Hedges' g with a 95% Confidence Interval (CI). ES ranges from 0.2 to 0.49 were considered small, from 0.5 to 0.79 were considered moderate, and values > 0.8 or above were considered large (Faraone, 2008). Study heterogeneity was assessed using the Inconsistency test (I^2). I^2 values, indicating heterogeneity, were interpreted as follow: 0–40% - not relevant; 30–60% - moderate; 50–90% - substantial; 75–100% - considerable (JPT and J T, 2022).

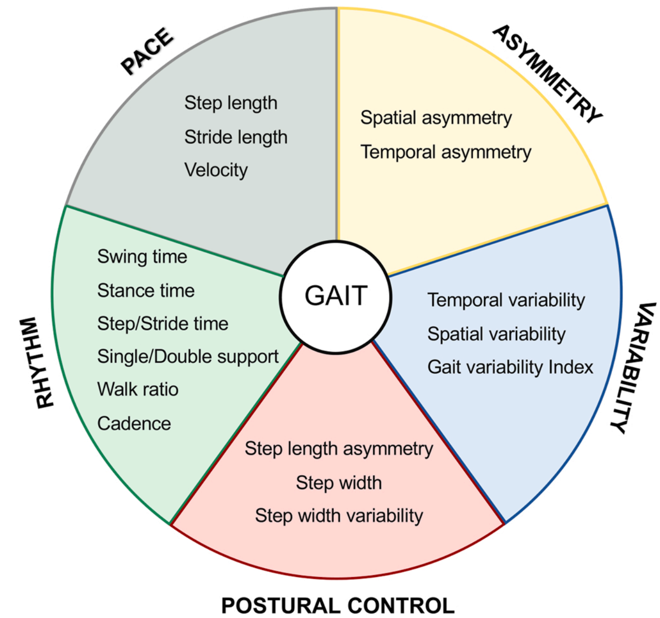


Fig. 1. Gait domain: spatio-temporal parameters classified into five independent domains.

The median was assimilated to the mean, and standard deviation (SD) was calculated considering that interquartile range = 1.35xSD, when data were reported as median and interquartile range. If SDs were not provided, they were calculated from the Standard Error (SE) (SD=SE x $\sqrt{N}$) (JPT and J T, 2022) or the range, assuming that 95% of values were within 2xSD of the mean. In the case of SE and range were not reported, and at least ten studies were included in the MA, the highest SD value of the meta-analysis was imputed. Missing data were extracted from images using WebPlotDigitizer (Drevon et al., 2017), whenever possible. Data were analyzed with Review Manager 5.3 (RevMan) software (Collaboration, 2020).

For the sake of clarity, the studies included in the meta-analyses were reported as follows: first author's surname, publication year, cueing type (capital), - cueing modalities [cues and/or task details] (e.g., (Barthel et al., 2018) VISUAL-laser [shoes]).

3. Results

Our search strategy identified a total of 822 results, of which 371 duplicates were excluded, and 393 studies were rejected after reading titles and abstracts. Full texts of the remaining 58 articles were assessed for eligibility. At the end of the screening phase, 33 studies were included in the systematic review (Fig. 3 and S4_Reasons for exclusion doc).

To the sake of clarity, below, our findings are presented into three Section (1. Gait initiation, 2. Walking, and 3. Turning). Studies overview and narrative results were given first, then, whenever possible, results were presented following this order: FOG-related gait parameters (ON and OFF phase) and then FOG-measures (ON and OFF). Relevant results obtained from the studies not pooled in the meta-analyses were described narratively.

3.1. Gait initiation

3.1.1. Studies overview

Details of the studies are shown in table (S5_Gait initiation studies characteristics). Below, data are reported as mean ± SD. Six studies (Delval et al., 2014; Jiang and Norman, 2006; Lu et al., 2017; McCandless et al., 2016; Schlenstedt et al., 2020; Russo et al., 2022) tested cueing effectiveness during gait initiation with a total of 106 PD

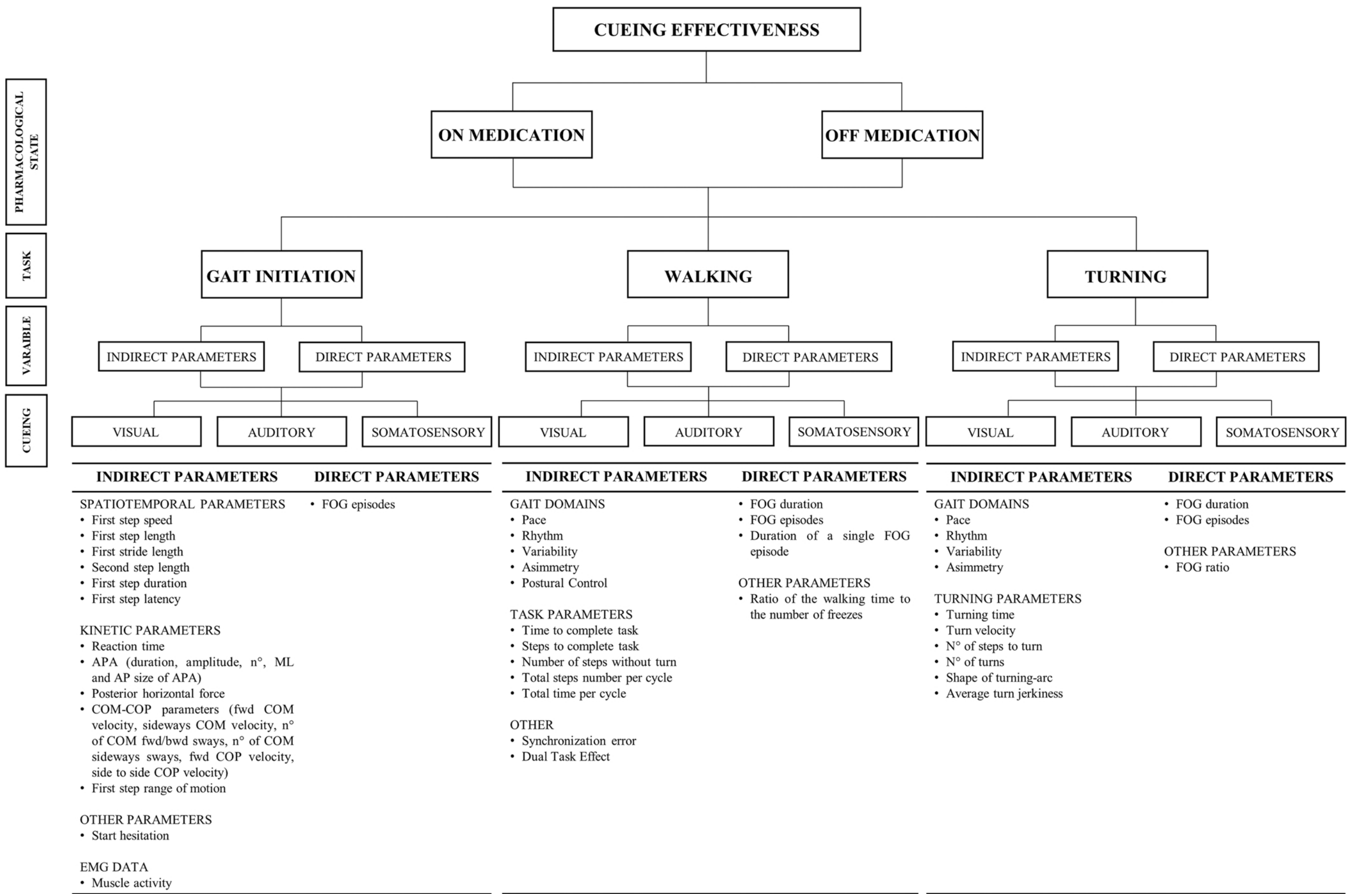


Fig. 2. Methods description: flowchart of data synthesis procedure.

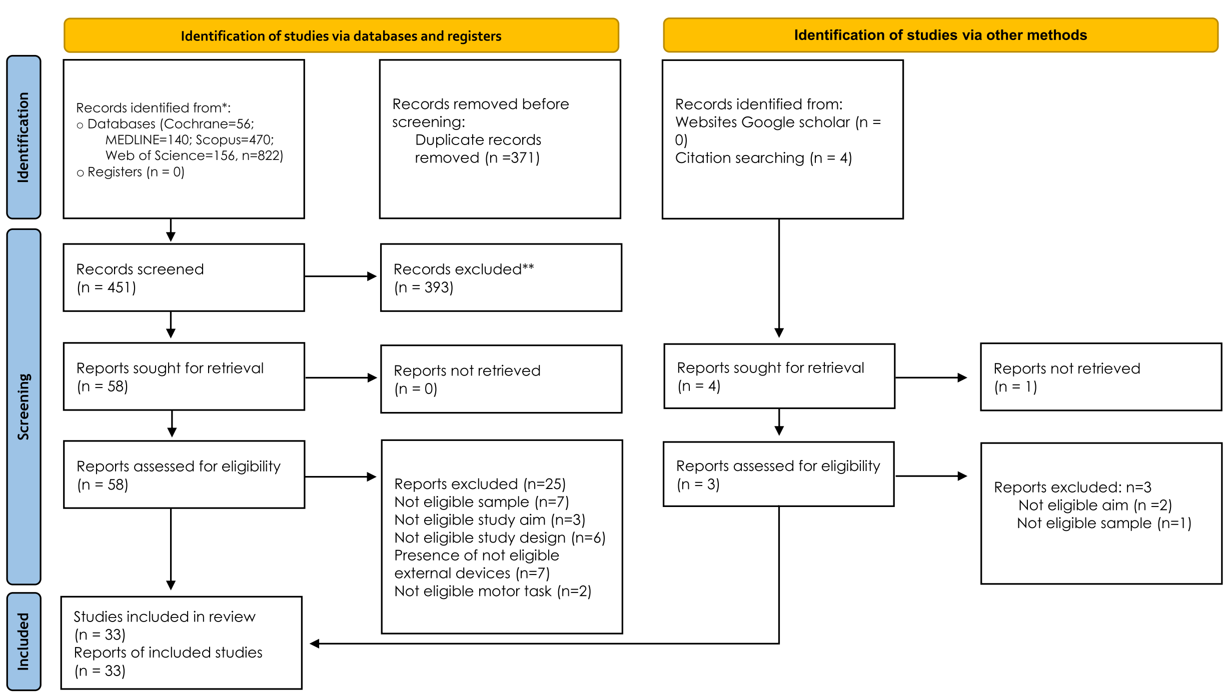


Fig. 3. PRISMA 2020 flowchart describing the results of the search and selection process.

patients with a mean age of 67.0 ± 7.8 years. Men:women ratio, computed on available data, was about 3:2 (67:39), and sample sizes ranged from 7 to 30. Three (Lu et al., 2017; Schlenstedt et al., 2020; Russo et al., 2022) studies assessed FOG severity using NFOGQ (score: 16.7 ± 4.9) and one (Delval et al., 2014) with FOGQ (score:14 ± 3). Disease duration was 9.9 ± 5.1 years, and H&Y scale ranged from II to III. Two out of five studies reported UPDRS-part III (score: 27.9 ± 10.3), whereas two (Schlenstedt et al., 2020; Russo et al., 2022) trials used MDS-UPDRS part III (score: 41.1 ± 6.6). Only one study (Lu et al., 2017) reported Levodopa Equivalent Daily Dose (LEDD, mg: 1059.8 ± 395.8). Four studies evaluated cognitive impairment using the Montreal Cognitive Assessment (MoCA) (Lu et al., 2017; Schlenstedt et al., 2020; Russo et al., 2022) (score: 26.6 ± 2.2) or the Mini-Mental State Examination (MMSE) (Delval et al., 2014) (score: 28 ± 1.5). Three studies (Delval et al., 2014; Jiang and Norman, 2006; Russo et al., 2022) evaluated the effect of cueing in the ON-phase whereas 3 in the OFF-phase.

3.1.2. Narrative results

All the included studies (n.6) evaluated the effect of cueing on the preparation phase (e.g., APA and COM measures), whereas five studies collected data related to the execution phase also (e.g., first and second steps length and duration).

Regarding the preparation phase, all the studies (Jiang and Norman, 2006; Lu et al., 2017; McCandless et al., 2016; Russo et al., 2022) applying visual cues reported significant changes in kinetic data (i.e., APA or COM data or reaction force), regardless of the medication state. Similarly, significant improvements in the anticipatory phase of the first step were reported in three studies (Delval et al., 2014; Lu et al., 2017; McCandless et al., 2016) evaluating the effectiveness of auditory cues in the ON (Delval et al., 2014) and in OFF (Lu et al., 2017; McCandless et al., 2016) phase. Differently from visual and auditory cues, findings for somatosensory cueing were less consistent. Schlenstedt et al. (2020) did not report significant changes in APA-related measures when somatosensory cues were applied, whereas Lu et al. (2017) showed a reduced incidence of incomplete APA but no changes in their amplitude and duration. Similarly, a vibrating metronome at the pelvis (McCandless et al., 2016) increased forward COP velocity significantly, but not the other COM-related parameters.

For the execution phase, five studies (three in the ON (Delval et al., 2014; Jiang and Norman, 2006; Russo et al., 2022) and two in the OFF (McCandless et al., 2016; Schlenstedt et al., 2020) phase) investigated the effect of cueing on the first and second steps (i.e., step length (Delval et al., 2014; Jiang and Norman, 2006) and first step range of motion and duration (Russo et al., 2022)). Data collected in OFF-phase (McCandless et al., 2016) revealed that both visual and somatosensory cues can improve the length of the first and second steps. Positive changes in step duration were also reported when somatosensory cues were applied at the wrists (Schlenstedt et al., 2020). Conversely, auditory cues appeared to be not superior compared to no cues condition. Step length data in ON-phase, were pooled in a meta-analysis and resulted are reported hereafter.

3.1.3. Meta-analysis results

3.1.3.1. FOG-related gait initiation parameters: ON-medication state

3.1.3.1.1. First step length. The meta-analysis was based on data obtained from 2 studies (Delval et al., 2014; Jiang and Norman, 2006), with 37 participants, which enabled three comparisons. Both trials evaluated the effect of auditory cues on step length, and one (Jiang and Norman, 2006) also tested the effect of visual cues (Fig. S9_Panel A). Pooled estimates of the ES showed no significant differences between cueing and no cueing conditions on step length (ES= 0.20 [−0.67, 1.06]; $p = 0.66$). The heterogeneity between the individual trials was substantial ($I^2 = 65\%$ $p = 0.06$), and evidence suggests that the effect of the two types of cueing on first step length differed ($I^2 = 79.1\%$ $p = 0.03$).

Subgroup analysis

To assess the effect of different types of cueing on gait initiation performance, we conducted a subgroup meta-analysis: auditory cueing (2 studies (Delval et al., 2014; Jiang and Norman, 2006), 2 comparisons), and visual cueing (1 study (Jiang and Norman, 2006), 1 comparison). Subgroup's analysis showed no effect of auditory cues whereas visual cueing revealed a trend towards cueing effectiveness (ES auditory= −0.27[−0.73, 0.19], $p = 0.25$, $I^2 = 0\%$; ES visual= 1.12 [−0.04, 2.27], $p = 0.06$).

3.2. Walking

3.2.1. Studies overview

Details of the studies are shown in S6_Walking studies characteristics. Below, data are reported as mean ± SD. Twenty trials (Arias and Cudeiro, 2010; Barthel et al., 2018; Beck et al., 2015; Bryant et al., 2010; Bunting-Perry et al., 2013; Cao et al., 2020; Cubo et al., 2003; Gál et al., 2019; Holmes et al., 2015; Horin et al., 2020; Kompoliti et al., 2000; Lebold and Almeida, 2010; Lee et al., 2012; Rosenthal et al., 2018; Poláková et al., 2020; Sijobert et al., 2017; Willems et al., 2006; Stuart et al., 2021; Zhao et al., 2016; Janssen et al., 2017) assessed cueing effectiveness on FOG exclusively during walking tasks, while one study (Russo et al., 2022), tested the effect of cues during gait initiation and walking. The total sample was 353 PD patients with FOG with an overall mean age of 69.8 ± 7.9 years. Men:women ratio, computed on available data, was about 3:1 (206:63), and sample sizes ranged from 6 to 32. Ten studies measured freezing severity using the FOGQ (Arias and Cudeiro, 2010; Bryant et al., 2010; Bunting-Perry et al., 2013; Gál et al., 2019; Lee et al., 2012; Rosenthal et al., 2018; Poláková et al., 2020; Willems et al., 2006; Stuart et al., 2021; Janssen et al., 2017) (score: 14.3 ± 4.6), and 6 studies used the NFOGQ (Russo et al., 2022; Barthel et al., 2018; Cao et al., 2020; Horin et al., 2020; Zhao et al., 2016; Janssen et al., 2017) (score: 18.8 ± 6.4). Disease duration was 11.2 ± 6.2 years, and H&Y scale ranged from II to IV. Fourteen studies (Beck et al., 2015; Bryant et al., 2010; Bunting-Perry et al., 2013; Cao et al., 2020; Cubo et al., 2003; Holmes et al., 2015; Horin et al., 2020; Kompoliti et al., 2000; Lebold and Almeida, 2010; Lee et al., 2012; Poláková et al., 2020; Willems et al., 2006; Zhao et al., 2016; Janssen et al., 2017) evaluated disease severity (motor examination) with UPDRS part III (score: 31.3 ± 12.1), 5 with the MDS-UPDRS part III (Russo et al., 2022; Barthel et al., 2018; Gál et al., 2019; Sijobert et al., 2017; Stuart et al., 2021) (score: 35.1 ± 11.9), whereas in 2 studies (Arias and Cudeiro, 2010; Rosenthal et al., 2018) data related to disease severity were not reported. LEDD was collected in 38% of the studies (Cubo et al., 2003; Horin et al., 2020; Lebold and Almeida, 2010; Lee et al., 2012; Poláková et al., 2020; Stuart et al., 2021; Zhao et al., 2016; Janssen et al., 2017) (8/21) with a mean of 935.2 ± 523.5 mg. Cognitive status was measured with MMSE (score: 27.8 ± 3.2) in 6 studies (Bunting-Perry et al., 2013; Cao et al., 2020; Horin et al., 2020; Lee et al., 2012; Willems et al., 2006; Janssen et al., 2017) and with MOCA (score: 25.8 ± 2.8) in 6 studies (Russo et al., 2022; Beck et al., 2015; Cao et al., 2020; Gál et al., 2019; Sijobert et al., 2017; Stuart et al., 2021). Also, three studies (Barthel et al., 2018; Zhao et al., 2016; Janssen et al., 2017) tested cognitive abilities with the Frontal Assessment Battery (FAB, score: 15.1 ± 6.9), one (Beck et al., 2015) with the Trail Making Test (TMT, Part A: 51 ± 14.8 s; Part B: 144.8 ± 64), and one (Beck et al., 2015) with the Digit Memory Test (DMT, score Forward: 10.6 ± 2.3; Backward: 5.9 ± 1.5). Finally, twelve studies (Russo et al., 2022; Beck et al., 2015; Bunting-Perry et al., 2013; Cubo et al., 2003; Gál et al., 2019; Holmes et al., 2015; Horin et al., 2020; Kompoliti et al., 2000; Lebold and Almeida, 2010; Rosenthal et al., 2018; Willems et al., 2006; Stuart et al., 2021) evaluated the effect of cueing in the ON-phase, 6 (Arias and Cudeiro, 2010; Cao et al., 2020; Lee et al., 2012; Poláková et al., 2020; Zhao et al., 2016; Janssen et al., 2017) in the OFF-phase and 3 (Barthel et al., 2018; Bryant et al., 2010; Sijobert et al., 2017) in both phases (ON and OFF).

3.2.2. Narrative results

In most of the studies (Russo et al., 2022; Arias and Cudeiro, 2010; Barthel et al., 2018; Beck et al., 2015; Bryant et al., 2010; Cao et al., 2020; Gál et al., 2019; Holmes et al., 2015; Horin et al., 2020; Lebold and Almeida, 2010; Lee et al., 2012; Poláková et al., 2020; Willems et al., 2006; Stuart et al., 2021; Zhao et al., 2016; Janssen et al., 2017) walking performance was measured using various gait analysis systems (e.g., motion analysis, inertial sensors).

Step and stride length, and velocity (domain: pace) were collected in 16 studies (Russo et al., 2022; Arias and Cudeiro, 2010; Barthel et al., 2018; Beck et al., 2015; Bryant et al., 2010; Cao et al., 2020; Gál et al., 2019; Holmes et al., 2015; Horin et al., 2020; Lebold and Almeida, 2010; Lee et al., 2012; Poláková et al., 2020; Willems et al., 2006; Stuart et al., 2021; Zhao et al., 2016; Janssen et al., 2017), and 3 meta-analyses were performed (details are reported below). Also, one meta-analysis was run for step length variability data. Data on other gait parameters (i.e., cadence, double support, step time and its variability) were not pooled because of the different outcome measures reported (e.g., % or sec.), thus results have been described narratively.

Regarding cadence both visual and auditory cues were applied. For visual, three studies showed (Lebold and Almeida, 2010; Lee et al., 2012; Janssen et al., 2017) a significant reduction, compared to no-cueing condition when stripes lines or bars on the floor were applied (Lebold and Almeida, 2010; Lee et al., 2012; Janssen et al., 2017), whereas in four trials (Barthel et al., 2018; Bryant et al., 2010; Cao et al., 2020; Poláková et al., 2020) any significant was detected. For auditory cueing, 3 studies (Arias and Cudeiro, 2010; Willems et al., 2006; Janssen et al., 2017) reported a significant increase in cadence (metronome set a +10% or preferred pace), 1 (Lee et al., 2012) revealed a significant reduction (metronome set from −10% to −20% of usual pace) and 1 (Janssen et al., 2017) did not report any difference between cueing and no-cues condition.

From the included studies, results on double limb support are controversial. Indeed, in ON-phase, three out of four (Barthel et al., 2018; Beck et al., 2015; Lebold and Almeida, 2010; Stuart et al., 2021) showed a significant effect of visual cues (Barthel et al., 2018; Beck et al., 2015; Stuart et al., 2021) (mainly stripes lines). In contrast, no studies in the OFF-phase (Cao et al., 2020; Lee et al., 2012; Poláková et al., 2020) revealed a greater effect of visual stimuli compared to no cueing condition. Finally, no difference on double limb support between cueing and no-cueing was seen when auditory stimuli were used, regardless of the medication state (Lee et al., 2012; Willems et al., 2006).

The effect of visual cues on step time and its variability was investigated in 5 studies (Barthel et al., 2018; Beck et al., 2015; Cao et al., 2020; Lebold and Almeida, 2010; Poláková et al., 2020), while only one trial (Horin et al., 2020) examined auditory cues effectiveness. No studies, except one (Beck et al., 2015), reported changes in step time when visual or auditory cues were applied whereas Horin et al. (2020) reported a significant decrement of gait variability induced by musical stimuli.

Lastly, six studies (Bunting-Perry et al., 2013; Gál et al., 2019; Holmes et al., 2015; Kompoliti et al., 2000; Rosenthal et al., 2018; Sijobert et al., 2017) reported as outcome measures the overall time to complete the task. Four out of six studies (Bunting-Perry et al., 2013; Holmes et al., 2015; Kompoliti et al., 2000; Sijobert et al., 2017) reported no significant change, while the remaining two showed an improvement induced by visual (Gál et al., 2019) and somatosensory (Rosenthal et al., 2018) cues. However, here, it should be noted that results might be influenced by the type of task applied in the experimental protocol.

Finally, the effectiveness of cues on FOG duration and episodes was investigated in a total of 13 studies (Arias and Cudeiro, 2010; Barthel et al., 2018; Beck et al., 2015; Bryant et al., 2010; Bunting-Perry et al., 2013; Cubo et al., 2003; Gál et al., 2019; Kompoliti et al., 2000; Lee et al., 2012; Rosenthal et al., 2018; Sijobert et al., 2017; Zhao et al., 2016; Janssen et al., 2017). Data obtained from most of the studies were inserted in the meta-analyses, and details of the results are given in the following session.

3.2.3. Meta-analysis results

3.2.3.1. FOG-related gait parameters: ON-medication state. Based on data from the included studies, five meta-analyses related to 3 different gait domains (i.e., pace, rhythm, variability) were performed.

3.2.3.1.1. Gait domain: Pace

3.2.3.1.1.1. Effect of cueing on step velocity

Ten studies (Russo et al., 2022; Barthel et al., 2018; Beck et al., 2015; Bryant et al., 2010; Gál et al., 2019; Holmes et al., 2015; Horin et al., 2020; Lebold and Almeida, 2010; Willems et al., 2006; Stuart et al., 2021) with a total of 170 participants were included in this meta-analysis. The overall effect of cues was evaluated by pooling a total of 28 comparisons. The pooled estimate of the ES was not significant (ES= 0.06 [−0.06, 0.18]; p= 0.31), revealing no significant improvements in step velocity induced by cueing compared to no cue condition.

No heterogeneity was found between the individual trials ($p = 1$, $I^2 = 0\%$), nor there was a significant effect between across the subgroups ($p = 0.75$, $I^2 = 0\%$). Results are shown in supplementary materials (S8_Forest plot PANEL B).Subgroup analysis

To assess the effect of each cueing type, the studies were grouped into two main categories: visual cueing (8 studies (Russo et al., 2022; Barthel et al., 2018; Beck et al., 2015; Bryant et al., 2010; Gál et al., 2019; Holmes et al., 2015; Lebold and Almeida, 2010; Stuart et al., 2021), 22 comparisons), and auditory cueing (2 studies (Horin et al., 2020; Willems et al., 2006), 6 comparisons). Subgroup's analysis did not show significant differences between cueing and no cue condition in any type of cueing (ES visual= 0.05 [−0.07, 0.18], $p = 0.41$, $I^2 = 0\%$; ES auditory= 0.11 [−0.22, 0.44], $p = 0.51$, $I^2 = 0\%$).

3.2.3.1.1.2. Effect of cueing on step length

The meta-analysis was based on data obtained from 5 studies (Barthel et al., 2018; Beck et al., 2015; Gál et al., 2019; Holmes et al., 2015; Lebold and Almeida, 2010), with a total of 92 participants. In all, 18 comparisons were computed since all the included studies tested the effect of several visual cue modalities. Results revealed a strong trend towards cueing effectiveness in improving step length as compared to no cueing condition (ES= 0.15 [−0.01, 0.30]; p= 0.06). The level of heterogeneity between the individual trials was not relevant (I^2= 21%, p= 0.20). Subgroup analysis was not performed because all the trials included in this meta-analysis tested the use of visual cueing only (S8_Forest plot PANEL B).

3.2.3.1.1.3. Effect of cueing on stride length

Six studies (Russo et al., 2022; Beck et al., 2015; Bryant et al., 2010; Horin et al., 2020; Willems et al., 2006; Stuart et al., 2021) with a total of 98 participants were included in this meta-analysis (S8_Forest plot PANEL B). The effect of cueing was evaluated by pooling a total of 12 comparisons, and the overall pooled estimate of the ES was in favor of cueing (ES= 0.43 [0.21, 0.65]; p= 0.0001) compared to no cues. Level of heterogeneity across the trials was not relevant (I^2= 0%, p= 0.50), whereas heterogeneity between types of cueing was considerable and significant (I^2= 79.6%, p= 0.03).Subgroup analysis

Based on cueing types, studies were grouped into two main categories: visual cueing (4 studies (Russo et al., 2022; Beck et al., 2015; Bryant et al., 2010; Stuart et al., 2021), 6 comparisons) and auditory cueing (2 studies (Horin et al., 2020; Willems et al., 2006), 6 comparisons). Subgroup's analysis revealed greater improvement in stride length when visual cues were applied (ES= 0.66 [0.36, 0.95]; $p < 0.0001$, $I^2 = 0\%$). No significant differences between cueing and no cue condition were found when auditory stimuli were used (auditory ES= 0.15 [−0.18, 0.49], $p = 0.37$, $I^2 = 0\%$).

3.2.3.1.2. Gait domain: variability

3.2.3.1.2.1. Effect of cueing on step length variability

Two studies (Beck et al., 2015; Lebold and Almeida, 2010) with 35 participants were included in this meta-analysis (S8_Forest plot PANEL B). Both trials evaluated the online effect of visual cues on step length variability using different cues modalities and tasks (e.g., single and dual tasks) and four comparisons were extracted. Statistical analysis did not reveal significant difference between cueing and no cues condition (ES= −0.16 [−0.67, 0.34]; p= 0.52). The heterogeneity between individual trials was moderate but not significant (I^2= 55%, p= 0.09). Subgroup analysis was not performed because all the trials included in this meta-analysis tested visual cueing strategy only.

3.2.3.2. FOG-related gait parameters: OFF-medication state. Data from the included trials, testing the effect of cueing during the OFF-phase, allowed for three meta-analysis on the following gait domains: pace and rhythm.

3.2.3.2.1. Gait domain: pace

3.2.3.2.1.1. Effect of cueing on step velocity

Six studies (Barthel et al., 2018; Bryant et al., 2010; Lee et al., 2012; Poláková et al., 2020; Zhao et al., 2016; Janssen et al., 2017) were included in this meta-analysis, with data from 92 participants (S8_Forest plot PANEL C). In all, 22 comparisons were extracted. Results revealed a trend in favor to no cueing condition (ES= −0.15 [−0.31, 0.01]; p = 0.07). Level of heterogeneity between individual trials was not relevant (I^2 = 0%, p = 0.98), whereas level of heterogeneity between cueing types was moderate but not significant (I^2 = 38.3%, p = 0.20). Subgroup analysis

To assess the effect of each cueing type, the studies were grouped into two main categories: visual cueing (6 studies (Barthel et al., 2018; Bryant et al., 2010; Lee et al., 2012; Poláková et al., 2020; Zhao et al., 2016; Janssen et al., 2017), 16 comparisons) and auditory cueing (3 studies (Lee et al., 2012; Zhao et al., 2016; Janssen et al., 2017), 6 comparisons). Subgroups analysis revealed that auditory cueing did not have any effect on step velocity (ES= 0.02 [−0.29, 0.32]; p = 0.91, I^2 = 0%), whereas visual cueing reported significant results in favor of no cueing condition (ES= −0.21 [−0.40, −0.03]; p = 0.03, I^2 = 0%).

3.2.3.2.1.2. Effect of cueing on stride length

Four studies (Bryant et al., 2010; Lee et al., 2012; Zhao et al., 2016; Janssen et al., 2017) were included in this meta-analysis, with a total of 53 participants (S8_Forest plot PANEL C). The effect of cueing was evaluated by pooling a total of 20 comparisons, and the pooled estimate of the ES did not show a superior effect of cueing (ES= 0.08 [−0.10, 0.25]; p = 0.39). The level of heterogeneity between individual trials was not relevant (I^2 = 0%, p = 0.82), such as level of heterogeneity between subgroups (I^2 = 0%, p = 0.85).Subgroup analysis

Based on cueing types, studies were grouped into two categories: visual cueing (4 studies (Bryant et al., 2010; Lee et al., 2012; Zhao et al., 2016; Janssen et al., 2017), 14 comparisons) and auditory cueing (3 studies (Lee et al., 2012; Zhao et al., 2016; Janssen et al., 2017), 6 comparisons). Statistical analysis revealed that the ES was not significant neither for visual nor for auditory strategies with respect to no cueing condition (ES= 0.06 [−0.14, 0.27]; p = 0.54, I^2 = 0% and ES= 0.10 [−0.21, 0.40]; p = 0.52, I^2 = 0%, respectively).

3.2.3.3. FOG measures: ON-medication state. In all, 8 studies (Barthel et al., 2018; Beck et al., 2015; Bryant et al., 2010; Bunting-Perry et al., 2013; Cubo et al., 2003; Gál et al., 2019; Kompoliti et al., 2000; Rosenthal et al., 2018) investigated the effect of cueing on FOG episodes and FOG duration in ON-medication state and two meta-analyses were performed.

3.2.3.3.1. Effect of cueing on FOG episodes. All studies (Barthel et al., 2018; Beck et al., 2015; Bryant et al., 2010; Bunting-Perry et al., 2013; Cubo et al., 2003; Gál et al., 2019; Kompoliti et al., 2000; Rosenthal et al., 2018) were included in this meta-analysis (S8_Forest plot PANEL B) and the effect of cueing was evaluated by pooling a total of 23 comparisons. The pooled estimate of the ES showed a tendency towards cueing effectiveness (ES= −0.28 [−0.59, 0.03]; p = 0.08). The level of heterogeneity between individual studies was substantial and significant (I^2 = 63%, $p < 0.0001$), whereas the heterogeneity between cueing types was not relevant (I^2 = 9.5%, p = 0.29).

Subgroup analysis

Based on cueing type, studies were grouped into two categories: visual (7 studies (Barthel et al., 2018; Beck et al., 2015; Bryant et al., 2010; Bunting-Perry et al., 2013; Cubo et al., 2003; Gál et al., 2019; Kompoliti et al., 2000), 22 comparisons) and somatosensory cueing (1 study (Rosenthal et al., 2018), 1 comparison). Subgroups analysis revealed that the ES of trials applying both visual (ES= −0.25. [−0.57, 0.06]; p = 0.12, I^2 = 63%) and somatosensory (ES= −0.83 [−1.87, 0.20]; p = 0.11) cueing did not show a significant effect on n° of FOG episodes.

3.2.3.3.2. Effect of cueing on FOG duration. Three trials (Beck et al., 2015; Cubo et al., 2003; Gál et al., 2019), investigating the effect of visual cues on FOG duration, were included in this meta-analysis. Fourteen comparisons were computed because several cue modalities were applied. Pooled estimates of the ES of cueing effectiveness showed no significant results (ES= −0.02 [−0.32, 0.27]; p = 0.87). The level of heterogeneity between individual trials was low (I^2= 0%, p=1.00).

Because all the studies included in this meta-analysis assessed visual cueing only, subgroup analysis was not performed. Results are reported in S8_Forest plot PANEL B.

3.2.3.4. FOG measures: OFF-medication state. In all, five studies (Arias and Cudeiro, 2010; Barthel et al., 2018; Bryant et al., 2010; Lee et al., 2012; Janssen et al., 2017) investigated the effect of cueing in PD patients with FOG during the OFF-medication state. Data extraction allowed to run two meta-analyses and the results are reported below.

3.2.3.4.1. Effect of cueing on FOG episodes. In this meta-analysis 5 studies (Arias and Cudeiro, 2010; Barthel et al., 2018; Bryant et al., 2010; Lee et al., 2012; Janssen et al., 2017) were included and the overall effect of cueing was evaluated by pooling a total of 9 comparisons (S8_Forest plot PANEL C). Results showed no effect of cueing in reducing FOG episodes compared to no cue condition when patients were tested in OFF-medication state (ES= −0.01 [−0.30, 0.29]; p = 0.96). Level of heterogeneity between individual studies was low (I^2 = 28%, p = 0.20) and evidence suggested that cueing effect on FOG episodes did not differ (I^2 = 0%, p = 0.70).

Subgroup analysis

Studies were grouped into two categories based on cueing type: visual (3 studies (Barthel et al., 2018; Bryant et al., 2010; Janssen et al., 2017), 6 comparisons) and auditory cueing (3 studies (Arias and Cudeiro, 2010; Lee et al., 2012; Janssen et al., 2017), 3 comparisons). Subgroups analysis revealed that the ES was not significant neither for visual nor for auditory strategies (ES= 0.03 [−0.33, 0.39]; p = 0.86, I^2 = 26% and ES= −0.11 [−0.73, 0.51]; p = 0.73, I^2 = 51% respectively).

3.2.3.4.2. Effect of cueing on FOG duration. Two studies (Arias and Cudeiro, 2010; Janssen et al., 2017) were included in this meta-analysis and five statistical comparisons were performed (S8_Forest plot PANEL C). Pooled estimates of the ES showed a tendency towards no cueing condition (ES= 0.20 [−0.10, 0.51]; p = 0.19). Both the level of heterogeneity between individual studies and subgroups was not relevant and not significant (I^2 = 2%, p = 0.40; I^2 = 8%, p = 0.30 respectively).

Subgroup analysis

Studies were clustered into two categories based on cueing type: visual cueing (1 study (Janssen et al., 2017), 3 comparisons) and auditory cueing (2 studies (Arias and Cudeiro, 2010; Janssen et al., 2017), 2 comparisons). The ES of visual cueing showed a tendency towards cueing effectiveness (ES= 0.34 [−0.03, 0.71]; p = 0.07, I^2 = 0%). No significant effect was found for auditory cueing effectiveness (ES= −0.14 [−0.96, 0.68]; p = 0.74, I^2 = 55%).

3.3. Turning

3.3.1. Studies overview

Details of the studies are described in S7_Turning studies characteristics. Below, data are reported as mean ± SD. Seven trials (Mancini et al., 2018; Spildooren et al., 2017; Spildooren et al., 2012; Nieuwboer et al., 2009; Tang et al., 2017; Willems et al., 2007; Das et al., 2022) assessed cueing effectiveness on FOG exclusively during turning tasks. Plus, five studies (Arias and Cudeiro, 2010; Bryant et al., 2010; Gál et al., 2019; Holmes et al., 2015; Sijobert et al., 2017), already included in the previous section, reported also data on turning performance. Therefore, 12 studies, with a total sample of 245 PD patients with FOG (age 69.4 ± 9.2 years) were considered. Men:women ratio was about 2:1 (122:71), and sample sizes ranged from 6 to 68. Seven studies (Arias and Cudeiro, 2010; Bryant et al., 2010; Gál et al., 2019; Holmes et al., 2015; Nieuwboer et al., 2009; Willems et al., 2007; Das et al., 2022) assessed FOG severity using FOGQ (score: 14.5 ± 4.7). Disease duration was 10.2 ± 5.9 years, and H&Y scale ranged from II to IV. Four studies (Gál et al., 2019; Sijobert et al., 2017; Mancini et al., 2018; Das et al., 2022) used the MDS-UPDRS part III (score: 29.8 ± 10.8), seven (Bryant et al., 2010; Holmes et al., 2015; Spildooren et al., 2017; Spildooren et al., 2012; Nieuwboer et al., 2009; Tang et al., 2017; Willems et al., 2007) used the UPDRS part III (score: 33.8 ± 11) and only two studies reported LEDD data (Nieuwboer et al., 2009; Das et al., 2022) (748.9 ± 367.5 mg). Four (Gál et al., 2019; Sijobert et al., 2017; Mancini et al., 2018; Das et al., 2022) studies evaluated cognitive impairment using MOCA (score: 25.5 ± 4) and four (Spildooren et al., 2017; Spildooren et al., 2012; Nieuwboer et al., 2009; Willems et al., 2007) studies with the MMSE (score: 27.6 ± 2.3). Six (Gál et al., 2019; Holmes et al., 2015; Nieuwboer et al., 2009; Tang et al., 2017; Willems et al., 2007; Das et al., 2022) out of 12 assessed the effect of cueing in the ON-phase, four trials (Arias and Cudeiro, 2010; Mancini et al., 2018; Spildooren et al., 2017; Spildooren et al., 2012) in the OFF-phase, one in both the ON and OFF phases (Bryant et al., 2010), and one did not report the medication state during which participants were tested (Sijobert et al., 2017).

3.3.2. Narrative results

Turning time was the most used parameter for assessing the effectiveness of cueing. Data obtained from 6 studies (Bryant et al., 2010; Holmes et al., 2015; Sijobert et al., 2017; Nieuwboer et al., 2009; Willems et al., 2007; Das et al., 2022) were combined in a meta-analysis, and results revealed a significant reduction of the time spent on turning when cueing strategies were applied compared to no cue condition (see below). In line with this result, other studies not included in the meta-analysis, also demonstrated a significant decrease in turning time induced by auditory (metronome) (Arias and Cudeiro, 2010) and visual cueing (rhythmic laser) (Tang et al., 2017) both in ON (Tang et al., 2017) and OFF (Arias and Cudeiro, 2010) pharmacological phase.

In ON-phase, the number of steps during the turning task, was measured in 4 studies (Bryant et al., 2010; Gál et al., 2019; Spildooren et al., 2012; Willems et al., 2007). Data from two studies (Bryant et al., 2010; Gál et al., 2019) applying visual cues were pooled in the meta-analysis, but any difference between cueing and no cues conditions was found (details are reported below). Regarding the other two studies, testing auditory cues, the results did not report any improvement (Willems et al., 2007).

Several spatio-temporal gait parameters were also measured (Mancini et al., 2018; Spildooren et al., 2012; Tang et al., 2017; Willems et al., 2007). Briefly, results showed that auditory cues can reduce turn velocity (Mancini et al., 2018) and cadence (Spildooren et al., 2012), whereas no changes were found for step length and step width (Willems et al., 2007). Differently, no substantial change in velocity of 360° turning was detected when visual cues (i.e., taped black lines on the floor in a starred pattern) were applied (Mancini et al., 2018).

Finally, two studies (Mancini et al., 2018; Willems et al., 2007) evaluated other turning-related parameters. Mancini and co-workers (Mancini et al., 2018) showed that both auditory (i.e., speaker set at the participants' preferred frequency) and somatosensory (i.e., phase-dependent foot vibration biofeedback to the wrist) cueing could improve turn jerkiness in the OFF state. Differently, in ON-phase, no significant changes in the shape of turning-arc (Willems et al., 2007) were found when auditory (i.e., fixed preferred frequency) cues were applied.

Regarding the effectiveness of cueing in reducing FOG episodes during turning, two studies (Nieuwboer et al., 2009; Tang et al., 2017) were conducted in the ON, 3 (Mancini et al., 2018; Spildooren et al., 2017; Spildooren et al., 2012) in OFF, and 1 (Bryant et al., 2010) both in ON and OFF medication states. Altogether the results showed a decrease in freezing episodes when cueing were applied. Precisely, in the OFF medication state, all type of cues (auditory: unilateral cue or speaker; visual: green light beam; somatosensory: vibrotactile biofeedback to the wrist) were able to reduce FOG episodes, whereas, in ON-phase, significant improvements were seen when rhythmic laser cues were used.

3.3.3. Meta-analysis results

3.3.3.1. FOG-related gait parameters: ON-medication state

3.3.3.1.1. Gait domain: Rhythm

3.3.3.1.1.1. Effect of cueing on step time

In all, data for a total of 32 participants were included in the meta-analyses, and the effect of cueing was evaluated by pooling a total of 3 comparisons from two studies (Tang et al., 2017; Willems et al., 2007) (S8_Forest plot PANEL D). Pooled estimate of the ES was not significant (ES= 0.51 [−0.15, 1.17]; p= 0.13) showing no difference between cueing and no cueing conditions. Levels of heterogeneity between individual studies (I^2= 63%, p= 0.07) and across the two types of cues (I^2= 62.8%, p= 0.10) were substantial but not significant.Subgroup analysis

To assess the effect of different types of cueing we conducted a subgroup meta-analysis: visual cueing (1 study (Tang et al., 2017), 2 comparisons), and auditory cueing (1 study (Willems et al., 2007), 1 comparison).

Statistical analysis showed a significant effect of visual cueing (laser) (ES= 0.75 [0.11, 1.39]; p = 0.02, I^2 = 55%), whereas any difference was detected for auditory cueing (ES= −0.19 [−1.12, 0.74]; p = 0.69).

3.3.3.1.2. Gait domain: variability

3.3.3.1.2.1. Effect of cueing on step time variability

The same studies (and comparisons) were pooled to assess cueing effectiveness on step time variability (S8_Forest plot PANEL D). Results were in favor of cueing effectiveness (ES= −0.59 [−1.05, −0.13]; p= 0.01). The level of heterogeneity between individual studies was moderate (I^2= 27%, p= 0.25). Results showed also no difference between the two types cueing effectiveness (I^2= 0%, p= 0.86).Subgroup analysis

The ES was not significant neither for visual nor for auditory strategies (ES= −0.62 [−1.31, 0.08]; p = 0.08, I^2 = 63% and ES= −0.51 [−1.46, 0.43]; p = 0.29).

3.3.3.1.3. Turning parameters

3.3.3.1.3.1. Effect of cueing on turning time

This meta-analysis was based on 12 comparisons obtained from data of 6 trials (Bryant et al., 2010; Holmes et al., 2015; Sijobert et al., 2017; Nieuwboer et al., 2009; Willems et al., 2007; Das et al., 2022), with a total of 112 participants (S8_Forest plot PANEL D). Pooled estimates of the ES showed a greater effect of cueing compared to not cue condition in reducing turning time (ES= −0.23 [−0.40, −0.06]; p= 0.008). The level of heterogeneity was low between the individual trials (I^2= 0%, p=0.99) and across types of cueing (I^2 = 0%, p= 0.70).Subgroup analysis

Based on cueing types, studies were grouped into three main categories: visual (4 studies (Bryant et al., 2010; Holmes et al., 2015; Nieuwboer et al., 2009; Das et al., 2022), 8 comparisons), auditory (2 studies (Nieuwboer et al., 2009; Willems et al., 2007), 2 comparisons), and somatosensory (2 studies (Sijobert et al., 2017; Nieuwboer et al., 2009), 2 comparisons). Subgroup's analysis revealed a trend towards effectiveness for auditory and somatosensory cueing (auditory ES= −0.31[−0.64, 0.03], $p = 0.07$, $I^2 = 0\%$; somatosensory ES= −0.29 [−0.63, 0.04], $p = 0.09$, $I^2 = 0\%$), whereas no effect was found when visual strategies were applied (ES= −0.16 [−0.40, 0.09], $p = 0.21$, $I^2 = 0\%$).

3.3.3.1.3.2. Effect of cueing on number of steps

This meta-analysis was based on 12 comparisons obtained from 2 studies (Bryant et al., 2010; Gál et al., 2019), with a total of 38 participants. Pooled estimates of the ES showed no significant results for cueing effectiveness (ES= −0.03 [−0.18, 0.12]; p= 0.70). Level of heterogeneity between studies was not relevant (I^2= 0%, p= 0.96). Subgroup analysis was not performed because all the included studies used visual cueing strategy. Results are reported in the supplementary materials (S8_Forest plot PANEL D).

3.4. Critical appraisal

3.4.1. Reporting

Results are reported in Fig. 5. The aim was clearly described in most of the studies, except for three (Delval et al., 2014; Barthel et al., 2018; Sijobert et al., 2017). In contrast, participants' demographics and clinical information were poorly described in about 61% of the studies. Moreover, in those studies where clinical characteristics were more detailed, a large heterogeneity among participants (e.g., disease duration, FOG severity) was often present. Concerning pharmacological treatment, all but one study (Sijobert et al., 2017) indicated the medication state (ON-OFF phase) during which cueing effectiveness was assessed. However, the Levodopa Equivalent Daily Dose (LEDD) was missing in about 58% of the cases. Details of the experimental tasks and cueing modalities were clearly described in all included studies.

3.4.2. Risk of bias

The risk of bias summary is reported in Fig. 5. None of the studies had a low risk of bias for all the methodological items. Therefore, the quality of the included studies was poor. The 45% of the studies had a high risk of bias for the randomization, because the inclusion of the OFF medication state in the randomization process could have led to a carry-over effect. Most of the included studies (22/33) had a low risk of bias for outcome measures. Regarding the outcome data domain, three studies (Bryant et al., 2010; Spildooren et al., 2017; Spildooren et al., 2012) did not report the necessary information to evaluate the risk of bias, whereas 8 (Arias and Cudeiro, 2010; Cao et al., 2020; Kompoliti et al., 2000; Lebold and Almeida, 2010; Lee et al., 2012; Sijobert et al., 2017; Zhao et al., 2016; Das et al., 2022) out of the remaining 33 had a high risk of bias.

The selective reporting bias was unclear for most of the included studies due to the absence of a registered study protocol (27/33). In the remaining six, the risk was judged as high because of inconsistencies between the material & methods and the results section. Details of the results for each included study are reported in the Supplementary Material (S11_Risk of bias graph).

4. Discussion

This systematic review with meta-analysis aimed to summarize and analyze the results of studies assessing the online effectiveness of single session adopting external cues on FOG and FOG-related gait parameters in PD subjects. Precisely, we were interested in answering the following three questions. First, to determine whether one session of online cueing can reduce FOG symptoms and improve gait performance during usual walking or during well-known FOG-provoking circumstances (e.g., gait initiation, turning, narrow passages). Second, to identify which – if any – of cueing strategies is the most effective in PD patients with FOG. Third, if cueing effectiveness is influenced by medication state (ON and OFF). These research questions were addressed in three primary gait tasks (i.e., gait initiation, walking, and turning).

In all, a total of 607 PD participants with FOG from 33 studies were included in the systematic review. Relevant results obtained from the studies not pooled in the meta-analyses were described narratively, and whenever possible, subgroup meta-analyses were run to assess the effectiveness of cueing type on each outcome measure (Fig. 4).

4.1. Gait initiation

Gait initiation, frequently defective in PD patients with FOG, is characterized by two distinct phases: (1) the preparatory phase, which precedes the initiation of stepping, and (2) the execution phase, which propels the body in the intended direction (Rogers et al., 2011; Rosin et al., 1997).

In all, five studies (Delval et al., 2014; Jiang and Norman, 2006; Lu et al., 2017; McCandless et al., 2016; Schlenstedt et al., 2020), with a total of 86 participants, were included in this analysis. Motion capture systems or force platforms were used to measure gait initiation performance, and various spatio-temporal and kinetic parameters were collected.

Concerning the preparatory phase of gait initiation, all the included studies tested the effect of cueing on postural control (e.g., APA and COM measures). Due to the variety of the outcome measures collected, data were not pooled into a meta-analysis, but some findings are worth commenting on. For auditory cueing, all the studies, except one (Jiang and Norman, 2006), showed significant improvements in postural control in freezers, regardless of participants' medication state. Delval et al. (Barthel et al., 2018) showed that an external triggered condition, which consisted in taking a step forward as soon as possible after hearing the sound signal, resulted in a quicker release of lower-amplitude APAs. Likewise, in the OFF-phase, Lu et colleagues (Lu et al., 2017) demonstrated that auditory cues significantly reduced the incidence of incomplete APAs. These effects were greater using predictable timing (i.e., a fixed delay or countdown strategies) with respect to random auditory cues. However, these latter results referred to all PD participants, and no specific analysis was conducted in the cohort of freezers. Similar findings were also reported by McCandless et al. (McCandless et al., 2016) showing that COM velocity and sways were improved by fixed auditory signals (from 50 to 70 bpm metronome).

Significant improvements in the preparation phase were also reported when visual cues were applied. In this case, most of the studies were conducted in OFF condition (Lu et al., 2017; McCandless et al., 2016), and only one (Jiang and Norman, 2006) in ON medication state in a small cohort of freezers (n = 7 participants), therefore it is difficult to determine whether the pharmacological treatment could somehow affect cueing effectiveness. Differently, results from somatosensory cues were not consistent. Two of the three studies showed that vibrotactile tools could improve some APA and COM parameters. Finally, no changes in the preparation phase were seen when tactile vibration was applied at the participants' wrist (Schlenstedt et al., 2020).

Taken together, our results support the hypothesis that cues, and principally auditory stimuli might facilitate the selection and the sequence of the motor output necessary to generate proper APAs during gait initiation. Precisely, temporal cueing could address the defective automatic coupling of postural control and stepping that is regulated by the brainstem postural and locomotor centers (Nonnekes et al., 2014; Nieuwboer et al., 2007) and is considered one of the causal factors of gait initiation difficulties in PD.

Related to the execution phase, data extraction allowed us to run one meta-analysis (in ON-phase) concerning the effect of cueing on step length. The pooled data did not reveal a greater effect of cues compared to no cue condition. However, it should be noted that only two studies (Delval et al., 2014; Jiang and Norman, 2006) (for a total of three comparisons) were included in the meta-analysis and results were different depending on the type of cues applied (i.e., visual, and

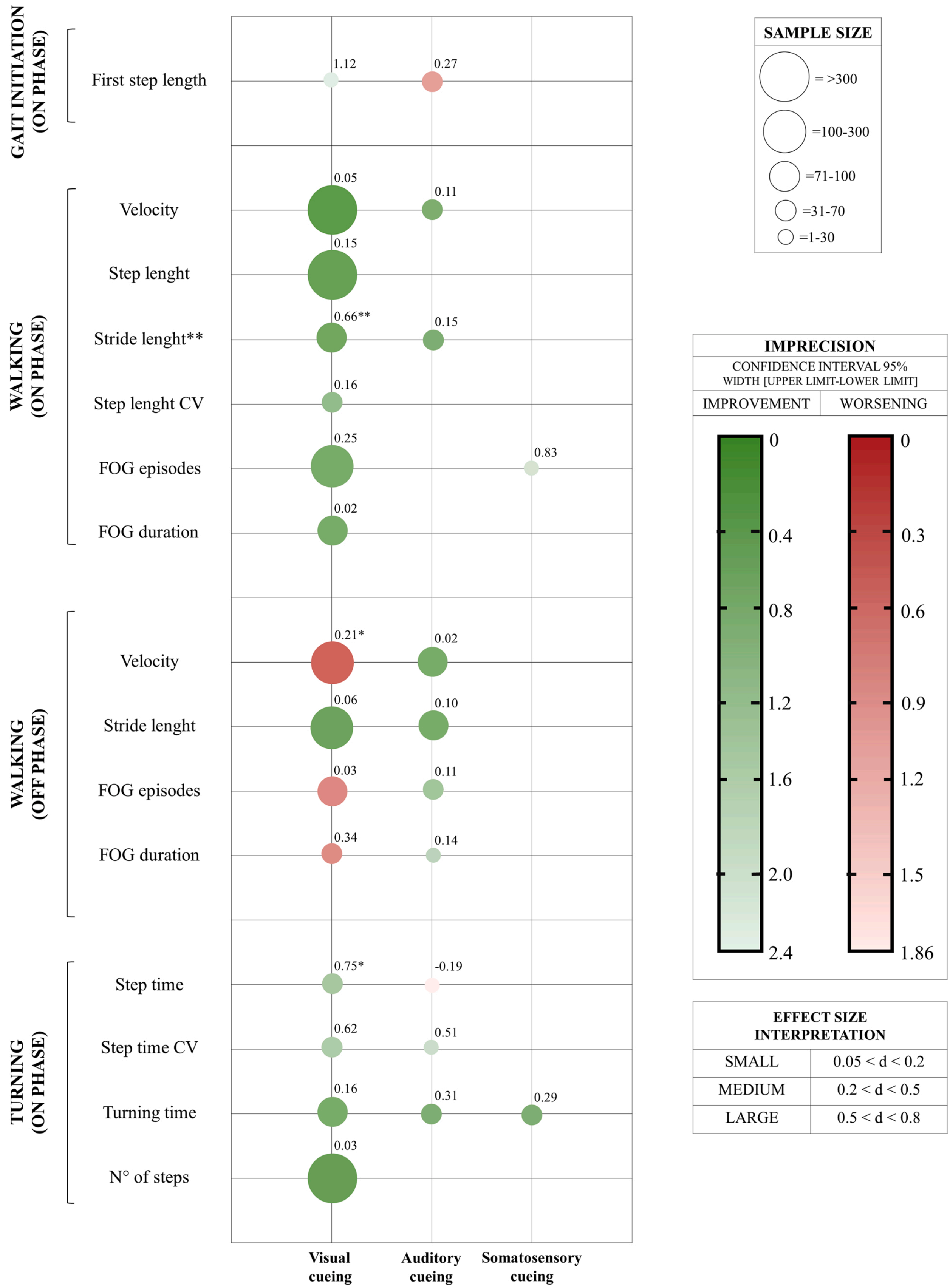


Fig. 4. Bubble plot. This graph depicts all the ES; grouped by cueing type; obtained by pooling available data for each outcome measure. The ES is illustrated above the bubble. Bubble size correspond to sample size. The color gradient represents the imprecision: the more is dark the more the CI is small. Green bubble shows ES in which cueing effect improves the parameter. Red bubble shows ES in which cueing effect decreases the parameter. Significant forest plot and significant ES were expressed with * when $p < 0.05$ and with * * when $p < 0.001$. The last box plot explains how to interpret Cohen's *d* effect size.

REPORTING

	GAIT INITIATION						WALKING																				TURNING						
	Delval, 2014	Jiang, 2006	Lu, 2017	McCandless, 2016	Russo et al., 2022	Schlenstedt, 2020	Arias, 2010	Barthel, 2018	Beck, 2015	Bryant, 2010	Bunting-Perry, 2013	Cao, 2020	Cubo, 2003	Gal, 2019	Holmes, 2015	Horin, 2020	Janssen, 2017	Kompoliti, 2000	Lebold, 2000	Lee, 2012	Polakova, 2020	Rosenthal, 2018	Sijobert, 2017	Stuart, 2021	Willems, 2006	Zhao, 2016	Das et al., 2022	Mancini, 2018	Nieuwboer, 2009	Spildooren, 2012	Spildoreen, 2017	Tang, 2007	Willems, 2006
Study Objective	NO	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Clinical and demographics characteristics	NO	NO	NO	NO	YES	YES	NO	NO	NO	NO	YES	YES	NO	YES	NO	YES	YES	NO	NO	YES	NO	NO	NO	YES	YES	NO	YES	NO	YES	NO	NO	NO	YES
Pharmacotherapy: LEDD	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	NO	NO	YES	NO	YES	YES	NO	YES	NO	NO	NO	NO
Pharmacotherapy: ON-OFF phase	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Cueing modalities description	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Motor task description	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
Outcomes measures	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES

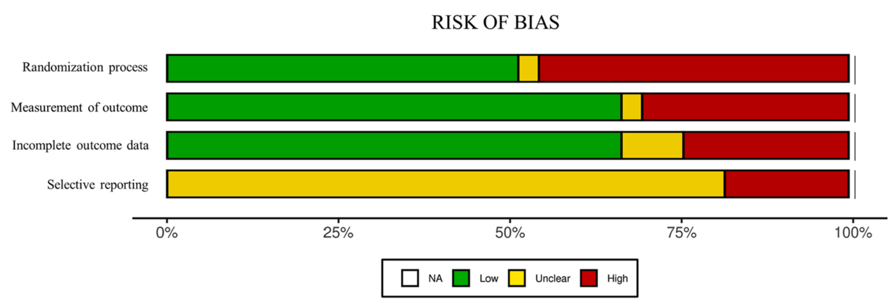


Fig. 5. Risk of bias summary: weighted bar plots of the distribution of risk of bias judgements within each bias domain. Table of reporting quality: authors judgement about each reporting item for each included study.

auditory). Indeed, auditory cues were not effective in improving step length, whereas data from one study (Jiang and Norman, 2006) showed that visual cue (stripes lines) significantly increased the length of the first step.

The poor effectiveness of auditory cueing on step length is not surprising. Indeed, previous studies demonstrated that training based on auditory stimuli could improve more temporal parameters of gait (e.g., gait speed) rather than other gait features (Ghai et al., 2018). Regarding visual cues, the positive results reported by Jiang and Norman (2006) in ON medication state were also confirmed by a study conducted in OFF medication state (McCandless et al., 2016). Indeed, McCandless et al. (2016), showed that somatosensory and visual cues were able to improve the first step length, but only visual stimuli increased the length of the second step, in the OFF medication state.

A general positive effect of visual external stimuli on pace parameters (i.e., step length) in PD is widely described in scientific literature and our results are in line with this finding. However, most of the previous evidence emerges from studies evaluating usual or complex walking rather than gait initiation tasks (Nieuwboer et al., 2007). This because studies assessing cueing effect on gait initiation usually collect outcome measures related to postural control (e.g., APA or sway area). Moreover, in a recent paper (Russo et al., 2022) no changes in step length were reported when visual cues were applied during a gait initiation task. As suggested by the authors, a possible explanation of this result might be related to the distance set for the visual stimuli. Indeed, significant changes in first step length were found when the visual cues were placed at the 100% of the participants' step length (Jiang and Norman, 2006): subjects with PD were able to exceed the cue so as to increase their step length. In contrast, when visual stimuli were set above the usual step size (about 120%), the results showed that PD subjects were more focused on controlling balance and avoiding a marked forward movement, thus performing the first step before the first line of tape (Russo et al., 2022). Therefore, although some positive results on visual cues have been described, available data are not sufficient to clarify whether the execution phase (i.e., first step) can be improved by external stimuli, and further studies are required to clarify this hypothesis.

Finally, it should be noticed that only one study (McCandless et al., 2016) reported the effect of cueing in a gait initiation task on direct measure of FOG. McCandless et al. (2016), showed that visual cues had a greater effect compared to auditory and somatosensory stimuli in reducing FOG. However freezing episodes were seen during the task only in 12 out of 20 participants.

The lack of direct FOG measures in the included studies could be explained in two ways. First, PD patients, to accomplish the required task, might have switched from habitual to goal-oriented behavior, thus decreasing the likelihood of FOG occurring, regardless of whether the stimuli were provided. Alternatively, the use of cueing per se, might have reduced the episodes of freezing, by enabling motor or cognitive response generation (executive role).

Gait initiation: Take home messages

Cueing effect on FOG and on kinetic and spatio-temporal parameters

- FOG severity (i.e., episodes and duration) has been insufficiently assessed, so the effectiveness of cueing on improving freezing cannot be yet determined.
- Preparation (e.g., APA and COM) and execution (step length) phases appear to be improved by specific cues strategies

Cueing type effectiveness

- Visual cueing seems to improve the preparatory phase and the execution phase (i.e., first step length) when visual stimuli are set about 100% of the usual length of each participant.
- Auditory cueing (i.e., "go" signals, and rhythmical stimuli) shows to impact on preparatory phase (APA and COM).
- Somatosensory cueing could improve the preparation phase, however results are weaker and sometimes controversial.

Influence of medication state on cueing effectiveness

- Available data did not allow determining if and how medication state could affect cueing effectiveness.

4.2. *Walking*

Data from 21 studies, with a total of 353 PD participants with FOG, allowed us to run a total of 12 meta-analyses. As reported in the results section, several analyses (n = 7) did not show differences between cues and no cues conditions, whereas the rest (n = 2) were in favor of cueing or revealed a trend toward significancy (n = 3). The general lack of significant findings was far from our expectation. However, by inspecting results of the meta-analyses, it emerged a substantial variety among tasks (e.g., single, or dual task) and cueing modalities (e.g., metronome set at +20% or −20% of gait speed) used in the included studies. Thus, in our opinion, to interpret these findings correctly, it is important being aware of the results emerging from individual studies along with the overall effect.

The effect of cueing on spatio-temporal parameters during gait was assessed in 6 meta-analyses, (4 from studies in ON-phase, 2 in OFF-phase) related to two gait domains (i.e., pace and variability).

Regarding gait parameters of the pace domain, a significant effect size was found only for stride length data when cues were applied in the ON medication state, and subgroup analysis showed that visual cues (mostly stripes lines) were more effective compared to auditory cues. Also, our results revealed a strong trend (p = 0.06) in favor to cues strategies for step length data, whereas no effect was found for velocity. It is noteworthy to note that we did not find effectiveness of visual cues on stride length in the OFF-phase. However, this result should be interpreted with caution, since it might have been driven by the nature of the task rather than by the OFF medication state. Indeed, it was when freezers in the OFF-state were asked to use visual cues in walking paths more complex than usual walking (e.g., narrow turn or doorway) that step length increased more in the no cueing with respect to cueing condition. Conversely, when freezers in the OFF state were asked to walk straight following a laser light on the floor (i.e., laser cane) step length increased. Thus, further studies aimed at investigating whether cueing effectiveness on step length is influenced by the pharmacological treatment are needed.

As general effect on gait, external cueing, rather than enhancing attention per se, may generate proper amplitude (visual) and timing (auditory) of steps, thus decreasing the likelihood that gait would break down. Specifically, in PD subjects, visual cues act by increasing and normalizing steps length, thus improving gait performance (Ginis et al., 2018). In freezers, the underlying mechanism of visual cues effectiveness has often been linked to the "sequence effect" phenomenon, that refers to the decrement in amplitude and speed of steps during walking (Tinaz et al., 2016). This is because reducing step-to-step amplitude and increasing step frequency are factors that often trigger freezing episodes. Therefore, external cues may act making the sequence effect less significant thus reducing the chance of freezing episodes to occur (Cao et al., 2020).

The lack of meaningful difference between visual cues and no-cueing condition on velocity, both in the ON and the OFF medication state, is not surprising since visual cues, the most frequent cues adopted in the studies we reported, are able to supply spatial information for correcting amplitude generation during gait (Spaulding et al., 2013). Backwards, the lack of improvements induced by auditory cues was not expected. Indeed, results from rehabilitative studies (Ghai et al., 2018), showed improvements on gait speed when auditory stimuli were applied, supporting the idea that these types of cues might compensate a defective "internal clock", switching gait control from the defective automatic control to the preserved goal directed control. Furthermore, by carefully inspecting the studies included in this sub-analysis, it emerges that the results are often controversial. As an example, Willems et al. (Willems et al., 2006), reported a significant increase in gait velocity in the ON-phase, when the rhythmical stimuli were set at a higher rate than of subjects' usual speed. Vice versa, when the metronome was set at − 10% or − 20% of participants' usual pace, velocity improved more when no cues were provided. Therefore, the overall results suggest that to improve gait speed, by using auditory cues, it is crucial to set a proper rhythm; otherwise, they would lose their therapeutic effect.

Related to the other domains (i.e., rhythm and variability), the effect of cueing on spatio-temporal parameters (i.e., cadence, double support, step time and its variability) were not pooled due to the different methods used to assess the data or to the impossibility to compare the studies' results. A parameter that in our opinion is worthy to be commented on is the one related to cadence.

First, we must say that although several studies (n = 12) reported data on cadence any meta-analysis was run. This is because it is not possible to determine a priori what changes are indicative of improved cadence. Cadence is a spatio-temporal parameter strictly related to step length and velocity. Thus, to ascertain any improvement, changes in cadence have to be linked with those for the other gait parameters. Indeed, in PD patients with severe freezing, who exhibit a gait pattern characterized by short steps with a high frequency, a cues-induced decrement of cadence, along with an increase of step length, should be considered an improvement. In contrast, a reduction of cadence in freezers manifesting a "bradykinetic gait pattern" with slow speed and reduced step length should be interpreted as a decline of gait performance. This issue may explain why the results of single studies here included were quite heterogeneous and, as reported from previous evidence, results of cueing on cadence are still challenged. Therefore, for both cadence and the spatio-temporal data not pooled in the meta-analysis (i.e., double support, step time and its variability) the results are still inconclusive, and drawing conclusions is premature.

Concerning direct FOG parameters (i.e., n° of FOG episodes and its duration), a total of 4 meta-analyses were conducted (2 in ON and 2 in OFF-phase) but any significant results emerged. This finding might have several explanations. First, capturing freezing in the laboratory is known to be difficult. Indeed, freezing episodes are often triggered by specific circumstances, such as gait initiation, turning, narrow passages, or dual tasking, rather than straight walking in wide space (e.g., gait lab). Therefore, to test the effectiveness of cueing strategies on freezing during straight ahead gait is demanding. Second, also cognitive or emotional status of participants might exacerbate (e.g., talking while walking or anxiety) or lighten (e.g., attention) freezing symptoms. In this case, as previously reported, we can speculate that participants use a higher-level of attention in executing the task, than when they walk in a more habitual context (e.g., at home). Finally, cueing itself can reduce freezing episodes, as commented above, thus decreasing the chance of FOG occurring.

Walking: Take home messages

Cueing effect on FOG and spatio-temporal gait parameters

- The analysis of available data does not show a significant effect of cueing on reducing FOG symptoms.
- Results indicate an effect of cues on some spatio-temporal parameters of walking task.

Cueing type effectiveness

- Visual cueing (i.e., stripes lines) improve step or stride length, perhaps avoiding sequence effect phenomenon, which is a major trigger of FOG. However, the application of these specific visual stimuli out of laboratory settings appears improbable.
- The effectiveness of somatosensory and auditory stimuli is uncertain and available data are insufficient to determine whether and which spatiotemporal parameters might benefit from this specific cue modalities.

Influence of medication state on cueing effectiveness

- Meta-analysis results suggest a positive effect of cueing in improving step length (i.e., visual) when individuals with PD were in ON medication state. Improvements on gait velocity seem more evident when visual cueing (i.e., laser cues) are applied in OFF state.

4.3. Turning

Turning, which accounts for more than 20% of daily walking, is a demanding activity requiring a complex integration of different control mechanisms. Also, turning is a strong trigger for FOG episodes (Spildooren et al., 2018), highly increasing the risk of falls. For these reasons, identifying which cues modalities could improve turning performance and decrease the occurrence of FOG in PD patients is still a relevant topic.

In this review 12 studies, including 245 participants, assessed the effectiveness of online cueing during turning. Turning was evaluated with different gait analysis systems and a wide range of turning-related parameters was reported depending on the experimental task (e.g., 180° or 8-shaped turning). The most reported turning parameters were the turning time (9 studies (Arias and Cudeiro, 2010; Bryant et al., 2010; Holmes et al., 2015; Sijobert et al., 2017; Spildooren et al., 2012; Nieuwboer et al., 2009; Tang et al., 2017; Willems et al., 2007; Das et al., 2022)) and the number of steps (4 studies (Bryant et al., 2010; Gál et al., 2019; Spildooren et al., 2012; Willems et al., 2007)), whereas for gait-related parameters the step time and its variability (2 studies (Tang et al., 2017; Willems et al., 2007)). In all, 4 meta-analyses were performed. Results from meta-analysis revealed that turning time was significantly reduced when cueing were applied compared to no cueing condition. This finding was in line with those obtained from studies not included in the meta-analyses both in the ON (Tang et al., 2017) and OFF (Arias and Cudeiro, 2010; Spildooren et al., 2017) medication state. In contrast, results on step numbers were not significant. Decreased turning time and unchanged number of steps could be explain by the "executive mechanism" of cueing (Nieuwboer et al., 2009), where motor performance (here, turning) is facilitated by requiring less attention to gait, thus resulting in faster turn time. Vice versa Mancini (Mancini et al., 2018) (i.e., auditory and somatosensory), and Spildooren (Spildooren et al., 2017) (i.e., auditory) reported that cues reduced turn velocity. A possible explanation of these results is that reducing turn velocity may be a strategy to decrease FOG occurrence, to lessen fall risk in PD by improving balance, as the center of gravity remains between the two feet.

Additional spatio-temporal gait parameters, collected during turning tasks, were analyzed with two meta-analyses. For step time, any significant effect size was found. Indeed, only one study (Tang et al., 2017) reported significant improvement when rhythmic laser cue was applied. Conversely, a significant effect size was found for step-time variability, but it should be noted that only data from two studies (Tang et al., 2017; Willems et al., 2007), allowing 3 comparisons, were pooled. Thus, despite a significant effect of cueing was detected, available data are still limited to determine whether and what type of cues is able to reduce step-time variability during turning.

Direct measures of FOG were collected in 7 (Arias and Cudeiro, 2010; Bryant et al., 2010; Mancini et al., 2018; Spildooren et al., 2017; Spildooren et al., 2012; Nieuwboer et al., 2009; Tang et al., 2017) out of 11 studies and in most cases (5 studies (Bryant et al., 2010; Spildooren et al., 2017; Spildooren et al., 2012; Nieuwboer et al., 2009; Tang et al., 2017)) the number of episodes was used as outcome measure. However, due to the lack of available data, any meta-analysis was run. Among the 7 studies assessing the effectiveness of cueing in reducing FOG, five (Arias and Cudeiro, 2010; Bryant et al., 2010; Mancini et al., 2018; Spildooren et al., 2017; Tang et al., 2017) reported a significant abatement of freezing episodes or its duration when visual and auditory cues were applied.

As mentioned earlier, FOG is a complex phenomenon and several internal (focused attention / impaired executive functions) or external (dual tasking / emotional state) factors might attenuate or exacerbate its clinical manifestation. Therefore, testing the online effect of cueing on a complex motor task, such as turning, which is also known to be a trigger for FOG episodes, is challenging and results might be positively or negatively influenced by several components. However, our findings are in line with previous results reporting that freezing, along with turning execution, improved when visual cues were applied (Muñoz-Hellín et al., 2012). Improvement in FOG episodes during turning and turning execution may be the consequence of the ability of visual cues of shifting movement control from habitual to a goal-directed control, as already discussed for walking improvements under external cues.

Turning: Take home messages

Cueing effect on FOG and spatio-temporal parameters

- Our results indicate a possible effect of cueing in reducing FOG episodes during turning.
- Turning time could benefit from external cues
- Cueing applied to modulate turning velocity (to increase or to decrease) should be chosen according to patients' need.

Cueing type effectiveness

- Both visual and auditory cues appeared to act on turning time and to decrease step time variability.

Influence of medication state on cueing effectiveness

- In ON-phase, cues reduce time spent to complete the turning, whereas in the OFF-phase turning time diminished probably to allow a better control of balance.

4.4. Study limitations

Several potential limitations deserve to be discussed. First, the selected study design, although suitable for our research questions, yields low quality evidence. Thus, GRADE assessment was not performed. Second, the number of potential meta-analyses was decreased due to the heterogeneity of the outcome measures across the included studies. Third, direct measures of FOG were often missing. This presumably happened because it is difficult to trigger FOG episodes in the laboratory setting. Fourth, incomplete clinical information reporting hinders proper interpretation of the results and decrease the likelihood of determining which PD subjects might benefit from a specific cues modality the most. Lastly, gait assessment was often limited to one or two of the five gait domains (Gouelle and Mégrot, 2017). Walking performance is multidimensional, and it can't be fully understood by collecting few or partial features (Lord et al., 2013). Finally, it is worth noting that our findings derive from single session studies and the results may change (both ways, improve or worsen) when cues are delivered for multiple sessions.

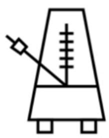
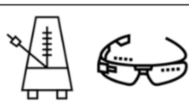
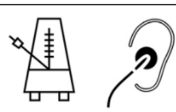
4.5. Gaps

The findings of the present systematic review shed some light on which are the issues we still have to face when applying cueing strategies in the clinical practice.

First, *in PD with FOG one cue does not fit all.* The selection of cue should take into account: (i) the specific mechanism of cues (i.e., executive, stabilizing, preparatory roles); (ii) the best behavioral strategies (i.e., rescue or preventing strategies) according to FOG features; (iii) the specific gait metrics that need to be addressed and (iv) the cueing-response congruency (e.g. auditory cues typically influence the timing of gait whereas visual cues mainly seem to regulate the amplitude generation during walking) (Ginis et al., 2018).

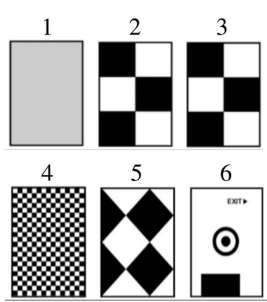
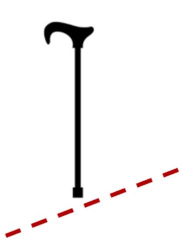
Second, *FOG severity is just the tip of the iceberg.* Freezing of gait is multifaceted phenomenon and quantifying its severity via NFOGQ can't be enough to thoroughly understand the extent of this symptom. Several further key factors should be considered when designing a FOG-tailored cue trial: FOG subtypes (Martens et al., 2018) (asymmetric motor,

Table 1
Cues: description of all cueing setting proposed in the included studies grouped by type.

AUDITORY CUEING	
MODALITIES	**SETTING**
METRONOME 	GAIT INITIATION • From 50 to 70 bpm (McCandless et al., 2016) WALKING • -10% and -20% of preferred cadence(Willems et al., 2006) • Preferred cadence (Willems et al., 2006), • +10% of preferred cadence (Arias and Cudeiro, 2010; Janssen et al., 2017; Willems et al., 2006) • +20% preferred cadence (Willems et al., 2006) TURNING • -10% preferred stride frequency (Spildooren et al., 2017, 2012) • Preferred cadence (Willems et al., 2007)
SMART GLASSES + METRONOME 	WALKING • Preferred cadence (range = 50 - 150 cues/min) [no visual display](Zhao et al., 2016)
METRONOME + EARPHONE 	TURNING • Preferred cadence (Nieuwboer et al., 2009)
SPEAKERS 	GAIT INITIATION • Warning tone → Sound intensity: 80 dB Go tone → Sound intensity: 90 dB (Lu et al., 2017) • Sound intensity: 105-dB Duration of the sound signal: 0.20 s (Delval et al., 2014) TURNING • Self-selected cue rhythm (Mancini et al., 2018)
BUZZER BEEP 	GAIT INITIATION (Jiang and Norman, 2006) Duration of the sound signal: 0.40 s Sound interval: set at the average step time of each subject
MUSIC 	WALKING • Piano arrangement of children's song with salient beat ('Row, Row, Row, Your Boat')(Horin et al., 2020)

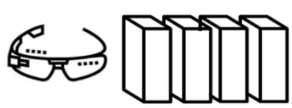
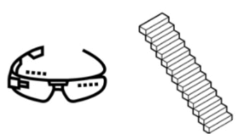
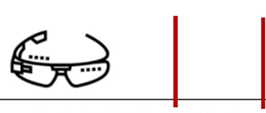
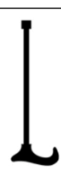
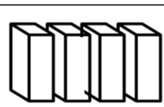
(continued on next page)

Table 1 (*continued*)

VISUAL CUEING	
MODALITIES	**SETTING**
LASER SHOES 	WALKING • Laser beam projection: orthogonally to the contralateral foot Frequency: each heel strike (Barthel et al., 2018)
STRIPES LINES 	GAIT INITIATION • First stripe location: average first step length of each subject (Jiang, 2006) • First stripe location: 120% of the baseline step length (Russo et al., 2022) WALKING • Inter-stripes distance: 65 cm (Beck et al., 2015) • Inter-stripes distance: 40% of the subject's height/preferred step length (Cao et al., 2020) • Inter-stripes distance: 65 cm (Lebold, 2010) • Inter-stripes distance: determined by the normalized step length (Lee et al., 2012) • Inter-stripes distance: +20% of normal step length (Stuart et al., 2021)
FLOOR PATTERN 	WALKING (Gál et al., 2019) 1. No pattern. 2. Real 50 x 50 cm chessboard. 3. Virtual 50 x 50 cm chessboard. 4. Virtual 5 x 5 cm chessboard. 5. Virtual 50 x 50 cm diagonal chessboard. 6. Irregular virtual pattern.
LASER CANE 	GAIT INITIATION • Laser location: projected horizontally from the cane tip on the floor (Sijobert et al., 2017) WALKING • Laser location: projected onto the floor, perpendicular to the cane. Frequency: triggered by patient when FOG occurred (Kompoliti et al., 2000) • Laser location: red and green light beams projected perpendicular to the cane (Bryant et al., 2010)

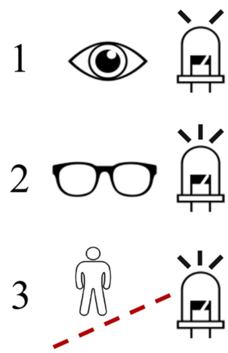
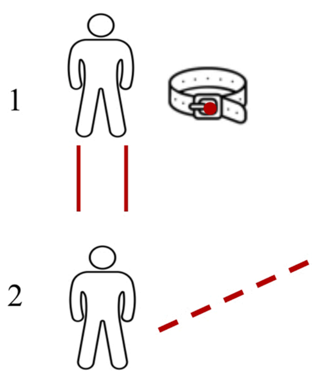
(*continued on next page*)

Table 1 (*continued*)

VISUAL CUEING	
MODALITIES	**SETTING**
ROLLER WALKER 	WALKING • a) Laser beam projection: between the walker rear wheels (Holmes et al., 2015) b) Laser beam projection: at a distance equivalent to mean sex specific step length in front of the center of the rear wheels (Holmes et al., 2015) c) Laser beam projection: at a distance equivalent to mean sex specific stride length in front of the center of the rear wheels (Holmes et al., 2015) • Laser beam on wheeled walker turned on during the trial (Cubo et al., 2003) Frequency condition1: continuous • Frequency condition2: triggered by patient when FOG occurred Laser beam projection: horizontal red beam at ankle level (Bunting-Perry et al., 2013)
SMART GLASSES 1  2  3  4 	WALKING 1. *Augmented transverse bar* (Janssen et al., 2017) Inter-bars distance: 40% of the participant's height Position: adjusted in real time according to walking speed and head orientation 2. *Augmented staircase* (Janssen et al., 2017) Setting: according to real staircase measures Position: adjusted in real time according to walking speed and head orientation 3. *Rhythmic cue*: rhythmic led Frequency: preferred (from 50 to 15 cue/min) (Zhao et al., 2016) 4. *Optic flow cue*: vertical lines on both sides of the screen moved forward at a fixed speed Frequency: preferred (from 50 to 15 cue/min) (Zhao et al., 2016)
INVERTED CANE 	WALKING • Device description: slat of wood attached at the bottom of the rod, at a right angle to it and parallel to the floor (Kompoliti et al., 2000)
SQUARE RODS 	WALKING • Inter-rods distance: 60 cm (Poláková et al., 2020) N° of rods: 16

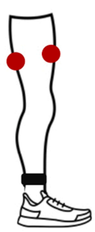
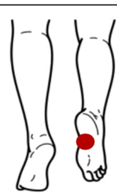
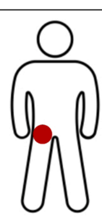
(*continued on next page*)

Table 1 (*continued*)

VISUAL CUEING	
MODALITIES	**SETTING**
SMART GLASSES  	GAIT INITIATION 1. Light location: at eye level (Lu et al., 2017) Device: vertical array Warning cue: yellow Go cue: green Duration: 100 ms WALKING 2. Device: motorized laser device Laser beam projection: 65 cm in front of the participant Frequency: 1 cycle per second (Lebold, 2010) TURNING 3. Device location: attached to glasses Frequency: preferred step frequency (Nieuwboer et al., 2009)
LASER DEVICE  	WALKING 1. Device location: waist belt Laser beam projection: two parallel transverse laser lines in front of the participant (Cao et al., 2020) TURNING 2. Device location: over the sternum Frequency of rhythmic laser: -10% preferred stride cadence Laser beam projection: one step length in front of the patient's feet (Tang et al., ,2017)
STARRED LINES 	TURNING • Disposition of black lines: 1m from the center of the star, providing 8 points (Das et al., 2022) Wide: four two-inch Verbal command: participants were asked to step over the cue when turning

(continued on next page)

Table 1 (*continued*)

SOMATOSENSORY CUEING	
CUEING LOCATION	**SETTING**
LATERAL MALLEOLUS 	GAIT INITIATION • Frequency: 250 Hz for 100 ms (Lu et al., 2017) Timing of application: initial stance leg
WRIST 	GAIT INITIATION • Frequency: during each stance phase of the L and R foot (Schlenstedt et al., 2020) TURNING • Frequency: during each stance phase (Mancini et al., 2018) • Frequency: preferred cadence (Nieuwboer et al., 2009)
HARMSTRING OR QUADRICEPS 	WALKING • Frequency: 0.7 step/sec (Rosenthal et al., 2018)
FEET 	WALKING • Frequency: at heel off detection from IMU signal Electrode location: cathode (arch of the foot) anode (dorsum of the foot) (Sijobert et al., 2017)
PELVIS 	GAIT INITIATION • Frequency: from 50 to 70 stimuli/min Vibrating metronome location: anteriorly over the right side of the pelvis (McCandless et al., 2016)

McCandless et al., 2016, Willems et al., 2006, Arias and Cudeiro, 2010; Willems et al., 2006; Janssen et al., 2017 Spildooren et al., 2017; Spildooren et al., 2012 Willems et al., 2007, Zhao et al., 2016, Delval et al., 2014, Mancini et al., 2018, Jiang and Norman, 2006, Horin et al., 2020, Barthel et al., 2018, Jiang and Norman, 2006, Russo et al., 2022, Beck et al., 2015, Cao et al., 2020, Lebold and Almeida, 2010, Lee et al., 2012, Stuart et al., 2021, Gál et al., 2019, Sijobert et al., 2017, Kompoliti et al., 2000, Bryant et al., 2010, Holmes et al., 2015, Cubo et al., 2003, Bunting-Perry et al., 2013, Janssen et al., 2017, Poláková et al., 2020, Lu et al., 2017, Nieuwboer et al., 2009, Tang et al., 2017, Das et al., 2022, Schlenstedt et al., 2020, Rosenthal et al., 2018 anxious, sensory-attention), FOG triggers (e.g., walking through a doorway, sloped surfaces) and FOG modulators (e.g, DT, anxiety) that may both decrease or increase the threshold for manifesting FOG (Weiss et al., 2019).

Third, *one point of view does not show the whole picture.* To customize training based on cueing, clinical (e.g., MDS-UPDRS scores) and mobility-related (e.g., gait and balance) information along with cognitive profile (e.g., MOCA or Parkinson's Disease Cognitive Rating Scale, PD-CRS), acknowledged as key prognostic factors, have to be necessarily collected.

Finally, related to mechanistic underpinnings of cues, there is evidence that the use of internal and external cues enhances cortical activation in the motor areas compared to baseline gait (Wu et al., 2015; Tosserams et al., 2022). In addition, frontal brain areas are more active during the application of internal cueing, and parietal and occipital areas are activated more during both cueing strategies compared to baseline (Wu et al., 2015; Tosserams et al., 2022). Cerebellar-cortical pathways seem to be recruited in both internal and external cues (Wu et al., 2015). Cueing seems not to be univocally fitting and, to date, there are no data in the literature to potentially predict whom would benefit from cueing and whom not.

One possible explanation for this limitation in the use of cues may be related to the heterogeneity of PD phenotype, including FOG subtypes. Evidence for distinct asymmetric-motor, anxious, and sensory-attention phenotypes within FOG has been recently provided (Martens et al., 2018). The freezing phenotypes identified may represent cohorts with distinct upstream dysfunctions in which pathophysiological mechanisms overwhelm specialized neural circuitry unique to each phenotypic subtype, which then ultimately manifests via a common inhibitory brain stem pathway that arrests ongoing gait processes. In a larger scenario FOG subtypes may correspond to clinical subtypes of PD. Indeed, PD is a highly heterogeneous disease characterized by a wide range of motor and non-motor symptoms. The most recent studies, based on hierarchical cluster analysis, have described a benign subtype characterized by mild motor symptoms ("mild motor-predominant" subtype) and a "diffuse malignant" subtype characterized by the coexistence of severe motor and non-motor symptoms at disease onset (Fereshtehnejad et al., 2017). In addition, clinical subtypes have been linked with variable neurodegeneration trajectories, with frontal, parietal, orbital and temporal areas variably involved in relation to phenotype (Inguanzo et al., 2021; Albrecht et al., 2022).

From the above-reported considerations, we can make a hypothesis of why response to cues is extremely variable. If cues exploit alternative pathways to promote motor action performance, it is also possible that the responsiveness of these alternative pathways varies in relation to neurodegeneration trajectories.

It would be really of impact for clinical implementation of cues, to unravel whether responsiveness to cues can be predicted by clinical phenotype information.

4.6. *Future perspectives*

To date, further steps must be taken to increase the effectiveness of cueing in reducing FOG and to promote their use in everyday activities (both indoor and outdoor) (Inguanzo et al., 2021). Indeed, the limit of the cueing strategies explored in this systematic review is that cueing paradigms are very basic, adopting, as an example, fixed auditory rhythm of metronome or transverse lines on the floor. Innovative technologies, such as wearable sensors (e.g., IMUs, vibrotactile) present exciting potential in this domain. Results from a trial, testing the different types of cueing over a period of 6 weeks, showed that "intelligent cueing" (Ginis et al., 2017) (i.e., auditory feedback provided when specific gait alterations occur) may decrease the cue-dependency in freezer, even if their efficacy was dependent on the cognitive abilities.

Furthermore, there are interesting reports in the literature related to "ecologically valid" cues as, for example gravel sounds (Young et al., 2014) described a novel cueing strategy using ecologically valid 'action-related' sounds (footsteps on gravel) that convey both spatial and temporal parameters of a specific action within a single cue. Results showed that PD patients were able to significantly adapt a spatial parameter of gait (step length) in accordance with the information conveyed in footstep sounds, demonstrating that an ecologically valid acoustic cue is also able to impact on spatial parameters of gait in addition to temporal ones. It would be interesting in future studies to have more data on the effect of "intelligent" and "ecologically valued" cues on FOG and FOG-related gait parameters, also in relation to PD patient' and FOG' characteristics to apply them in the clinical practice.

Furthermore, taking advantage of novel technologies (e.g., wearable sensors), it will be crucial to develop new tools able to objectively measure FOG episodes and its severity (e.g., in a ecological setting), in order to have reliable data and evidence on cues effectiveness. (Table 1).

5. Conclusions

As far as we know, this is the first systematic review evaluating the immediate effectiveness of online cueing on freezing and gait-related parameters.

Although our findings show that available evidence is still insufficient to clearly determine the effectiveness of cueing on freezing and FOG gait-related parameters our finding provide insights for the potential application of cues in the clinical practice and bring to light the current limitations associated with their use. Results revealed that visual and auditory cues, when applied during gait initiation, improve APAs but has no effect on FOG. Related to walking, visual cues improve step or stride length, but has no effect on FOG symptom. In turning, visual and auditory cues improve turning time and step time variability and may reduce FOG episodes during turning.

Despite these results several issues have been raised we still have to face when using cueing strategies in the clinical practice. Particularly, it emerged the urgent need to develop ecologically- valid and "intelligent" cues and to tailor cue strategies in relation to FOG phenotype that includes a number of factors ranging from FOG subtype to FOG triggers and modulators.

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Conflict of interest

The Authors have no financial or other conflicts of interest associated with this publication to declare.

Data availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2023.105189.

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