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PAPER

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E-mail: s.janssen-2@utwente.nl**Keywords:** Parkinson disease, cues, virtual environment, freezing of gait, gait disorders**Abstract**

Objective. Elucidating how cueing alleviates freezing of gait (FOG) in Parkinson's disease (PD) would enable the development of more effective, personalized cueing strategies. Here, we aimed to validate a visual cueing virtual environment (VE) paradigm for future use in e.g. neuroimaging studies and behavioral studies on motor timing and scaling in PD patients with FOG. **Approach.** We included 20 PD patients with FOG and 16 age-matched healthy control subjects. Supine participants were confronted with a VE displaying either no cues, bars or staircases. They navigated forward using alternate suppression of foot pedals. Motor arrests (as proxy for FOG), and measures of motor timing and scaling were compared across the three VE conditions for both groups. **Main results.** VE cues (bars and staircases) did not reduce motor arrests in PD patients and healthy control subjects. The VE cues did reduce pedal amplitude in healthy control subjects, without effects on other motor parameters. **Conclusion.** We could not validate a visual cueing VE paradigm to study FOG. The VE cues possibly failed to convey the necessary spatial and temporal information to support motor timing and scaling. We discuss avenues for future research.

Abbreviations

FAB	Frontal Assessment Battery
FOG	freezing of gait
MMSE	mini-mental state examination
N-FOGQ	New Freezing of Gait Questionnaire
PD	Parkinson's disease
UPDRS-part III	Unified Parkinson's Disease Rating Scale part III (motor examination)
VE	virtual environment.

1. Introduction

One of the most disturbing motor symptoms of PD is FOG, defined as a 'brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk' [1]. Freezing is not restricted to gait and can also occur in speech [2], upper limb [3] and alternate foot movements [4]. Gait initiation, approaching doorways and cognitive dual tasks can

trigger FOG [1]. Conversely, external stimuli called 'cues', such as transverse bars on the floor or the sound of a metronome, can reduce FOG, and facilitate gait initiation [5, 6] and continuation [7] by increasing step length [8–10], and decreasing cadence [9, 10] and step length variability [7, 8, 11].

Different mechanisms may explain the beneficial effects of external cues. First, external cues shift automated movements, which are typically affected in PD, to goal-directed movements, which are preserved [12]. Second, cues might attract attention to the task at hand [13]. Third, visual cues deliver spatial information aiding in the scaling of movement [10, 14]. Fourth, auditory cues can restore motor timing dysrhythmia [7, 10, 15]. Lastly, external cues can improve anticipatory postural adjustments preparing for step initiation [5]. Despite the wealth of hypotheses on the mechanisms underlying externally cued gait in PD, their neurophysiological grounds await to be unveiled [7]. Patients respond heterogeneously to the various

Table 1. Clinimetrics.

	PD patients Median (Q1–Q3)	Healthy controls Median (Q1–Q3)	<i>p</i> -value
Number of participants ^a	20	16	
Age (years)	70.5 (62.8–73.0)	68.0 (65.3–70.8)	0.3
Gender (% male)	85	44	0.01
Disease duration (years)	11.0 (7.3–17.0)		
LEDD (mg d ⁻¹)	1128 (897–1360)		
MDS-UPDRS-part III	39.5 (31.3–47.8)		
Hoehn and Yahr (II/III)	12/8		
MMSE	29 (27–30)		
NFOGQ	21 (16–25)		
FAB	16 (15–17)		

The median and first (Q1) and third (Q3) quartiles are given, unless stated otherwise. A *p*-value < 0.05 indicates a significant difference between PD patients and healthy control subjects.

^a Number of included participants, including five PD patients who were excluded from analyses because of insufficient signal quality. PD, Parkinson's disease; LEDD, levodopa equivalent daily dose; MDS-UPDRS-part III, Movement Disorder Society—Unified Parkinson's Disease Rating Scale part III (range 0–132); MMSE, mini-mental state examination (range 0–30); N-FOGQ, New Freezing of Gait Questionnaire (range 0–28); FAB, Frontal Assessment Battery (range 0–18). All questionnaires were rated while participants were OFF medication.

cueing modalities [16, 17]—e.g. some patients profit mostly from visual cues while others respond better to auditory cues—suggesting that different neurophysiological pathways are involved. Elucidating the neuronal pathways that ‘bypass’ or modify defective pathways would enable a mechanistic and hypothesis-driven rather than trial-and-error based development of personalized cueing strategies.

To date, neuronal structures involved in externally cued movement have been studied in healthy persons [18, 19], to a lesser extent in PD patients [20–22], and rarely in PD patients with FOG [23, 24]. Considering the structural and functional cerebral changes in PD patients with FOG, the findings in healthy individuals and PD patients without FOG cannot necessarily be extrapolated to PD patients with FOG. Furthermore, only a single previous study explored the neural networks involved in visually cued movements in persons with PD [25]. This study applied colored target zones serving as visual cues to support handwriting, and did not apply rhythmic visual cues such as bars on the floor to support walking. The neural networks involved in visually cued lower limb movements in PD patients are yet unexplored.

A validated paradigm to study visually cued lower limb movement in a neuroimaging study is not yet available. A VE paradigm has proven valuable to study FOG [4, 26–31]. Specifically, participants navigated through a VE using alternate depression of foot pedals. Motor arrests occurring during foot pedaling were considered equivalents of FOG episodes [4, 26]. Functional magnetic resonance imaging studies that employed this VE paradigm provided relevant insights into the pathophysiology of FOG [28, 31]. By incorporating visual cues into the VE, this paradigm could serve to study the neurophysiological mechanisms involved in visual cueing, and to investigate motor timing and scaling in PD patients with FOG.

In this study, we aimed to validate a visual cueing VE paradigm for use in future neuroimaging studies and behavioral studies on motor timing and scaling in PD patients with FOG. Our objectives were to assess: (a) whether visual cues in a VE altered measures of motor arrests (as a proxy for freezing severity); (b) whether these VE cues altered motor timing and scaling; and (c) whether the effects of VE cues were different between PD patients and healthy control subjects. We hypothesized that VE visual cues would reduce the percent time spent on motor arrests, and the number and duration of motor arrests; improve motor timing by reducing cadence, step time variability, and start latency; and improve amplitude generation by increasing pedal amplitude and reducing its variability. These effects were expected to be larger in PD patients than in healthy control subjects, because of their larger dependency on external rhythm generation and thus benefit of external cues.

2. Methods

2.1. Participant selection

We included 20 PD patients and 16 age-matched healthy control subjects (table 1). Inclusion criteria for patients were a diagnosis of PD according to the UK Brain bank criteria [32], and a subjective experience of FOG episodes (defined as a score ‘1’ on question 1 from the NFOG-Q [33]) more than once per day (score ‘3’ on question 2 from the NFOG-Q [33]). Exclusion criteria included: significant cognitive impairment (MMSE ≤ 24 or FAB score ≤ 8); comorbidity causing severe gait impairments; inability to lie supine for the duration of the experiment; and severe visual impairments precluding the participant from seeing the VE cues. PD patients were tested ‘Off’ medication after overnight withdrawal of dopaminergic medication (>12 h after last intake).



Figure 1. Virtual environment experimental set-up. Experimental set-up (A) in which participants were lying supine with the knees slightly bent and the feet on foot pedals. The alternate suppression of the foot pedals led to a forward movement through a VE environment displayed on a screen in front of their faces. The VE consisted of a corridor with either (B) no visual cues, (C) transverse bars, or (D) staircases. Experiments were divided into six sessions (E), each subdivided into two blocks, with three trials per block. A trial was performed under one of the three cueing conditions (C, control; B, bars; S, staircase), with each condition occurring once per block. The order of the cueing conditions was randomized per block (the depicted order of trials is an example).

This is important because previous studies employing the VE paradigm found that freezing-related features are more prominent during ‘Off’ states compared to ‘On’ states [27, 29]. Patients fulfilled the following clinical assessments: NFOG-Q [33], MDS-UPDRS part III [34], MMSE [35] and FAB [36].

2.2. Virtual environment experimental set-up

Participants were positioned lying on their backs, the knees slightly bent, and the feet on foot pedals (figure 1(A)). The foot pedals had an upward basic position and could be depressed independently by light force. A tablet computer (surface pro 4, Microsoft) displayed a three-dimensional VE from a first-person perspective, built with the game engine Unity (version 5, Unity Technologies) in combination with Visual Studio (2015, Microsoft) for script editing.

The VE resembled a corridor (corresponding to a width of 4 m and height of 4 m) with plain white walls, a grey carpet on the floor, unobtrusive objects like plants and furniture at irregular distances, and wide doorways every 20 m (except in the staircase condition). In the control condition, no visual cues were

displayed (figure 1(B)). The experimental VE cueing conditions displayed either regularly spaced white transverse bars (corresponding to a width of 0.9 m) at 40% of the participant’s height (figure 1(C)), or a staircase (corresponding to a width of 0.9 m) every 25 m (figure 1(D)).

Pedal angles were converted to voltages by flex sensors (4.5”, Antratek) attached under each foot pedal. An Arduino-based single-board microcontroller converted these signals from analog to digital. The Arduino sent four bytes containing ASCII encoded signals to custom software built in Unity (version 5, Unity Technologies) installed on the tablet computer. Two bytes carried data on the current state (‘up’ or ‘down’) of the pedals and were used for real-time translation into forward progression through the VE. The other two bytes contained pedal angle data which were used for post hoc signal analyses (described at ‘Signal preprocessing’). The signals corresponding to the downward position of the left and right pedals were considered to signal ‘steps’. ‘Step duration’ was calculated as the time interval between steps from the left and right foot. The mean ‘step frequency’ was calculated as the multiplicative inverse of the mean

step duration. The movement speed through the virtual environment was calculated by multiplying the mean step frequency with 0.7 (the estimated length of a single step [37]). Forward movement through the virtual environment was initiated by the consecutive suppression of the left and right foot pedals, at an initial virtual movement speed calculated from the step duration of the first steps. Continued alternate pedal depressions (i.e. left–right or right–left) resulted in continuation of forward progression through the virtual environment at a speed calculated from the mean step duration of the last four steps. In this way, the continuous alternating pedal movements gave the impression of walking through the corridor in fluent motion, without being jerky or too slow in response to changes in stepping speed. Non-alternate pedaling (i.e. left–left or right–right), or a time interval exceeding twice the mean step duration (indicating that the participant had stopped pedaling), resulted in cessation of the forward movement. To mimic normal vertical head movements during gait, the view during forward progression through the virtual environment moved 6 cm up and down, with a 0.5° rotation clockwise and counterclockwise around the y -axis (in the frontal plane).

Participants were instructed to look at the VE without specific instruction on where to focus their gaze at, and to ‘walk’ through the corridor by the alternate depression of the foot pedals at a self-selected pace.

The original VE paradigm applied a virtual Stroop task to increase cognitive load and induce freezing-related motor alterations [4, 26]. To prevent interference with the effects of the visual cues presented in the VE, we applied an auditory Stroop task [38] instead. The Stroop task consisted of congruent word pairings (a male voice saying ‘man’, or a female voice saying ‘woman’) signaling the participant to start or resume walking/pedaling (‘WALK’), and incongruent word pairings (a male voice saying ‘woman’ or vice versa) signaling to stop walking/pedaling (‘STOP’). These Stroop signals were clustered into three different ‘Stroop events’: (a) a single WALK; and paired signals with (b) a WALK, or (c) STOP followed within 1–4 s by a WALK. Per trial, three to four Stroop events occurred at random time intervals of which at least one was a paired STOP/WALK event.

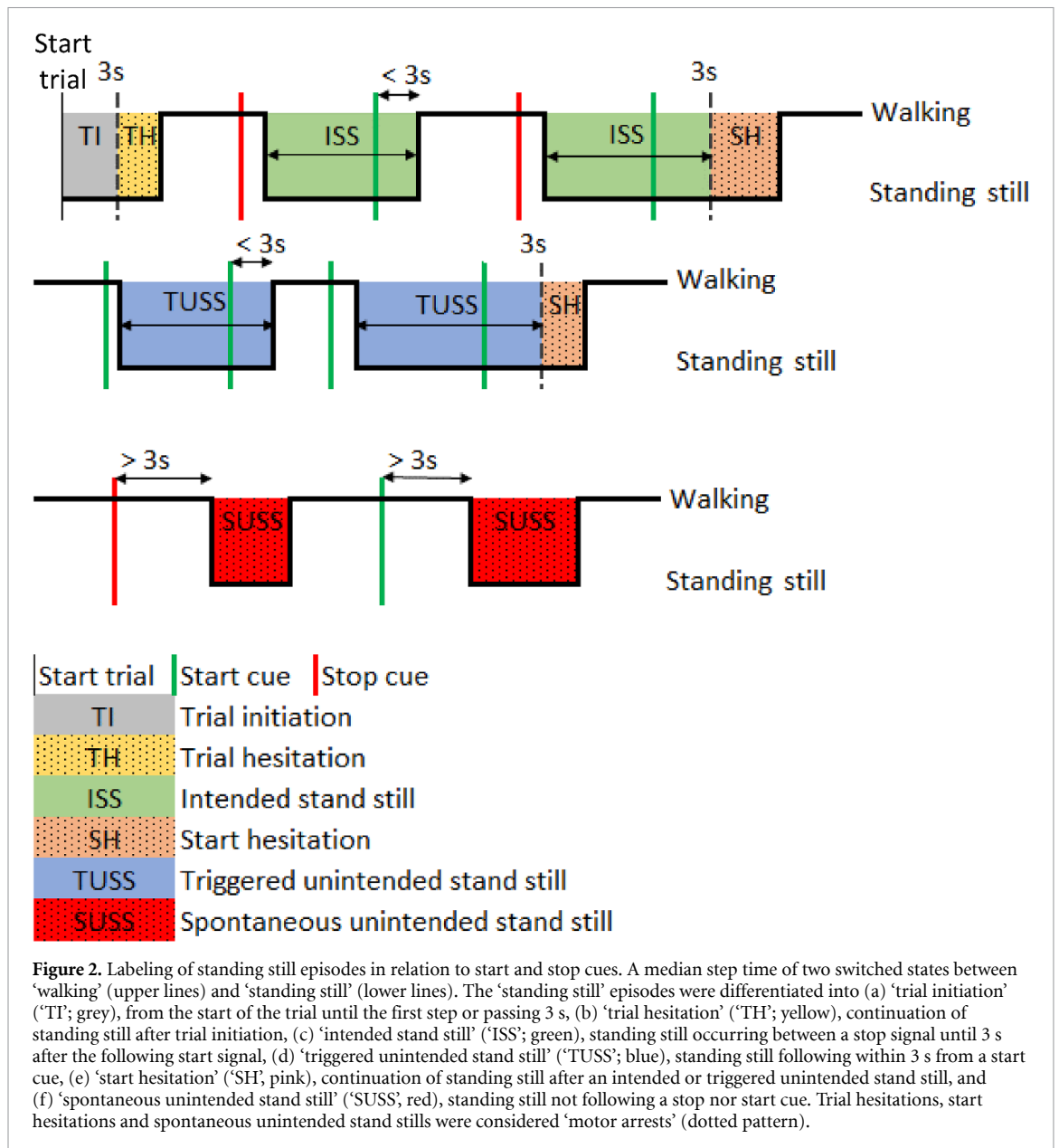
The VE experiment was divided into a training session and six experimental sessions. In the training session, participants were allowed to practice until they felt comfortable with the task and conditions. Each experimental session was subdivided into two blocks. Each block consisted of three randomly ordered trials under one of the three cueing conditions (‘Control’, ‘Bars’, and ‘Staircase’). Therefore, each cueing condition occurred 12 times per experiment. Each trial lasted 30 s, with its start and end indicated by a voice record saying ‘start’ and ‘stop’.

Participants were suggested to take a short break of approximately 1 min in between blocks, and longer breaks of approximately 5 min in between experimental sessions, but were allowed to rest as long as needed. Experiments were executed in a single visit.

2.3. Signal preprocessing

The raw pedal angle data were preprocessed offline using MATLAB R2017b (Mathworks, Inc, Natick, MA, USA) to differentiate valid peaks (representing steps) from false peaks (i.e. noise). The pedal angle signals were resampled at 50 Hz. A sliding window of 2.5 s and an overlap of 25% was applied. The signals from both feet were normalized per window by subtracting their means. Positive and negative peaks were detected as the maximum absolute amplitudes. Two runs of peak removal were executed on the normalized pedal data. In the first run, the median time interval between two alternate valid peaks was calculated. In the second run, false peaks (i.e. noise) were removed from the original normalized pedal data. In both runs, peaks were removed if they (a) occurred in a time frame without crossing of the signals from the left and right foot lasting either (1) >2 s (first run), or (2) >2 times the median time interval between two alternate valid peaks as calculated in the first run (second run); (b) co-occurred within three samples of a peak of the opposite foot (‘in phase’, typical of noise); (c) had an amplitude $<30\%$ of the median amplitude, and/or a peak width ≤ 5 samples (i.e. ≤ 0.1 s); or (d) occurred in sequence with a higher peak from the same foot. If over 75% of detected peaks were removed, data were considered of insufficient quality and the trial was marked invalid. Participants were excluded from analyses if more than half of the trials in at least one condition were invalid.

Then, the preprocessed data were segmented into various step events. ‘Step time’ was defined as the temporal interval between two alternate (i.e. left–right or right–left) valid peaks. A threshold calculated as two times the median step time was used to differentiate ‘walking’ from ‘standing still’. The ‘standing still’ episodes were further differentiated into (a) ‘trial initiation’, from the start of the trial until the first step or passing 3 s, (b) ‘trial hesitation’, continuation of standing still after trial initiation, (c) ‘intended stand still’, standing still occurring between a stop signal until 3 s after the successive start signal, (d) ‘triggered unintended stand still’, standing still following within 3 s from a start cue, (e) ‘start hesitation’, continuation of standing still after an intended or triggered unintended stand still, and (f) ‘spontaneous unintended stand still’, standing still not following a stop nor start cue (figure 2). Trial hesitations, start hesitations and spontaneous unintended stand stills were considered ‘motor arrests’. Parameters for motor timing and scaling were calculated over the ‘walking’ episodes.



2.4. Study parameters

Measures of freezing severity were: percentage of time in a trial spent on motor arrests, and mean number and duration of motor arrests per trial. Parameters for motor timing and scaling were cadence, step time coefficient of variation (COV), pedal amplitude, pedal amplitude COV, and latency to start walking after an intended stand still (as equivalent to gait initiation).

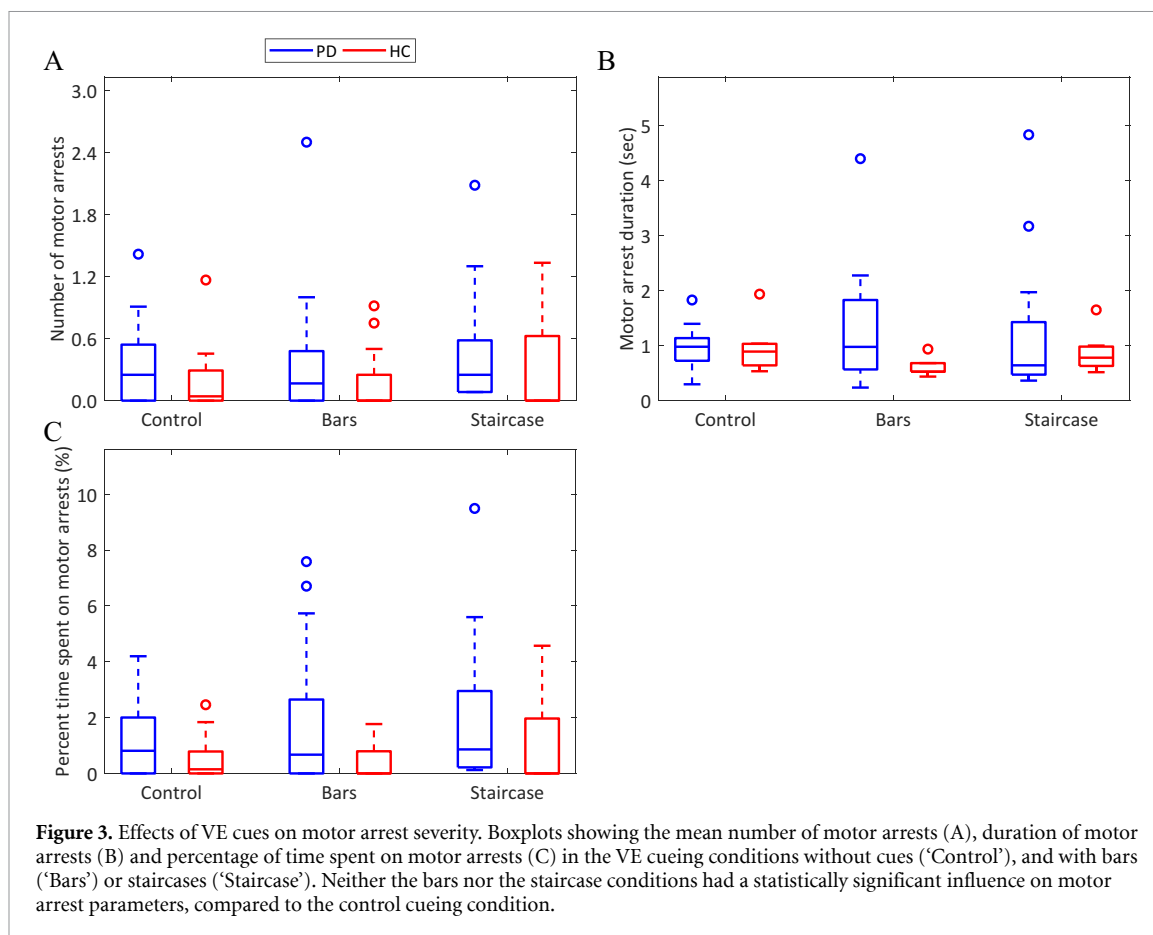
2.5. Statistical analyses

All data analyses were performed with MATLAB R2017b (Mathworks, Inc, Natick, MA, USA; statistics toolbox installed). Alpha was set at 0.05 unless stated otherwise, and adjusted with the Bonferroni–Holmes method for post hoc planned comparisons. Normality of distributions was assessed by visual inspection of histograms and Q–Q plots, and tested by Shapiro–Wilk tests.

Clinimetrics were compared with Mann–Whitney U tests and Fisher’s exact tests.

Motor arrest parameters were not normally distributed regardless of transformations which were therefore not applied. Interactions between cues and participant class were not assessed for motor arrest parameters due to the unavailability of a suitable non-parametric test. Motor arrest parameters were tested with the Friedman test and post hoc Wilcoxon–signed rank tests for the effect of cues (within-factor) per category of the participant class, and with the Mann–Whitney U test for the effect of participant class (between-factor) per category of cues.

Parameters for motor timing and scaling were normally distributed. Interactions between cues and participant class were assessed with a two-way mixed ANOVA (within-factor ‘cues’; between-factor ‘participant class’). In the presence of outliers (defined as values outside $1.5 \times$ interquartile range below the



first or above the third quartile), the parametric analyses were repeated without outliers and reported if this changed statistical significance. Homogeneity of variances was assessed by Levene's test, homogeneity of covariances (alpha 0.001) with the Box's M test. If Mauchly's test indicated that the assumption of sphericity was violated, p values were corrected with epsilon calculated according to Greenhouse and Geisser. The effects of cues on motor timing and scaling parameters were analyzed with one-way repeated measures ANOVAs and post hoc paired t -tests, either per category of participant class (in the presence of an interaction), or for both participant classes together (in the absence of an interaction). The effects of participant class were tested with one-way ANOVAs, either per category of cues (in the presence of an interaction) or for all cues together (in the absence of an interaction).

3. Results

Data of 5 out of 20 PD patients, but none of the control subjects, were excluded from analyses because of low signal quality. Trials with insufficient data quality were equally distributed over the cueing conditions. The clinimetrics of excluded participants did not differ significantly from the PD patients included for analyses. Excluded participants scored slightly worse (mean 2.3 points) on item '3.7 toe tapping' from the

MDS-UPDRS-part III compared to included participants (mean 2.0 points), a non-statistically significant difference ($p = 0.27$). Upon inspection of the data, excluded participants displayed extremely low pedal amplitudes and failed to alternate the pedaling movements, resulting in a low signal to noise ratio.

3.1. Effects of VE cues on motor arrest severity

The Friedman test showed a non-statistically significant effect of the various cues on percentage of time spent on motor arrests (PD $\chi^2(2) = 5.286$, $p = 0.07$; HC $\chi^2(2) = 5.353$, $p = 0.07$), the number of motor arrests (PD $\chi^2(2) = 3.660$, $p = 0.16$; HC $\chi^2(2) = 3.938$, $p = 0.14$) in both PD patients and healthy control subjects, and the duration of motor arrests in PD patients ($\chi^2(2) = 0.889$, $p = 0.64$) (figure 3). Whilst the Friedman test did show a statistically significant effect of the cueing conditions on duration of motor arrests in healthy control subjects ($\chi^2(2) = 6.400$, $p = 0.04$), post hoc analysis with Wilcoxon signed-rank tests did not show statistically significant differences between the control versus the bars condition ($p = 0.35$), nor between the control versus the staircase condition ($p = 0.50$).

3.2. Effects of VE cues on motor timing and scaling

A two-way mixed ANOVA showed an interaction between 'cues' and 'participant class' for pedal amplitude ($F(2, 58) = 3.995$, $p = 0.03$), although not

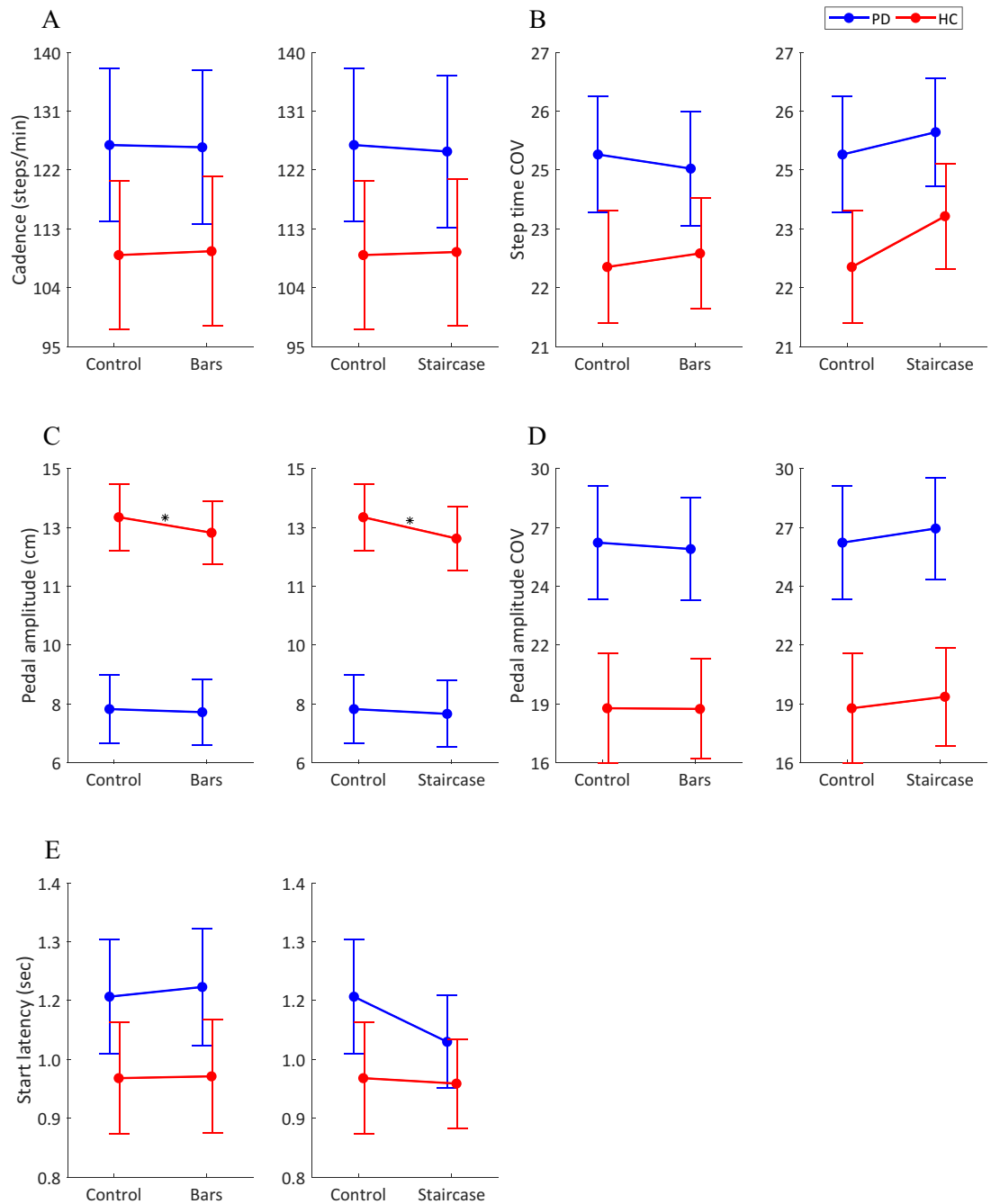


Figure 4. Effects of VE cues on motor timing and scaling. Profile plots showing the group mean (●) and standard error of the mean (vertical bars) for cadence (A), step time COV (B), pedal amplitude (C), pedal amplitude COV (D), and start latency (E) in the different VE cueing conditions in PD patients (blue) and healthy control subjects (red). The control condition is compared to the bars condition (left subplots) and the staircase condition (right subplots). Asterisks indicate a statistically significant ($p < 0.05$) contrast within the specific participant group. Significant differences between conditions with fused participant groups (i.e. in the absence of an interaction effect) were not present. All participants were included in the plots.

if outliers (i.e. one healthy control subject with high pedal amplitudes in each cueing condition) were excluded ($F(2,56) = 3.28$, $p = 0.057$). A repeated measures ANOVA with a Greenhouse–Geisser correction determined that pedal amplitude differed statistically significantly amongst cueing conditions in healthy control subjects ($F(2, 30) = 10.266$, $p < 0.01$), but not in PD ($F(2, 28) = 0.926$, $p = 0.39$). Post hoc tests using the Bonferroni–Holmes correction of

alpha revealed that both bars ($p = 0.001$, adjusted alpha = 0.05) and the staircase ($p < 0.001$, adjusted alpha = 0.025) reduced pedal amplitude compared to the control condition in healthy subjects (figure 4).

There were no statistically significant interactions between cues and participant class for the other motor timing and scaling parameters. Therefore, PD patients and healthy control subjects were grouped for the analyses of the effects of cues. Repeated

measures ANOVAs showed a statistically significant effect of cues for step time COV ($F(2, 58) = 3.594$, $p = 0.03$), but not for cadence ($F(2, 58) = 0.134$, $p = 0.88$), pedal amplitude COV ($F(2, 58) = 1.715$, $p = 0.19$) and latency to start walking after an intended stand still ($F(2, 58) = 1.034$, $p = 0.36$). Post hoc tests failed to show statistically significant differences in step time COV between the control condition and the bars ($p = 0.99$, adjusted alpha = 0.05) or the staircase ($p = 0.03$, adjusted alpha = 0.025) condition (figure 4).

If outliers (two PD participants) were excluded, there was a statistically significant effect of cueing condition on pedal amplitude COV ($F(2, 56) = 4.389$, $p = 0.02$). The post hoc tests showed a statistically significant increase of pedal amplitude COV in the staircase versus control condition ($p = 0.021$, adjusted alpha = 0.025).

3.3. PD patients versus healthy control subjects

The assumptions of homogeneity of variances and covariances were violated for pedal amplitude COV and start latency. If outliers (three PD participants) were excluded, the assumption of homogeneity of variances was violated for start latency.

PD patients experienced a significantly higher number of motor arrests ($p < 0.01$) and greater percentage of time spent on motor arrests ($p < 0.01$), but a non-significantly different duration of motor arrests ($p = 0.46$), determined by Mann–Whitney U tests (figure 3) compared to healthy control subjects.

Given the interaction between cues and participant class for pedal amplitude described above ('Effects of VE cues on motor timing and scaling'), the effects of participant class were analyzed for the three cueing conditions separately for pedal amplitude, and with the cueing conditions grouped for the remaining motor scaling and timing parameters. One-way ANOVAs revealed lower pedal amplitudes in PD patients than in healthy control subjects in the control ($F(1, 29) = 16.255$, $p < 0.01$), bars ($F(1, 29) = 15.704$, $p < 0.01$), and staircase ($F(1, 29) = 14.229$, $p < 0.01$) conditions (figure 4). Pedal amplitude COV was significantly higher in PD participants versus healthy control subjects ($F(1, 29) = 5.096$, $p = 0.03$, cueing conditions grouped) (figure 4), although not if outliers (two PD participants) were excluded ($F(1, 27) = 3.178$, $p = 0.086$). Other motor scaling and timing did not significantly differ between the participant groups (figure 4).

4. Discussion

We aimed to validate a VE paradigm to enable future neuroimaging studies of visual cueing in patients with PD and FOG. Measures of motor arrests (as a proxy for FOG), and motor timing and scaling were compared between a control condition without cues, and across two experimental VE cueing conditions ('bars'

and 'staircase'), in both PD patients with FOG and healthy control subjects. In contrast to our hypotheses, we found that VE visual cues gave no improvements in motor arrest severity or motor timing and scaling in patients and control subjects. We discuss several considerations with regard to this lack of effectivity.

First, the VE cues may not have conveyed the necessary information required to facilitate the scaling and timing of foot pedaling. The spatial information provided by the VE cues might have been perceived as unrelated to the foot pedaling movements. The control over the forward progression through the VE could be reinforced by calculating movement speed through the VE (=step frequency \times step length) with a step length based on a variable derived from the pedal amplitude, rather than on a constant. In addition, the perceived coupling between foot pedaling and walking through the VE could be strengthened by integrating footstep projections in the VE, representing the current positions of the feet in response to the foot pedal movements. Accurate control over these footprints would consolidate the perception of stepping across the bars serving as visual cues in the VE. In addition, such footprints in VE could intrinsically serve as temporal cues (e.g. if the appearance of the footprints is controlled by step timing) as well as spatial cues (e.g. if the position of the footprints is controlled by pedal amplitude) [39].

Second, the VE cues were, in hindsight, perhaps ill chosen. Indeed, a previous study found that augmented reality bars or staircases did not improve FOG and gait, although this was perhaps attributable to the bulky smart glasses that distracted subjects from the walking task [40]. However, in real life, transverse bars on the floor [9, 41], climbing staircases [42, 43] and passing a painted staircase illusion [44] were effective in improving FOG. An augmented reality tiled floor increased gait velocity and stride length in PD patients [45, 46] and FOG [47], although effects on the FOGQ were marginal and not significant for freezing frequency [47]. Considering that augmented reality tiles provide similar spatial information to VE bars or staircases, we do not expect those to be more effective.

Third, the calculation of the parameters might have influenced the ability to measure effects. In our definition of motor arrests, unintended stand stills triggered by cognitive stimuli were not included. According to current insights, cognitive tasks can overload the neural conflict resolution capacity leading to freezing [48]. Therefore, stand stills triggered by the cognitive task might be mediated by the same neural pathways as freezes during gait. Alternatively, however, a stand still following a Stroop-stimulus could be erroneous, hence being more informative about cognitive performance than the mechanisms underlying freezing. Furthermore, although we attempted to closely approximate the definition of

motor arrests to real freezing behavior, those remain different behaviors. This is demonstrated by the occurrence of motor arrests in healthy participants, who naturally do not experience freezing of gait. That healthy control subjects displayed motor arrests might have been due to cognitive errors (i.e. start cues being misinterpreted as stop cues), slow responses to start cues (causing ‘start hesitations’) and suboptimal performance of alternate pedal movements at a sufficiently constant speed (causing ‘spontaneous unintended stand stills’). These, on their turn, are likely to have been influenced by attention, cognitive capacity, and physical tiredness. Finally, the stringent preprocessing criteria applied might have caused motor arrests embedded in a stretch of noisy data to be discarded as ‘noise’. This may have decreased the number of motor arrests detected, hence decreasing statistical power. However, this stringent preprocessing strategy minimized the risk of mislabeling noise as motor arrests, which was a genuine risk especially in PD patients because of lower pedal amplitudes and lower signal-to-noise ratios.

Fourth, displaying the VE through a virtual reality headset rather than a screen might provide a more immersive experience, although a virtual reality-headset would raise issues with compatibility in neuroimaging studies. Fifth, participants might not have looked at the VE visual cues with full attention, as they were not specifically instructed to do so. A recent study investigating cycling in a VE on a stationary bike showed that PD patients only increased their motor output when explicitly instructed to attend to the VE visual cues [49]. Sixth, participants might have been unresponsive to visual cues in general. Certainly, PD patients vary in their responses to cues [16]. We did not select participants based on their response to, or familiarity with, cues. Testing those patients with a known effect to visual cues could enhance a response to VE visual cues, to the cost of reducing generalizability of the results to PD patients with FOG without a defined response to visual cues. Seventh, the group sizes might have been too small to find statistically significant effects. Finally, since the neural circuitry underlying visual cueing has not yet been fully elucidated, it cannot be excluded that dopamine modulates the response to visual cues. Our PD patients were tested ‘Off’ medication, so this could have diminished the response to cues. However, the scarce literature comparing responses to external cues during ‘On’ and ‘Off’ suggests that the effects of cues are not mediated by dopamine [50–52].

In our study, data of five PD participants were discarded because of insufficient data quality. That these participants struggled to execute alternate pedaling movements of sufficient depth can be attributed to rigidity and dysrhythmia, which are common in persons with PD and FOG [15]. That clinimetrics did not differ between participants who succeeded and those

who failed on the pedaling task hampers the prediction of which participants are capable of performing the pedaling movements in the experiment.

A limitation of the current study is that the effects of VE cues were not compared to those of real visual cues in an overground experiment. Such direct comparison would have strengthened the validation of VE cues. Furthermore, our study did not include a control group of PD patients without freezing. Including such control group would allow to determine whether findings are related to PD, or to FOG.

5. Conclusion

We were unable to validate a virtual environment paradigm for investigating the neurophysiological mechanisms involved in visual cueing in PD patients with FOG. The original virtual environment paradigm that we based our virtual environment cues upon has earned its spurs in investigating the neural mechanisms underlying FOG. Adding effective visual cues to the paradigm would be a giant leap in disentangling the neurophysiological pathways mediating the effects of external cues. These insights would empower a mechanism-based development of effective cueing devices, with a final goal of improving gait in PD patients with FOG.

Data availability statements

The dataset generated and analyzed during the current study is stored in the Donders repository (<http://hdl.handle.net/11633/aactf4ln>).

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Ethical statement

This study was performed in accordance with the guidelines of the Declaration of Helsinki (1964), approved by the medical ethics committee Twente (NL60687.044.17) and registered in the Dutch trial registry (NTR6409; 2017-02-16). All participants provided written informed consent prior to their inclusion in the study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

MB was not employed by VicarVision at the time of his active role in the study (see author contributions). VicarVision has had no role in the study design, in the collection, analysis and interpretation of data, in the decision to publish, nor in the preparation of the manuscript.

Author contributions

SJ was involved in the conception and design of the study, the acquisition, analysis and interpretation of the data, writing of the manuscript and editing of the final manuscript for submission.

JH contributed to the analysis and interpretation of the data, and to the writing of the manuscript.

MB and ED developed the software used in the experiments.

BB was involved in the critical appraisal of the manuscript.

RvW and TH were involved in the conceptual design and set-up of this study, the analysis and interpretation of the data, critical revision of the manuscript, and supervision over the study.

All authors read and approved the final manuscript.

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