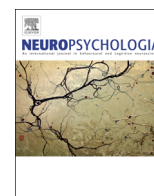




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Auditory cueing in Parkinson's patients with freezing of gait. What matters most: Action-relevance or cue-continuity?

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ABSTRACT

Gait disturbances are a common feature of Parkinson's disease, one of the most severe being freezing of gait. Sensory cueing is a common method used to facilitate stepping in people with Parkinson's. Recent work has shown that, compared to walking to a metronome, Parkinson's patients without freezing of gait (nFOG) showed reduced gait variability when imitating recorded sounds of footsteps made on gravel. However, it is not known if these benefits are realised through the continuity of the acoustic information or the action-relevance. Furthermore, no study has examined if these benefits extend to PD with freezing of gait. We prepared four different auditory cues (varying in action-relevance and acoustic continuity) and asked 19 Parkinson's patients (10 nFOG, 9 with freezing of gait (FOG)) to step in place to each cue. Results showed a superiority of action-relevant cues (regardless of cue-continuity) for inducing reductions in Step coefficient of variation (CV). Acoustic continuity was associated with a significant reduction in Swing CV. Neither cue-continuity nor action-relevance was independently sufficient to increase the time spent stepping before freezing. However, combining both attributes in the same cue did yield significant improvements. This study demonstrates the potential of using action-sounds as sensory cues for Parkinson's patients with freezing of gait. We suggest that the improvements shown might be considered audio-motor 'priming' (i.e., listening to the sounds of footsteps will engage sensorimotor circuitry relevant to the production of that same action, thus effectively bypassing the defective basal ganglia).

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1. Introduction

1.1. Background

Parkinson's disease is a neurodegenerative disorder characterized by a substantial loss of dopaminergic cells in the basal ganglia resulting in deficient communication between subcortical and cortical structures (Jankovic et al., 2007) and inadequate activation of the SMA, anterior cingulate cortex and left putamen during the performance of self-paced actions (Jahanshahi et al., 1995). This impaired output from the basal ganglia can lead to movement slowness (bradykinesia), reduced movement amplitude (hypokinesia) and problems initiating movements (akinesia) (Blin et al.,

Abbreviations: nFOG, the participant group without freezing of gait; FOG, the participant group self-reporting freezing of gait; CV, coefficient of variation

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1991; Bloem et al., 2004; Schaafsma et al., 2003). For example, Parkinson's patients will often exhibit reduced walking speed and step length, alongside increased temporal and spatial gait variability compared to healthy controls (Hausdorff et al., 1998). Furthermore, approximately 50% of people with advanced Parkinson's will experience freezing of gait (Giladi et al., 2001a, 2001b); the episodic sensation of one's feet being 'glued' to the floor, preventing the initiation of a step. Parkinson's patients with freezing of gait also exhibit pathological gait between freezing episodes, demonstrating increased step coefficient of variation (CV) (Almeida and Lebold, 2010), asymmetry, rhythmicity (Hausdorff et al., 2003; Nantel et al., 2011) and deficits in bi-lateral co-ordination (Plotnik et al., 2008), compared to patients without freezing pathology.

There is growing evidence that Parkinson's compromises the execution of movements that are highly automatized and self-paced, whereas the performance of goal-directed or externally-paced movements can remain relatively unaffected (Redgrave,

2010, Torres, 2011). This distinction is based on studies showing that performance of self-paced actions, like walking (Rubinstein et al., 2002) or reaching (Majsak, 1998; Bieńkiewicz et al., 2013), significantly improves under conditions where relevant external information is available for a patient to follow; a phenomenon termed '*kinesia paradoxica*'. These studies demonstrate that the neural processes underpinning goal-directed movements are fundamentally different to those governing habitual/automatic movements. Further, it is suggested that improved motor output observed when patients 'follow' external sensory cue information can be rationalized as a shift between these neural processes, effectively bypassing defective basal ganglia circuitry (Morris et al., 1996).

The notion of sensory cueing in Parkinson's relates to the provision of either spatial cues that inform *where* movements should be guided (e.g., horizontal lines placed on the floor), or temporal cues that inform *when* a movement should be executed (e.g., an auditory metronome). Improvements in motor performance achieved through the use of simple sensory cues are well-documented and the subject of several review papers (Rubinstein et al., 2002, Rocha et al., 2014; Spildooren et al., 2012; Nieuwboer, 2008). Such improvements are often demonstrated in the context of reducing gait variability when patients walk on static visual targets and/or attempt to step in time to a metronome (Rubinstein et al., 2002). Compelling examples of *paradoxical kinesia* can also be found in specific case studies. Snijders and Bloem (2010) showed that a patient was able to freely ride a bicycle despite experiencing severe freezing of gait during self-paced gait. Another example shows a patient overcoming freezing of gait by kicking a ball attached to some string (Asmus et al., 2008). Severe gait deficits such as freezing of gait often persist despite optimal pharmacological (Giladi et al., 2001a; Bloem et al., 2004) or surgical intervention (Ferraye et al., 2008; Fasano et al., 2011). Consequently, there is a clear need to conceive of new and improved sensory cueing techniques available for patients, especially for those with freezing of gait pathology (Nieuwboer, 2008).

1.2. Auditory cueing

When walking, people often need to visually search their intended path (Patla and Vickers, 1997). Therefore, visual cueing strategies inevitably impose various impracticalities for use in daily life. While auditory cueing largely bypasses this problem, attempts to develop acoustic cues for Parkinson's may have been discouraged by a reported detrimental influence of listening to music whilst walking (Brown et al., 2009). Apart from providing rhythmic temporal information, musical sounds have little relevance to specific actions concurrently attempted by listeners. However, there is an alternative; imitating the sounds of real actions, where the dynamic content of the acoustic information is directly relevant to the actions performed. Furthermore, action-relevant sounds not only specify temporal, but also spatial information (Gaver, 1993; Young et al., 2013).

Recent evidence suggests that, when walking to auditory cues, improvements to gait in Parkinson's patients are directly influenced by the specific nature of auditory information presented. Young et al. (2014) showed that when Parkinson's patients (without freezing of gait pathology) listened to the sound of footsteps made on a gravel path and attempted to imitate the action they heard, not only did they successfully recreate steps at an appropriate step duration and length, but the variability of gait reduced significantly compared to when walking to a metronome played at the same cadence (Young et al., 2014; Rodger et al., 2014). The authors speculated that the benefits observed when walking to 'action-relevant' sounds were due to the putative function of so-called 'sensori-motor' neurons (Young et al., 2013;

2014) i.e., that auditory perception of stepping actions would elicit relevant pre-motor activity required for the performance of that same action (Bidet-Caulet et al., 2005; Buccino et al., 2001; Rizzolatti and Craighero, 2004). Consequently, Young et al. (2014) claimed that specific Parkinson's-related deficits in eliciting sufficient cortical activity (required for efficient movement co-ordination) might be compensated for by instigating relevant cortical activity directly through action-observation.

Aside from the action-relevance of sound cues, a second fundamental difference exists between the metronome and the footstep sounds used by Young et al. (2014). Whereas a metronome comprises discrete bursts of noise separated by silence, the footstep sounds contained no periods of silence and therefore represented a continuous source of acoustic information (for a detailed description see Young et al., 2013). The importance of cue-continuity has previously been demonstrated for visual cues. Azulay et al. (1999) showed that benefits derived from stepping on static visual targets placed on the floor were lost when the continuity of the information was disrupted using stroboscopic lighting. However, it is not currently known if the importance of cue-continuity observed in the visual domain extends to auditory cues. After all, it is possible that improvements to gait observed when patients walked to footstep sounds (Young et al., 2014) were achieved by virtue of the acoustic continuity of the footstep sounds, rather than the action-relevance and presumed audio-motor priming. Therefore, the current study incorporated four different types of auditory cues that varied in accordance with their action-relevance and/or acoustic continuity (see Fig. 1). The sounds of footsteps in a corridor were used as an action-relevant and non-continuous (discrete) cue and a metronome was used as a non-action-relevant and discrete comparison. In contrast, recordings of footsteps on gravel were used as action-relevant and continuous cues (see Young et al., 2013 for full description), and continuous non-action-relevant counterparts were synthesized by

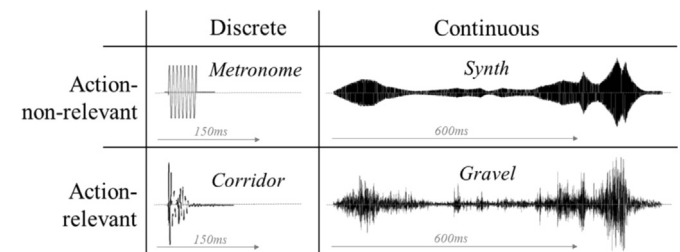


Fig. 1. The four types of auditory cues. The 'Gravel' footsteps used in the current study were identical to the 'Medium step length' sounds used previously (Young et al., 2013; 2014). To record these sounds, a young healthy male was asked to walk (on horizontal visual cues placed 70 cm apart at a cadence specified by an auditory metronome) along a 6 m path containing a single 60 cm² section that had been removed and filled with coarse gravel. The sounds of individual footsteps made on this gravel surface were recorded over twenty walks of the path using a pair of Rode NT2 microphones. This process was repeated for nine different step durations between 500 ms, and at 50 ms intervals, up to 900 ms. This created a database of individual footstep sounds that were subsequently concatenated according to the relevant step duration (500, 550, 600, 650, 700, 750, 800, 850 and 900 ms), resulting in a continuous representation of a person walking on a gravel surface at a specific step length and duration (for further details see Young et al., 2013). The 'Corridor' footstep sounds were recorded for the purpose of the current study using the same protocol and equipment, as described for Gravel sounds, but in a corridor with a solid wooden floor throughout. Whereas footsteps on gravel produces a continuous noise throughout each stance phase, the corridor footsteps only produced a significant sound at heel-contact for 80–140 ms, followed by silence until the onset of the heel-contact of the opposite limb. Both 'Metronome' and 'Synth' sounds were generated using acoustic editing software (SONAR, Cakewalk Inc.). The duration of each metronome beat was also matched to approximate the sound of heel-contacts present within Corridor cues. For each Gravel footstep sound recorded, we generated a noise signal with an equivalent duration and sound intensity envelope. This was carried out for samples recorded at all step durations. These synthesized samples were then concatenated using the same protocol as described above for the recorded footstep sounds.

generating bursts of white noise containing a comparable sound intensity profile and duration compared to the Gravel sounds (see Fig. 1 caption).

Previous studies using action-relevant sound cues have focussed exclusively on Parkinson's patients without freezing of gait pathology (nFOG) (Rodger et al., 2014; Young et al., 2014). Therefore, the current study included two groups: (1) nFOG, and (2) Parkinson's patients self-reporting freezing of gait (FOG). The purpose of this research was to interactively examine the two specific cue-parameters of action-relevance and cue-continuity (see Fig. 1), to observe which of these specific parameters contributed to improved temporal regulation in stepping, and to compare the effects between nFOG and FOG groups.

1.3. Stepping in place task

Freezing of gait is notoriously difficult to provoke in a controlled manner (Nieuwboer and Giladi, 2008; Snijders et al., 2008; Plotnik et al., 2007; Nantel et al., 2011; 2012; Almeida and Lebold, 2010) possibly due to heightened attention associated with participants being observed (Nieuwboer and Giladi, 2008). Nantel et al. (2011) showed that freezing of gait can be provoked in a repetitive, alternating Stepping In Place (SIP) task, where Parkinson's patients make alternate steps on two forceplates; a paradigm previously employed to mimic gait in below knee amputees (Centomo et al., 2007) and to evaluate the podokinetic reflex in healthy adults (Reed-Jones et al., 2009). Not only does the SIP paradigm provide measures of common gait variables such as step CV, swing CV, rhythmicity and asymmetry, but it also provides an objective measure of freezing of gait that correlates with self-reported freezing of gait with a high degree of specificity and sensitivity (87% and 93% respectively) (Nantel et al., 2011). Nantel et al., (2011) also formerly observed patients performing a 125 m walk that included gait initiation training, disruption of visual information and dual-tasking. However, according to the authors, none of these attempts to induce freezing of gait were as successful or informative as those recorded during the SIP protocol (Nantel et al., 2011). In addition to these issues, researchers have reported an intricate link between increasing step length and reducing variability of step frequency when walking (Hausdorff et al., 1998). The SIP task controls for the potentially confounding influence of step length on temporal variability. Therefore, we deemed the SIP task to be the most appropriate paradigm for evaluating the influence of the various sound cues (described in Fig. 1) on temporal regulation of stepping.

We predicted that in all trials containing an auditory cue, both FOG and nFOG groups would demonstrate significant reductions in temporal variability relative to Baseline trials (stepping without a cue). However, we expected that action-relevant cues (regardless of cue-continuity) (see Fig. 1) would induce proportionately greater benefit. Consequently, in the FOG group, the time spent stepping before the onset of the first freeze would be significantly longer when walking to action-relevant cues, compared to their non-action-relevant counterparts. Further, as temporal gait variability was likely to be higher in the FOG group at Baseline, we predicted that the benefits to gait observed in the FOG group would be comparatively higher compared to nFOG.

2. Materials and methods

2.1. Participants

Nineteen subjects with Parkinson's disease (mean age: 62 ± 11 (nFOG) and 63 ± 9 (FOG)) were recruited from the Stanford Movement Disorders Clinic and participated in a single research

session. All participants gave written informed consent. With the exception of one participant, all were in an OFF medication state (long-acting dopaminergic medications were stopped ≥ 24 h prior, and short-acting medications were stopped ≥ 12 h prior to testing). Participants were excluded from the study if they had dementia, significant hearing loss, or reported any musculoskeletal or neurological issue (other than Parkinson's) that significantly affected their walking. The study protocol received institutional ethical approval and was carried out in accordance with the principles laid down by the Declaration of Helsinki. After data were collected for four patients (FOG only), a sample size calculation was performed on data representing percentage changes in Step CV relative to Baseline trials (details of this variable are provided in Section 2.4). For this calculation we performed a within-subject comparison between trials containing metronome and gravel footstep sounds (as per Young et al., 2014). This analysis revealed that only 9 FOG participants were required to obtain a statistically significant effect. However, it should be acknowledged that the effect sizes observed in the full cohort were notably smaller than that observed within this sample size calculation.

All participants were divided into two groups based on their response to question #3 of the Freezing of Gait Questionnaire: *Do you feel that your feet get glued to the floor when walking, turning or when trying to initiate walking? Possible responses were: 0= never; 1= about once a month; 2= about once a week; 3= about once a day; 4= whenever walking.* Participants were categorized as a 'freezer' (FOG group) if their response was equal to or greater than 2 (Giladi et al., 2009), otherwise they were placed in a 'non-freezer' (nFOG group). In our cohort, all participants reported a score of either 0 or 3 (see Table 1).

2.2. Experimental design: SIP protocol

In the SIP protocol participants were instructed to step in place on two adjacent AMTI forceplates customized to fit a SMART EquiTest (Neurocom, USA). The protocol consisted of an initial appraisal of step duration (see below) followed by 6 full trials. At the start of each full trial participants were instructed to stand still with their eyes open and to start stepping at a comfortable pace once they heard a *beep* (occurring after 10 s) played through a pair of headphones that were worn throughout. Participants were instructed to keep stepping until they heard a second *beep* (occurring after 80 s). In Baseline trials, participants listened to an audio file that contained no sound other than the two beeps. In trials containing auditory stepping cues, the sound files contained the stepping cue throughout the entire track with the beeps embedded at 10 s and 80 s. Before the start of each cued trial participants were given the following instruction: "If you hear a sound please try to synchronise your own stepping in time to that sound. If you do not hear any sound, just step normally. Please start stepping when you hear the beep". Participants were given the option of sitting down and resting between every trial. The first of the 6 full trials was a familiarization/practice trial, where participants were asked to SIP at a self-selected pace (i. e., under Baseline conditions). This was done to allow the experimenter to confirm that participants understood all the instructions and to give

Table 1
Participant characteristics.

Measure (range of possible scores)	nFOG (n=10)	FOG (n=9)
Age (years)	61.68 \pm 11.13	62.82 \pm 8.82
UPDRS motor examination	31.8 \pm 21.81	32.6 \pm 21.33
H&Y	2.2 \pm 0.45	2.4 \pm 0.53
Years since diagnosis	6.46 \pm 5.42	10.71 \pm 6.01
FOG questionnaire: Q3	0 \pm 0	3 \pm 0

participants the opportunity to ask any questions after having attempted a whole trial. The remaining 5 trials were used for data analysis. These trials contained one Baseline and the four different auditory cues (Fig. 1), the order of which was randomised.

2.3. Appraisal of step duration

The step duration presented within the auditory cues was matched to participants' step duration observed in Baseline conditions. To appraise each participant's baseline step duration, a tri-axial accelerometer was attached to participants' right heel and data were recorded over a 20 s SIP trial. If a participant froze during the stepping frequency appraisal, the process was repeated. Peaks in the vertical acceleration profile of the heel were used to approximate the mean duration between heel-contacts in the right foot (stride duration) over 6 gait cycles. This value was divided by 2 to provide an indication of mean step duration. It is suggested that to address motor deficits contributing to rhythmic disturbances, sensory cues aimed at stabilizing motor output are best presented at Baseline frequencies (Nieuwboer, 2008). Therefore, in the current study we selected auditory cues that best represented each participant's Baseline step duration. With the range of available cues differing by 50 ms (see Fig. 1), the maximum error between participant's actual Baseline step duration and that presented in the cue was 25 ms. This resulted in the following cues being used in the FOG group: 2×450 ms, 2×500 ms, 2×550 ms and 4×600 ms, and the nFOG group: 3×450 ms, 3×500 ms, 1×550 ms, 2×650 ms and 2×700 ms.

2.4. Data analysis

The following stepping characteristics were calculated using force plate data from the EquiTest and an algorithm specified by Nantel et al., (2011) (see Fig. 2(a)): (1) Step time CV (of both legs); (2) Swing time CV (of both legs); (3) Rhythmicity (defined as the mean stride time CV of both legs); (4) Asymmetry (defined as $100 \times |\ln(SSWT/LSWT)|$, where SSWT and LSWT correspond to the leg with the shortest and longest mean swing time over the trials,

respectively).

The onset time and duration of freezes were calculated using the computerized algorithm described by Nantel et al. (2011). In every trial, participants were formerly observed by a trained clinician, who created a report for each trial detailing observations of freezing of gait. These reports were later corroborated by visual inspection of video recordings of participant's feet during each trial. These reports were used to verify the output of the freezing of gait-detection algorithm (see Fig. 2(b)).

Statistical tests were performed in two stages. First, mean data for each stepping metric (Step CV, Swing CV, Rhythmicity, Asymmetry) were entered into separate mixed ANOVA ($2 \times$ group, $5 \times$ cue parameter ($4 \times$ experimental conditions + $1 \times$ Baseline)). One difficulty presenting results from this analysis is that within-subject changes can be masked by substantial between-subject variability. Therefore, in a second stage of analysis, stepping metrics from each cued trial were expressed as a percentage change relative to that observed at Baseline (no cue) for each participant. As described by Young et al., (2013, 2014), this process of normalising data allows a more insightful comparison between conditions. These percentage values were entered into a second mixed ANOVA ($2 \times$ group, $4 \times$ cue parameter) and repeated for each stepping metric including the time to the first freeze. All post hoc analyses were performed using Bonferroni corrected *t*-tests. For all analyses, if participants failed to start stepping at any point within a trial, no data were included in the analysis for that trial for any dependent measure. This occurred in four trials ($1 \times$ Metronome, $1 \times$ Corridor, $2 \times$ Gravel). For data concerning the time spent stepping prior to the first freeze and freeze duration, data were analysed in accordance with both stages described above and entered into repeated-measure ANOVA (5 and $4 \times$ cue parameter for analysis of mean values and percentage change in values relative to Baseline, respectively). Data were only entered into these analyses for those patients who froze during Baseline and at least one cued trial.

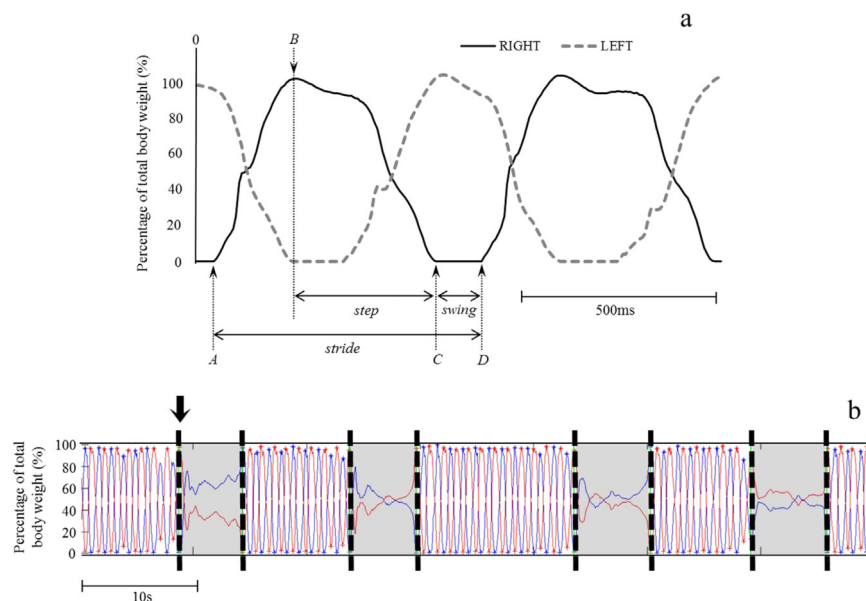


Fig. 2. Analysis of forceplate data. a) vertical forces (expressed as a percentage of participant's body weight) recorded by separate force plates under each foot. The solid black line represents the right foot and the dashed grey line represents the left. A & D = right foot contact on force plate; B = time when percentage of body weight on left foot reaches 0% and the right force plate will register ~100%; C = onset of swing in the right foot, where percentage of body weight reduces to 0% on the right force plate. The stride phase is defined as the time between A and D. Step time is defined as the duration between foot contacts between feet (i.e., between B and C). The swing phase occurs between C and D. b) Force traces for both feet over a whole trial. Data are representative from a patient with freezing of gait. Vertical dashed lines indicate the onset and offset of freezing episodes over the whole trial. The vertical arrow indicated the time of the first freeze (see Fig. 4).

3. Results

3.1. Mean stepping metrics

Results for Step CV showed a two-way interaction between group and cue-parameter ($F_{(4,52)}=3.083$, $p=.025$, $\eta_p^2=.219$). Post hoc analysis revealed that the FOG group significantly reduced Step CV in the Corridor and Gravel conditions compared to Baseline (see Table 2). There were significant main effects of group and cue parameter on Swing CV ($(F_{(1,11)}=6.523$, $p=.027$, $\eta_p^2=.372$) and ($F_{(4,44)}=2.937$, $p=.031$, $\eta_p^2=.372$), respectively), where the FOG group demonstrated significantly higher variability compared to nFOG across all conditions. Post hoc analysis showed no significant differences between cue parameters.

The Rhythmicity metric showed a significant two-way interaction between group and cue-parameter ($F_{(4,52)}=3.612$, $p=.011$, $\eta_p^2=.217$). Post hoc analysis showed a significant reduction in Rhythmicity in Corridor, Synth and Gravel (but not Metronome) conditions compared to Baseline, but only in the FOG group (see Table 2). There were no significant differences in the nFOG group. Results for Asymmetry showed no significant main effects or interactions.

3.2. Relative change in stepping metrics compared to Baseline

Results for Step CV showed a two-way interaction between group and cue-parameter ($F_{(3,39)}=4.02$, $p=.015$, $\eta_p^2=.268$). When stepping to the Gravel cue the FOG group produced relatively greater reductions in Step CV compared to nFOG. In the nFOG group, reductions in Step CV compared to Baseline were greater in the Synth, compared to the Gravel cue condition. In the FOG group, reductions in Step CV were significantly greater in both Corridor and Gravel conditions, compared to trials containing non-action-relevant cues (Metronome and Synth) (Fig. 3(a)). These between-cue differences were only found in data representing percentage change relative to Baseline trials, and not mean Step CV.

Results for Swing CV showed a main effect of both group ($F_{(1,17)}=8.370$, $p=.013$, $\eta_p^2=.411$) and cue-parameter ($F_{(3,39)}=4.918$, $p=.006$, $\eta_p^2=.291$), where FOG showed overall significantly greater reductions in Swing CV compared to nFOG (across all cue-parameters). Across both groups, reductions in Swing CV were greater in the Synth and Gravel conditions compared to Metronome (Fig. 3(b)). Although not significant when comparing mean values, when calculating percentage changes

relative to Baseline, Corridor cues induced relatively greater reductions in Swing CV compared to Metronome, demonstrating that for discrete cues, action-relevance imparts an additional benefit.

For rhythmicity there was a significant two-way interaction between group and cue-parameter ($F_{(3,39)}=4.961$, $p=.005$, $\eta_p^2=.262$) (Fig. 3(c)). There were no significant differences between cue-parameters in the nFOG group. However, FOG significantly improved Rhythmicity when stepping to the Corridor and Gravel cues compared to the Metronome. FOG also demonstrated significantly greater reductions in Rhythmicity compared to nFOG in the Gravel condition. There was no significant effect of group or cue-parameter on stepping asymmetry.

3.3. Time spent stepping before first freeze

For the FOG group, calculations of the time spent stepping before the onset of the first freeze showed a significant effect of cue-parameter ($F_{(4,16)}=2.986$, $p=.044$, $\eta_p^2=.427$). Post hoc analyses showed that patients stepped for significantly longer durations when listening to the Gravel cues compared to Metronome and Corridor cues (see Fig. 4). This main effect and post hoc analyses were preserved when calculating this time as a percentage change relative to Baseline ($F_{(3,18)}=4.730$, $p=.021$, $\eta_p^2=.542$). When stepping to Gravel cues, patients stepped for approximately 35% longer durations before the first freeze compared to Baseline. However, this difference was not statistically significant. No significant differences were found among cue-parameters in the number of freezes in each trial, or the total time spent in a freeze.

4. Discussion

4.1. Action-relevance vs acoustic continuity

This study evaluated the utility of different auditory cue-parameters in people with Parkinson's with and without freezing of gait pathology. Whereas nFOG did not significantly improve any metric of stepping performance using auditory cues relative to Baseline (Table 2), FOG demonstrated remarkable improvements in temporal regularity, particularly during trials containing action-relevant cues. In the FOG group, improvements in Step CV were greater in both Corridor and Gravel trials compared to their non-action-relevant counterparts (Metronome and Synth) and Baseline

Table 2
Mean stepping metrics.

	Group	Baseline	Metronome	Corridor	Synth	Gravel
Step CV ^{a,*}	nFOG	6.45 ± 2.03	5.87 ± 1.29	5.02 ± 2.16	5.12 ± 2.04	6.37 ± 1.52
	FOG	28.63 ± 18.64	19.45 ± 18.3	15.53 ± 10.79 ^{d,*}	20.04 ± 18.49	9.55 ± 3.45 ^{d,*}
Swing CV ^{a,*}	nFOG	10.32 ± 2.9	13.57 ± 11.75	9.77 ± 2.27	9.62 ± 2.59	9.91 ± 2.07
	FOG	21.63 ± 9.17	20.66 ± 8.9	18.39 ± 6.84	16.0 ± 4.95	14.4 ± 2.57
Rhythmicity ^{c,*}	nFOG	4.56 ± 1.63	3.68 ± 0.75	5.8 ± 6.28	3.84 ± 0.97	4.21 ± 0.77
	FOG	24.05 ± 17.74	19.53 ± 13.52	14.88 ± 9.76 ^{d,*}	16.14 ± 16.02 ^{d,*}	15.61 ± 17.22 ^{d,*}
Asymmetry	nFOG	8.33 ± 3.71	8.48 ± 3.58	11.06 ± 5.07	9.49 ± 5.72	6.99 ± 2.8
	FOG	12.39 ± 10.87	19.04 ± 8.77	13.8 ± 10.58	17.78 ± 10.99	14.67 ± 8.0
Time to first freeze (s) ^b	FOG	31.1 ± 17	24.1 ± 12	22.7 ± 15	30.8 ± 19.8	44.9 ± 15.5

^a Main effect of group.

^b Main effect of cue-parameter.

^c Two way interaction between group and cue-parameter.

^d Significant difference to Baseline condition.

* $p < .05$.

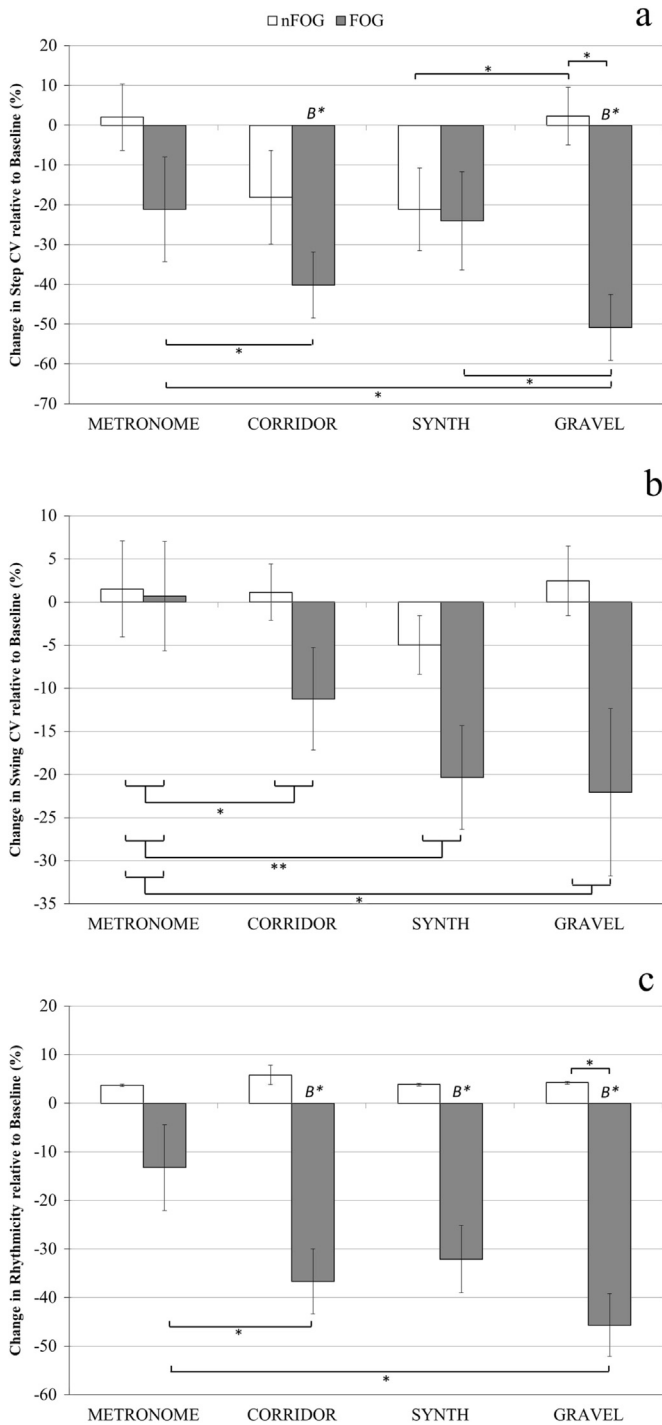


Fig. 3. Percentage changes in: a) Step CV, b) Swing CV, and c) Rhythmicity, relative to Baseline. Error bars represent standard error of the mean. B=significant change relative to Baseline, as determined by analysis of mean stepping metrics (see Table 2). $p < .05^* p < .005^{**}$.

trials (Fig. 3(a)). These results support previous claims that action imitation can enhance motor performance in Parkinson's patients to a greater extent compared to traditional auditory cueing methods (i.e., walking to a metronome) (Young et al., 2014; Rodger et al., 2014). Prior to the current study there was no information to suggest whether additional benefits to gait derived from Gravel cues (Young et al., 2014) were a consequence of the action-relevance or the continuity of the auditory information. The current results demonstrate that even when action-relevant sounds are presented in an intermittent form (Corridor), benefits to Step CV

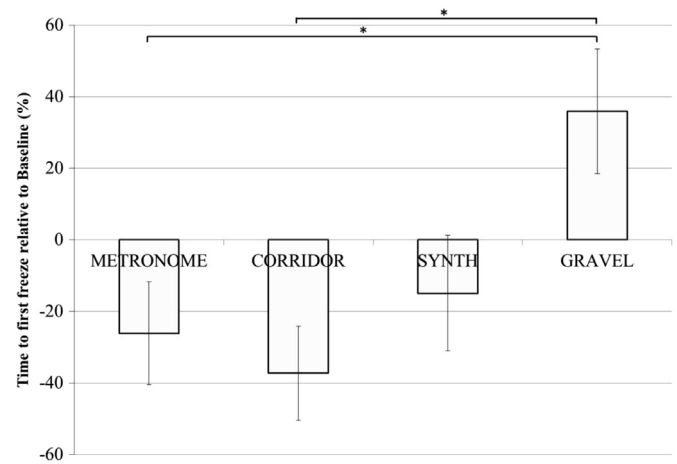


Fig. 4. Percentage change in the time spent stepping before the onset of the first freeze in the FOG group. Error bars represent standard error of the mean. $p < .05^*$.

are preserved. In contrast, Synth cues did not induce benefits of the same magnitude (Fig. 3(a)), asserting that action-relevance could be a more dominant factor in enhancing motor performance in FOG compared to acoustic continuity.

Whereas action-relevance appears to represent the most meaningful factor in promoting regular stepping in FOG, acoustic continuity did impact on the variability of time spent in swing (Fig. 3(b)). We suggest that this result can be explained through a simple interpretation of how the information presented in each cue translates to the sequence of temporal events within each gait cycle. When walking in a corridor, only the heel contact phase of gait produces a significant sound, meaning that no information is provided for patients about when each foot should leave the ground to start swinging. In contrast, when walking on gravel, sound is continuously produced throughout stance until toe-off (Farnell, 2007; Visell et al., 2009). Therefore, reductions in swing phase variability during Synth and Gravel trials are likely to be a consequence of toe-off times being specified within the cue (unlike Metronome and Corridor), as opposed to the continuity of the acoustic information *per se*. Azulay et al. (1999) demonstrated the importance of presenting visual cue information in a continuous manner. In the current study, cue-continuity did not significantly impact on Step CV or Rhythmicity (Fig. 3(a) and (c)), suggesting that conclusions drawn from visual cueing paradigms do not fully extend to the auditory domain.

With reference to non-action-relevant cues, it seems that Parkinson's patients with freezing of gait can only improve aspects of the gait cycle that are represented within the acoustic information, regardless of cue-continuity (Fig. 3(a)). In contrast, there appear to be properties of action-relevant cues that transcend this rule. Corridor cues led to greater reductions in Step CV and Swing CV compared to the Metronome (Fig. 3(b)) (i.e., the timing of each toe-off with respect to the preceding heel-contact was improved). As described above, Corridor cues did not directly specify toe-off times, only heel-contact times. These results demonstrate that through auditory perception of action relevant sounds, listeners can gain insight into aspects of actions that are not directly specified in the cue (i.e., a listener only 'hears' heel-contacts, but they perceive the entire action). This concept of 'filling in the gaps' during action observation is reminiscent of the phenomenon of 'Apparent Motion' described in the domain of visual perception (Shiffrar and Freyd, 1990) (see Young et al., 2013 for further discussion in the context of stepping sounds).

The apparent superiority of action-relevant stepping cues can be interpreted with reference to the putative function of sensorimotor neurons whereby listening to the sounds of actions can

induce activity in pre-motor areas required for movement planning (Aziz-Zadeh et al., 2006; Pizzamiglio et al., 2005; Bidet-Caulet et al., 2005); activity that is ordinarily deficient in Parkinson's due to malfunctioning basal ganglia circuitry (Jankovic et al., 2007). Consequently, action-relevant cues may provide a way of bypassing the defective basal ganglia and exploiting relatively preserved audio-motor circuitry to enhance movement co-ordination (Bucino, 2014). This approach represents an exciting opportunity for the design of future sensory cues that may contain a relatively small amount of acoustic information, yet maximise details of the perceived/required action and facilitate corresponding motor performance in listeners.

4.2. Freezing of gait

During Gravel trials the FOG group significantly extended the time spent stepping prior to the first freeze compared to Metronome and Corridor trials, and by 35% compared to Baseline (no significant difference) (Fig. 4). Whereas cue-continuity and action-relevance differentially improved specific aspects of stepping variability (Fig. 3), these individual acoustic attributes are seemingly not sufficient to enable patients to step for a longer period when provided independently. In fact, there appears to be a differential effect of cue parameter in this regard, as all cues except Gravel had a detrimental effect on the time spent walking before the first freeze.

Our current knowledge regarding the mechanisms underlying freezing of gait is very limited and the literature is dominated by hypotheses surrounding specific motor and non-motor factors known to elicit freezing of gait, such as walking through narrow spaces, turning, dual-tasking (Nieuwboer, 2008), increased anxiety (Martens et al., 2014), and deficits in cognitive flexibility (Amboni et al., 2008), set-shifting (Naismith et al., 2010), block design and matrix reasoning (Nantel et al., 2012). With so many factors being associated with freezing of gait, it is difficult to isolate individual perceptual, cognitive and/or motor processes that must have been altered through our manipulations of action-relevance and cue-continuity. Nevertheless, we can speculate as to the underlying mechanisms and identify specific areas that should be addressed in future research.

Attentional processes are known to heavily influence freezing of gait, as gait deficits increase when attention is divided between walking and a second cognitively demanding task (Giladi and Hausdorff, 2006). Therefore, finding ways to help patients with freezing of gait focus on walking and/or reduce the associated attentional costs (Canning, 2005) will likely lead to a reduction in stepping variability and consequently delay onset of freezing of gait. In our opinion, the simplest and most compelling explanation for the observed results is that cueing through continuous action-sounds may serve to lessen attentional costs associated with planning/monitoring actions by virtue of audio-motor action priming (Young et al., 2013). A practical illustration of this suggestion can be found when people walk side-by-side for an extended time, as they will often subconsciously start to walk in synchrony (Glass, 2001). Furthermore, people with severe gait disturbances often demonstrate improved stepping characteristics when walking with a partner (Hadar-Frumer et al., 2004).

In conjunction with concepts of motor priming, our results might also be interpreted through reference to other action domains founded on associating specific gestures with sounds. For example, for the perception and production of speech it is widely considered that, by generating so-called 'forward models' within the motor system, listeners can transform acoustic information into a 'phonetic code' (Skipper et al., 2007), which can then be compared (via efference copy) against internal candidate representations of speech gestures (Wilson and Iacoboni, 2006). As

such, acoustic input can be compared and contrasted against predicted acoustic consequences of the motor representation/intended motor output, thus generating a potential 'error signal' for use in adapting/correcting the motor representation/perceived acoustic gesture (Iacoboni, 2008; Wilson and Iacoboni, 2006). Assuming these processes are also used when perceiving sounds of nonverbal actions (such as the stepping sounds used here), it is possible that the cyclical perception of consecutive footsteps would allow patients to perform periodic spatial and temporal adjustments to improve the synchrony with the perceived actions. Based on the current results, we speculate that the Gravel sounds were the only cue to provide the continuous, dynamic and spectral information necessary to establish these processes (Young et al., 2013), thereby improving several metrics of variability and postponing the onset of freezing.

4.3. Limitations and implications for further research

When considering previous findings concerning the use of action sounds for walking in Parkinson's the current study contains important discrepancies that require clarification and discussion. Young et al. (2014) observed significant benefits (increased step length and reduced variability) of using the same Gravel cues in Parkinson's without freezing pathology. However, our results showed that nFOG derived no clear benefit from any of the auditory cues. When considering that sensory cueing often leads to increased gait variability in healthy controls (Young et al., 2014) one would expect that the benefit derived from sensory cueing would be proportionate to the magnitude of the gait deficits at Baseline. Therefore, we propose that benefits to stepping would have been observed in nFOG had their gait deficits at Baseline been more pronounced. This finding emphasizes the suggestion that sensory cueing is only appropriate in patients with pronounced gait disturbances. However, it also implies that the proportionately greater benefits observed in the FOG group may not relate directly to FOG pathology *per se* but rather increased disease severity.

In the current study, footstep sounds (and their synthesized counterparts) were based on recordings of forward walking, yet participants were required to SIP. Young et al. (2013) demonstrated that young healthy adults can perceive spatial information from the Gravel sounds used in the current study. Within the SIP task, this may have introduced a degree of conflict between the spatial characteristics of the action perceived within the cue and the action participants were instructed to perform. Nantel et al. (2012) showed that freezing of gait was associated with deficits in block design and matrix reasoning. There is also evidence that perceptions of sound intensity/volume (fundamental information for perceiving spatial information concerning gait (Young et al., 2013)) is deficient in Parkinson's patients (Ho et al., 2000). Therefore, it is plausible that such deficits would compromise the perception of spatial characteristics of the stepping actions heard, thus reducing 'spatial conflict' and enhancing motor performance in Gravel trials (Figs. 3 and 4). Conversely, if we presume that perceptions of spatial information/matrix reasoning were relatively superior in nFOG (Nantel et al., 2011) any resultant spatial conflict would serve to compromise motor performance. As such, aside from issues relating to potential group differences in disease severity, we suggest that spatial conflict is a likely candidate for the lack of significant improvements currently observed in nFOG. According to this rationale, we might expect that motor enhancements would be greater in both groups during forward walking, similar to that shown by Young et al. (2014), compared to SIP. Nevertheless, it is important to consider that in the FOG group, the most pronounced improvements were observed in the action-relevant cues, particularly in Gravel; presumably the only cue capable of

affording spatial information necessary to cause spatial conflict. This consideration bolsters the notion that action-relevance plays a more dominant role in enhancing motor performance compared to acoustic continuity.

Aside from possible issues relating to spatial conflict, the SIP task did not involve typical walking actions and the environment was not representative of daily life. As such, there is a clear need to carry out an equivalent study using forward walking in settings with greater ecological validity. Further work is also necessary to evaluate how attentional factors interact, not only with processes involved in action imitation, but also motor and non-motor symptoms commonly associated with Parkinson's disease and freezing of gait. Without this future research we cannot conclude that action-relevant and/or continuous sounds will deliver functional benefits for users. Nevertheless, the current study provides an indication that there is clear potential for these benefits to be realised. Furthermore, it provides examples of how specific acoustic manipulations can influence various aspects of motor performance.

It is important to acknowledge that the sound cues selected in the current study differed not only in regards to action-relevance and continuity, but also in terms of context (i.e., the sounds also differed qualitatively by virtue of the different walking surfaces and synthesis techniques used). It would have been possible, for example, to record both discrete and continuous stepping sounds on gravel. Our rationale for maintaining these qualitative differences related to the integrity of the perceived action. For example, to produce a discrete sound on gravel one would need to significantly alter several aspects of gait (i.e., walk with 'flat-footed' steps and avoid producing any downward pressure at toe-off). Our concern was that listeners would perceive and attempt to imitate this altered style of walking (Young et al., 2013). Therefore, we chose to generate our discrete sounds on a solid walking surface (Corridor), as one can walk without producing significant sounds following foot contact, and hence the 'style' of walking can be kept relatively consistent between cue-parameters.

Opportunities for future research include the recording and synthesis of sounds representing other actions important for daily living, such as reaching and grasping. However, there are important factors to consider. For example, walking sounds are especially conducive to recording and using as a cue because they typically produce sounds that people learn to associate with the respective actions. However, reaching and grasping do not consistently produce sounds that are sufficiently distinct to recognise and imitate. Therefore, future attempt to cue upper limb movements might primarily consider easily recognizable sounds that clearly afford information relevant to both spatial and temporal constraints (e.g. the sound of pulling a zipper).

There are countless factors that will likely influence the efficacy of specific cue types, including disease severity, cognitive deficits, mood state, and musical experience and preference. Therefore, we suggest that future research should not solely endeavour to identify a single optimal cue for all potential users. Instead, an opportunity exists to exploit: (1) the versatility of modern sound engineering techniques; and (2) the emergence of low-cost motion sensing technology, to create versatile cueing options that meet the preferences of specific users.

4.4. Conclusions

Action-relevant sensory cues induced greater reductions in temporal variability during a stepping in place (SIP) task in the FOG group compared to cues that do not represent an action. Even when listening to discrete footstep sounds that only represented the heel-contact phase of stepping (Corridor), FOG improved aspects of their stepping that were not directly represented within

the acoustic information (swing CV, Fig. 3(b)). Neither cue-continuity nor action-relevance was independently sufficient to increase the time spent stepping before freezing. However, combining both attributes (Gravel) did lead to significantly longer duration of SIP before the first freeze (compared to Metronome and Corridor cues). Collectively, these findings represent an exciting opportunity to develop new auditory cues that exploit the neural processes involved in perceiving actions through sound. The results of this study also suggest that the only auditory cue widely used by clinicians to date (Metronome) is the cue that produces the poorest results (Fig. 3). However, this claim should be treated with caution when considering the small cohorts used in the current study and others that support this claim (Rodger et al., 2014; Young et al., 2014).

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