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Can 'action-relevant' visual cues improve walking performance and reduce freezing of gait in Parkinson's disease?

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Summary

Gait impairments are a common symptom of Parkinson's disease (PD), one of the most severe being freezing of gait (FOG). PD compromises the execution of automated movements while goal-directed movements stay relatively unaltered, a phenomenon that is exploited by sensory cueing techniques. The presentation of 'action-relevant' information (i.e. information about someone else's past actions) may be an effective cueing technique which may activate the mirror neuron system. The aim of this thesis is to study how visual action-relevant cues can improve gait dynamics and reduce doorway-provoked FOG. The two experiments of this thesis were conducted using an immersive virtual reality environment. In Experiment 1 Healthy Controls (N=5), and idiopathic PD patients (N=5), walked using visual action-relevant cues (footprints) containing spatial (115% and 130% baseline step length), and temporal (No temporal information, 100% baseline cadence and 125% baseline cadence) information. The cues showed to be effective in increasing step length and step velocity while reducing overall gait variability in the PD group. In the first part of Experiment 2, virtual doorways (100% shoulder width and 125% shoulder width) were presented to the same two groups. Similar to past results using real doors, the virtual doorway reduced step length and step velocity while increasing overall gait variability. The doorways also induced FOG in one PD patient. In the second part of Experiment 2, the visual cues examined in Experiment 1 were tested while the participants crossed the virtual doorways. In the PD groups, the cues increased step length and step velocity while reducing overall gait variability. They were also effective in reducing the duration and frequency of the FOG episodes. These results showed that these action-relevant visual cues were an effective way of cueing normal walking and doorway crossing in PD patients.

Key words (max 5)

Parkinson Disease; Freezing of Gait, Doorway, Visual Cues; Virtual Reality.

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1 Introduction

Parkinson's disease (PD) is characterized by the loss of dopamine-generating cells in the basal ganglia (Jankovic, 2008) and dysfunctional activation of supplementary motor areas, anterior cingulate cortex, and left putamen during self-paced actions (Jahanshahi et al., 1995). These impairments in the basal ganglia can lead to bradykinesia (movement slowness), hypokinesia (reduced movement amplitude), akinesia (problems initiating movement), tremor, rigidity, and postural instability (Blin et al., 1991; Bloem, et al., 2004; Schaafsma et al., 2003). For example, patients with PD will often exhibit reduced walking speed and step length, as well as exhibiting increased temporal and spatial gait variability compared to healthy controls (Hausdorff et al., 1998). Moreover, approximately half of the patients with advanced PD experience freezing of gait (FOG) (Giladi et al., 2001). FOG events involve a brief, episodic absence, or marked reduction, of forward progression despite the intention to continue walking (Bloem et al., 2004). Whilst experiencing these episodes the patients usually report the feeling of their feet being glued to the floor.

Growing evidence suggests that PD compromises automated and self-paced movements while the production of goal-directed movement or externally paced movements stays relatively unaltered (Redgrave, 2010; Torres, 2011). This phenomenon is known as 'kinesia paradoxica' (Young et al., 2016) and is based on studies showing that self-paced movements, e.g. walking (Rubinstein et al., 2002; Lim et al., 2005) or reaching (Majsak, 1998; Bieńkiewicz et al., 2013), improve when relevant external information is present. An impressive example of this is the overcoming of FOG observed when a patient kicks a ball attached to a string (Asmus et al., 2008). This evidence suggests that the neural mechanism behind self-paced movement is different to the one that underlies externally controlled movements (Young et al., 2016). Furthermore, it suggests that in these instances there is a shift in the neural mechanisms employed to control movement that effectively bypasses defective basal ganglia circuitry (Morris et al., 1996).

Sensory cueing is related to the provision of either spatial cues that give information about where movements should be guided, or temporal cues, that give information about a rhythm (Young et al., 2016). The advantages of spatial cues are usually related to an improvement in step length and a reduction in step length variability (Azulay et al., 1999; Lewis et al., 2000; Morris et al., 1994a, 1994b, 1996). By contrast, the delivery of temporal cues has been shown to improve cadence (i.e. faster walking) and reduced variability (Hausdorff et al., 2007; McIntosh et al, 1997; Suteerawattananon et al., 2003). Traditionally cues have been understood as discrete events that help direct the focus of attention to specific processes of the gait dynamics (Azulay et al., 2006). For this reason, cues are kept as simple as possible, with a metronome being the usual way of delivering temporal information (Rodger, & Craig, 2016), while horizontal stripes have been the most common spatial cue.

However, our perceptual experience is not a succession of discrete events, but rather a continuous unfolding flow, populated by meaningful happenings. In this framework perception can be conceived as the pick-up of affordances, understood as possibilities for action (Gibson, 1979). If we think of sensory cues as affordances, it is relevant to study how events are specified in perception, the action-possibilities that are afforded by the cue, and the capabilities of the perceiver to detect and act upon such an event (Steenson & Rodger, 2015). For example, when walking to auditory cues, improvements in the gait of PD patients is directly influenced by the specific nature of the auditory information presented (Young et al., 2014). In Young et al. (2014) study, PD patients walked using the guide of a metronome (containing only temporal information) or of the sound of footsteps over gravel (containing not only temporal information but also spatial information). The footsteps were not only able to affect the step cadence and step cadence variability of PD patients (like a metronome) but also produced changes in step length and step length variability. Unfortunately, in the case of visual cues, little attention has been directed to the nature of the information being delivered through them. Therefore, there is a need to study the type of information delivered in visual cues, whether patients are able to attune to this information, and how the nature of this information improves the gait cycle.

If we look at the information delivered in visual cues, most studies have presented lines perpendicular to the walking direction of the participant. These studies use different distances in between the lines without any prior justification (e.g. 45 cm between the lines [Azulay et al., 1999], 40% of the height of the participant [Suteerawattananon et al., 2003], age and height step length matched to control participants [Morris et al., 1994a, 1994b, 1996]). Unlike the auditory cues used by Young et al. (2014), this type of visual cue only provides spatial information while the sound of footsteps over gravel contain rich information about a past action of a walker. This additional information has been defined as 'action-relevant' information (Young et al. 2014). The use of auditory action-relevant cues has already shown to be a more effective cueing method than a classical metronome, producing greater reductions of gait variability (Rodger et al, 2014, Young et al. 2014) and effectively reducing FOG (Young et al. 2016). The authors of these studies argue that these improvements are due to the putative function of 'sensory-motor' neurons (Young et al., 2013; 2014), also known as the mirror neuron system. It is hypothesized that the perception of stepping actions elicits relevant pre-motor activity required for the performance of that same action (Buccino et al., 2001; Rizzolatti & Craighero, 2004). It is possible that this neural system is activated by the action-relevant information afforded by the footprints, while horizontal lines will fail to convey this type of necessary information.

The aim of this master's thesis was the development of an action-relevant visual cue and the testing of this intervention under a key situation that has shown to be problematic for PD patients. Although auditory action-relevant cues have demonstrated to be an effective cueing method, there is no study that has tested a similar approach with visual cues. Moreover, cueing techniques are usually tested in a laboratory where participants have to walk over a treadmill or in another controlled situation. Although these artificial situations allow for a high experimental control (Loomis et al., 1999), they do so by compromising the ability to reproduce the situations in which PD patients experience their symptoms -like turning, sitting or crossing through narrow spaces-thereby reducing ecological validity. The few studies that tested visual cueing under ecologically representative designs found problems to produced reliable results (Griffin et al., 2011; Nieuwboer et al., 2007) due to the loss of experimental control. This may have hampered the study of the applicability of these kinds of methods in the real life of the patients.

Immersive interactive virtual reality (VR) provides a unique opportunity to overcome these difficulties. This technology allows for the precise control of the perceptual information presented to a participant immersed in the virtual environment while still allowing participants to freely interact and move within it. Therefore, we can present strictly controlled designs while keeping the ecological validity of the task very high (Loomis et al., 1999). This implies that virtual environments could be created that are representative of hazardous situations that in real life have shown to be problematic for PD patients. This would mean an increase of the experimental power due to an increase in the experimental realism. Furthermore, this technology also allows for a quick and personalized manipulation of the information delivered in the cues (Schultheis, & Rizzo, 2001). Thus, personalized cues can be created that are adapted to the patients' current walking capabilities as assessed by a short baseline measurement. Taking into account that perception has been shown to be scaled to the action-capabilities of each perceiver (Kamp et al., 1998; Mark, 1987; Warren, 1984; Warren & Wang, 1987), this is expected to allow researchers to create optimal cues that should be easier to reenact than cues that are fixated at a common distance for all participants.

2 Experiment 1

In this study different types of action-relevant visual cues were developed and tested in an immersive interactive VR environment that looked like a regular hallway. Participants coordinated their gait so that they stepped on various visual action-relevant cues. Taken into account that perception is scaled to the capabilities of the perceiver, the cues were built individually for each participant based on baseline measures that were taken at the start of the session. It was assumed that personalizing the cues maximized their effectivity, making them easier to use. The cues consisted of left and right black footprints (Figure 1) containing different spatial (115% or 130% of a baseline measure of the participant's own step length) and temporal information (No temporal information, 100% or 125% of the participant's baseline cadence). When temporal information was presented, footprints changed color to red with a rhythm as if they were reacting to someone walking slightly ahead of the participant with an imposed cadence. As the aim of this experiment was to test if the intervention was able to improve walking performance in PD, all results are presented as a ratio of change from the baseline condition that was used to create the cues.

Patients were expected to be able to tune into the two types of information (spatial and spatio-temporal) delivered by the visual cues, resulting in improvements in the gait parameters, namely step length, step cadence, step velocity and the variability of each of these gait parameters. In particular, the footprints with only spatial information should improve in step length, step velocity and the variability of these parameters. The footprints that delivered spatio-temporal information were anticipated to also improve step cadence variability and increase in step cadence as a function of the rhythm presented in the cues. Furthermore, the improvements in step length and step velocity were hypothesized to vary between the cues as a function of the different spatial information that they contained. Finally, as PD patients are expected to have larger gait variability in their baseline measures than healthy control (HC) participants, the decreases in variability are expected to be larger in this group than in the HC group (Young et al. 2014).

2.1 Methods

Participants: Two groups of participants participated: One group of HC (N=5; mean age= 68.0 yr.; SD= 8.6 yr.), and one group of PD patients (N=5; mean age= 70 yr.; SD=6.8) were recruited from the Parkinson's UK association. Motor disability was assessed using part III of the MDS-UPDRS questionnaire (Goetz et al., 2008). This test consists of 33 items each of which is scored from 0 to 4. Higher results in this test meant that the patients were experiencing more motor symptoms, while lower results meant the patients were experiencing fewer motor symptoms. 'The freezing of gait questionnaire' (FOGQ; Giladi et al., 2000) was used to asses if the patients had experienced freezing in the week prior to the experiment. Mean scores higher to two meant that the patient had experienced FOG episodes regularly last week. The results of these tests are presented in Table 1, along with demographic information about the PD patients. Before the start of the experiment, the shoulder width of the participants was measured using a tape measure. One healthy adult quit the experiment before ending the study. Furthermore, one PD patient was not able to complete the study due to the severity of his symptoms and his data has not been included in any of this analysis nor in Table 1. These two participants were replaced by a new Healthy Control and a new PD patient.

Participants	Age (years)	Gender	Years from diagnose	Clinical state	UPDRS Part III	FOG-Q
PD1	*61*	*Female*	*7*	*ON*	*10*	*0.33 (0.51)*
PD2	*68*	*Female*	*6*	*OFF*	*35*	*3.00 (0.63)*
PD3	*75*	*Male*	*8*	*ON*	*34*	*2.80 (0.23)*
PD4	*77*	*Male*	*6*	*OFF*	*29*	*0.66 (1.02)*
PD5	*64*	*Female*	*2*	*ON*	*18*	*0.33 (0.52)*
PD6	*76*	*Male*	*5*	*ON*	*28*	*3.16 (0.40)*

Table 1: Demographic information about PD patients. The clinical state is related to the effect of the medication; an 'on' state meaning the PD patient is responding well to the medication while an 'off' state meant they were not responding to their medication. The results of the FOG-Q are presented as the mean (SD) of all the results in the test. PD 1 to 5 were the participants of Experiment 1. PD6 was included in the sample due to the data of PD3 not being usable in Experiment 2 (See Methods of Experiment 2 for more information).

Apparatus: The experiment was performed using immersive interactive VR technology housed within the Movement Innovation lab at Queen's University Belfast. The tracked space in this laboratory is 8m long by 5m wide. The virtual environment was constructed using a game developer program (Unity 5.4.1f1). The environment consisted of a hallway of 20m long and 2.5 m high. A red line, representing the end of the trial, was presented 6.5 m away from the starting point that was represented by a yellow line. The width of the hallway in all trials was equivalent to 5 shoulder widths of the current participant. This virtual representation of the hallway was presented to the participant using a head-mounted display (Oculus Rift DK2; Oculus VR, Irvine, California, USA), containing two color micro-displays. The images were refreshed at 120 Hz to generate the illusion of movement inside the virtual environment. Spatially offset images were sent to each display producing a binocular view.

Head position and orientation were tracked using an Intersense head tracker (IS900) attached to the head mounted display. This system uses a mix of ultrasound and inertial sensors to detect position and orientation (InterSense Inc., Bedford, Massachusetts, USA). Head position and orientation were used to determine the participant's viewpoint in the virtual world and record the walking path. This information was updated in real time.

The kinematic data of the participants was recorded using 12 Qualysis (Oqus3) infrared motion capture cameras (Qualisys Ltd., Göteborg, Sweden). On their foot participants wore rigid bodies, with three reflective markers each, which were detected by the system with a sampling frequency of 100 Hz. In order to allow participants to see their own feet in the virtual environment, we used a routine that streamed the data online from the infrared motion capture system into the virtual environment (Qualisys Unity SDK), with a sampling frequency of 30 HZ. The position of the rigid bodies was detected by the system, using its position to control the position of two blue rectangular boxes that represented the feet of the participants in the VR environment. This accurate representation of their foot position in the VR environment allowed participants to see where they were stepping in the virtual environment.

Figure 1: Picture of the footprints that were used as visual cues in the experiments.

Procedure: Throughout the experiment, two experimenters were present. One controlled the virtual environment and the motion capture system while the other walked by the participants all the time in order to ensure their safety. First, participants completed four familiarization trials to get used to walking in the VR system. After this, participants performed four walking trials without cues to get a baseline measure of step length and step cadence (see Table 2 for the baseline results). These measures were used to construct personalized parameters for each participant for both the spatial and spatio-temporal cues. After this, participants walked eight more times guided by visual cues containing either spatial or spatio-temporal information. These cues were different to the ones used in the experimental trial (they contained slightly different spatial and temporal parameters) and were intended to train the participant in the use of the visual cues. Each trial consisted of a 6.5 m walk towards the red line that marked the end of the trial. After this, participants turned with the help of an experimenter. Once they had completed the turn a new trial started in which they again walked to the red line. At the end of the block of practice trials, participants were allowed to rest for two minutes.

In the experiment there were two different distances between successive footprints (115% of baseline step length (‘normal’; N)), 130% of baseline step length (‘long’; L)) that were crossed with three different types of temporal information (No temporal information (NT), 100% of baseline cadence (100%), and 125% of baseline cadence (125%)). This means that there were six different conditions in the experiment, two spatial conditions (N-NT and L-NT) and four spatio-temporal conditions (N-100%, N-125%, L-100%, and L-125%). The footprints consisted of black pictures of right and left black footsteps 25.5 cm long and 12.75 cm width (the equivalent to a regular 40 European shoe size; see Figure 1; see https://www.youtube.com/watch?v=9n29zjS9KXQ for an example of a spatial trial). In the spatio-temporal conditions, one footstep at a time changed color from black to red to specify a cadence, as if the change of color was due to an invisible person walking in front of the participant. The changes happened ahead of the participants in order to allow them to look ahead (see https://www.youtube.com/watch?v=vql_CE69y0Y for an example of a spatio-temporal trial). Each of the cues was presented in one of six walking trial blocks with the type of cue in each block being determined randomly. Participants walked to the red line, and then turn, with the help of one of the experimenters; after this, a new trial started. Each block consisted of 8 trials. After each block had ended participants rested for some time in order to avoid any residual effects of the cues. Participants were instructed to walk on the footsteps on the floor, and to try to match their rhythm to the rhythm imposed by the change in color of the footsteps, if such a change was present. Before the start of the block participants were informed of the type of cue (spatial or spatio-temporal) that they were going to face.

Dependent variable	**Group**	**Baseline results**
Step length	*HC*	*0.56 m (0.13 m)*
	PD	*0.49 m (0.10 m)*
Step cadence	*HC*	*1.74 Hz (0.21 Hz)*
	PD	*1.70 Hz (0.23 Hz)*
Step velocity	*HC*	*1.00 m/s (0.19 m/s)*
	PD	*0.89 m/s (0.21 m/s)*
Step length CV	*HC*	*0.07 (0.03)*
	PD	*0.23 (0.12)*
Step cadence CV	HC	*0.07 (0.04)*
	PD	*0.23 (0.21)*
Step velocity CV	*HC*	*0.11 (0.05)*
	PD	*0.27 (0.10)*

Table 2: Baseline results for the two groups for the six relevant gait parameters. The results of the variability are presented using the coefficient of variation (CV) and therefore are expressed in a dimensionless ratio. Results are presented as mean (SD).

Data analysis: The Qualysis data were analyzed using custom-made Matlab (Matlab 2016b; Mathworks, inc, Natick, Massachusetts, USA) routines. The program first filtered the data using a low-pass butterworth filter with a cutout frequency of 10 Hz. After this, the heelstrikes were marked automatically. These heelstrikes were defined as the moment when the velocity of the marker that was nearer to the heel reached 0 in the vertical direction. At the end of the analysis, the first and last steps were removed. These heelstrikes were used to calculate the relevant gait parameters.

The relevant gait parameters were step length, step cadence, step velocity, and the variability of these variables. Step length was defined as the distance between two successive heelstrikes in the direction of walking. Step cadence was formalized as the inverse of the time between two successive heelstrikes. Finally, the step velocity was calculated by dividing the step length by the time the same step took to be completed. The coefficient of variation (CV) was used to calculate the variability of each of these parameters. This coefficient is defined as the ratio between the standard deviation and the mean.

All results were expressed as a ratio created by dividing them by the corresponding baseline measure as obtained by each individual participant. Thus, values above 1 indicated that the results were higher than the associated baseline measures, while values under 1 meant that the results were smaller than the baseline measures. Finally, results equal to 1 meant that there were no changes from the baseline trial.

Statistical analysis: One-sample t-tests on the individual results of each group for step length and step cadence were run comparing its mean results to the imposed step length and step cadence of the corresponding blocks. The objective of these tests was to see if participants were adhering to the step lengths and cadences impose by each cue. The confidence intervals (95%) for each block in each group were presented in the graphs. If 1 was not included in the confidence intervals the results were significantly different to the baseline results. This allowed us to see if the cues produced improvements in the gait parameters of the participants. Three-way mixed ANOVAs with the between-subjects factor Group (HC, PD) and within-subjects factors Spatial information (N, L) and Temporal information (NT, 100%, and 125%) were carried out on the results for all the gait parameters. The results were considered significant when $p<0.05$. Taking into account the small size of the sample, trends were also presented. A result was considered to be a trend when $0.05<p<0.1$. Post-hoc analyses turned out not to be necessary. Results are presented as mean ± standard deviation.

2.2 Results

The t-tests showed that HC step length was not different from the imposed mean in any of the conditions. In the case of PD patients, their step length was different to the imposed mean in the N conditions (t (14) = 2.17, p=0.047; 1.21±0.12) but not in the L conditions, implying that they had a larger mean than the impose step length for the N conditions but not for the L conditions. When performing the t-tests for step cadence it was found that the two groups could adapt to the 100% condition, but neither of the groups adapted to the 125% condition (HC: t (9) =3.47, p=0.007, 1.10± 0.29; PD: t (9) = 5.10, p< 0.001, 1.00± 0.15).

As can be seen in the confidence intervals of Figure 2A, all the cues were effective in increasing step length in the two groups. In the case of step cadence (Figure 2B) none of the conditions produced changes from the baseline condition in the two groups. For step velocity (Figure 2C) all the spatio-temporal conditions increased the velocity in the PD group, but none of the two spatial conditions produced these increments. In the HC group all conditions produced increments in step velocity with the exception of the N-NT, and N-100% conditions. For step length CV (Figure 2D) and step velocity (Figure 2F) all the conditions produced improvements in the PD group, but none of the condition produce these improvements in the HC group. Finally for the step cadence CV (Figure 2E) the improvements all the spatio-temporal conditions improved variability in the

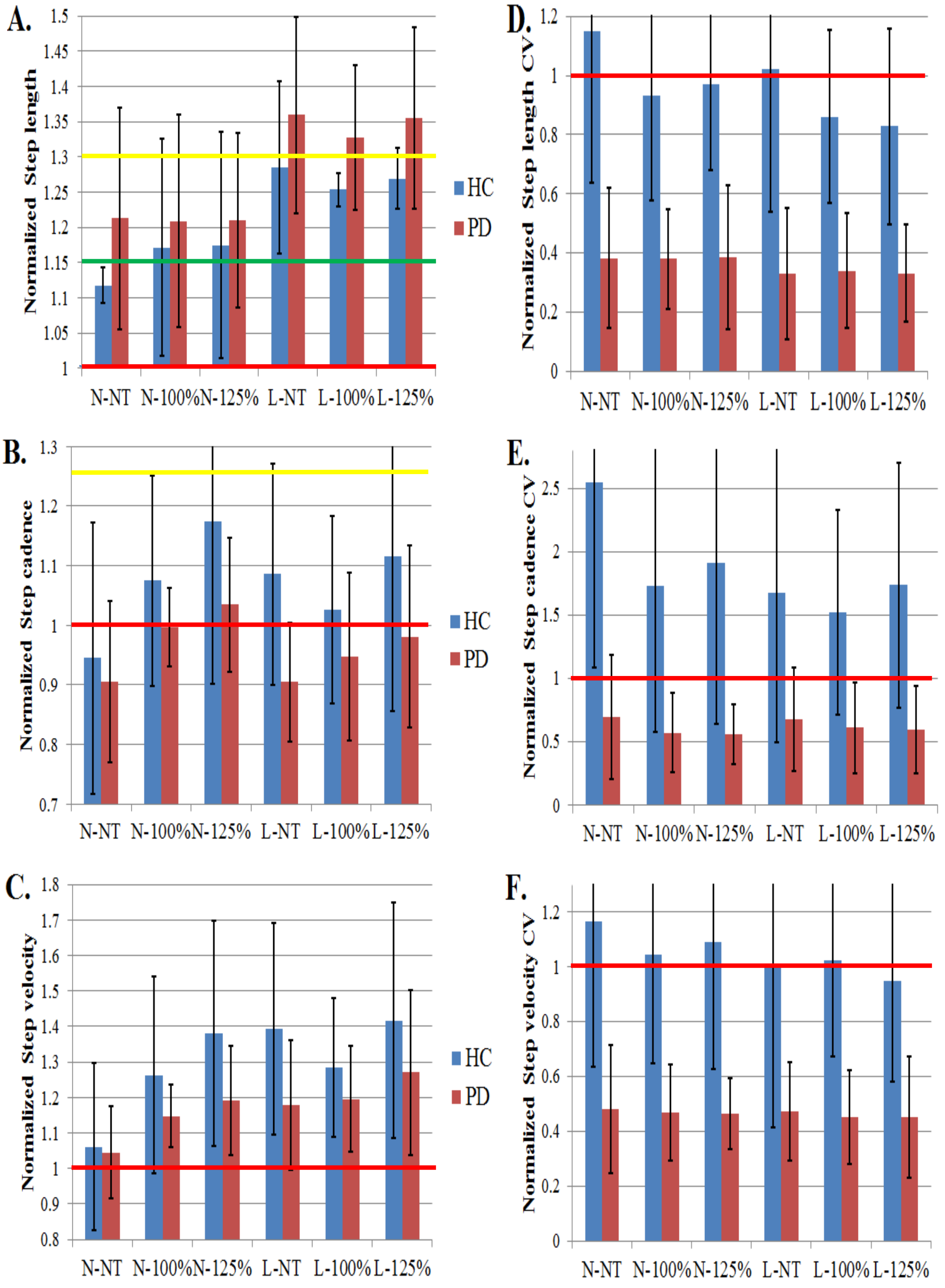

Figure 2: Normalized results for step length (A), step cadence (B), step velocity (C), step length CV (D), step cadence CV (E), and step velocity CV (F) for the PD and the HC groups in the six different blocks. The results are presented as a normalized result derived by scaling the results of each block to the baseline individual measurements. The red lines represent in all graphs the result that would mean no change from the baseline measures. In figure (A) the green and yellow lines represent the step length prescribed in the N and L conditions respectively. In figure (B) the red and yellow lines represent the step cadence prescribed in the 100% and 125% conditions respectively. The error bars represent the confidence intervals (95%) of the mean.

PD group, but none of the two spatial conditions produced these improvements. None of the conditions produced improvements in variability in the HC group, the N-NT condition even producing increments in variability.

The results of the ANOVA for step length (see Figure 2A) showed a significant effect of factor Spatial information ($F_{(1, 9)} = 24.85$, $p<0.001$) showing that participants had a larger improvement while walking in the L condition (1.31 ± 0.09) than in the N condition (1.18 ± 0.11). There was also a significant effect of factor Group ($F_{(1, 9)} = 7.04$, $p= 0.011$) revealing that the PD patients (1.28 ±0.12) showed larger improvements while walking on the cues than the HC group (1.21 ±0.1). The results of the ANOVA for step cadence (see Figure 2B) showed that the effect of factor Temporal information tended towards significance ($F_{(2, 9)} = 3.04$, $p=0.057$). This suggested that the faster temporal condition (125%) increased the step cadence of the participants (NT: 0.94 ± 0.17; 100%: 1.00 ± 0.12; 125%: 1.05 ± 0.15). In addition, there was a significant effect of factor Group ($F_{(1, 9)} = 5.91$, $p= 0.019$), demonstrating that the HC (1.04 ± 0.17) showed larger improvements than the PD patients (0.95± 0.11). The results of the ANOVA for step velocity (see Figure 2C) showed that there was a significant effect of factor Spatial information ($F_{(1, 9)} = 6.14$, $p=0.020$) meaning that the participants moved faster in the L conditions (1.29 ±0.20) than in the N conditions (1.17 ±0.20). The effect of factor Temporal information tended towards significance ($F_{(2, 9)} = 2.44$, $p= 0.090$). This suggested that the participants moved faster when the temporal information was added, moving faster as the temporal rhythm got higher (NT: 1.17 ± 0.16; 100%: 1.22 ± 0.14; 125%: 1.30 ± 0.21). Finally, there was a significant effect of factor Group ($F_{(2, 9)} =8.43$. $p= 0.005$), demonstrating that the HC group (1.30 ±0.24) showed larger improvements in velocity due to the cues than the PD patients (1.16 ±0.14). The results of the ANOVAs for the three CV (see Figures 2D, 2E, and 2F) only showed significant effects of the group (step length CV: $F_{(1, 9)} = 36.90$, $p<0.001$; step cadence CV: $F_{(1, 9)} = 19.47$, $p<0.001$; step velocity CV: $F_{(1, 9)} =52.14$, $p<0.001$) meaning that the PD patients (step length CV: 0.38 ±0.23; step cadence CV: 0.62 ±0.28; step velocity CV: 0.48 ±0.20) had much larger improvements than the HC group (step length CV: 0.97 ±0.44; step cadence CV: 1.80 ±1.32; step velocity CV : 1.04 ±0.34).

2.3 Discussion

The results showed that participants could adapt to the different information contained in the cues. Even if the participants failed to replicate the exact step length and step cadence that were contained in the cues, the change of the information contained in the cues produced changes in the behavior of the participants. These changes were the ones that were expected by the intervention: the manipulation of spatial information produced changes in step length, while, although only a tendency effect was found, the manipulation of temporal information seemed to induce changes in step cadence. Furthermore, all visual cues showed to be effective in increasing step length (in the two groups) and reducing step length and step velocity CV (only in the PD group). The addition of temporal information expanded these benefits to step velocity (with the exception of the N-100% condition in the HC group) and step cadence CV (in the PD group). These results may sound contradictory with the results of the ANOVAs and therefore must be taken cautiously, especially taking into account the small size of the sample of the experiment. The absence of advantages experience from the visual cues in the HC group is probably due to a ceiling effect. The baseline results (see Table 2) for the gait variability in the HC group were so small that it is possible that they could not get smaller.

In contrast to what was expected there were no differential effect in step length and step cadence variability of the spatial and spatio-temporal cues in the PD patients. It is possible that the absence of a difference between the visual cues in the PD group is due to a similar effect. The final results for the gait parameters variability are very similar in the two groups (step length CV: [HC: *0.07 ± 0.04, PD: 0.08 ± 0.02*]; step cadence CV: [HC: *0.126 ± 0.25, PD: 0.125 ± 0.12*]; step velocity: CV [HC: *0.11 ± 0.15, PD: 0.13 ± 0.06*]). Furthermore, this showed that in the PD group the final results were nearly identical to the baseline results of the HC group. Therefore, if the HC group was experiencing a ceiling effect, is possible that the PD group was experiencing the same phenomenon when walking with the guide of the visual cues. These suggest that all cues may be sufficient for the optimal improvement of the gait variability in the PD group. The only exception found was the step cadence CV results, were the improvements were smaller than for the two other parameters meaning that PD patients could potentially still improve their cadence variability.

Finally, PD patients did not exactly reenact the information contained in the visual cues. In the N condition the PD group walked with a higher step length that the one contained in the visual cues of this condition. Furthermore, the two groups failed to reenact the 125% condition implying that the rhythm in this cue was probably too high to be replicated by the participants. Taking into account the short training period, only 8 trials, it is also possible that this cue needed a longer training period. This may hint that PD patients benefit of the visual cues even when not been able to replicate the exact action they contain. In the PD group the visual cues reduced gait dynamics variability to less than half the variability they exhibited in their baseline measures. PD patients gait exhibits a dysfunctional variability when walking (Hausdorff et al., 1998). Thus, these results (improvements in velocity and step length with reductions in gait variability) show that all the visual cues were an effective intervention in improving gait dynamics in PD patients even if not perfectly reenacted.

3 Experiment 2

In Experiment 1 the visual cues showed to be an effective way of improving gait dynamics in PD. In Experiment 2 the same cues were tested under a situation in which PD patients have shown to experience problems. In several studies, small doorways were demonstrated to produce reductions in step length and velocity and increments in variability (Almeida & Lebold, 2010, Cowie et al., 2010), with one study even showing that small doors can induce FOG (Cowie et al., 2012). Taking into account the difficulties found in creating tasks that induce freezing (Nieuwboer, & Giladi, 2008), developing a VR task that could produce FOG would prove useful in furthering the research in this elusive symptom. The aim of the first part of this second experiment was to see if virtual doorways produce the same effects as real doors in a small group of PD patients. Therefore, in the first part of this experiment, participants walked through virtual doorways of 100% or 125% of the shoulder width of the participant, as well as in a no-door condition. It was predicted that virtual doorways will produce FOG episodes similar to real doors and also induce shorter steps, reductions in velocity and cadence while increasing the variability of gait. This is expected as real doors of the same width as our virtual doors have shown to produce similar gait perturbations (Almeida, & Lebold, 2010, Cowie et al., 2010 2012). To anticipate, the results from the first part of this experiment showed that virtual doors indeed produced similar effects as real doors.

Therefore, in the second part of this experiment, it was tested if the visual action-relevant cues presented in Experiment 1 could reduce, or even prevent, the occurrence of these symptoms by improving the aspects of the gait dynamics affected by the doorways. The efficacy of the different forms of information, namely spatial or spatial-temporal, was determined. Participants walked through the same doorways as in Part 1 while guided by the cues tested in Experiment 1. It is expected that gait improvements would be brought about through the action-relevant nature of the information presented in the spatial or the spatio-temporal cues. The visual cues of Experiment 1 were action-relevant to the task of crossing a door as they specify an optimal path through the door. The visual cue was positioned in the floor symmetrically at both sides specifying a center of walk. This center of walk was positioned in the real center of the hallway and the door. This meant that if participants walked while stepping on top of the footprints they would be walking in the center of the hallway and the center of the doorway. Taking into account that PD patients veer to one side while walking in a hallway (Davidsdottir et al., 2008) a cue that specifies a way of walking in the center of the doorway should prove useful by affording a less energetically and cognitively demanding behavior. This could potentially help PD patients cross the door and therefore, perhaps, reduced their symptoms (e.g. shuffling, FOG, slowness).

3.1 Methods

Participants: The same group of HC and PD patients participated in this experiment. The data of one of the PD patients was eliminated because the participant did not change his behavior or move his shoulders when the doors were presented. This suggested that the participant was ignoring the doors, making his data not reliable. This PD participant, PD3, was replaced by PD6 (see Table 1). It is important to note that despite three participants having a high score on the FOG-Q, all of these participants but one were in the ‘on’ state. Being in an ‘on’ clinical state meant that the medication was working at that point making the symptoms lesser, especially when it comes to FOG. On the other hand an ‘off’ clinical state means the medication is not working at the moment. Only one participant was in an ‘off’ state and had a mean result higher than 2 in the FOG-Q (Giladi et al., 2000), and therefore could potentially suffer from FOG.

Apparatus: The apparatus was the same as in Experiment 1.

Procedure: At all moments two experimenters were present. One controlled the virtual environment and the motion capture system while the other walked by the participants all the time in order to ensure their safety.

Part1: There were three virtual doorway conditions (No door, 100% shoulder width (Small Door), 125% shoulder width (Medium Door)). The doorways consisted of two posts of 5 cm each with the top of the door frame being positioned 2 m above the floor (see https://www.youtube.com/watch?v=0Hrzr2iDXyw for an example of a trial). Participants walked 6.5m through the doorway to the red line that was on the other side of the doorway. The doorway was presented 4 meters away from the start of the trial, leaving 2.5 m of walk after the doorway was crossed. The participants then turned around with the help of one experimenter and a new trial started. Before the start of the experimental trials participants walked eight times in the virtual hallway with doors of slightly different widths to the ones used in the experimental trials in order to get used to the virtual environment. The three experimental conditions were presented six times each in a random order resulting in a total of 18 trials. Participants were instructed to walk to the line and pass through the virtual doorway as they would normally pass through a doorway in real life. Finally, after six trials had been completed participants were allowed to rest for 2 minutes in order to avoid problems with fatigue.

Part 2: The same virtual doorways (Small Door and Medium Door) were presented along with the same spatial and spatio-temporal cues from Experiment 1 (see https://www.youtube.com/watch?v=u6iT5eTyMwA for an example of a trial). Before the start of the experimental trials participants walked eight times guided by visual cues through doorways. The visual cues used in these practice trials contained slightly different spatial and temporal information than the cues used in the experimental trials. The doorways had also a slightly different width than the doorways that were used in the experimental trials. The baseline measures obtained in Experiment 1 were used to create the visual cues of this experiment[1]. There were the same 6 visual conditions as in Experiment 1: two spatial cues (N-NT, and L-NT) and four spatiotemporal cues (N-100%, N-125%, L-100% and L-125%). Each door condition with each visual cue was presented 6 times, giving a total of 72 trials. The cue conditions were blocked in blocks of twelve trials with the door presentation being randomized within these blocks. Participants were instructed to walk to the red line and pass through the virtual door as they would normally pass through a doorway in real life. After this they turned with the help of one of the experimenters and a new trial started from that position. Participants were instructed to walk on the footsteps on the floor, and to try to match their rhythm to the rhythm imposed by the change in color of the footsteps, if such a change was present. Before the start of the block participants were informed of the type of visual cue presented in the block. Participants were able to rest for two minutes at the end of the blocks in order to avoid problems with fatigue and residual effects of the other cues.

Data analysis:

Part 1: The same analysis as in Experiment 1 was conducted to detect the heelstrikes. As in Experiment 1 in the No Door condition the first and last steps were removed from the analysis. The remaining heelstrikes were used to calculate step length, step cadence, step velocity, and the variability of these parameters. See Experiment 1 for the definitions of these gait parameters. Again, the CV was used to calculate the variability of each parameter. This coefficient is defined as the ratio between the variability and the mean. The aim of this experiment was to see how the gait parameters were affected by the doors. For this reason in the trials where there was a door, an area of 3.5 meters before the door, and 1 meter after the door was selected. The gait parameters were only calculated in this area as this was the part of the trial affected by the virtual door.

Part 2: The same analysis and gait parameters as in the first part of this experiment were used. The results in all the gait parameter were divided by the mean result in Part 1 in the same doorway condition. This meant that the results told us how much the gait parameters were affected by the presentation of the visual cues. Similarly, as in the first experiment, a result less than 1 meant that the gait parameter value was smaller when the cue was presented than when there was no cue. Results larger than 1 meant there was an increase in the gait parameters in the cue condition compared with the no cue condition. Finally, results equal to 1 will mean there was no change from the no-cue condition.

Freezing-like events: PD2 had very high scores on the FOG-Q while also being in an ‘off’ state. Therefore it was believed that she would probably experience FOG while crossing the smaller doorways. For this reason, an objective definition of FOG was used on the results of PD2 to establish when she was experiencing FOG. This definition was derived from Cowie et al., (2012) and categorized FOG in terms of a

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[1] *For PD6 the baseline measures were taken following the same procedura as in Experiment 1.*

velocity drop under 10% of the mean results in the no door condition. Using this definition, the mean velocity in the no door condition was established and FOG events were classified as those trials in which the velocity dropped under 10% of the mean velocity in the no door condition. If there were less than three strides between two FOG events they were considered as belonging to the same freezing event. After establishing in what trials she froze, the percentage of trials in which she experiences these episodes under each condition was calculated. The mean duration of these episodes and its standard deviation were also calculated. As we only had a participant in an off state this analysis was merely descriptive.

Statistical analysis:

Part 1: Two-way mixed ANOVAs with the between-subjects factor Group (HC, PD) and within-subjects factor Door (No Door, Small Door, Medium Door) was carried out on the results for the different gait parameters. The results were considered significant when $p<0.05$. Taking into account the small size of the sample trends were also presented. A result was considered to be a trend when $0.05<p<0.1$. When needed post-hoc Tukey analyses were run in order to explore what levels were different inside factors with significant main effects. Results are presented as mean ± standard deviation.

Part 2: The confidence intervals (95%) for each block in each group were presented in the graphs. If 1 was not included in the confidence intervals the results were significantly different to the same Door condition in Part 1 of this experiment. This allowed us to see if the cues produced improvements in the gait parameters of the participants compared to Part 1 of this experiment. Four-way mixed ANOVAs with between-subjects factor Group (HC, PD) and within-subjects factors Door (Small Door, Medium Door), Spatial information (N, L) and Temporal information (NT, 100%, 125%) was carried out on all the kinematic data leading up to the doorways. The results were considered significant when $p<0.05$. Taking into account the small size of the sample trends were also presented. A result was considered to be a trend when $0.05<p<0.1$. Post-hoc analysis turned out not to be necessary. Results are presented as mean ± standard deviation.

3.2 Results

3.2.1 Part 1: Doors without cues

For the results of the ANOVA for step length (see Figure 3A) there was a significant effect of factor Door ($F_{(2, 9)}$ =3.72 p=0.040). Post-hoc analysis revealed that step length was significantly smaller in the Small Door condition (0.46 m± 0.16 m) that in the No Door condition (0.62 m ±0.10 m). For the results of the ANOVA for step cadence (see Figure 3B) there was a significant effect of factor Group ($F_{(1, 9)}$ = 4.34 p= 0.048) implying that the HC group (1.9 Hz ±0.04 Hz) had a higher cadence compared to the PD group (1.76 Hz ± 0.06 Hz). Finally, for the results of the ANOVA step velocity (see Figure 3C) there was a significant effect of factor Door ($F_{(2, 9)}$ = 4.72 p=0.020). Post-hoc analysis revealed that step velocity was significantly lower in the Small Door condition (0.85 m/s ± 0.27 m/s) that in the No Door condition (1.16 m/s ±0.20 m/s). There was a significant effect also of factor Group ($F_{(1, 9)}$ =5.29 p=0.031), demonstrating that the PD group (0.91 m/s ±0.28 m/s) always moved with a lower velocity than the HC group (1.10 m/s ± 0.21 m/s).

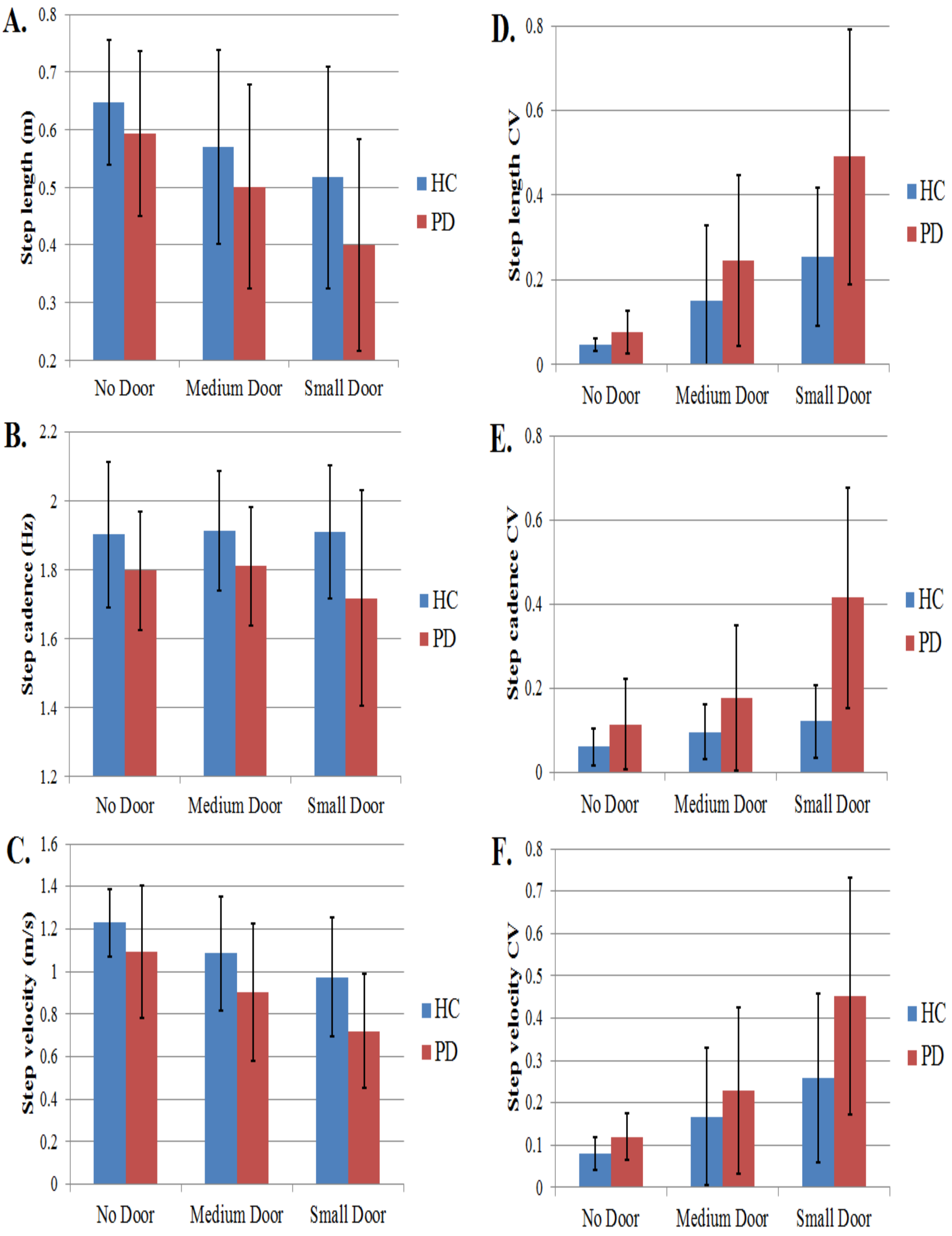

Figure 3: Results for step length (A), step cadence (B), step velocity (C), step length CV (D), step cadence CV (E), and step velocity CV(F) for the two groups, in the three different doorway conditions.The data for seplength is presented in meters, the data of step cadence is presented in hertz, while the data for the step velocity is presentd in meter/seconds. The error bars represent the confidence intervals(95%) of the mean.

For the results of the ANOVA for step length CV (see Figure 3D) a significant effect of factor Door was found ($F_{(2, 9)}$ = 6.58 p=0.005). Post-hoc analysis revealed that step length CV was significantly larger in the Small Door condition (0.37 ±0.28) that in the No Door condition (0.06 ±0.03). The results of the ANOVA for step cadence CV (see Figure 3E) showed that there was a significant effect of factor Group ($F_{(1, 9)}$ =4.37, p=0.047) signifying that the variability was always higher in the PD group (0.23 ±0.27) than in the HC group (0.09 ±0.06). Lastly, for the results of the ANOVA for step velocity CV (see Figure 3F) there was a significant effect of factor Door ($F_{(2, 9)}$ =4.72 p=0.019). Post-hoc analysis revealed that step velocity CV was significantly larger in the Small Door condition (0.36 ±0.24) that in the No Door condition (0.10 ±0.04). There was also a significant effect of factor group ($F_{(1, 9)}$ = 5.29 p=0.033), signifying that the variability was always higher in the PD group (0.23± 0.27) than in the HC group (0.09± 0.06).

3.2.2 Part 2: Doors with cues

` As it can be observed in Figure 4A, all cue conditions while crossing the Small Door, with the exception of N-NT, produced increases in step length in the PD group. On the Medium Door conditions, only L-NT and L-100% conditions produced improvement in the PD group. In the HC group (see Figure 5A) all conditions in the two Door conditions produced improvements in step length. For step cadence, none of the cues produced improvements in step cadence in neither of the two groups (see Figure 4B for the PD group, and Figure 5B for the HC group). Furthermore, as Figure 4C demonstrates in the PD group all cue conditions while crossing the Small Door, with the exception of N-NT, produced increases in step velocity. On the Medium Door conditions, only L-NT condition produced improvement in the PD group. For the HC group (see figure 5C) only condition L-NT in the two Door conditions, and conditions N-NT and L-100% in the Small Door condition produced improvements in step velocity. For step length CV in the PD group (see Figure 4D) all cue conditions produced improvements in the Small Door condition, but only the N-100% and the L-100% conditions produced significant improvements in the Medium Door conditions. In the case of the HC group (see Figure 5D) only the N-NT condition and the L-100% significantly reduced step length CV in the Small Door condition while no cue condition produced improvements in the Medium Door condition. For the step cadence CV in the PD (see Figure 4E) group only conditions N-100% and L-100% produced significant improvements in the Small Door condition. In the HC group (see Figure 4E) none of the conditions produced improvements in variability. Finally, for step velocity CV in the PD group (see Figure 4F) all conditions, with the exception of L-NT produced improvements in the Small Door condition, while none produced improvements in the Medium Door condition. In the HC group (see Figure 5F) none of the cue conditions produced improvements in step velocity CV in none of the two Door conditions.

The ANOVA for the step length (see Figures 4A and 5A) showed a tendency towards significance for the influence of factor Spatial information ($F_{(1, 9)}$ = 3.69 p=0.057), suggesting that the increments in step length were marginally bigger for the L conditions (1.38 ± 0.20) than for the N conditions (1.30 ± 0.28). Furthermore, there was an effect of factor Door ($F_{(1, 9)}$ =22.67 p<0.001) implying that the increments were bigger for the Small Door (1.44 ±0.26) than for the Medium Door (1.24 ±0.19). Finally, there was an effect of factor Group ($F_{(1, 9)}$ =9.10 p=0.003) demonstrating that the increments were bigger in the PD group (1.40 ±0.30) than in the HC group (1.28 ±0.16). The ANOVA for step cadence (see Figures 4B and 5B) showed no significant effect of any of the factors. The ANOVA for step velocity (see Figure 4C and 5C) revealed a significant effect of factor Door

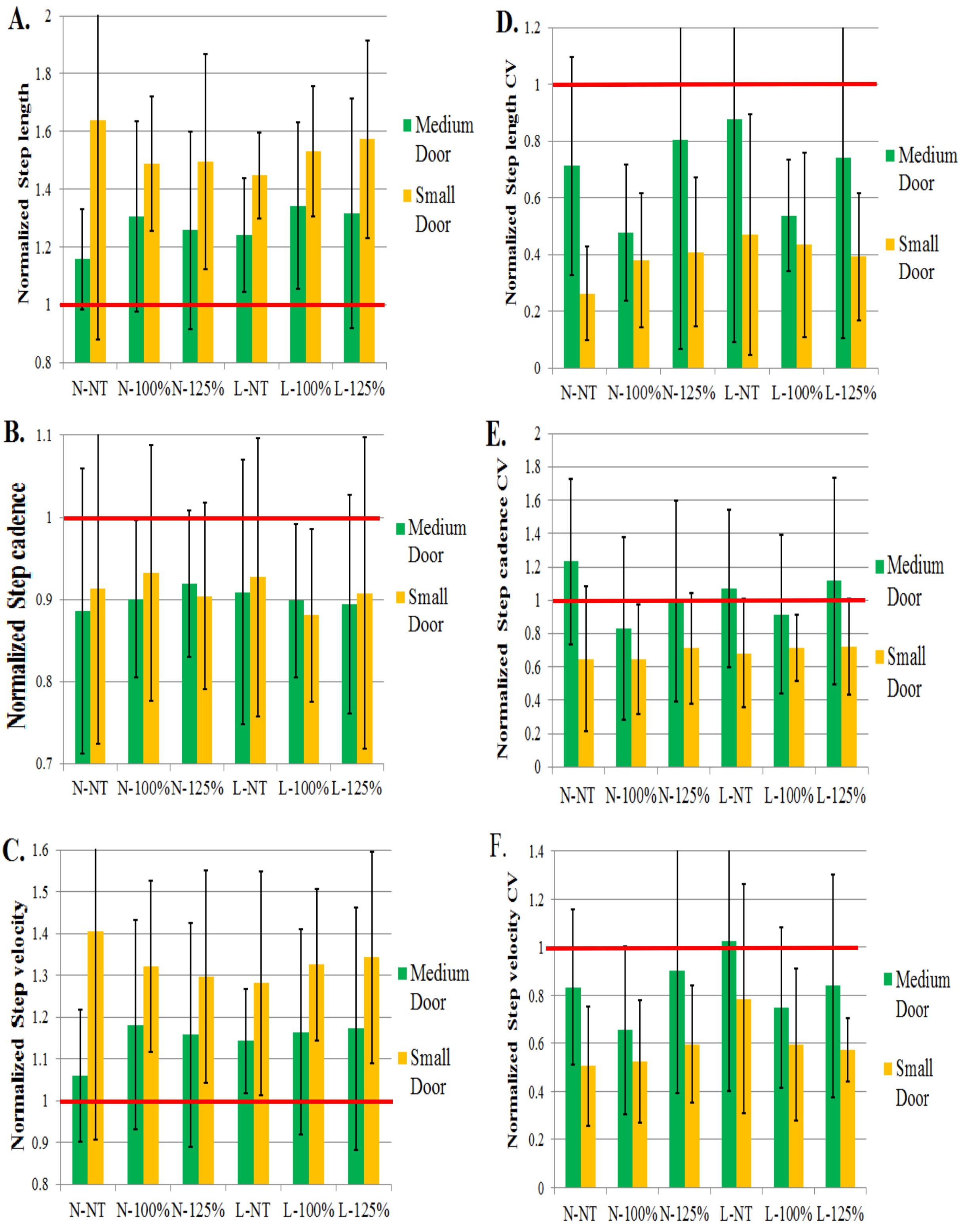

Figure 4: Normalized results for step length (A), step cadence (B), step velocity (C), step length CV (D), step cadence CV (E), and step velocity CV (F) for the PD group in the six different blocks in the two different Door conditions. The results are presented as a normalized result derived by scaling the results of each Door condition in each block to the results of the same Door condition in Part 1. Therefore, the results of the Small Door condition in each block were scaled to the results of the Small Door condition in Part 1, and the results of the Medium Door condition in each block were scaled to the results of the Medium Door condition in Part 1. The red lines represented the result were there was no change from the Part 1 results. The error bars represent the confidence intervals (95%) of the

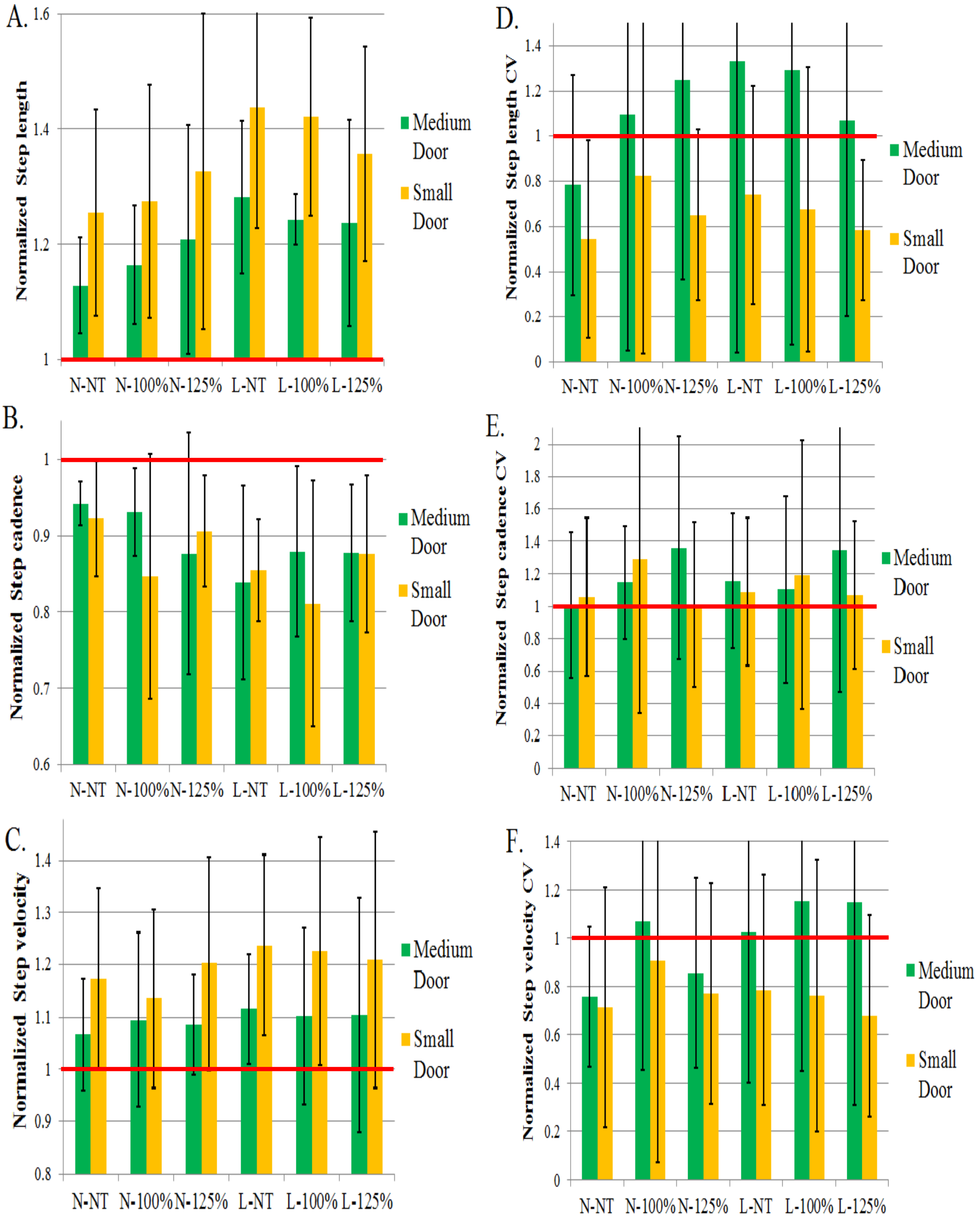

Figure 5: Normalized results for step length (A), step cadence (B), step velocity (C), step length CV (D), step cadence CV (E), and step velocity CV (F) for the HC group in the six different blocks in the two different Door conditions. The results are presented as a normalized result derived by scaling the results of each Door condition in each block to the results of the same Door condition in Part 1. Therefore, the results of the Small Door condition in each block were scaled to the results of the Small Door condition in Part 1, and the results of the Medium Door condition in each block were scaled to the results of the Medium Door condition in Part 1. The red lines represented the result were there was no change from the Part 1 results. The error bars represent the confidence intervals (95%) of the mean.

(F $_{(1, 9)}$ = 16.02 p<0.001) showing that the increments in velocity were larger for the Small Door (1.26 ±0.21) than for the Medium Door (1.12 ±0.15). Finally there was an effect of factor Group (F $_{(1, 9)}$ = 7.96 p=0.006) demonstrating that the increments were larger for the PD group (1.24± 0.23) than for the HC group (1.14 ±0.14).

The ANOVAs for step length CV (see Figure 4D and 5D), step cadence CV (see Figure 4E and 5E) and step velocity CV(see Figure 4F and 5F), rendered significant effects of factor Door (step length CV: [F $_{(1, 9)}$ =14.55 p<0.001]; step cadence CV: [F $_{(1, 9)}$ =6.19 p=0.015]; step velocity CV: [F $_{(1, 9)}$ =10.32 p=0.002]) demonstrating that the variability became more reduced in the Small Door (step length CV: [0.53 ± 0.36]; step cadence CV: [0.90 ±0.44]; step velocity CV: [0.67 ± 0.34]) than in the Medium Door (step length CV: [0.91 ± 0.68]; step cadence CV [1.10 ± 0.45]; step velocity CV [0.90 ±0.43]). There were also significant effects of factor Group (step length CV: [F $_{(1, 9)}$ = 13.31 p<0.001]; step cadence CV: [F $_{(1, 9)}$ =13.96 p<0.001]; step velocity CV: [F $_{(1, 9)}$ =7.86 p=0.006]) implying that the reductions were larger for the PD group (step length CV: [0.54 ± 0.39]; step cadence CV: [0.85 ± 0.39]; step velocity CV: [0.68 ±0.32]) than for the HC group (step length CV: [0.90 ± 0.67]; step cadence CV: [1.15 ± 0.46]; step velocity CV: [0.89 ±0.46]).

Cue condition	**Door condition**	**% of trials with an FOG episode**	**Mean duration of FOG episode**	**Max duration of FOG**	**Min duration of FOG**
Non-cue condition	*Small Door*	*100 %*	*7.64 s ± 5.26 s*	*17.93 s*	*2.63 s*
	Medium Door	*33%*	*5.46 s ± 4.07 s*	*8.972 s*	*1 s*
N-NT	*Small Door*	*100%*	*2.32 s ± 1.8 s*	*4.66 s*	*0.51 s*
	Medium Door	*0 %*	*NA*	*NA*	*NA*
N-100%	*Small Door*	*66 %*	*2.6 s ± 1.77 s*	*4.61 s*	*0.78 s*
	Medium Door	*0%*	*NA*	*NA*	*NA*
N-125%	*Small Door*	*66%*	*2.9 s ± 1.26 s*	*3.58 s*	*1.66 s*
	Medium Door	*0%*	*NA*	*NA*	*NA*
L-NT	*Small Door*	*83%*	*4.12 s ± 2.92 s*	*8.18 s*	*0.58 s*
	Medium Door	*33 %*	*4.92 s ± 4.06 s*	*7.79 s*	*2.05 s*
L-100%	*Small Door*	*83%*	*5.92 s ± 5.02 s*	*13.03 s*	*0.648 s*
	Medium Door	*0 %*	*NA*	*NA*	*NA*
L-125%	*Small Door*	*83 %*	*2.12 s ± 1.17 s*	*3.55 s*	*1.21 s*
	Medium Door	*0 %*	*NA*	*NA*	*NA*

Table 3 *Results of the analysis done on the FOG episodes that PD2 experience in Experiment 2. The results include: the percentage of trials where patients experience freezing for each cue condition; The mean duration of these episodes in each condition; and the maximum and minimum duration of the episodes in each condition. NA mean that there was no FOG episodes in that condition.*

3.2.1 FOG

Table 3 presents the results of the FOG episodes for PD2. Part 1 showed that the virtual doorways, especially the Small Doors, induced FOG: These episodes lasted for more than 5 s being as long as 18 s in one case. The addition of the cues in Part 2, in general, reduced the occurrence of these episodes. In all cases but one, the cues completely aborted them in the Medium Door condition. Additionally, in the Small Door condition, all visual cues but one reduced the occurrence of these episodes. In most cases, the cues reduced the duration of these episodes. In four of the six cue types, the episodes ended up being of less than 3 seconds, while in the two other cases the duration was reduced to less than 6 seconds. Therefore, the visual cues seem to reduce the occurrence of FOG, reducing also the duration of these episodes.

3.3 Discussion

The first part of this study showed that virtual doorways produced similar gait adaptations as real doors. Participants move slower when a Small Door was presented, also showing a reduction in step length. The presentation of the Small Door also increased the gait variability. These effects were present in the two groups although the PD group always presented a higher variability, a slower velocity, and a smaller step length than the HC group. These results are consistent with other studies (Almeida, & Lebold, 2010, Cowie et al., 2010, 2012) that have used real doors of the same width as the virtual doors in this experiment.

In Part 2, the visual cues produced (with the exception of N-NT) increases in step velocity and step length in the vicinity of the Small door. In the Medium Door condition only conditions L-NT and L-100% produced increases in step length in the PD group while only condition L-NT produced increases in step velocity. Furthermore, the variability of gait in the PD group was reduced to less than 60% of the variability they had in the same door condition without cues. These decreases in step length CV and step velocity CV in the PD group were significant in most cases for the Small Door condition but mostly not for the Medium Door condition. Only two cues showed to be effective in reducing step cadence CV in the PD group in the Small Door condition. The failure of most visual cues to produced improvements in the Medium Door conditions may be due to the small size of the sample and the small effect of the Medium Doors in Part 1(patients did not have a significant difference between the No Door condition and the Medium Door condition). Although the confidence intervals show some differential effect of the cues, the experiment failed to show a superiority of any of the cues, pointing to their similar effectiveness. The difference in between these two statistical tests may be due to the small size of the sample. Nevertheless, the visual action-relevant cues showed to be an effective intervention in the PD group. Generally, the visual cues did not show to be beneficial for the HC group. As in Experiment 1, it is possible that this is due to a ceiling effect that does not allow the HC group to experience any improvements.

Furthermore, the virtual environment induced freezing-like episodes, although the sample size was one patient. These episodes ranged from about 3 s to 18 s, with a median around 8 s. These results replicate the findings of Cowie et al. (2012) using the same size real doors that showed that the current VR paradigm was able to produce FOG. Thus**,** this virtual environment is a representative design of the task of crossing a narrow space (Brunswick, 1955), indicating it could be used to induce freezing in PD patients that tend to experience this symptom while performing this type of task. In the second part of this experiment, PD2 also experience benefits from the presentation of the visual cues. Although this is the data of a single patient, the number of

FOG episodes and the intensity of these episodes reduced when visual cues were presented. This may suggest that this action-relevant visual cueing intervention could be used to improve quality of life in PD patients that experience FOG.

4 General Discussion

In this master's thesis, an action relevant visual cue was developed and tested while PD patients walked and crossed a virtual doorway. In Experiment 1, the visual cues showed to be in general very effective in improving the walking dynamics in the PD group. Specifically PD patients' improved step length, step velocity, and reduced overall gait variability. HC also improved step length, and step velocity but did not show any improvements in gait variability. All these improvements occurred even if patients did not walk with the exact step length and cadence contained in the cues. No differential effect in step cadence variability was found for the two types of visual cues (spatial and spatio-temporal cues). Walking is a spatio-temporal task (it contains a temporal [the cadence], and a spatial [the step length] component), therefore, the spatio-temporal cues were expected to have had a more profound effect on the variability than the spatial cues due to its higher action-relevance. Although the addition of temporal information produced significant improvements in velocity and step cadence CV not present in the spatial conditions, the failure of the ANOVAs to show any effect of the Temporal information factor raises questions about the statistical power of the confidence intervals. Therefore, it is believed that our results do not support a superiority of the spatio-temporal information compared to spatial information.

In the first part of Experiment 2, an immersive VR task was developed that was representative of a real-life situation, crossing a doorway, which participants face daily. The results found mimicked the impairments and adaptations produced in PD patients and a HC group while crossing real doorways (Almeida, & Lebold, 2010, Cowie et al., 2010 2012). Specifically, when crossing the virtual doorways participants reduced their step length and velocity, while variability increased. Further research may try to create immersive VR environments that are representative of other problematic situations for PD patients (like initiating gait, turning, etc.). The furthering in the comprehension of the different problematic tasks for PD could allow for the development of visual cues that adapt to their functional demands. Furthermore, this VR tasks allows for testing the effects of visual cues under highly controlled experimental setups that would also be ecologically valid (Loomis et al, 1999).

In the second part of Experiment 2 the visual cues were tested while participants crossed the doorways developed in part 1. Once more, the action-relevant visual cues showed to be equally effective in reducing overall variability and increasing step length and step velocity. If the virtual environment indeed is representative of the task of crossing a doorway, the behavior observed could potentially resemble how the cues would affect a patient while performing this task in real life. Therefore, further research may find ways of implementing this type of action-relevant visual cues in the real life of patients (see Practical implications, for an example). To our knowledge this is the first study to show PD patients benefit from the use of visual cues when crossing a doorway.

The task was also able to induce freezing-like episodes in PD2, the only PD patient with high results in the FOG-Q (Giladi et al, 2000) who was also in an 'off' clinical state. Taking into account the problems found in producing FOG in a controlled manner in the lab (Nieuwboer, & Giladi, 2008), these results point out that this designs could prove useful in creating setups to the study of this symptom. Furthermore, the action-relevant visual cues showed to be effective in reducing the duration of these episodes, while also reducing the percentage of trials where they were present. To our knowledge, this is the first study to prove that visual cues are able to reduce doorway-provoked FOG. These results point to the potential of action-relevant information in reducing FOG. These results add up to the recent discoveries that had shown that action relevant cues (in their case auditory) were able to reduce the time between FOG episodes (Young et al., 2016). Unluckily, the results of this thesis are limited by the small size of the sample (only one patient). In the future, this study could be replicated controlling also the medication regime of PD patients. In this way it could ensure that the sample is experiencing FOG, optimizing the possibilities to test the effect of our VR environment and visual cues.

As expected the behavior of the participants was affected by the information presented in the visual cues producing the Spatial information changes in step length, and the Temporal information changes in step cadence. But, although the spatio-temporal cue contained more action-relevant information than the spatial cue, no differential effect of the two types of cues was found in the overall variability of gait. This happened not only for the normal walking trials but also for the doorways of Experiment 2. This could potentially mean the action-relevance nature of the cues was not the most relevant feature. Alternatively, it could be due to the way in which the visual cues were created. Young et al. (2014) found that their action-relevant cues were only effective when the cues were created using real biological movement, not when created using a synthesizer. Taking into account that the visual cues of this study were not created using real biological motion it is possible that they did not replicate relevant information (e.g. the natural noise related to healthy movement (Goldberger, 1996, 2006) contained in biological movement needed to allowed PD patients to use the cues optimally. Furthermore, in the case of Experiment 2 it is possible that the spatio-temporal cue did not add any further effects to the spatial cue for a similar reason. HC naturally slow down when approaching a narrow space (Almeida, & Lebold, 2010, Cowie et al., 2010 2012), allowing them to cross the doorway safely. If the spatio-temporal cues would have been created using a healthy adult dynamics, the cues would have slowed down when approaching the door, recovering its full speed only when the door had been crossed. On the other hand, the visual cues (especially the spatio-temporal cues that both constrained step length and step cadence) of this study maintained the same speed (or the same step length in the spatial cues) throughout all the trial, raising questions regarding the action-relevance nature of the visual cues for the task of crossing a doorway. In the future, research could develop visual cues crafted using biological real movement (e.g. of a healthy young adult), and test them against synthesize cues to see if this effect could explain this phenomenon. Next, a theoretical discussion will be developed on what this thesis could potentially mean to the state of the art of visual cues.

4.1 Theoretical implications

Usually, visual cues are assumed to work as a way of directing attention to gait characteristics that are impaired (Azulay et al., 2006; Morris et al., 1996). Visual cues would serve as a way of correctly activating the motor set related to walking (Morris et al. 1994b) by centering the focus of attention on the part of the gait that is impaired. Supporting this hypothesis some studies have shown that the advantage experienced while walking using visual cues gets aborted while performing a dual task (Morris et al. 1994a, 1994b). In these studies, visual cues usually consisted of lines perpendicular to the walking direction of the participant, positioned at different distances. By centering the debate on interior cognitive processes, the study of the information delivered in the cues was overlooked, hampering the creation and development of cueing techniques.

On the other hand visual cues can be built shifting the focus away from the internal processes of the patients (Morris et al. 1994a, 1994b, 1996) and back to the functional characteristics of the task (the informational constrains of the task; Bieńkiewicz et al., 2013; Rodger & Craig, 2016; Rodger et al, 2014; Young et al, 2013, 2014, 2016). By redirecting the focus to the information contained in the cues, a novel intervention was created that showed not only to be effective in improving unconstrained gait but also proved effective while crossing a virtual doorway. By furthering the research in the functional constrains of other problematic tasks, like turning, starting movement, and sitting, novel cues (e.g visual, auditory, olfactory) could be developed that could afford an energetically and cognitively optimal behavior. For example, following the suggestion made by Steenson and Rodger (2015) for sound, if the visual information contained in the cues is conceived as aspects of an affordance, one could imagine using footprints that follow a smooth path around furniture to afford a healthy turning behavior, or one may think of the development of visual cues that help a patient initiate its gait. Auditory cues built under this framework have already shown to be more effective than a classic metronome in reducing variability of gait (Rodger et al, 2014, Young et al., 2014), but this superiority needs to be examined for visual cues in a study that directly compares the footprints developed in this thesis with the more conventional perpendicular lines.

If we talk about the information contained in cues, the effects of these visual cues in improving normal walking performance could be related to two potential reasons: 1) *The action-relevant nature of the information delivered.* Our visual cues were built to keep characteristics that a past walker would have produced. In contrast to other studies that used horizontal lines (Azulay et al., 1999; Lewis et al., 2000; Morris, et al., 1994a, 1994b, 1996; Suteerawattananon et al, 2000), stepping stones (Bank, Roerdink, & Peper, 2011) and our footprints are a more ecological cue, more representative of a normal human gait. Perpendicular lines don't preserve the lateral symmetry of walking, while the footprints of this study (or other action-relevant cues like stepping stones), would keep this lateral symmetry having a higher action-relevance than perpendicular lines. This means that the task is more specified in the cue, making it an easier intervention to attune to. 2) *The visual cues contained 'action-scaled' information*. The visual cues of this thesis were built using a pi ratio, a dimensionless number that expresses a percentage of improvement over the baseline measures of the participant (Warren, 1995). This was a very simple process: a baseline measure was established; after this a ratio was applied to the spatial and temporal (e.g. 1.3 baseline step length or 1.25 baseline step cadence) characteristics of the gait producing a visual cue that always meant an improvement for the patient while staying in a range easy to reproduce. In this way it is also avoided to create cues that are potentially too large for the shorter participants, or too short for the participants that are taller.

In Experiment 2 of this thesis visual cues were applied to examine whether they improved the gait dynamics while crossing doorways, as they would theoretically make the task easier for patients. They were meant to improve step length, increased velocity and reduce overall variability of gait, all parameters that had shown in the past (Almeida, & Lebold, 2010, Cowie et al., 2010 2012) to be affected while crossing a doorway. Furthermore, the visual cues contained information about a center of walk that when correctly positioned (in the center of a door) could potentially afford an optimal path (energetically and cognitively) through the doorway. As this source of information was not directly tested in this thesis further research could study the differential effects of the different sources of information contained in these action-relevant visual cues. For example, an experiment could be designed that tested while crossing a doorway 4 different cues that contained only step length information (e.g. perpendicular lines; Figure 6A), only the center of walk (e.g. continuous parallel lines; Figure 6B), these two sources combines (e.g. discontinuous parallel lines at an specific step length; Figure 6C), and a cue containing also action-relevant information (e.g. the footprints of this thesis; Figure 6D). In this way the effect of different types of information could be study isolated allowing to understood better the effect of each of these sources of information.

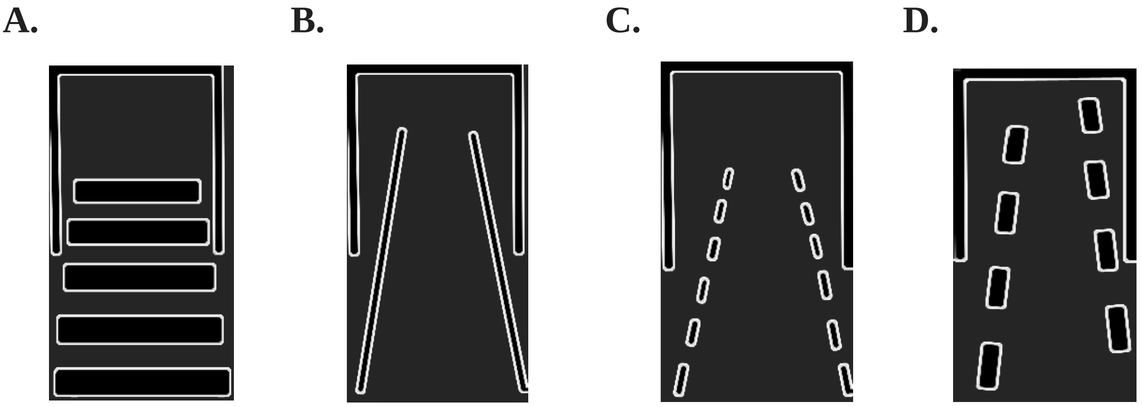

Figure 6 Schematic representation of an experimental design testing only step length information (A), only information about a center of walk (B), step length and a center of walk (C), and this two types of information plus action-relevant information(D).

These principles are not the only possible ways of thinking of the information contained in visual cues, but they already show the benefits of focusing on the information that unfolds during the task rather than on internal cognitive processes. This focus would allow for the development of more complex cueing techniques that may alleviate the functional demands of problematic tasks. Future experiments may explore new sources of information that could help, for example, when turning, standing up, or initiating gait. For this purpose immersive VR environments could show its full potential by allowing the isolation and testing of different sources of information under representative designs (Loomis et al., 1999). But it will stay still a challenge to produce interventions based on the principles discovered by this line of research. The next section explores the practical implications of the use of immersive VR environments in PD research, while also exploring a possible way to develop a cueing intervention that could be applied in the real life of PD patients.

4.2 Practical implications

Immersive VR technology can be used as a tool that allows for high ecological validity while allowing to easily test different types of information under different types of tasks constrains (Schultheis, & Rizzo, 2001). This may further the research in cueing techniques by allowing the creation of specific cues that afford certain complicated actions, like turning, sitting, or crossing through narrow spaces. This technology further allows training the patients in the use of the different cues under virtual highly representative situations of relevant daily live tasks. This training is not meant as a way of improving walking performance in the long term, but rather as a way of ensuring that patients use the cues to its full potential. This way it would be ensured that the cues are being used to its full potential when applied as an intervention. Finally, VR allows for the creation and adjustment of each cue in such a way that can be easily optimized for each patient. This could allow VR to work as a way of adjusting and testing the real intervention. Although visual cues seem to be an effective way to improve gait dynamics, it is unclear to what extent these kinds of interventions produced any long-term effects or if they could have any benefit in the real life of PD patients. These doubts are raised because cueing techniques have failed to show any long-term retention of the temporary benefits experience while walking in top of them (Morris et al., 1996). As we see**,** although immersive VR could further the research of cueing techniques, it still fails to create any intervention that could alleviate the symptoms of patients in their regular life.

To create effective cueing interventions a way of delivering the cues while patients are experiencing their symptoms in real life must be found. In order to do so, we could try to use augmented reality glasses (Jansen et al., 2017). These glasses allow delivering visual information that is superimposed on the visual field of the patient. This promising technology may allow us to deliver the intervention while the patient is naturally interacting with his/her environment. In addition, some of these glasses are able to scan the environment and record data. This will allow us to create systems that by the measurement of the behavior of the patient and its current position in the environment can deliver cues specific to the current functional constrains that the patient is experiencing. The software of such a system could benefit from the use of neuronal networks. Such networks could adjust and create personalize thresholds for each patient by producing the optimal configuration controlled by algorithms that use the recorded behavioral and environmental data. This may allow us to create highly complex interventions (that contain a high number of specific cues) that are highly personalized to the needs of each patient. It is not less important to take into account that we are experiencing the emergence of an information society, increasingly based on the production and exchange of information. Therefore, Human-Computer interacting devices provide exciting new opportunities to benefit various patients groups in flexible and highly specific manners.

5 Conclusions

In this thesis, action-relevant visual cues (footprints in the floor) were developed based on considerations regarding the information the visual cues could potentially convey. In Experiment 1, the visual cues showed to be effective in increasing step length, step cadence, step velocity, and reducing overall variability of gait, although no difference was found between the cues containing more action-relevant information (spatio-temporal cue) and the ones containing less (spatial cue). In the first part of Experiment 2, a virtual representative design of the task of crossing a doorway was developed and tested. The results showed that the presence of virtual doorways reduced step length and step velocity while producing an overall increase in variability. This method even induced FOG in PD2, a patient with a history of FOG. The same visual cues used in Experiment 1 were tested while the participants crossed virtual doorways. Once again, the cues increased step length, step velocity, and reduced overall gait variability. The action-relevant visual cues also reduced the overall percentage of trials with FOG, and the duration of these episodes in PD2. These results show that these action-relevant visual cues were effective not only in improving normal walking but also while crossing a virtual doorway, in patients with PD.

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