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Biologically-variable rhythmic auditory cues are superior to isochronous cues in fostering natural gait variability in Parkinson's disease

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ABSTRACT

Introduction: Rhythmic auditory cueing improves certain gait symptoms of Parkinson's disease (PD). Cues are typically stimuli or beats with a fixed inter-beat interval. We show that isochronous cueing has an unwanted side-effect in that it exacerbates one of the motor symptoms characteristic of advanced PD. Whereas the parameters of the stride cycle of healthy walkers and early patients possess a persistent correlation in time, or long-range correlation (LRC), isochronous cueing renders stride-to-stride variability random. Random stride cycle variability is also associated with reduced gait stability and lack of flexibility.

Method: To investigate how to prevent patients from acquiring a random stride cycle pattern, we tested rhythmic cueing which mimics the properties of variability found in healthy gait (biological variability). PD patients ($n = 19$) and age-matched healthy participants ($n = 19$) walked with three rhythmic cueing stimuli: isochronous, with random variability, and with biological variability (LRC). Synchronization was not instructed.

Results: The persistent correlation in gait was preserved only with stimuli with biological variability, equally for patients and controls (p's < 0.05). In contrast, cueing with isochronous or randomly varying inter-stimulus/beat intervals removed the LRC in the stride cycle. Notably, the individual's tendency to synchronize steps with beats determined the amount of negative effects of isochronous and random cues (p's < 0.05) but not the positive effect of biological variability.

Conclusion: Stimulus variability and patients' propensity to synchronize play a critical role in fostering healthier gait dynamics during cueing. The beneficial effects of biological variability provide useful guidelines for improving existing cueing treatments.

1. Introduction

Rhythmic auditory cues (e.g., repeated tones or music) can improve gait in Parkinson's disease (PD) [1]. Such non-invasive stimulation leads to an immediate increase of cadence, stride length, and/or speed [2,3] which might extend to non-cued gait following training [4]. Benefits from cueing may be related to patients' rhythmic skills [5]. These findings suggest that a portable device can serve as a technological aid in assisting patients in their daily lives and delivering a training program [6]. This use of cueing implies that many of the patients may aim to walk in synchrony with the stimulus. Success of an isochronous stimulus (i.e., tones separated by a constant time interval) is defined in terms of removing all temporal variation. Is it beneficial, however, to

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repetitively execute a stereotypical movement without any variation?

Computational models suggest that motor variability linked to basal ganglia activity fosters more effective motor learning [7]. Slow variation in a repetitive reaching task in monkeys or in baseball pitching is a part of the process of learning and practicing [8]. At the other extreme, forced long-term stereotypy can lead to loss of behavioral repertoire and even undesirable cortical reorganizations leading to focal dystonia [9]. Thus, variability in training is recommended as a general principle of rehabilitation practice [10].

The temporal properties of variability are particularly important when the motor behavior necessarily involves repetition, such as the case of gait. Typically, however, only an averaged characterization of the gait cycle in terms of mean stride length, speed, and cadence has been used while studying the effects of rhythmic auditory cueing. This fails to reveal the influence of the temporal structure of cueing on the temporal dynamics of gait (i.e., the change of the gait cycle) throughout the trial.

In healthy individuals, the temporal dynamics of gait, expressed in terms of the inter-stride-intervals (ISI), exhibits non-random variability characterized by a persistent trend called long-range correlation (LRC). The LRC property of healthy gait, herein referred to as 'biological variability' because of its ubiquitous character in physiological processes [11,12], is characterized by persistent trends unfolding on multiple temporal scales (i.e., it possesses fractal properties). LRC means that the ISI characterizing a given gait cycle depends on all previous ISIs. A random ISI would not depend on the previous ISIs. LRC is deemed an optimal form of control of physiological processes because LRC is a functionally beneficial combination of stability (persistent control) and variability (flexibility) [11]. It has been associated with tolerance to errors and resistance to perturbations [12,13]. Biological variability distinguishes faller from non-faller patients with so-called higher-level gait disorder (HLGD) [14]. Thus, the disappearance of LRC with advanced PD [15] is a clinically relevant symptom.

In spite of its beneficial effect on averaged measures, isochronous cueing may exacerbate certain PD symptoms related to the dynamics of these measures. Stimuli with isochronous beats remove LRC in healthy individuals [16] and in PD patients [17]. This could be avoided by embedding biological variability in the stimulus. We tested this strategy in a group of PD patients. The auditory stimuli also varied in terms of their musical complexity (a sequence of tones or music). This was to test the independence of the effect of variability from the characteristics of the auditory stimulus such as pitch, rhythmic features, and motivational factors (music is expected to be more motivating than a metronome) [18].

The interval between the sounds or musical beats was either fixed (standard cueing), non-biologically variable (random uncorrelated noise), or biologically variable (with embedded LRC). The latter was hypothesized to preserve LRC of gait in patients with PD while also maintaining the other beneficial effects expected from standard cueing.

2. Methods

2.1. Participants

Nineteen non-demented patients with PD were recruited in the Department of Neurology of a Regional University Hospital of Montpellier, and in the neurological unit of another local hospital (Beau Soleil Clinic). The clinical diagnosis of PD was based on the Queen Square Brain Bank criteria. At the time of testing, all patients scored above the recommended cutoff for dementia (21/30) on the Montreal Cognitive Assessment (MoCA) for screening cognition in PD. Patients were assessed on revised Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) when in "ON" state, and were assessed in terms of their Hoehn and Yahr stage. The levodopa equivalent daily dose (LEDD) was calculated both for dopamine agonists (DA-LEDD) and dopamine agonists plus L-dopa (total LEDD) [19]. Inclusion criteria consisted of presence of gait disorders and absence of hearing impairments. All patients were examined by neurologists with extensive experience in movement disorders.

Nineteen sex-, age- and education level-matched healthy controls were also recruited. Controls had no history of neurological or psychiatric disorders, showed no hearing impairment and had no complaint about gait. They were also evaluated using the MDS-UPDRS and the MoCA. Demographic information, clinical details, and medication at pre-test for patients and controls are presented in Table 1. Patients differed from controls in terms of MDS-UPDRS scores.

All participants provided written informed consent prior to the experiment. They received financial compensation for their participation. The study was approved by a national ethics committee in conformity with the Declaration of Helsinki.

2.2. Rhythmic auditory cueing

Rhythmic auditory cueing was provided via 1) a sequence of tones (metronome), 2) musical excerpts, and 3) amplitude-modulated noise (AMN) derived from the same musical excerpts. The metronome was a sequence or repeated tones with a triangle timbre. Musical excerpts were four highly familiar military marches (e.g., Mozart's Turkish March). They were selected in a pilot study for their salient beat structure and positive emotional connotation. AMN stimuli were transformations of the music stimuli. The amplitude envelope (RMS, 25 ms windows) extracted from each musical excerpt was applied to a noise with a matching power spectrum. This stimulus resembles a drum ensemble and has the advantage to preserve the rhythmical structure of the musical stimuli while discarding the tonal information, thus lacking the associated motivating and affective aspects.

Cueing was presented in three variability conditions: 1) no variability, 2) biological variability (LRC), and 3) non-biological variability (random variability). Custom Matlab scripts generated the stimuli by manipulating computer-generated versions of the original musical pieces. The desired variability was embedded at the *beat* level. Stimulus rate was set to 10% faster than each participant's preferred cadence which was measured at pre-test. Magnitude (coefficient of variation of the inter-beat interval, CV) of biological and non-biological variability corresponded to 2% of the inter-beat-interval (IBI). Cues were delivered using headphones via a wireless sound monitoring system.

2.3. Gait measurement

Gait data were recorded with small inertial measurement units (IMU sensors including 3D accelerometers and 3D gyroscopes sampled at 128 Hz, MobilityLab, APDM Inc., Portland, OR) strapped over the left and right phalanges of the feet, anterior side of left and right tibia, and sternum. Recordings were processed off-line to extract a series of left and right ISIs from the left and right foot falls. Trial averages of stride length (SL, m), velocity (v, m/s), and cadence (steps/min) were also estimated. Gait variability was measured in terms of the coefficient of variation of ISIs (SD of the inter-stride-intervals divided by the mean ISI).

The temporal structure of gait variability within a trial–whether ISIs in that trial contained biological variability or non-biological random variability–was quantified using a standard method for estimating LRC. The α scaling exponent represents the short-and long-term trends in the series of ISIs. It is calculated using

Table 1
Demographic and clinical data.

	Patients with PD (N = 19)		Healthy Controls (N = 19)			
	Median	Range	Median	Range	*z*	*p*
Demographical data						
Age, years	60	37–78	60	39–79	−0.02	0.98
Years of education	12	4–22	12	6–19	−0.70	0.48
Male sex, %	63		63			
MoCA	28	22–30	28	24–30	−0.38	0.71
Height, m	1.71	1.44–1.87	1.69	1.56–1.83	−0.54	0.59
Weight, kg	72	41–86	81	57–107	−1.81	0.06
BMI, kg/m^2	24	20–31	27	20–36	−2.18	0.03
Clinical assessment						
Age of disease onset	55	38–67				
Disease duration, years	6	3–20				
DA-LEDD, mg/day	246	0–600				
Total LEDD, mg/day	1030	248–1984				
Hoehn and Yahr stage	2	1–3				
MDS-UPDRS						
Part I	11	1–18	2.5	0–9	−4.49	<0.001
Part II	12	3–18	0	0–6	−5.17	<0.001
Part III	18	1–57	2.5	0–7	−5.09	<0.001
Part IV	1	0–10	0	0–0	−3.72	<0.001

Abbreviations: BMI, Body mass index, DA = Dopaminergic agonist, LEDD = L-Dopa equivalent daily dose, MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale, Part I, Non-Motor Experience of Daily Living, Part II, Motor Experiences of Daily Living, Part III, Motor Examination, Part IV, Motor Complications, MoCA, Montreal Cognitive Assessment.

detrended fluctuation analysis (DFA) [20] applied to the series of ISIs. In this analysis $.5 < \alpha \leq 1$corresponds to LRC, $\alpha = 0.5$ to random fluctuations (i.e., non-biological variability), and $\alpha < 0.5$ to anti-persistent fluctuations (alternations of shorter and longer intervals). Measures were calculated from the patient's more severely affected side where laterality was a relevant factor, namely when computing SL and α. Controls were assigned to the lateralization of their corresponding PD match.

2.4. Analysis of synchronization to the cues

Synchronization of the steps to the cues may be a critical element in explaining the effects of the cueing. The alignment between the time of the footfalls and the beats was estimated with beats as reference [21] and circular statistics then provided a measure of synchronization performance ranging from zero (lack of alignment between footfalls and the beats, no synchronization) to one (consistent alignment, maximal synchronization). This measure ("synchronization consistency") has proven very sensitive to individual differences in synchronization skills in a variety of populations [22]. When used as input in further statistical analyses, synchronization consistency was submitted to the *arcsine* transformation [22].

2.5. Procedure and design

The study was performed in the research division of the university hospital. Testing was performed in a quiet hospital hall where participants walked around an elliptical area (6×3.6 m). A three-minute pre-test assessment without auditory stimulation was performed to identify baseline gait spatio-temporal parameters. Participants then performed 18 test trials consisting of two trials, turning left and right, in each of the nine conditions of a factorial design resulting from the full crossing of three stimulus types (metronome, music, and AMN) and three variability conditions (no variability, biological variability, and random variability). The participants were asked to walk as comfortably as possible with the auditory stimuli; they were not explicitly instructed to synchronize heel strikes to the stimulus beats. To avoid effects of fatigue trials were run in three separate sessions,

Table 2
Spatio-temporal gait parameters (Mean ± SD) across groups (PD, n = 19, and Control, n = 19) in pre-test and the three experimental conditions of stimulus variability. (Cad is Cadence, spm.)

Group		Pre-test	Cueing		
			Isochronous	Random	Biological Variability
PD	Cad	101.7 (12.2)	109.0 (10.4)	109.2 (10.8)	109.3 (10.2)
	SL $^{\$\nabla}$	1.32 (0.15)	1.33 (0.18)	1.33 (0.19)	1.33 (0.19)
	CV $^{\diamond}$	1.40 (0.70)	2.42 (0.78)	2.64 (1.40)	2.59 (0.95)
	$\alpha^{\dagger}$	0.70 (0.18)	0.58 (0.20)	0.65 (0.17)	0.69 (0.15)
	Sync $^{\diamond\dagger}$	–	0.42 (0.41)	0.39 (0.37)	0.37 (0.36)
Control	Cad	104.7 (8.)	107.3 (9.5)	107.1 (9.5)	107.3 (8.9)
	SL $^{\$\nabla}$	1.45 (0.10)	1.48 (0.09)	1.47 (0.10)	1.48 (0.10)
	CV $^{\diamond}$	1.06 (0.30)	2.19 (0.66)	2.18 (0.61)	2.2 (0.55)
	$\alpha^{\dagger}$	0.64 (0.17)	0.65 (0.18)	0.68 (0.15)	0.72 (0.14)
	Sync $^{\diamond\dagger}$	–	0.23 (0.35)	0.18 (0.30)	0.19 (0.27)

Main effects of Group in Pre-test $^{\$}(p < 0.01)$, Group in Cueing $^{\diamond}(p < 0.05)$, $^{\nabla}(p < 0.01)$, Cueing variability: $^{\dagger}(p < 0.001)$.

approximately thirty minutes each, during two consecutive days. Order of conditions was randomized but trials were blocked per stimulus type.

2.6. Statistical analyses

PD patients were compared to controls at pre-test for demographic variables and gait parameters using *t*-tests (see Tables 1 and 2). Mixed ANOVAs tested for differences in spatio-temporal gait parameters and LRC among the nine experimental conditions and two groups (patients vs. controls).

As PD patients are typically very heterogeneous, we adopted an additional statistical approach, linear mixed-effect models (LMEM), which account for individual differences as well [23]. It parsimoniously takes into account group and trial condition as well as individual variables such as individual intercept and degree of synchronization. It is ideally suited to identify individual biases that might affect the dependence of gait parameters on cueing characteristics.

Longitudinal LMEM modeling was applied to the series of one pre-test and 18 test trial α scores using a dedicated statistical package (lme4) [24] for R. The coefficients (βs in Table 3) that maximized the model fit were obtained following a recommended model selection method [23]. Conceptually they resemble regression slopes and intercepts. The predictors comprised trial number (accounting for the effect of trial), presence of cueing (comparing cueing in experimental conditions vs. pre-test), specific cueing condition, and group. Synchronization was included as a trial-varying predictor. Note that instead of running one test to compare baseline to averaged cueing trials and then another one to compare among cueing conditions using synchronization as a covariate of α, the LMEM model merges the two tests. It treats each participant's trials as a trajectory of successive observations and uses dummy variables to represent conditions of performance and synchronization as trial-varying predictors, except for group which is constant. Predictors could be continuous or binary. As in regression, the results are interpreted by substituting the estimated parameters into the final selected model,

$$\alpha_{ij} = \beta_0 + \sigma_{0i} + \beta_1 T_{ij} + \beta_2 G_{ij} + \beta_3 C_{ij} + \beta_4 G_{ij} C_{ij} + \beta_5 R_{ij} + \beta_6 B_{ij} + \beta_7 G_{ij} R_{ij} + \beta_8 G_{ij} B_{ij} + \beta_9 S_{ij} + \beta_{10} S_{ij} R_{ij} + \beta_{11} S_{ij} B_{ij} + \sigma_{ij}.$$

Here i is participant, j is trial, β_0 is a global baseline, σ_{0i} is variability in the individual baseline, σ_{ij} is the residual. Latin letters indicate the predictors. G (group), C (cueing trial), R (random variability), and B (biological variability) were coded as binary dummy variables (details in Table 3) indicating the group and conditions of performance on a given trial for a given participant. For instance, C is a 38 × 19 (participants × trials) matrix of zeros in the first column (pre-test) and ones in all other columns. In this way, the coefficient β_3 estimates the change from pre-test to cued walking trials.

Table 3
Linear mixed-effects model specified by the estimated predictors coefficients for the outcome α. Boldface indicates significant *t*-test. Categorical predictors are coded for each trial in terms of binary variables: Group = 0 (control) and 1 (PD); Cueing = 0 (pre-test) and 1 (test). The coefficients for Cueing and Group estimate the change from pre-test to cueing trials and between control and PD participants, respectively. Stimulus variability was coded for each trial in terms of two binary dummy variables: Rand and Biological. Rand = 1 in the random variability condition and 0 otherwise. Biological = 1 in the biological variability condition and 0 otherwise. The coefficients for Rand and Biological describe how the respective conditions differ from the No variability condition.

Predictor	Estimate	*SE*	*t*
β_0: Intercept (Pre-test)	**0.638**	**0.032**	**20.00**
β_1: Trial	**0.003**	**0.001**	**2.99**
β_2: Group	0.055	0.045	1.21
β_3: Cueing	0.056	0.031	1.77
β_4: Cueing * Group	−0.060	0.043	−1.42
β_5: Rand	−0.004	0.017	−0.24
β_6: Biological	−0.010	0.017	−0.59
β_7: Group * Rand	0.017	0.024	0.73
β_8: Group * Biological	−0.031	0.024	−1.30
β_9: Synchronization * No Var	**−0.264**	**0.019**	**−14.62**
β_{10}: Synchronization * Rand	**0.100**	**0.026**	**3.77**
β_{11}: Synchronization * Biological	**0.286**	**0.028**	**10.29**

3. Results

The analysis of gait parameters at pre-tests showed that patients' stride length was significantly shorter relative to controls ($p < 0.01$) by 9%. The two groups were comparable in the other gait parameters including LRC (see Table 2).

The effects of cueing conditions are summarized in Table 2. The statistics were based on data averaged across left and right turning trials and across the three stimulus types (metronome, music, AMN) because statistical analyses did not reveal any effects or interactions for these factors. Cadence did not differ between the groups and was not affected by stimulus variability. Irrespective of stimulus variability, stride length was shorter ($p < 0.01$) and gait variability (CV) was higher in patients than in controls ($p < 0.05$). Patients synchronized their steps to the cueing stimuli more often than controls did ($p < 0.05$) (see Fig. 1).

No correlations were found (all p = NS) between average synchronization and clinical characteristics such as disease severity (MDS-UPDRS-III), disease duration, or treatment (L-dopa and L-dopa equivalent dose).

3.1. Effects of cueing and synchronization on α

The final LME-model reduces to $\alpha_{ij} = \beta_0 + \sigma_{0i} + \beta_1 T_{ij} + \beta_9 S_{ij} + \beta_{10} S_{ij} R_{ij} + \beta_{11} S_{ij} B_{ij} + \sigma_{ij}$ because the non-significant coefficients (see Table 3) can be assumed to be equal to zero. α tended to increase with trial at a rate of about 0.003 per trial. Group, cueing, variability type, or interaction between group and variability in themselves did not affect α. Synchronizing with the non-variable stimulus tended to reduce α by about $\beta_9 = -0.264$ units per one unit of synchronization (the arcsine-transformed measure varies from zero for no synchronization to approximately 1.57 for perfect synchronization). This tendency was weaker with embedded random variability, $\beta_9 + \beta_{10} = -0.164$, and completely overcome, $\beta_9 + \beta_{11} = 0.022$, with biological variability. Solving the final LME model for level of synchronization and setting α = 0.5 (uncorrelated random variability) shows that in isochronous trials α is expected to cross from LRC into the anti-persistent domain ($\alpha < 0.5$) at synchronization consistency values ranging from 0.52 to 0.67 depending on trial number. In random cueing this ranges from 0.77 to 0.93. In biological variability the model predicts that $\alpha > 0.5$ across the full synchronization range.

The same relation between synchronization and drop in α is seen in terms of the best-fit lines in Fig. 2 (PD data only) where α correlates negatively with synchronization (arcsine-transformed) in isochronous cueing, $r = -0.730$, $p < 0.001$, and slope $b = -0.269$, less negatively in non-biological variability, $r = -0.541$, $p < 0.001$, $b = -0.190$, and no such correlation was found in biological variability, $r = 0.029$, $p = 0.77$, $b = 0.010$. Control participants produced the same pattern of correlations and slopes in the three conditions, $r = -0.687$, $p < 0.001$, $b = -0.265$, $r = -0.380$, $p < 0.001$, $b = -0.152$, and $r = 0.167$, $p = 0.08$, $b = 0.072$, respectively. (The maximum-likelihood-estimated LMEM coefficients and the least-squared-error fit slopes are numerically comparable but not equal because of the different fitting methods and ways of accommodating individual and trial variability.)

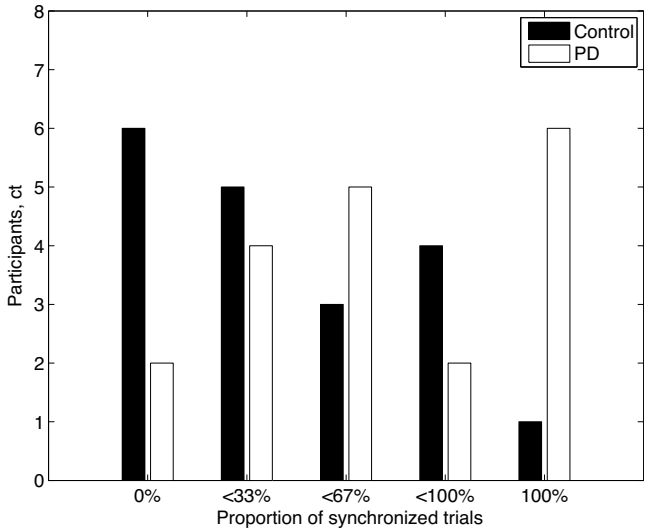

Fig. 1. Different propensities of PD patients and controls to synchronize with the stimulus. The histogram shows the number of participants per proportion of synchronized trials.

4. Discussion

LRC typical of healthy gait has been linked to increased adaptive stability to perturbations [12,13], to movement efficiency in terms of kinetic energy re-use [25], and lowered risk of falls [26]. The goal of the present study was to test whether biological variability embedded in the cueing stimulus can overcome the deleterious side-effects of standard isochronous cueing. Our findings confirm two important hypotheses. First, consistent with previous studies [4], patients' gait loses its natural pattern if they synchronize with an isochronous cue or a random pattern and acquires the random stride-to-stride fluctuations characteristic of advanced gait disorders. Thus, the use of standard cueing comes at the price of sacrificing the temporal flexibility of the stride cycle. On the contrary, stimulation with embedded biological variability preserves the natural pattern of gait variability. To our knowledge this is the first study with PD patients that explores how biological variability of the stimulus interacts with synchronization (for studies focusing solely on the variability properties, see [27,28]).

The PD patients in this study were selected to represent an early phase of the disease. They differed from controls in terms of standard parameters such as stride length and velocity. However, no difference in baseline LRC was observed [15]. Arguably, this suggests that the persistence in stride-to-stride control may be of biomechanical [25,29] and not higher cortical origin. Interestingly, PD patients showed greater propensity to be entrained by the beat in comparison to healthy controls. This appears paradoxical at first because basal ganglia are structures strongly involved in generating and responding to rhythmic patterns [30]. It follows that the insufficiency of internal rhythm generation may make PD patients *more dependent* on external rhythmical patterns. This propensity is a double-edge sword. It makes long-term training through portable rhythmic stimulation devices possible but also makes patients more likely to be entrained by an exogenous rhythm that is not optimized for their individual characteristics.

Finally, the null effect of stimulus type (not shown) suggest that the rhythmic and not the musical or tonal properties of the stimulus are responsible for the efficacy of cueing.

4.1. Limitations

Contrary to expectations, cueing did not lead to an overall improvement of patients' gait. This could be due to the relatively early disease stage of the recruited patients. In this context, we expect the relationship between synchronization and gait variability to be augmented in the advanced stage because there the reliance on environmental structure to cue action is even greater, as suggested by the tricks employed by patients with freezing [31].

The variability of gait parameters in the present study could have been compressed by the pathway layout. In a previous study involving healthy young adults, we found that walking in an elliptical trajectory (same dimensions as here) reduced velocity, stride length, and α relative to open track walking. Arguably, constant steering links additional biomechanical degrees of freedom to environmental constraints and thus constrains gait variability by reducing motor redundancy [32].

Patients exhibiting falling and freezing of gait (FoG) were not tested in the present study to ensure uninterrupted trials permitting the determination of LRC. It is known that the risk of falling is related to the amount of variability of gait parameters and, furthermore, cueing reduces this variability in patients who already suffer from increased variability (cueing increases variability in healthy participants) [26]. The anti-persistent variability observed here for synchronization with an isochronous cue implies that corrections are being made at each stride to compensate for the inherent variability of gait. We could speculate that patients with falling incidence and FoG might benefit from the biological cueing method inasmuch as it reduces the cognitive demands associated with the corrections.

The present study reveals only immediate and likely transient effects of cueing. Future training programs can test whether biological variability would lead to persistent effects, also extending to a reduction of FoG and to lower risk of falls.

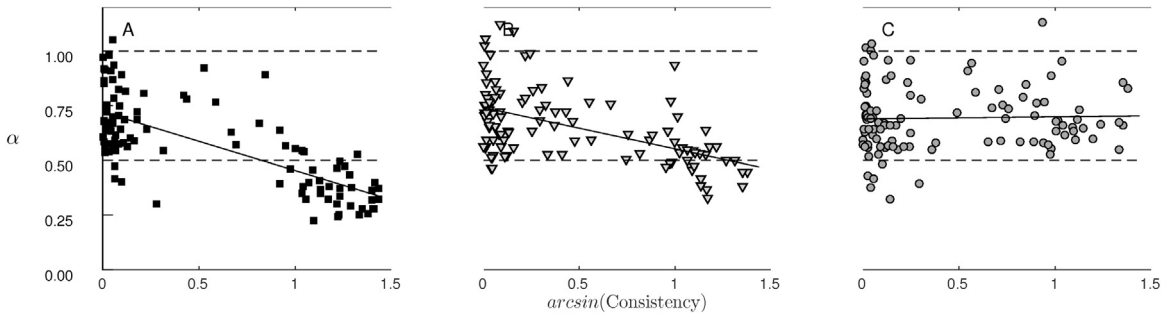

Fig. 2. Association between α and arcsine-transformed consistency (propensity to synchronize to the beat) where 0 = no synchronization, 1.57 = full synchronization. PD patient data and best-fit-lines (solid) are shown in the No variability (A), Random (non-biological) variability (B), and LRC (Biological) variability (C) conditions. Data points are trials. Dashed lines indicate the ideal theoretical LRC and random variability levels.

5. Conclusion

The correlation between synchronization and negative impact of isochronous cueing reveals the following dilemma: recommend synchronization but sacrifice natural variability or spare natural variability but diminish the positive effects of synchronizing with the cue. While there might not be an immediate negative consequence of acquiring a more random gait pattern it is safe to assume that the long-term consequences will be substantial. Embedded biological variability should be introduced in programs for gait rehabilitation in PD because it promises to solve this dilemma.

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