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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 $\alpha$ scaling exponent represents the short-and long-term trends in the series of ISIs. It is calculated using