### Positive effects of auditory cue in locomotor pattern of people with Parkinson's disease (off and on medication)

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#### **Abstract**

Gait disorders are identified in people with Parkinson's disease. The aim of this study was to investigate the effect of auditory cues and medication on kinematic, kinetic and EMG parameters, during different gait phases of people with PD and healthy elderly. Thirty subjects distributed in two groups (Group 1, PD patients off and on medication; Group 2, healthy elderly) participated in this study and were instructed to walk in two experimental conditions: non-cued and cued. Therefore, kinematic, kinetic and electromyography analyses were utilized to investigate the locomotor pattern. Changes in locomotor pattern (greater muscular activity) with auditory cue were observed for PD patients. Regarding the medication, locomotor parameter improvement was observed after levodopa intake in association with the auditory cue. These results confirm the hypothesis about the external cues therapy that could be used as a complement to drug therapy to achieve improvement in the locomotor pattern of PD patients.

KEY WORDS: Walking; Levodopa; Biomechanics; External cue; Aging.

#### Introduction

The dysfunctions in spatial, temporal, kinetic and electromyographic parameters in the gait of people with Parkinson's disease (PD) have been widely described in literature<sup>1-5</sup>. Dopaminergic medication has a positive effect on the length and velocity of the stride and on the ability to produce muscle strength<sup>6-9</sup>, however, cadence and double support does not alter in response to medication<sup>10</sup>.

Moreover, therapy with auditory cues is also used as a sensory reinforcement for improving gait kinematic parameters of people with PD<sup>11-12</sup>. Recently, Rochester et al. found that auditory cues have a positive role in gait kinematic parameters, which are resistant to dopaminergic treatment people with PD<sup>13</sup>.

However, it is important to analyze the effect of auditory cues on electromyographic and kinetic

parameters in different gait phases in people with PD. Thus, these variables could identify changes in the pattern of muscle activation during different gait phases and a better understanding of how the movements are controlled under an external sensory stimulation. From this analysis, it would be possible to understand more comprehensively the associative effects between medication and auditory cue in the gait of people with PD. Thus, we ask: Could auditory cues associated with levodopa make people with PD improve the locomotor parameters? The aim of this study was to investigate the effect of auditory cues and medication on kinematic, kinetic and EMG parameters, during different gait phases of people with PD and healthy elderly.

#### **Method**

#### **Participants**

30 subjects participated in this study: Group 1 - 15 people with and Group 2 - 15 healthy elderly (control group). PD patients presented the UK Parkinson's disease Society Brain Bank Diagnostic Criteria. Both groups were matched in relation to age, gender, height and weight (TABLE 1). The patients were diagnosed with idiopathic PD by a neurologist and they did not suffer from severe dyskinesia or freezing that would impair their ability to walk. The inclusion criteria were: a) they should be diagnosed in the stages which varied from 1 to 3 as assessed by the Hoehn and Yahr Scale 14; b) they

should receive regular pharmacological treatment with levodopa; c) they should not present indication of dementia according to the Mini-Mental State Examination (MMSE). Besides that, the disease severity was measured by the Unified Parkinson's Disease Rating Scale Section III (motor subscale) (UPDRS-III)<sup>15</sup>.

It was confirmed that participants had no other neurological disease, including hearing and musculoskeletal disorders that would influence walking tasks with the metronome (auditory cue). This study was approved by the Local Ethics Committee (Protocol # 2635). All participants signed a Free Informed Consent Form.

TABLE 1 - General characteristics of the healty control and PD patients.

Values represent means with SDs in parentheses.

	PD (n=15)	Healthy Control (n=15)	
Age (years)	69.27 (5.75)	70.3 (6.03)	
Gender (men/women)	(8/7)	(8/7)	
Height (cm)	160.95 (8.70)	161.82 (10.08)	
Weight (kg)	68.55 (12.22)	67.10 (9.85)	
Mini-Mental (ptos)	27.7 (1.59)	27.7 (1.59)	
Hoehn and Yahr scale	1.60 (0.76)	NA	
UPDRS motor (ON state)	22.60 (11.17)	NA	
Disease Duration (years)	6.26 (2.74)	NA	
Daily dose of dopaminergic medication (mg)	506.6 (173.1)	NA	

#### **Procedures**

The clinical scales were done only in the on medication state<sup>16</sup>. Data collection of people with PD was performed in the morning and in two stages: first, patients were without medication (12 hours) - off medication state; in the second stage, one hour after taking the medication - on medication state, the same experimental task was done. Subjects were asked to walk on a pathway 8 m long by 1.4 m wide in all experimental conditions. They realized two experimental conditions, non-cued and cued condition. For the cue condition, an auditory cue was provided by a metronome (software Metronome plus). The instruction given to the subjects was to synchronize each footstep in time to the metronome. The frequency of auditory cues was administered at 10% above the baseline stride11. Before the data collection, some practice trials were provided

for the subjects. It was realized 3 trials for each condition and it was completely randomized.

For the kinematic analysis, four infra-red emitting diode (IREDs) were placed on each subject's lower limbs at the following locations: head of the fifth right and of the first left metatarsal and lateral face of the right calcaneous and medial face of the left calcaneous. The surface electromyographic data were collected from tibialis anterior, gastrocnemius medialis and lateralis, vastus lateralis and medialis and biceps femoris in the lower right limb. The electrodes were positioned according to the recommendation made by the project SENIAM<sup>17</sup>.

#### **Equipment**

One Optotrak Certus System (Northern Digital Inc., Waterloo, Canada) was positioned in the

sagittal plane to track all IREDs at a sampling rate of 100 Hz. Two force plates (AccuGait, Advanced Mechanical Technologies, Boston, MA) - 50 cm x 50 cm -, embedded in the pathway (covered with the black rubber carpet), were positioned approximately in the middle of the walkway to record ground reaction forces during task execution at a frequency of 200 Hz. At the beginning of each data collection, subjects were weighed on both force platforms. This weight (BW) was used to normalize kinetic variables<sup>18</sup>.

The EMG signals were recorded using electromyography (EMG System of Brazil), which was linked to a computer for conversion of analog data into digital data with a sampling frequency of 2000 Hz. All data acquisition was electronically synchronized.

#### Data analysis

Kinematic data was filtered using a 2<sup>th</sup> order Butterworth filter with 6 Hz cutoff frequency. For kinetic analysis, it was used a 4<sup>th</sup> order Butterworth filter with 4 Hz cutoff frequency. For EMG analysis, it was used a 4<sup>th</sup> order Butterworth filter with 10 Hz cutoff frequency. The following dependent variables were calculated on the central stride (from one heel contact to the next heel contact), removing effects of acceleration and deceleration:

- Kinematic variables: stride length and velocity, cadence, double and single support time;
- Kinetic variables: extracted from the force-time curves: braking and propulsive impulses in two directions (vertical and anterior-posterior [AP]). These variables were calculated for the central stride (first heel contact [force plate 1] and second heel contact [force plate 2]);
- Electromyographic variables: each gait cycle was normalized in 100%. Then, five selected phases of

gait cycle were computed: loading (0-10% of the gait cycle), mid-stance (11-30%), terminal-stance (31-60%), initial swing (61-86%) and terminal swing (87-100%)<sup>19</sup>. The muscles analyzed for each phase of gait cycle were: tibials anterior, medial gastrocnemius, lateral gastrocnemius, vastus lateralis, vasus medial, biceps femoris. In all these phases, Root Mean Square (RMS) and Linear Envelope were calculated to determine the co-activation index and the level of activation of each analyzed muscle (defined as the area under the curve), respectively. The co-contraction index was calculated between the agonist and antagonist muscles, taken in pairs (tibials anterior vs. lateral gastrocnemius) and (vastus lateralis vs biceps femoris)20.

#### Statistical analysis

The Kolmogorov-Smirnov and Levene tests showed that the data were not normally distributed and homogenous. For each analysis (kinematic, kinetic and EMG), Mann-Whitney tests were performed to investigate possible difference between groups ([control group x PD off], [control group x PD on]) in cued and non-cued conditions. Besides, Wilcoxon tests were performed for possible differences between conditions (with and without auditory cue) for all groups (control, PD off and PD on). Furthermore, to investigate the interaction between medication and auditory cue effects on gait of PD patients ([PD on x PD off] in cued and non-cued conditions), paired tests of Friedman with repeated measures were performed for each analysis. When necessary, "post hoc" tests with Bonferroni adjustments were performed. The significance level for all analyses was kept at 0.05.

#### Results

#### Changes in PD locomotor pattern in cued and non-cued condition before the medication intake

In cued and non-cued conditions, Mann Whitney test indicated that people with PD *off* medication showed shorter gait length ( $U=47,\ p=0.010$ ), velocity ( $U=37,\ p=0.003$ ) and double support ( $U=48.5,\ p=0.013$ ) than the control group (FIGURE 1). Regarding the first heel contact in the first

force plate, Mann Whitney test revealed for both conditions (cued and non-cued) that people with PD off medication showed lower braking and propulsive impulse (U = 37, p = 0.05) than control group. For the second heel contact on the second force plate without auditory cue, people with PD off medication showed lower propulsive impulse (U = 26, p = 0.04) than control group. However, with auditory cue, this effect was only observed for vertical braking impulse (U = 24, p = 0.01) (FIGURE 2).

Regarding electromyographic analysis, Mann Whitney test revealed that people with PD *off* medication showed higher co-contraction index between vastus lateralis and biceps femoris (swing phase) than control group with and without auditory cue (U = 51.5, p = 0.01). However, with auditory cue, the Mann Whitney test indicated that the PD *off* medication showed lower muscle activation for the following muscles: vastus lateralis (loading phase) (U = 57, p = 0.02), medial gastrocnemius (terminal stance phase) (U = 47, p = 0.05), vastus medial (initial swing phase) (U = 64, p = 0.04) and biceps femoris (terminal swing phase) (U = 63, p = 0.04) (FIGURE 3 and TABLE 2).

# Changes in PD locomotor pattern in cued and non-cued condition after the medication intake

Mann-Whitney test revealed that people with PD off medication showed shorter length (U = 49, p = 0.08) and velocity (U = 60, p = 0.029) stride (FIGURE 1), smaller braking impulse (kinetic analysis) of the first (U = 61.5, p = 0.05) and second heel contact on the force plate (U = 32.5, p = 0.02) than control group (FIGURE 2) without auditory cue. Provided with auditory cue, people PD off medication overstayed in double support when compared with control group (U = 60.5, p = 0.05) (FIGURE 1). As there was no significant difference between groups with auditory cue, it can be assumed that auditory cue caused some changes in the kinetic parameters of gait in people with PD on medication, since their locomotor pattern was similar to the control group. For electromyographic analysis, Mann- Whitney test revealed that PD on medication showed higher co-contraction index between vastus lateralis and biceps femoris (terminal swing) (U = 59, p = 0.02) than control group, without auditory cue. However, with auditory cue, Mann-Whitney test showed that PD on medication showed lower biceps femoris activation (loading phase) (U =

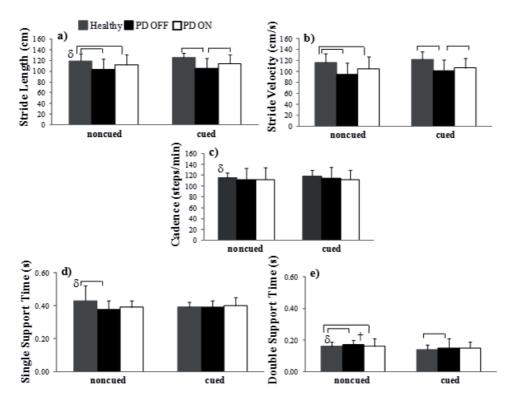
49, p = 0.01) and higher co-contraction index between vastus lateralis and biceps femoris (terminal swing) (U = 58.5, p = 0.04) than control group (FIGURE 3 and TABLE 2).

### Positive effect of cued condition in PD locomotor pattern

When people with PD were off medication, the beneficial effect of auditory cue was observed due to the reduction in double support time (Z = -2.42, p = 0.015) and an increased in vastus medial (swing phase) (Z = -2.49, p = 0.012) and tibialis anterior activation (terminal swing phase) (Z = -2.44, p = 0.015). However, after taking the medication, reduction was observed in co-contraction index between vastus lateralis and biceps femoris (terminal swing phase) (Z = -2.41, p = 0.016) and co-contraction index between vastus lateralis and biceps femoris (swing phase) (Z = -1.98, p = 0,02) (FIGURES 1, 3 and TABLE 2).

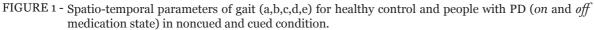
## Association effects between medication and cue conditions for people with PD

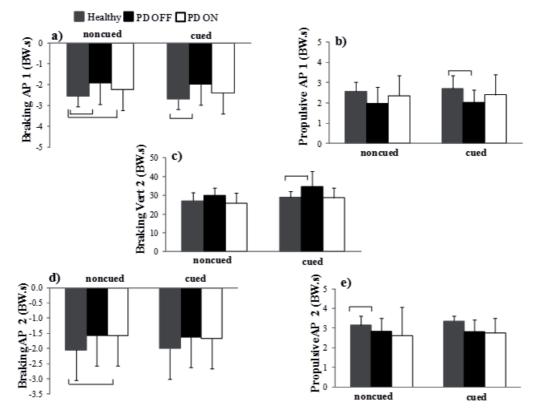
In order to investigate the effects of medication and auditory cue on the gait of people with PD, Friedman test revealed an increase in length ( $X^2(2) = 11.08$ , p = 0.01) and velocity ( $X^2(2)$  = 11.08, p = 0.01) stride after medication intake with auditory cues. Besides, it was observed an increase of biceps femoris activation in the loading phase of gait cycle ( $X^2(2) = 13.64$ , p = 0.003). Wilcoxon "post hoc" tests showed that with auditory cue, after intake the medication, people with PD had increased length (p = 0.001) and velocity (p = 0.01) stride. Furthermore, people with PD showed greater biceps femoris activation (p = 0.01) after medication intake. Also, biceps femoris showed higher activation when patients were in the off state medication (with auditory cue) compared to the on state medication (without auditory cue) (FIGURES 1 and 3, TABLE 2).



\*Brackets indicate significant differences between healthy control and people with PD (off and on medication) (p  $\leq 0.05$ );

δ and † indicate positive effect of auditory for healthy control and people with PD off medication, respectively.





\*Brackets indicate significant differences between healthy control and people with PD (off and on medication) (p  $\leq$  0,05);

Numbers indicate the force plate 1 and 2.

FIGURE 2 - Antero-posterior and vertical impulses of force ground reaction (a,b,c,d,e) for healthy control and people with PD (*on* and *off* medication state) in noncued and cued condition.

TABLE 2 - Mean and  $(\pm SD)$  for gait cycles phase for healthy control, PD off medication and PD on medication in cued and noncued conditions.

\*Difference between control and PD *off* medication ( $p \le 0.05$ ) in cued condition.

Positive effect of medication for PD off medication (p  $\leq$  0.05).  $\neq$ Difference between PD off medication (cued condition) and PD on medication (noncued condition).

Phase of gait cycle	Muscle	<b>Healthy Control</b>		PD off		PD on	
		noncued	cued	noncued	cued	noncued	cued
Loading response (0-10%)	Vastus Lateralis	267.1 (99)	318.8 (107)*	152.6 (98.6)	161.7 (89.7)	241.3 (100)	281.8 (96.4)
	Biceps Femoris	220.5 (95.5)	226.4 (93)**	207.2 (91.2)	208.8 (93)	221.7 (102.4)	291.9 (99.8)
Mid-stance (10-30%)	Biceps Femoris	231.57 (107)	277.4 (91.8)	392.6 (95.4)	415.8 (99)***	336.6 (98.3) ¥	305.1 (107.8)
Terminal stance (30-60%)	Medial Gastrocne- mius	633.6 (197.5)	839.5 (150)*	529.9 (158.7)	535.3 (157)	539.5 (113)	600.8 (118.3)
Initial swing (60-73%)	Vastus Medial	21.5 (9.2)	20.3 (10.4)*	15.4 (9)†	23.4 (9.2)	16.5 (7.4)	21.9 (10.8)
Terminal swing (87-100%)	Biceps Femoris	287.4 (101.3)	290 (100.8)*	203.9 (99.1)	151.8 (81)	251.4 (99)	266.5 (92.1)
	Tibialis Anterior	365.2 (97.2)	432.9 (103.2)	294.7 (94.7)†	336.5 (98.5)	302.1 (98.3)	349.8 (99.6)

\*Brackets indicate significant differences between healthy control and people with PD (off and on medication) (p  $\leq 0.05$ );

‡indicate positive effect of auditory cue for people with PD *on* medication.

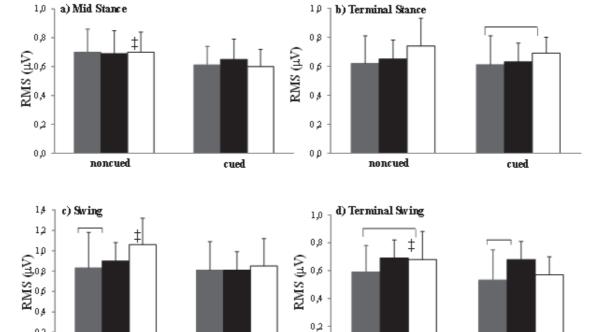


FIGURE 3 - Muscular co-contraction index between vastus lateralis and biceps femoris (a,b,c,d) for healthy control and people with PD (*on* and *off* medication state) in noncued and cued condition.

cued

0,0

noncued

cued

noncued

0,2 0,p

<sup>\*\*</sup>Difference between control and PD on medication ( $p \le 0.05$ ) in cued condition.

<sup>\*\*\*</sup>Positive effect of medication (p  $\leq$  0.05) in cued condition.

#### **Discussion**

The aim of this study was to investigate the effect of auditory cues and medication on the kinematic, kinetics and EMG parameters, during different phases of gait in people with PD. The results of this study are in agreement with literature which has reduced kinematic, kinetic and electromyographic variables, for PD patients compared to elderly<sup>5,21-22</sup>. This is one of the first studies to identify changes in muscle activation patterns in PD patients in different phases of gait with auditory cue. Del Olmo and Cudeiro showed that with auditory cue it was possible to observe positive changes on standard muscle (tibialis anterior and gastrocnemius) of PD patients, however, in this study it was not possible to identify in which gait phase this change took place<sup>22</sup>.

In the present study, patients with PD showed higher knee co-activation and lower muscle activation than control group, especially in the phases of balance and final balance. This increase in the co-activation index of PD patients may indicate motor coordination problems, muscle function inefficiency and high energy expenditure<sup>3</sup>. The swing phase, since it generates imbalance, proves to be more challenging for patients with PD, regardless of the condition of the medication, when compared to healthy elderly. This result can be explained by loss of function of the basal ganglia, pushing the motor cortex to send motor commands with noise to the effector system, so that agonists and antagonists are activated simultaneously and inefficiently.

In relation to medication intake, some studies have shown improvements in spatial and temporal parameters and in the ability to increase muscle activation pattern during gait in PD patients after ingestion of the medication<sup>23-25</sup>. The present study also found changes in gait parameters in PD patients after taking the medication, however, these changes were only observed with auditory cue, that indicated a better performance in the locomotor pattern of people with PD.

Therefore, we observed an increase on the activation of eccentric biceps femoris muscle during single support when patients were in the *off state* medication and were provided with auditory cue. In this gait phase, the biceps femoris acts as a stabilizer of the knee to sustain body weight and propel the next step. This is an important finding because in a situation of freezing gait, where both feet are adhered to the ground, auditory cue may facilitate removal of

the foot from the ground, freeing patients from this conflicting situation. Another interesting finding is that people with PD *off* medication showed higher biceps femoris activation with auditory cue than without auditory cue.

These results may help people with PD to use this sensory stimulation when they are *off* medication, e.g., during daily activities and motor intervention sessions. Thus, the auditory cue pulse makes that the motor impulses bypass the damaged circuitry in basal ganglia, and the medication acts in this damaged area, that even in this situation may not improve muscle activation. Besides that, these results can be explained by the demand for attentional and sensory resources stimulating the motor cortex, which subsequently sends commands to the spinal cord, without basal ganglia participation<sup>26</sup>. Therefore, in addition to medication therapy, patients with PD require a sensory reinforcement for improving some gait parameters.

When conditions were compared, improvements on kinematic, kinetic, and electromyographic parameters people with PD were evident. For patients with PD, significant difference was found only for the double support. This study revealed a reduction in double support values, indicating a positive result for the dynamic stability. Moreover, provided with auditory cue, a similar behavior was observed in braking and propulsion impulses in the first and second steps of the gait cycle in people with PD (on medication) and in healthy individuals. These results can be explained by the increase in muscle activation of the vastus medialis (swing phase) and the tibialis anterior (terminal swing phase). As a consequence, in the swing phase, the greatest activation of the vastus medialis may have caused patients to elevate the leg over the ground, increasing the propulsion and reducing the double support. Subsequently, patients activated mostly the tibialis anterior muscle to perform ankle dorsiflexion and ensure that the heel touches the ground. Yet, the rate of knee joint muscle co-activation decreased in the presence of auditory cue, indicating better motor coordination and even alleviating the problems of muscle stiffness. Thus, auditory cue resulted in greater consistency in the motor recruitment by means of motor neuron excitability through the reticulum spinal route<sup>27</sup>, deflecting circuit from the dopamine deficits basal ganglia<sup>28</sup>.

Besides these changes in the gait of people with PD in the presence of auditory cue, it seems that people with PD *on* medication state, adopted a

locomotor pattern similar to the control group. For example, without auditory cue, there was no significant difference between the on and off medication state, but provided with auditory cue, this difference was observed, and people with PD on medication showed better locomotor performance. Besides medication therapy, people with PD require a sensory reinforcement to improve some gait parameters, such as reduction in coactivation rates. This is an important variable that indicates improvement in motor coordination. For rehabilitation, in addition to auditory cue, it is important that attentional cues synchronize movement with auditory cue<sup>29</sup>, which facilitates positioning of the foot on the ground. Finally, this study presents unprecedented results that auditory cue may help patients with PD in the most challenging phases of gait (initial and terminal swing phase), being an important factor for motor rehabilitation. Furthermore, it is important to

emphasize that these stages patients with PD require greater sensory stimulus to overcome hypermetria, muscular rigidity and postural instability.

We can conclude that auditory cue resulted in improvements in muscle activity of people with PD patients that indicates a better locomotor pattern. Auditory cue can act as an external rhythmic generator and alleviate some PD symptoms such as bradykinesia and muscle rigidity. Moreover, this sensory stimulation caused changes in the motor system of these patients, such as increased recruitment of motor units, facilitating movement, especially in the most challenging phase of gait (swing). Consequently, we emphasize the use of auditory cue as a complementary therapy to levodopa to achieve improvement in the gait of patients with PD, since they can benefit from this sensory stimulation during daily activities and during motor interventions.

#### Resumo

Efeito positivo da dica auditiva no padrão locomotor de pacientes com doença de Parkinson

Mudanças na marcha são identificadas em pacientes com doença de Parkinson (DP). O objetivo deste estudo foi investigar o efeito da dica auditiva e do medicamento nos parâmetros cinemáticas, cinéticos e eletromiograficos durante diferentes fases da marcha em pacientes com DP e idosos sadios. 30 indivíduos distribuídos em dois grupos (Grupo 1, pacientes com DP; Grupo 2, idosos sadios) participaram deste estudo e foram instruídos a realizarem duas tarefas experimentais: marcha com e sem dica auditiva. Análise cinemática, cinética e eletromiográficas foram utilizadas para investigar o padrão locomotor. Mudanças no padrão locomotor (maior ativação muscular) foram observadas para os pacientes com DP. Em relação à medicação, melhoras no padrão locomotor foram observadas após a ingestão da levodopa em associação com a dica auditiva. Estes resultados confirmam a hipótese sobre a terapia com dicas externas, que pode ser utilizada como um complemento à terapia medicamentosa para melhorar o padrão locomotor de pacientes com DP.

Palavras-chave: Locomoção; Levodopa; Biomecânica; Dica externa; Envelhecimento.

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