Clinical Neurophysiology 130 (2019) 1789–1797

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Immediate effects of rhythmic auditory stimulation on gait kinematics in Parkinson's disease ON/OFF medication

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ARTICLE INFO

Article history:
Accepted 5 July 2019
Available online 25 July 2019

Keywords:
Parkinson disease
Rhythmic auditory stimulation
Kinematic
Gait analysis
Rehabilitation
Personalized medicine

HIGHLIGHTS

- Rhythmic Auditory Stimulation (RAS) instantly improves parkinsonian gait, regardless of the dopaminergic drug.
- A frequency of 110% of the preferred walking cadence is the most effective stimulus.
- RAS improves spatio-temporal parameters and gait phases distribution, but leaves joint kinematics unaltered.

ABSTRACT

Objective: Gait impairment is a highly disabling symptom for Parkinson's disease (PD) patients. Rhythmic auditory stimulation (RAS), has shown to improve spatio-temporal gait parameters in PD, but only a few studies have focused on their effects on gait kinematics, and the ideal stimulation frequency has still not been identified.
Methods: We enrolled 30 PD patients and 18 controls. Patients were evaluated under two conditions (with (ON), and without (OFF) medications) with three different RAS frequencies (90%, 100%, and 110% of the patient's preferred walking cadence). Spatial-temporal parameters, joint angles and gait phases distribution were evaluated. A novel global index (GPQI) was used to quantify the difference in gait phase distribution.
Results: Along with benefits in spatial-temporal parameters, GPQI improved significantly with RAS at a frequency of 110% for both ON and OFF medication conditions. In the most severe patients, the same result was observed also with RAS at 100%.
Conclusions: RAS administration, at a frequency of 110% of the preferred walking frequency, can be beneficial in improving the gait pattern in PD patients.
Significance: When rhythmic auditory stimulation is provided to patients with PD, the selection of an adequate frequency of stimulation can optimize their effects on gait pattern.

1. Introduction

Gait impairment is a main issue for patients with Parkinson's Disease (PD) (Boonstra et al., 2008), because it causes reduced mobility, loss of independence, and high risk of fall. The consequences include high morbidity and mortality (Moore et al.,

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https://doi.org/10.1016/j.clinph.2019.07.013
1388-2457/

2007; Muslimovic et al., 2008; Walton et al., 2015), and deterioration of patient's and proxy's quality of life.

Gait impairments can be continuous or episodic (i.e. festination and freezing of gait) (Ebersbach et al., 2013; Peterson and Horak, 2016). Continuous gait disturbances include a spectrum of gait alterations which can be divided in three main areas: (i) slowness of gait, (ii) increased variability and asymmetry, and (iii) poor postural control (Peterson and Horak, 2016; Smulders et al., 2016). In PD patients, step length and frequency are reduced, as well as arm swing amplitude, while step duration is increased (Morris et al., 1994b; Curtze et al., 2015; Galna et al., 2015). Moreover, reduced lower limb angular excursion and abnormal muscular co-contraction patterns (mainly because of increased muscle tone) have been reported (Wright et al., 2007; Baker, 2013). As a result, gait phases distribution is altered (Rinaldi et al., 2014; Skinnner et al., 2015), favoring a flat-footed gait with increased time spent with both feet on the ground (double support time, DST) (Nieuwboer et al., 1999; Peterson and Horak, 2016; Smulders et al., 2016). Finally, asymmetric upper and lower limb movements have been noticed during gait and a high variability of gait parameters is observed (Peterson and Horak, 2016). These alterations are determined by the dysfunction of both dopaminergic and non-dopaminergic neural circuits (Peterson and Horak, 2016; Takakusaki, 2017), and consistently with this hypothesis, gait impairment is only partially improved by the dopaminergic therapy.

Recently, attention has been focused on alternative gait rehabilitative strategies, such as external sensory cueing (Spaulding et al., 2013; Rocha et al., 2014). Rhythmic motor tasks, such as walking or speaking, require correct functioning of internal timing mechanisms. Two main timing modalities are generally identified, with two different underlying neural circuits: implicit and explicit (Nombela et al., 2013). Implicit timing involves automatic timing systems and relies on the external cues (Coull and Nobre, 2008), and is mainly driven by the cerebellum (Beudel et al., 2008; Ivry and Spencer, 2004; Merchant et al., 2015). Explicit timing is engaged whenever subjects make a deliberate estimation of discrete time duration by comparison with a previously memorized standard (Coull and Nobre, 2008); it relies on an internal sense of time and it is sustained by a network involving basal ganglia, supplementary motor cortex, premotor cortex, and cerebellum (Coull et al., 2011).

In PD, the explicit timing mechanisms are impaired, contributing to gait disturbance (Jones et al., 2008), while implicit timing seems to be spared. Various external sensory cues, such as visual, auditory, or tactile stimulations have been used as pacemakers to recalibrate the timing mechanisms and access motor programs (Nieuwboer et al., 2009; Nombela et al., 2013; Patel et al., 2014). Compared to the visual or tactile primary cortexes, auditory cortex has been shown to have shorter reaction times (Shelton and Kumar, 2010; Nombela et al., 2013). The effect of auditory cueing as a tool to restore locomotion timing, relies on the innate human capacity to extract rhythm from the external world (Ashoori et al., 2015), and on a mechanism called "entrainment", which provides the synchronization of movements to rhythm (Nombela et al., 2013; Moens and Leman, 2015). The neural basis of entrainment relies on the highly documented connections between the auditory and the motor systems (Mcintosh et al., 1997; Bengtsson et al., 2009; Grahn and Brett, 2009; Bijsterbosch et al., 2011).

Auditory cues, also referred to as rhythmic auditory stimulation (RAS), can be administered via metronome, counting, or music. Most studies evaluated the effects of RAS on spatial-temporal measures of parkinsonian gait, showing an increase of step cadence, stride length, and gait speed (Spaulding et al., 2013; Rocha et al., 2014; Ghai et al., 2018). Three studies focused on the effects of RAS on gait kinematics. Picelli et al. evaluated the effects of RAS on gait kinematics of 8 PD patients in ON phase with an optoelectronic system, showing a decrease of ankle range of motion (ROM) and DST, and an increase of hip joint power during the pull-off phase (Picelli et al., 2010). Rinaldi et al. investigated the immediate effects of RAS training and medication on kinematic, kinetics, and EMG parameters during different gait phases in PD, showing a RAS-induced change of muscle activation patterns with reduction of rectus femoris/biceps femoris co-contraction (knee extensors/flexors) in ON condition (Rinaldi et al., 2014). Pau et al. evaluated the effect of a 5-weeks combined classical gait training and RAS training on gait kinematics, showing a correct reweighting of swing/stance phase duration, and a significant improvement of a concise kinematic value (global profile score) up to 17 weeks, mainly due to a normalization of the hip flexion–extension movement (Pau et al., 2016).

To the best of our knowledge, studies evaluating the immediate effects of RAS on gait kinematics and the differential effects in OFF and ON conditions are still lacking. The aim of this study was to determine whether RAS could have an immediate effect on kinematic values of gait of PD patients, in both OFF and ON medication conditions, including the evaluation of lower limb joint angles and gait phases distribution.

2. Methods

2.1. Study sample

Thirty PD patients (Table 1) were enrolled among outpatients of the Movement Disorders Unit of the Fondazione Policlinico Universitario Agostino Gemelli IRCSS and Fondazione Don Carlo Gnocchi Onlus. Idiopathic PD was diagnosed according to Gelb criteria (Gelb et al., 1999). We included patients with clinically relevant response to levodopa (ON and OFF, Unified Parkinson's Disease Rating Scale (UPDRS) motor scale difference over 20%), able to walk unaided, with mini-mental state examination (MMSE) > 24/30 (Folstein et al., 1975). The patients with intracranial lesions, orthopedic comorbidities, severe psychiatric disorder (because of dopaminergic complications or idiopathic), and/or hypoacusia were excluded. The sample size was calculated using a repeated measure, within factor, ANOVA test (number of measurement = 4), assuming an effect size of 0.25, a significance level of 0.05, and a power of 0.9.

Eighteen age and sex-matched control subjects were included. The inclusion criteria for the control group were: absence of parkinsonism, MMSE > 24, ability to walk unaided.

The study protocol was approved by the Ethics and Medical Board of the IRCCS Fondazione Don Carlo Gnocchi (Prot. N.2/2017/CE_FdG/SA). The study was conducted in accordance with the International Conference on Harmonization Good Clinical practice guidelines and the Declaration of Helsinki. All participants gave written informed consent prior to study participation.

2.2. Study procedures

The following data were recorded for all study participants: age, sex, coping with daily living activities as assessed by the ADL-IADL scale (Katz, 1983), the MMSE (Folstein et al., 1975), age at PD onset; and disease duration, comorbidities, medications, number of falls, and near-falls in the last six months.

PD was assessed by the UPDRS (Fahn, 1987; Antonini et al., 2013), Hoehn and Yahr staging (Hoehn and Yahr, 1967), and the levodopa equivalent daily dose (LEDD, mg) calculated according to the published conversion factors for individual antiparkinsonian drugs (Tomlinson et al., 2010).

Table 1
Demographic and clinical characteristics of PD patients (*patient with "wrong sided tremor").

Patients	Age (years)	Sex	Side of onset	Most affected side	Disease Duration (years)	UPDRS III	
						OFF-med	ON-med
1	68	M	right	right	3	25	16
2	68	M	/	right	3	23	14
3	74	M	left	left	8	25	10
4	71	F	left	left	17	14	10
5	57	F	left	left	7	14	11
6	68	M	left	left	13	32	19
7	79	F	right	right	15	25	17
8	66	M	left	left	23	10	6
9*	78	F	right	left	7	26	23
10	76	F	/	left	17	15	12
11	78	F	/	left	5	32	23
12	70	M	right	right	7	18	8
13	69	F	left	left	3	27	20
14	66	M	left	left	12	35	24
15	69	M	right	left	4	20	18
16	73	M	left	left	13	28	20
17	64	M	right	right	9	40	25
18	79	F	left	left	18	36	26
19	81	M	left	left	10	24	18
20	79	M	left	left	22	27	14
21	76	M	right	right	7	33	22
22	63	M	right	right	12	38	20
23	77	M	/	left	15	40	32
24	63	M	left	left	13	42	31
25	74	M	left	left	17	31	19
26	79	M	left	left	10	30	19
27	71	F	left	left	14	29	19
28	76	F	right	right	17	43	20
29	75	M	left	left	10	37	26
30	64	M	right	right	23	36	28
Mean ± std	72 ± 6				12 ± 6	29 ± 9	19 ± 6

2.3. Experimental setup

Four force resistive sensors (FRSs, Wireless Wave EMG, Cometa – IT) were placed under each foot—in correspondence of the heel, the first metatarsophalangeal, the fifth metatarsophalangeal, and the toe—to estimate gait temporal parameters (Mileti et al., 2017). Two wireless modules, one for each foot, sampled the signal of the FRSs at a 2000 Hz rate, sending data to a base receiver. Seven wireless inertial measurement units (IMUs MTw, Xsens Technologies – NL) were placed on the insteps of feet, laterally on mid-shanks, laterally on mid-thighs of both sides, and on pelvis. Each IMU is equipped with a 3-axes accelerometer sensor (±160 m/s^2 FS), a 3-axes gyroscope (±1200°/s FS), and a 3-axes magnetometer (±1.5 Gauss). The sampling rate was set at 50 Hz. Elastic belts were used to fix IMUs on each body segment. IMUs were used to estimate the lower limb kinematics through the biomechanical model (details are reported in previous studies) (Palermo et al., 2014a; Pacilli et al., 2016). Body-to-sensors alignment and joint angles were obtained by applying a functional calibration (FC) procedure (Palermo et al., 2014a). FRSs and IMUs were synchronized in starting and stopping the acquisition. During the post-processing stage, IMU data were up-resampled and FRSs were down-sampled to match in rate at 200 Hz. A wireless FM headset (SHC5100, Philips – NL) and an ad-hoc developed by the LabVIEW software (v.2014, National Instrument, USA), were used to provide RAS to the participants.

2.4. Experimental procedure

Subjects were asked to walk along a 20 m pathway in four conditions:

(i) walking at their preferred speed without cues (preferred walking, PW);
(ii) walking with RAS at 90% of the PW (RAS90);
(iii) walking with RAS at 100% of the PW (RAS100); and
(iv) walking with RAS at 110% of the PW (RAS110).

The order of the last three trials was randomized among the subjects. FC was performed by all subjects before each walking trial, to compensate for magnetic field disturbances (Palermo et al., 2014b).

Each patient was evaluated in both OFF and ON medication conditions. OFF condition was tested in the morning after a twelve-hour levodopa wash-out; ON condition was tested one hour after the usual morning levodopa dose intake. After each trial, patients rested on a chair for at least two minutes to avoid fatigue effects.

2.5. Data analysis

Data were post-processed and analyzed using MATLAB software (MathWorks, 2012b, Natick, MA, USA). For each walking task, mean and standard deviation of the parameters were calculated by discarding the first and the last three strides to avoid acceleration and deceleration effects. Temporal parameters were detected through the identification of the following gait events on the FRSs output: (i) Heel strike, when the heel reached the ground and the sensor placed under the heel was pressed; (ii) Toe strike, when the toe reached the ground and the toe sensor was pressed; (iii) Heel off, when the heel was lifted and only the toe sensor was pressed; and (iv) Toe off, when the foot was landing and no sensor was pressed. A gait cycle was defined as the interval between two consecutive heel strikes. Stride time was defined as the overall gait cycle time expressed in seconds.

According to the four-phase model (Taborri et al., 2016), each gait cycle was divided into four phases: (i) Loading response, from heel strike to toe strike; (ii) Flat-foot, from toe strike to heel off; (ii) Pre-swing, from heel off to toe off; (iv) Swing, from toe off and the

following heel strike. Furthermore, Single support was defined as the time period, in which patients were in single stance condition during a gait cycle. Each gait phase was expressed as a percentage of the gait cycle. To quantify the difference of patients' phase distribution from those of the control group, the kinematic gait phases quality index (GPQI) was calculated as defined in another study (Mileti et al., 2018). The GPQI value represents the deviation between the abnormal and normal gait in terms of gait phases distribution. A GPQI value close to 0% represents a gait pattern more similar to the normal one.

Data were analyzed by dividing gait parameters in three groups, according to the classification reported by Peterson (Peterson and Horak, 2016): (i) slowness of gait, (ii) stride-to-stride variability, and (iii) gait asymmetry.

To quantify the slowness of gait, the following spatio-temporal parameters were computed: step length; stride length; cadence; walking speed; stride time; hip, knee, and ankle ROM angle in the sagittal plane (RoM_{Hip}, RoM_{Knee}, RoM_{Ankle}); loading response; flat-foot; pre-swing; swing, and GPQI. In particular, step length and stride length were normalized to the subjects' leg length. Joint angle curves related to each stride were normalized to the gait cycle.

To estimate stride-to-stride variability, the coefficient of variation (CoV) was computed for step length (^{CoV}StepLength), stride length (^{CoV}StrideLength), stride time (^{CoV}SrideTime), and swing (^{CoV}Swing). CoV values were computed (Mileti et al., 2016). To quantify the gait asymmetry, the symmetry index (SI) was evaluated for the step length (^{SI}SpL), and the range of motion of hip, knee, and ankle in the sagittal plane ($^{SI}ROM_{Hip}$, $^{SI}ROM_{Knee}$, $^{SI}ROM_{Ankle}$) (Motta et al., 2016). Values of SI close to 0% indicate full side-symmetry, whereas values of SI greater than 100% indicate full side-asymmetry.

2.6. Statistical analysis

To compare PD patients with controls, two unpaired *t*-test were performed between controls and PD patients' gait parameters in OFF and ON conditions.

To investigate the effects of RAS on the entire cohort of patients with PD (G1), gait parameters were analyzed by using a $2 \times 4 \times 2$ three-way repeated measures ANOVA, with *treatment condition* (two levels: ON and OFF), *RAS* (four levels: PW, RAS90, RAS100, and RAS110), and *side* (two levels: most and less affected) as between-subject factors. When appropriate, we performed post-hoc paired comparisons, with Fisher LSD correction for multiple comparisons. If the interaction effect LEVODOPA × RAS was significant, we broke down the interactions, comparing OFF and ON separately. More specifically, a two-way repeated measures ANOVA, with RAS (four levels: PW, RAS90, RAS100, and RAS110), and side (two levels: most and less affected) as between-subject factors, was performed both for OFF and ON conditions.

Furthermore, in order to deeper investigate the immediate effect of RAS, the three-way repeated measures ANOVA was performed on a subset of 12 patients (G2) presenting a high level of gait impairment, by gait sub-item of UPDRS-III value related to OFF condition equal to 2 or 3, i.e. half the range variation of our patients. Data were tested for normality with the Shapiro Wilk test. For all statistical tests, significance refers to a two-tailed *p*value < 0.05.

3. Results

3.1. Uncued gait analysis in PD patients and controls

In Table 2, mean and standard deviation of gait parameters were reported considering both PD in OFF and ON condition and healthy subjects. Furthermore, p-values and F values of the unpaired t-tests were reported. Compared to controls, PD patients in OFF condition showed significant reduction of step length, stride length, walking speed, ROM_{Hip}, ROM_{Knee}, ROM_{Ankle}, swing phase, single support phase; and a significant increase of GPQI, variability of step length and stride time, and the asymmetry of step length and ROM_{Ankle}. In ON condition, patients reported a reduction of step length, stride length, walking speed, ROM_{Hip}, ROM_{Knee}, ROM_{Ankle}; and an increase of GPQI, variability of stride time, and the asymmetry ROM_{Ankle}. All the remaining parameters did not show significant differences between the PD patients and the control group.

3.2. Effect of levodopa and RAS on gait of PD patients

In Table 3, mean and standard deviation of gait parameters were reported for the entire cohort of patients with PD (G1) con-

Table 2
Mean and standard deviation of gait parameters of PD patients and control group (CG) in preferred walking condition. *p*-values of two unpaired t-test between control group and PD patients in OFF and ON conditions are reported. *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.

					OFF-CG		ON-CG	
		OFF	ON	CG	*p*-values	*F*	*p*-values	*F*
Slowness of gait	Step Length	0.44 ± 0.19	0.51 ± 0.13	0.70 ± 0.06	<0.01***	17.27	<0.01***	1.49
	Stride Length	0.90 ± 0.38	1.04 ± 0.26	1.36 ± 0.14	<0.01***	9.97	<0.01***	2.88
	Cadence (step/s)	116.65 ± 30.68	113.51 ± 15.34	108.45 ± 10.06	0.97	2.81	0.25	1.28
	Walking Speed (m/s)	0.77 ± 0.32	0.88 ± 0.26	1.08 ± 0.19	<0.01**	7.16	0.02*	2.06
	Stride Time (s)	1.13 ± 0.17	1.09 ± 0.11	1.13 ± 0.10	0.94	1.62	0.26	0.36
	ROM_{Hip} (°)	27.42 ± 9.07	30.56 ± 7.95	36.89 ± 3.37	<0.01**	8.14	<0.01**	3.13
	ROM_{Knee} (°)	45.48 ± 9.51	49.64 ± 6.85	58.82 ± 6.13	<0.01***	1.67	<0.01**	0.92
	ROM_{Ankle} (°)	23.56 ± 6.77	27.68 ± 5.14	35.10 ± 6.27	<0.01***	0.49	<0.01**	0.01
	Loading Response (%)	5.63 ± 3.36	6.4 ± 2.43	6.85 ± 2.17	0.27	2.01	0.60	0.47
	Flat-Foot (%)	45.44 ± 13.00	40.5 ± 11.14	39.35 ± 7.41	0.15	3.85	0.75	1.88
	Pre-Swing (%)	17.34 ± 6.64	17.21 ± 6.65	16.15 ± 5.95	0.61	0.07	0.65	0.09
	Swing (%)	32.51 ± 10.53	36.75 ± 4.74	37.71 ± 2.89	0.01*	5.92	0.38	1.03
	Single Support (%)	64.79 ± 20.74	72.86 ± 12.44	75.63 ± 4.77	0.01*	8.80	0.48	2.25
	GPQI (%)	23.52 ± 15.69	18.89 ± 10.55	7.50 ± 3.16	0.01*	8.03	0.01*	2.15
Gait variability	^{CoV}Step Length (%)	10.85 ± 17.00	5.76 ± 3.96	2.71 ± 0.50	0.04*	4.75	0.01*	10.81
	^{CoV}Stride Length (%)	8.38 ± 13.57	4.41 ± 3.31	1.91 ± 0.76	0.13	4.44	0.02*	7.77
	^{CoV}Stride Time (%)	4.63 ± 4.03	3.84 ± 2.07	2.89 ± 0.72	0.02*	2.93	0.03*	6.03
	^{CoV}Swing (%)	19.39 ± 33.72	7.36 ± 3.75	5.37 ± 1.52	0.20	5.16	0.11	5.93
Gait asymmetry	^{SI}Step Length (%)	20.8 ± 23.94	14.01 ± 13.84	5.09 ± 3.00	0.04*	6.67	0.01	2.92
	$^{SI}ROM_{Hip}$ (%)	13.08 ± 8.28	12.61 ± 7.33	11.85 ± 7.94	0.22	0.74	0.39	0.30
	$^{SI}ROM_{Knee}$ (%)	11.04 ± 9.42	10.64 ± 9.54	5.40 ± 2.87	0.06	7.92	0.08	6.85
	$^{SI}ROM_{Ankle}$ (%)	14.09 ± 12.19	13.77 ± 9.63	7.10 ± 3.21	0.01*	3.11	0.03*	11.36

Table 3
Mean and standard deviation of gait parameters of the entire cohort of patients (G1) in PW, RAS-90, RAS-100 and RAS-110 conditions. *p*-values of the main effects *treatment condition* (Treatment) and RAS of the three way repeated measure ANOVA are reported. * stands for statistical differences in the post-hoc analysis comparing PW and each RAS condition.

							Treatment		RAS		Treat *Ras	
			PW	RAS 90	RAS 100	RAS 110	*P*	*F*	*p*	*F*	*p*	*F*
Slowness of gait	Step Length	OFF	0.44 ± 0.19	0.45 ± 0.18	0.46 ± 0.17	0.46 ± 0.17*	<0.01*	12.66	0.11	2.53	0.86	0.25
		ON	0.51 ± 0.13	0.52 ± 0.13	0.53 ± 0.13	0.53 ± 0.13*						
	Stride Length	OFF	0.9 ± 0.38	0.91 ± 0.34	0.92 ± 0.33	0.94 ± 0.34*	<0.01*	13.16	0.11	2.07	0.97	0.08
		ON	1.04 ± 0.26	1.05 ± 0.26	1.07 ± 0.25	1.06 ± 0.25*						
	Cadence (step/s)	OFF	116.65 ± 30.68	100.63 ± 18.82*	105.75 ± 15.43	112.06 ± 17.52	0.01*	3.39	<0.01*	11.29	0.09	2.30
		ON	113.51 ± 15.34	108.4 ± 22.92*	109.1 ± 23.89	116.68 ± 12.35						
	Walking Speed (m/s)	OFF	0.82 ± 0.41	0.70 ± 0.3*	0.73 ± 0.3	0.81 ± 0.31	0.01*	11.05	<0.01*	7.00	0.20	1.56
		ON	0.88 ± 0.26	0.83 ± 0.26*	0.87 ± 0.25	0.91 ± 0.26						
	Stride Time (s)	OFF	1.13 ± 0.17	1.26 ± 0.24*	1.19 ± 0.18*	1.12 ± 0.18	0.02*	6.30	<0.01*	20.50	0.50	1.95
		ON	1.09 ± 0.11	1.18 ± 0.15*	1.13 ± 0.16*	1.07 ± 0.11						
	ROMHip (°)	OFF	27.42 ± 9.07	27.24 ± 8.84	27.27 ± 9.15*	27.34 ± 9.83	<0.01*	9.87	0.12	2.04	0.94	0.12
		ON	30.56 ± 7.95	31.24 ± 8.66	31.13 ± 8.13*	31.14 ± 8.77						
	ROMKnee (°)	OFF	45.48 ± 9.51	43.39 ± 8.72*	45.04 ± 8.92	44.97 ± 9.84	<0.01*	12.00	0.01*	4.35	0.40	0.98
		ON	49.64 ± 6.85	48.24 ± 8.27*	49.05 ± 7.26	49.82 ± 8.47						
	ROMAnkle (°)	OFF	23.56 ± 6.77	23.89 ± 6.4	24.16 ± 5.69	24.02 ± 6.37	<0.01*	12.70	0.17	1.71	0.74	0.41
		ON	27.68 ± 5.14	26.96 ± 5.1	27.51 ± 5.07	27.49 ± 4.89						
	Loading Response (%)	OFF	5.63 ± 3.36	4.96 ± 3.04*	5.29 ± 2.92	5.38 ± 3.12	0.01*	9.11	<0.01*	4.84	0.35	1.11
		ON	6.4 ± 2.43	5.67 ± 2.49*	6.45 ± 2.43	6.41 ± 2.42						
	Flat-Foot (%)	OFF	45.44 ± 13.00	46.72 ± 12.81*	45.86 ± 11.64	45.64 ± 12.09	<0.01*	16.26	0.02*	3.37	0.87	0.22
		ON	40.5 ± 11.14	42.35 ± 11.12*	41.38 ± 11.26	40.82 ± 10.48						
	Pre-Swing (%)	OFF	17.34 ± 6.64	16.05 ± 6.3*	15.97 ± 5.64*	16.12 ± 6.84*	0.23	1.54	0.01*	4.94	0.45	0.88
		ON	17.21 ± 6.65	16.13 ± 6.25*	16.83 ± 7.21*	16.87 ± 6.18*						
	Swing (%)	OFF	32.51 ± 10.53	32.94 ± 9.09	33.53 ± 8.45	33.48 ± 8.27	0.01*	8.67	0.14	1.87	0.10	2.18
		ON	36.75 ± 4.74	36.52 ± 5.47	36.11 ± 5.51	36.57 ± 5.23						
	Single Support (%)	OFF	64.79 ± 20.74	65.73 ± 17.61	66.85 ± 16.69	66.63 ± 18.11	0.05*	9.23	0.25	1.39	0.17	1.69
		ON	72.86 ± 12.44	71.6 ± 12.73	72.42 ± 11.74	72.88 ± 11.54						
	GPQI (%)	OFF	23.52 ± 15.69	22.82 ± 14.43	21.03 ± 12.54	21.6 ± 12.62*	0.08	3.52	0.04*	2.71	0.08	2.28
		ON	18.89 ± 10.55	18.57 ± 9.02	18.84 ± 9.72	16.96 ± 8.86*						
Gait variability	^{CoV}Step Length (%)	OFF	10.85 ± 17.00	7.81 ± 9.31	6.33 ± 4.33	7 ± 9.41	0.12	2.59	0.11	2.03	0.19	1.59
		ON	5.76 ± 3.96	5.30 ± 2.48	5.32 ± 3.02	5.29 ± 3.19						
	^{CoV}Stride Length (%)	OFF	8.38 ± 13.57	6.62 ± 9.30	4.38 ± 2.15	6.13 ± 9.85	0.10	2.84	0.12	2.02	0.12	1.99
		ON	4.41 ± 3.31	3.97 ± 1.96	4.06 ± 2.73	3.69 ± 1.92						
	^{CoV}Stride Time (%)	OFF	4.63 ± 4.03	4.64 ± 3.25	4.3 ± 1.97	4.2 ± 2.49	0.08	8.23	0.62	0.60	0.95	0.10
		ON	3.84 ± 2.07	4.27 ± 2.21	3.93 ± 2.15	3.74 ± 1.61						
	^{CoV}Swing (%)	OFF	19.39 ± 33.72	13.09 ± 16.79	14.21 ± 19.8	13.24 ± 18.34	0.05*	4.04	0.05*	2.78	0.11	2.06
		ON	7.36 ± 3.75	6.79 ± 3.63	8.59 ± 5.83	7.39 ± 3.93						
Gait asymmetry	^{SI}Step Length (%)	OFF	20.8 ± 23.94	20.45 ± 30.11	14.59 ± 17.23*	20.12 ± 18.33	0.11	2.68	0.13	1.94	0.55	0.71
		ON	14.01 ± 13.84	12.00 ± 10.99	11.72 ± 10.59*	13.26 ± 14.68						
	^{SI}ROM$_{Hip}$ (%)	OFF	13.08 ± 8.28	10.78 ± 7.27*	12.35 ± 8.62	11.3 ± 7.89	0.69	0.17	0.16	1.78	0.21	1.53
		ON	12.61 ± 7.33	13.03 ± 8.47*	11.48 ± 7.59	13.45 ± 8.87						
	^{SI}ROM$_{Knee}$ (%)	OFF	11.04 ± 9.42	11.85 ± 11.06	9.82 ± 7.94	11.38 ± 11.78	0.54	0.37	0.16	1.77	0.51	0.78
		ON	10.64 ± 9.54	11.22 ± 11.61	10.1 ± 10.94	10.36 ± 9.89						
	^{SI}ROM$_{Ankle}$ (%)	OFF	14.09 ± 12.19	13.29 ± 9.18	13.08 ± 12.85	13.41 ± 9.28	0.90	0.02	0.11	0.32	0.64	0.56
		ON	13.77 ± 9.63	14.32 ± 11.32	15.99 ± 11.69	14.93 ± 10.91						

sidering both treatment condition, i.e. OFF and ON levodopa condition, and all walking conditions examined, i.e. walking at the preferred cadence (PW), and walking hearing RAS at 90% (RAS 90), at 100% (RAS100) and at 110% (RAS 110) of the preferred cadence. *P*-values and *F* values of the main effects treatment condition and RAS were also reported in Table 3 as results of the ANOVA test. Results of the interaction effects, i.e. treatment condition × RAS, were also showed. Similarly, results related to G2 were reported in Table 4.

Firstly, the interaction factors were found statistically significant only regarding the swing phase ($p = 0.03$) and its variability ($p = 0.01$) in the G2, meaning a different influence of RAS therapy depending on treatment condition. More specifically, a significant improvement of swing and its variability was observed walking with RAS at 100% of the preferred pace in the absence of levodopa treatment. According to the two-way ANOVA test, i.e. RAS (four levels: PW, RAS90, RAS100, and RAS110), and side (two levels: most and less affected) as between-subject factors, required by the significance of the interaction effect, the main effect RAS was statistically significant only in OFF condition (Swing: $p = 0.02$, ^{CoV}Swing: $p = 0.01$), and the post-hoc test unveiled significant differences only between PW and RAS100 (Swing: $p = 0.04$, ^{CoV}Swing: $p = 0.05$). As concern the remaining parameters, no significant interaction between treatment condition and RAS was observed attesting similar RAS effect on walking pattern, regardless levodopa condition. Thus in these parameters, the treatment condition, RAS and side main effects were considered in the following analysis.

In G1, levodopa caused a significant improvement for all parameters related to gait slowness, except for pre-swing phase and GPQI. In G2, levodopa administration significantly improved all parameters regarding slowness of gait area, except for stride time, loading response phase, and pre-swing phase. In both G1 and G2, levodopa did not cause any significant variation on stride-to-stride variability and gait asymmetry, except for ^{CoV}Swing, which improved with treatment in G1.

RAS influenced mostly the parameters related to gait slowness in a non-univocal way: in G1 RAS90 decreased cadence, walking speed, stride time, loading response phase, and flat-foot phase; and increased pre-swing. RAS100 statistically decreased stride time and increased pre-swing, whereas RAS110 statistically increased pre-swing and GPQI (effects of RAS on GPQI are shown in Fig. 1).

Table 4
Mean and standard deviation of gait parameters in patients presenting a high level of gait impairment (G2) in PW, RAS-90, RAS-100 and RAS-110 conditions. *p*-values of the main effects *treatment condition* (Treatment) and RAS of the three way repeated measure ANOVA are reported. * stands for statistical differences in the post-hoc analysis comparing PW and each RAS condition.

							Treatment		RAS		Treat *Ras	
			PW	RAS 90	RAS 100	RAS 110	*P*	*F*	*p*	*F*	*p*	*F*
Slowness of gait	Step Length	OFF	0.24 ± 0.13	0.28 ± 0.14*	0.30 ± 0.11*	0.29 ± 0.12*	0.01*	12.47	<0.01*	0.49	0.60	0.19
		ON	0.41 ± 0.10	0.44 ± 0.10*	0.42 ± 0.11*	0.42 ± 0.12*						
	Stride Length	OFF	0.50 ± 0.24	0.57 ± 0.23*	0.61 ± 0.19*	0.61 ± 0.21*	0.01*	13.21	<0.01*	0.03	0.36	1.09
		ON	0.83 ± 0.21	0.87 ± 0.21*	0.87 ± 0.21*	0.87 ± 0.22*						
	Cadence (step/s)	OFF	105.49 ± 15.92	95.4 ± 20.16	101.54 ± 17.02	110.07 ± 20.03*	0.05*	3.87	0.05*	4.85	0.24	1.45
		ON	108.6 ± 17.31	110.05 ± 33.04	105.09 ± 32.98	115.37 ± 13.42*						
	Walking Speed (m/s)	OFF	0.44 ± 0.19	0.43 ± 0.21	0.46 ± 0.19	0.53 ± 0.19*	0.09	11.51	0.02*	3.39	0.84	0.28
		ON	0.67 ± 0.2	0.68 ± 0.24	0.71 ± 0.2	0.73 ± 0.21*						
	Stride Time (s)	OFF	1.20 ± 0.22	1.29 ± 0.30*	1.22 ± 0.2	1.11 ± 0.18*	0.15	2.49	<0.01*	11.63	0.18	1.76
		ON	1.1 ± 0.09	1.18 ± 0.14*	1.1 ± 0.14	1.05 ± 0.11*						
	ROMHip (°)	OFF	18.6 ± 5.47	19.29 ± 5.65	19.37 ± 4.98	18.8 ± 6.15	0.01*	11.92	0.57	3.71	0.91	0.18
		ON	26.42 ± 6.43	26.6 ± 7.56	26.38 ± 6.76	25.9 ± 7.61						
	ROMKnee (°)	OFF	36.31 ± 7.86	37.06 ± 7.25	38.28 ± 7.2	37.21 ± 8.69	0.01*	10.89	0.46	0.88	0.13	2.04
		ON	47.54 ± 7.51	45.64 ± 7.82	46.15 ± 6.36	46.73 ± 8.12						
	ROMAnkle (°)	OFF	18.84 ± 7.44	19.52 ± 5.97	20.65 ± 5.67	19.86 ± 6.71	<0.01*	21.18	0.09	2.33	0.68	0.49
		ON	27.07 ± 5.49	26.98 ± 5.88	27.18 ± 5.55	27.32 ± 6.15						
	Loading Response (%)	OFF	3.49 ± 4.16	3.53 ± 3.73	3.89 ± 3.89	4.22 ± 4.21	0.06	4.42	0.07	2.65	0.73	0.42
		ON	5.08 ± 2.62	4.74 ± 2.45	5.81 ± 2.82	5.11 ± 2.62						
	Flat-Foot (%)	OFF	56.22 ± 9.24	56.25 ± 11.38	54.52 ± 9.71	54.32 ± 9.81	0.03*	15.18	0.52	0.77	0.49	0.82
		ON	46.12 ± 11.63	47.29 ± 9.91	46.57 ± 10.72	46.55 ± 8.98						
	Pre-Swing (%)	OFF	18.95 ± 7.57	16.36 ± 6.03	16.62 ± 4.55*	15.9 ± 7.26	0.53	0.42	0.11	2.17	0.56	0.69
		ON	17.22 ± 6.31	16.56 ± 4.89	16.92 ± 5.80*	17.19 ± 5.31						
	Swing (%)	OFF	22.73 ± 10.98	24.82 ± 9.04	26.01 ± 8.53*	26.46 ± 8.54	0.01*	10.30	0.07	2.60	0.03*	5.75
		ON	33.47 ± 2.41	32.89 ± 2.99	32.45 ± 3.54	32.36 ± 3.31						
	Single Support (%)	OFF	44.35 ± 18.52	49.08 ± 14.49	51.33 ± 13.7	50.58 ± 16.72	0.01*	9.64	0.16	1.83	0.10	4.55
		ON	64.15 ± 12.12	62.47 ± 10.19	63.44 ± 10.13	63.02 ± 8.91						
	GPQI (%)	OFF	36.07 ± 17.98	34.12 ± 16.29	30.25 ± 14.41*	30.19 ± 15.58*	0.03*	6.48	0.01*	4.49	0.09	2.41
		ON	22.53 ± 14.52	20.26 ± 11.67	21.11 ± 13.53*	19.03 ± 11.61*						
Gait variability	^{CoV}Step Length (%)	OFF	22.07 ± 23.72	14.38 ± 12.56	9.35 ± 3.96	12.64 ± 14.05	0.12	2.82	0.07	2.63	0.09	2.33
		ON	9.00 ± 4.44	6.77 ± 3.16	7.48 ± 3.69	7.92 ± 3.68						
	^{CoV}Stride Length (%)	OFF	17.41 ± 18.87	12.47 ± 13.16	6.69 ± 1.27	11.61 ± 15.04	0.10	3.29	0.09	2.39	0.08	2.47
		ON	6.88 ± 4.03	5.07 ± 2.62	5.98 ± 3.47	5.41 ± 1.93						
	^{CoV}Stride Time (%)	OFF	5.5 ± 1.33	6.12 ± 4.64	5.26 ± 1.42	4.75 ± 1.58	0.10	3.21	0.28	1.38	0.75	0.40
		ON	5.69 ± 2.02	5.62 ± 2.73	4.82 ± 2.48	4.8 ± 1.48						
	^{CoV}Swing (%)	OFF	40.78 ± 14.62	23.06 ± 7.61	24.84 ± 8.42*	21.7 ± 7.91	0.08	3.74	0.01*	4.49	0.04*	3.17
		ON	9.19 ± 2.91	8.13 ± 4.18	11.31 ± 6.66	9.51 ± 3.83						
Gait asymmetry	^{SI}Step Length (%)	OFF	37.22 ± 31.8	36.19 ± 43.6	24.88 ± 23.9*	30.63 ± 21.65	0.15	2.46	0.37	1.09	0.58	0.66
		ON	18.65 ± 20.49	15.27 ± 11.54	15.96 ± 12.6*	19.04 ± 20.78						
	^{SI}ROM$_{Hip}$ (%)	OFF	11.19 ± 7.71	6.78 ± 4.74	11.33 ± 7.75	9.61 ± 6.92	0.33	1.06	0.74	0.42	0.10	2.32
		ON	11.13 ± 6.13	14.43 ± 9.92	11.89 ± 7.97	15.77 ± 10.97						
	^{SI}ROM$_{Knee}$ (%)	OFF	13.33 ± 12.59	12.04 ± 15.02	10.5 ± 10.71*	15.48 ± 16.78	0.39	0.39	0.20	1.66	0.27	1.38
		ON	11.87 ± 11.98	12.44 ± 13.59	10.89 ± 12.33*	10.36 ± 10.86						
	^{SI}ROM$_{Ankle}$ (%)	OFF	19.34 ± 14.1	15.85 ± 7.92	12.26 ± 13.81	14.12 ± 8.19	0.98	0.01	0.56	0.69	0.54	0.73
		ON	14.85 ± 12.02	16.8 ± 14.04	16.7 ± 13.12	13.88 ± 9.04						

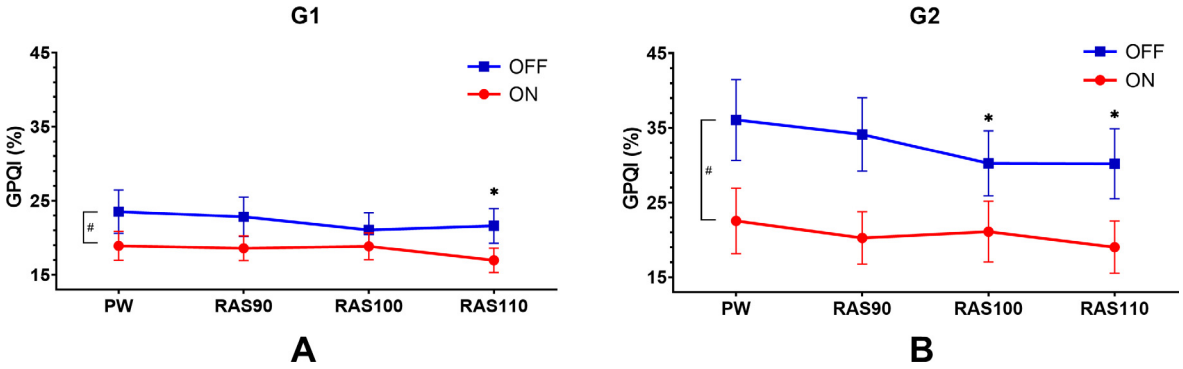

Fig. 1. (A) Mean and standard error of the GPQI in the whole group of patients (G1) obtained at the preferred walking speed (PW), and with rhythmic auditory stimulation (RAS) set a 90%, 100% and 110% of the PW (RAS90, RAS100 and RAS110, respectively). (B) Mean and standard error of GPQI in patients with high disease severity (G2) obtained in PW, RAS90, RAS100, and RAS110 conditions. Statistical differences between RAS and PW are starred. The symbol # indicates a statistically significant difference of the main effects treatments condition (ON vs OFF medication).

In G2, RAS90 statistically increased step length, stride length, and stride time. The improvements in step length, stride length, and GPQI were also found with RAS100. RAS110 improved all the spatial-temporal parameters related to hypo/bradykinesia subscore area. Furthermore, GPQI decreased, unveiling an improvement of gait phase distribution. The effects of RAS on GPQI in G1 and G2 are shown respectively in Fig. 1A and B.

For all the three frequencies, RAS had no effect on stride-to-stride variability and gait asymmetry both in G1 and G2, expect ^{CoV}Swing in G2 in OFF condition. The side differences were not statistically different among all parameters, both for G1 and G2.

The *p*-values of the post-hoc analysis of the three-way measure ANOVA are available in the Supplementary Material.

4. Discussion

The main contribution of this study was the evaluation of immediate effects of different frequencies of RAS on kinematic gait measures and gait phase distribution in PD, in both OFF and ON medication conditions. Although several studies evaluated the effects of RAS on spatial-temporal parameters (Spaulding et al., 2013; Rocha et al., 2014; Ghai et al., 2018), or on gait variability (del Olmo and Cudeiro, 2005; Almeida et al., 2007; Hausdorff et al., 2007), only three studies, as previously discussed, focused on the evaluation of the kinematic parameters (Picelli et al., 2010; Rinaldi et al., 2014; Pau et al., 2016). Furthermore, in all three studies, an optoelectronic gait analysis system was used, allowing evaluation on shorter distances, significantly reducing ecology of the measurement affected by the test effect. In this study, instead, we leveraged wearable inertial units, which allowed gait evaluation along a longer walkway (20 m), obtaining a more representative measure of actual symptomatic state of patients, without the need of several walking trial across the calibration volume. The foot insole pressure sensors also permitted detection of the gait phase distribution, according to the four-gait phase model.

As already reported in the literature, all PD patients, both ON and OFF medication, showed significantly lower spatial-temporal parameters, such as step/stride length and walking speed; and significant reduction of ROM of hip, knee, and ankle with respect to the control group. In line with a previous study (Morris et al., 1994a), cadence was not significantly different from the controls.

With regard to the gait phase analysis, PD patients group showed a significantly high GPQI value, indicating a deviation of gait phase distribution from normal values. More specifically, PD patients in OFF condition had a shorter swing phase, with a significantly reduced time in single support, indicating that patients tend to spend a longer part of the gait cycle in double support to increase stability, as previously described in another study (Peterson and Horak, 2016).

Hypometric steps, reduced ROM, altered gait phase distribution—as found in the studied group—are all major determinants of gait slowness in PD (Peterson and Horak, 2016). Indeed, significantly slowed gait speed was observed in PD patients in both ON and OFF conditions.

The analysis of the independent effect of the therapy on gait parameters of the studied group confirmed that the dopaminergic therapy improves all spatial-temporal gait parameters, increases joint ROM, ameliorates gait phase distribution with increase in swing time and single support time, and reduction of GPQI. The improvement of gait hypometria and joint rigidity caused by levodopa is in agreement with the literature and confirms that such gait alterations in PD are linked to the degeneration of dopaminergic circuits (Peterson and Horak, 2016; Takakusaki, 2017). This translates into a significant increase of PD gait velocity in both ON and OFF conditions; moreover, the positive effect of levodopa on some of the gait parameters also validates the patients' selection.

The data on effect of levodopa on the temporal parameters of gait are controversial in the available literature (Curtze et al., 2015; Sterling et al., 2015; Smulders et al., 2016). In our population, levodopa significantly reduced stride time, but with respect to asymmetry, we failed to observe the levodopa induced reduction of pace asymmetry reported by other authors (Galna et al., 2015). Moreover, the gait variability was not affected by levodopa, a finding in agreement with the hypothesis that the high gait variability in PD is not related to the dopaminergic circuitry impairment, but is secondary to the increase of voluntary cortical attentive gait control, reported in PD (Bohnen et al., 2013; Clark, 2015). As underlined in the cited works, high gait variability in PD seems to be caused by an increase of voluntary cognitive prefrontal attentive control on gait. As a consequence, as patients have to be more actively focused on how they walk, they tend to make steps all different from each other. The authors also underline how, since high gait variability is not caused by dopaminergic function degeneration, levodopa supply does not usually have an effect on gait variability (Bohnen et al., 2013; Clark, 2015). Our results, were in fact consistent with this hypothesis.

Regarding the auditory intervention, RAS, at all frequencies, improved step and stride length in the group of the most affected patients (G2), as observed in the previous studies (Ghai et al., 2018). In case of the temporal parameters, the effect of RAS was different according to the frequency. RAS had a significant effect on cadence and stride time, both in OFF and ON conditions. In particular, RAS90 reduced both the parameters in all patients; RAS110, on the contrary, increased cadence and stride time in the most affected patients. RAS100 left these parameters unaltered. The same effect was observed for the walking speed. Such a result, in agreement with previous research (Spaulding et al., 2013; Rocha et al., 2014), underlines the ability of the variable frequency RAS in modulating (accelerate and decelerate) gait velocity in PD patients, mainly influencing gait cadence and stride time. This enforces the hypothesis that a personalized RAS therapy, possibly utilizing faster frequencies for slower patients and slower frequencies for festinating patients, could help normalizing the gait patterns.

Our results unveiled a statistical improvement of motor aspects both considering spatio-temporal parameters and gait variability in PD patients with higher gait impairments while walking with RAS at 100%. Similar tendency was observed considering RAS at 110% of the preferred walking. However, different motor mechanisms were modified according to RAS rhythms. In fact, RAS100 presented the tendency to consolidate and stabilized gait rhythmic acting up step length, gait phases and variability. In addition to the normalization strategy imposed by RAS100, further motor improvements were observed considering RAS 110. More specifically, motor aspect was both normalized in term of step length and gait phases but also was speeded up. Increasing walking speed and reducing stride time, could have a great impact in reduction of bradykinesia symptoms, relieving discomfort in performing everyday movements in the daily life activities.

Kinematic parameters, such as ROM of the lower limb joints were not modified by RAS; a similar result was observed by Picelli et al. regarding the hip and knee joint, while they observed a reduction in ankle ROM with RAS110 (Picelli et al., 2010). On the contrary, as pointed out by Pau and colleagues, a chronic rhythmic training (5 weeks) with RAS can improve the hip ROM. These results suggest that RAS, although not causing an immediate improvement of the joint ROM, may induce it after a long-term training. Further "off-line" effects of RAS therapy were also observed in gait temporal parameters. Although, improvement of joint kinematics requires a long-lasting (5 weeks) rhythmic train-

ing (Pau et al., 2016), in the study of Hausdorff and colleagues (Hausdorff et al., 2007) a carryover effect was observed 15 min later the administration of RAS therapy at 110% of the preferred pace on temporal gait variability. Thus, immediate "on-line" RAS effects raised a gait stabilization strategy based on regularization of spatio-temporal parameters, as our results showed. "Off-line" RAS effects, instead, were observed to reduce gait variability and improve joint kinematics after RAS training. Despite in our study carryover effects cannot be assessed, our results combined with literature findings could support the hypothesis that RAS therapy is a pivot non-pharmacological treatment in the stimulation of motor plasticity of the networks controlling gait rhythmicity in PD.

Regarding the gait phases, walking with RAS at the same frequency improved the gait phase distribution (improved GPQI) in patients with severe gait impairments, while faster RAS normalized the phase distribution for the entire group. This result was motivated by a general normalization of the gait phase modulation, although only the pre-swing phase reduction was significant.

RAS90, on the contrary, did not modify GPQI, because of a hypothesized trade-off between the worsening of heel strike and flat foot phases, and the improvement of pre-swing phase.

In our study, RAS did not have a significant effect on the variability calculated for step/stride length, stride time, hip, knee, and ankle ROM. Otherwise, walking with RAS100 reduced variability of the swing phase in patients with severe gait impairments in OFF condition. This is in agreement with the finding of Hausdorff et al. that RAS at 110% of baseline step rate, significantly decreased the temporal variability (Hausdorff et al., 2007); and with the results of Almeida et al., who described a reduction of the temporal variability of patients in OFF medication condition with a high frequency RAS (100 bpm) (Almeida et al., 2007). Such a finding indicates an increase of the gait automaticity in association with RAS. In addition, as the swing phase variability has been associated with higher risk of fall (Hausdorff et al., 2001), its reduction is expected to foster a safer gait pattern and improved mobility.

Considering the interaction effects between treatments condition and RAS in Tables 3 and 4, only two indices were found statistically significant: the swing phase and its variability. The swing phase increases while swing variability decreases in walking condition at RAS100 during OFF periods. These results highlighted the tendency of RAS100 to regularize gait pattern both regarding the duration and the variability of parameters when it was administrated to subjects presenting a higher impairment. During ON period, the effect of Levodopa on this gait aspect was sufficient to restore a regular motor behavior, hiding the RAS effect. Since RAS therapy could assist PD patients when motor fluctuations appear, improving their motor capabilities, our results encourage the application of the non-pharmacological RAS therapy as a support for levodopa treatment in daily-life.

RAS is a useful, low cost, mildly intrusive rehabilitation tool to be implemented in PD, especially in cases of poor response of axial symptoms to dopaminergic treatment. Although some studies seem to suggest a low attentional cost of auditory cues (Baker et al., 2007), or even a reduction of attentional demand on walking in PD (Rochester et al., 2007), further studies are warranted to investigate whether RAS-related gait improvements persist in a daily life setting. An effort should be needed to design and produce dedicated unobtrusive devices to permit safe RAS integration in patients' daily life, adapting the auditory stimulus to the natural walking pattern.

Limitation of the study

A potential limitation of this study is that the ON-med and OFF-med conditions were not randomized. In fact, although randomizing those conditions would have enabled to avoid eventual practice effect, for logistic and ethical reasons we preferred to ask patients to do the required 12-h pharmacological wash out during night hours and to perform the evaluation in the morning. Moreover, to avoid both practice and fatigue effects, different RAS conditions were only investigated on one 20 m walk; however, it is worth noting that gait data were averaged on a number of strides which is relatively high with respect to similar studies.

5. Conclusion

The outcomes of our study confirm the role of RAS as a useful and effective tool to improve PD patients' gait pattern, independent from the effect of dopaminergic treatment. Furthermore, they suggest the efficacy of auditory cues in immediate normalization of gait phases, an aspect poorly investigated in the previous studies. The profile of RAS intervention on gait, especially its capacity of up and down regulation of walking speed, suggests that a personalized approach to each patient is likely to be implemented.

Declaration of Competing Interest

We confirm that none of the authors have potential conflicts of interest associated with this publication to be disclosed, and that there has been no significant financial support for this work that could have influences its outcome.

Acknowledgment

We would like to thank Dr Claudia Loreti for her technical support.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.07.013.

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