Highlights

- Faster RAS induced faster upper-limb movements on one-hand and both-hand tasks in patients with PD.
- Movement performance: Right-hand task > Left-hand task> Both-hand task.
- Healthy controls had better performance than patients with PD.

Effects of rhythmic auditory stimulation on upper-limb movements in patients with Parkinson's disease

Wei Fan[a], Jin Li[b], Wei Wei[c], Shao-Hua Xiao[d], Zhen-Jun Liao[d], Shu-Mei Wang[a,*], Kenneth N. K. Fong[a]

[a] *Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong*

[b] *Department of Neurology, General Hospital of the Yangtze River Shipping, Wuhan Brain Hospital, Wuhan, Hubei Province, China*

[c] *Department of Rehabilitation Medicine, General Hospital of the Yangtze River Shipping, Wuhan Brain Hospital, Wuhan, Hubei Province, China*

[d] *Department of Rehabilitation Medicine, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, China*

☒Correspondence to: Shu-Mei Wang, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, 11 Yuk Choi Rd, Hung Hom, Kowloon, Hong Kong.

Tel: +852-27664197

E-mail: shumei.wang@polyu.edu.hk.

ABSTRACT

Introduction: Rhythmic auditory stimulation (RAS) is an effective technique extensively used to alleviate lower-limb bradykinesia in patients with Parkinson's disease (PD). However, RAS effects on upper-limb bradykinesia have not been well studied. This study investigated immediate effects of RAS on upper-limb movements in PD patients and healthy people.

Methods: PD patients (n = 23) and age- and gender-matched healthy controls (n = 23) executed left-hand, right-hand, and both-hand movement tasks of the Purdue Pegboard Test when listening to the beats of RAS, including 100%, 110%, and 120% of the baseline tempo, which was fastest movement performance of each participant without the aid of RAS. Sequence of RAS and tasks was randomized for each participant.

Results: PD patients had slower upper-limb movements than did health controls. An interaction was found between RAS and tasks. In both patients and controls and for all task conditions, 120%RAS induced higher scores than did 110% RAS, and the latter induced higher scores than did 100%RAS. In both patients and controls and for all RAS conditions, the right-hand condition induced higher scores than did the left-hand condition, and the latter induced higher scores than did the both-hand condition.

Conclusions: RAS was effective in regulating upper-limb movements in PD patients, which may be explained by rich neural connections between auditory and motor cortical areas in humans. Clinical practitioners should consider using RAS in clinical therapy. Future neuroimaging studies are needed to explore neural mechanisms of RAS in PD patients.

Keywords: Acoustic stimulation, Parkinson's disease, Arm, Movement, Bradykinesia

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disease with prevalence of 0.3%–1%. PD is caused by age-related neurodegeneration of the substantia nigra of the basal ganglia, resulting in a decrease in dopamine levels. Decreased dopamine markedly diminishes signals from the thalamus to motor-related cortices, resulting in hypokinetic movements (such as bradykinesia, meaning slow movements). Bradykinesia adversely affects daily activities and thus quality of life in patients. In addition, the healthcare cost for treating PD is increasing annually, due to reduction in pharmacotherapeutic effects. It is warranted to develop effective therapies for bradykinesia in PD patients.

Rhythmic auditory stimulation (RAS) is a promising technique for improving movements in PD patients [1]. RAS provides rhythmic auditory cues when patients perform repetitive movements. In earlier studies, RAS tempi were adjusted to different levels, such as 100%, 110%, and 120% of the baseline tempo, meaning performance without the aid of RAS, to modulate movement speed in patients [2,3]. Generally, suitably faster RAS induces faster walking speed in PD patients, although investigation of who could and could not respond to faster RAS among PD patients has drawn research attention [4]. Basal ganglia regulate signals transmitted from the cortex and send these refined signals back to the cortical areas, so that rapid and coordinated movements are generated. However, in PD patients, dysfunctional basal ganglia destroy mediation of movements and cause movement symptoms, such as bradykinesia. It is suggested that manipulation of RAS may bypass impaired basal ganglia and activate neural pathways linking the auditory and motor cortices to improve movements in PD patients [1]. Earlier studies mainly targeted gait responses to RAS [5] and rarely examined upper-limb responses to RAS in PD patients, although rhythmic repetition of movements may be also needed in daily upper-limb

tasks and rehabilitation training tasks. To date, scarce studies have examined effects of RAS on upper-limb bradykinesia, which is common among these patients. One existing study testing RAS effects on upper-limb movements in PD patients [6] is a case report, recruiting three patients and lacking a control condition in the experiment. In addition, earlier research has indicated effectiveness of suitably faster RAS on inducing faster upper-limb movements in people with impaired basal ganglia [7]. It is worth examining RAS effects on upper-limb movements in PD patients.

To sum up, this study examined effects of RAS on upper-limb movements in PD patients . Because this study was exploratory in nature, we assessed responses of the right hand, left hand, and both hands to RAS, and recruited age- and gender-matched healthy controls to provide reference data of movements and responses to RAS. For our main research purpose regarding RAS effects on upper-limb movements in PD patients, we hypothesized that upper-limb movements were faster when PD patients listened to faster RAS.

2. Methods

2.1. Study design

This study investigated effects of RAS (100%RAS versus 110%RAS versus 120%RAS), tasks (the left-hand task versus the right-hand task versus the both-hand task), and groups (PD patients versus healthy controls) on upper-limb movements. Participants in each group was randomly allocated to one sequence of RAS (e.g., 100%-110%-120%) and one sequence of tasks (e.g., left-right-both). The participant executed the first task under three RAS conditions and repeated the same RAS sequence for the second and third tasks.

2.2. Participants

PD patients were recruited from hospitals. Inclusion criteria were (a) a PD diagnosis made by a neurologist according to the Movement Disorder Society Clinical Diagnostic Criteria; (b) the stage two or three on the Hoehn and Yahr scale, meaning that both hands were affected without severe disability; (c) a score ≥ 21 in the Montreal Cognitive Assessment to ensure comprehension of experimental instructions; (d) a score > 60 in the Edinburgh Handedness Inventory, meaning right handedness; (e) unchanged types and doses of medications for the past 1 month. Age- and sex-matched right-handed healthy controls who showed comprehension during communication with researchers were recruited from communities. Exclusion criteria for both patients and healthy controls were presence of medical conditions that may affect hand movements, vision, or hearing. This study was approved by an ethical review board (approval number: 2021-S079). All participants signed an informed consent form before participation.

2.3. Outcome measures

The Purdue Pegboard Test was used to assess movement speed of upper-limbs of participants. This study used left-hand, right-hand, and both-hand tasks to measure one-hand and bilateral-hand movements. This study did not include the assembly task of the Purdue Pegboard Test considering RAS may not be effective if movements heavily involve attention [8]. Participants were asked to use one hand (for the left- and right-hand tasks) or both hands (for the both-hand task) to pick one pin or pin pairs from the corresponding cups and insert them into holes in the board as quickly as possible within 30 seconds per task. The score of each task was the number of inserted pins (for one-hand tasks) or pin pairs (for the both-hand task). Higher scores reflected faster movements. The Purdue Pegboard Test showed excellent test-retest and interrater reliability in the PD population [9].

2.4. Procedure

Patients were assessed during the "ON" period of medication. The participant executed the left-, right-, and both-hand task without RAS first, to allow calculation of the baseline tempo on each task (no-RAS tempo), which was the task score multiplied by two (unit: beat per minute). This study provided three tempi of RAS: 100%RAS, 110%RAS, and 120%RAS, which were the baseline tempo multiplied by 100%, 110%, and 120%, respectively. RAS was generated using a metronome (SQ200, Seiko incorporated). The participant was asked to make a pin (or a pin pairs) touch a hole (or holes) (i.e., the movement of insertion) when hearing a beat of RAS. Three practical trials and then three formal trials under each RAS condition and each task condition were needed in this study. A short break was provided between RAS conditions to prevent influences of muscle fatigue on task performance. The average score of three formal trials under each task condition and each RAS condition was calculated to represent movement speed.

2.5. Statistical analysis

Differences in demographic data between groups were examined using the independent *t*-test or the chi-square test. Three-way repeated-measures analysis of variance was used to examine effects of groups (PD patients versus healthy controls), RAS (no RAS versus 100%RAS versus 110%RAS versus 120%RAS), and tasks (left-hand task versus right-hand task versus both-hand task). Dependent variables were scores of the Purdue Pegboard Test. The alpha level (two-tailed) was set at 0.05. Bonferroni correction was used in post hoc analyses.

3. Results

3.1. Demographic and clinical data in participants

Twenty-three PD patients and 23 healthy controls were recruited in this study. No group differences in age, education, and sex were found (Table 1).

3.2. Group differences in movements

No triple interaction was observed ($p = 0.800$). Among all interactions between any two factors, only the interaction between RAS and tasks was significant (RAS × task, $p = 0.008$; RAS × groups, $p = 0.920$; tasks × groups, $p = 0.763$). Group differences in movements were found ($F = 26.26$, $p < 0.001$), with patients showing lower scores than healthy controls.

3.3. Effects of RAS and tasks on movements

Because of the RAS × tasks interaction, further analyses were conducted under each RAS condition and under each task condition in each group (Table 2). In both patients and controls, RAS effects were found for three task conditions: 120%RAS induced higher scores than did 110%RAS, and 110%RAS induced higher scores than did 100%RAS. In both patients and controls, task effects were found for four RAS conditions: the right-hand condition induced higher scores than did the left-hand condition, and the left-hand condition induced higher scores than did the both-hand condition.

4. Discussion

This study found that faster RAS induced faster upper-limb movements for each task in both PD patients and in healthy people. In addition, the right-hand movements were faster than the left-hand movements, and the latter were faster than the both-hand movements in both PD patients and in healthy people when they listened to each tempo of RAS. Finally, healthy individuals had faster upper-limb movements than did PD patients.

We found that faster RAS induced faster upper-limb movements in PD patients and healthy individuals, which is consistent with earlier studies showing effects of fast RAS on gait velocity in PD patients [5]. This study extended earlier findings by showing that RAS was also effective in inducing faster upper-limb movements in the same population. PD patients have impaired basal ganglia and thus bradykinesia, which explains our results that upper-limb movements were slower in PD patients than healthy people. RAS, which involves rich neural connections between auditory and motor cortices, may still be able to rely on alternative neural pathways, such as the cortico-cerebellar-cortical network and cortical connections, to regulate motor areas in brains and modulate movements in PD patients [10]. Faster RAS may provide a timing template and guide PD patients to generate faster movements [1]. In addition, no interaction between RAS and groups was found, representing a similar response to RAS in PD patients and healthy people. This similar pattern of responses to RAS supported the aforementioned notion regarding neural mechanisms of RAS. Although PD patients have impaired basal ganglia, RAS may still be able to affect motor cortices through rich neural connections between the auditory cortex, activated by RAS, and motor cortices.

Right-hand movements were faster than left-hand movements, and then the latter were faster than both-hand movements, which is consistent with earlier results examining dominant-hand and both-hand movements in patients with impaired basal ganglia and bradykinesia [7]. Because of handedness, it is reasonable that right-hand movements were faster than left-hand movements in participants in this study. Compared with unimanual movements, both-hand movements require more attentional load to ensure coordination of left and right hands, resulting in reduced speed of both-hand movements [8].

This study has clinical implications. When tackling bradykinesia in upper-limbs in PD patients is the target, clinical practitioners should consider the use of fast RAS. This study had several limitations. First, we only examined immediate movement responses to RAS and did not examine effects of training programs. Future research should develop training involving RAS and examine its effects on movements in PD patients. Second, this study did not measure neural activity when participants listened to RAS and executed movements. Future studies should combine neuroimaging and behavioral measurement to elucidate neural mechanisms underlying effects of RAS on movements in PD patients. Third, this study design was unable to assess actual entrainment between movements and beats of RAS. In addition, considering speed-accuracy trade-off [11], it was possible that faster RAS induced faster but less accurate movements. This study did not assess movement accuracy or variability. Future research may consider using motion analysis to quantify movement procedures and detect RAS beats to measure the entrainment degree and movement accuracy. Fourth, research personnel checked if healthy people were able to follow experimental instructions only through communication and behavioral observations before experiments. Cognitive screening conducted on healthy controls is needed in future similar studies. Last, this study did not examine RAS effects on the assembly task of the Purdue Pegboard Test considering tasks that require multiple steps and thus are complicated may undermine beneficial effects of RAS on movements. Future research is suggested to further explore RAS effects on upper-limb movements with different degrees of complexity.

In conclusion, this was one of the pioneering studies demonstrating that RAS was a valid technique for modulating upper-limb movement speed in PD patients. Clinical practitioners should consider using RAS to regulate upper-limb movement speed in PD patients.

Author roles

Wei Fan: Study conception and design. Execution. Writing of the first draft.

Jin Li: Execution.

Wei Wei: Review and critique.

Shao-Hua Xiao: Review and critique.

Zhen-Jun Liao: Execution.

Shu-Mei Wang: study conception and design. Review and critique.

Kenneth N. K. Fong: Review and critique.

Funding source

This work was supported by Youth Scientific Research Project of Wuhan Municipal Health Commission (project number:WX18Q20): foundation of Tongji hospital of Tongji Medical College, Huazhong University of Science and Technology (project number: 2201300795).

Conflict of interest

The authors have no conflict of interest to report.

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Table 1. Demographic and clinical data in patients and healthy controls.

	Patients (n = 23)	Controls (n = 23)	t	*p*
	Mean ± SD	Mean ± SD		
Age (years)	67.30±7.86	64.13±5.59	1.58	0.122
Education (years)	11.35±3.76	10.04±3.42	1.23	0.225
UPDRS-III	27.96±12.26	--	--	--
MoCA	24.13±2.22	--	--	--
	n (%)	n (%)	χ^2	*p*
Male	8 (34.78%)	10 (43.48%)	0.37	0.546
H&Y stage				
2	15 (65.22%)	--	--	--
3	8 (34.78%)	--	--	--

Note: MoCA = the Montreal Cognitive Assessment; H&Y stage = the Hoehn and Yahr stage; UPDRS-III = Unified Parkinson's Disease Rating Scale – Part III.

Table 2. Results of RAS effects and task effects on upper-limb movements in PD patients and healthy controls.

Tasks		PPT scores under each RAS condition (Mean ± SD)[a]				RAS effects for each group and each task (post-hoc analysis)
		(1) No RAS[b]	(2) 100%RAS[c]	(3) 110%RAS[d]	(4) 120%RAS[e]	
(a) LH	PD	10.70±1.90	10.63±2.08	11.32±2.22	11.91±2.02	$F = 38.64$, $p < 0.001$ (1-3**; 2-3***; 1-4***; 2-4***; 3-4***)
	HC	13.44±1.61	13.36±1.62	14.09±1.59	14.82±1.65	$F = 35.73$, $p < 0.001$ (1-3**; 2-3***; 1-4***; 2-4***; 3-4**)
(b) RH	PD	11.80±2.05	11.75±2.08	12.53±2.29	13.11±2.28	$F = 41.91$, $p < 0.001$ (1-3***; 2-3***; 1-4***; 2-4***; 3-4**)
	HC	14.46±1.80	14.33±2.02	15.27±1.90	15.78±1.95	$F = 53.13$, $p < 0.001$ (1-3***; 2-3***; 1-4***; 2-4***; 3-4*)
(c) BH	PD	8.32±1.78	8.39±1.81	8.92±1.96	9.39±2.17	$F = 36.65$, $p < 0.001$ (1-3***; 2-3**; 1-4***; 2-4***; 3-4**)
	HC	10.99±1.60	10.97±1.62	11.41±1.58	11.96±1.52	$F = 27.31$, $p < 0.001$ (1-3*; 2-3***; 1-4***; 2-4***; 3-4***)

Note: PPT = The Purdue Pegboard Test; RAS = Rhythmic auditory stimulation; LH = Left-hand task; RH = Right-hand task; BH = Both-hand task; PD = Patients with Parkinson's disease; HC = Healthy controls.

[a]Performance within 30 seconds.
[b]For PD under the no RAS condition, task effects and post-hoc analysis: F = 127.30, $p < 0.001$ (a-b***; b-c***; a-c***)

For HC under the no RAS condition, task effects and post-hoc analysis: F = 156.20, $p < 0.001$ (a-b**; b-c***; a-c***)

[c]For PD under the 100%RAS condition, task effects and post-hoc analysis: F = 118.15, $p < 0.001$ (a-b***; b-c***; a-c***)

For HC under the 100%RAS condition, task effects and post-hoc analysis: F = 148.10, $p < 0.001$ (a-b**; b-c***; a-c***)

[d]For PD under the 110%RAS condition, task effects and post-hoc analysis: F = 122.68, $p < 0.001$ (a-b***; b-c***; a-c***)

For HC under the 110%RAS condition, task effects and post-hoc analysis: F = 200.35, $p < 0.001$ (a-b***; b-c***; a-c***)

[e]For PD under the 120%RAS condition, task effects and post-hoc analysis: F = 141.88, $p < 0.001$ (a-b***; b-c***; a-c***)

For HC under the 120%RAS condition, task effects and post-hoc analysis: F = 120.97, $p < 0.001$ (a-b*; b-c***; a-c***)

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.