

The Use of Rhythmic Auditory Stimulation on Gait Parameters in Parkinson's Disease: A Systematic Review

Aashna S. Agarwal, BHSc Student [1]*, Amrit Marwaha, BHSc Student [1],
Aleena Sajid, BMSc Student [2]

[1] Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada, L8S 4L8

[2] Department of Medical Sciences, Western University, London, Ontario, Canada, N6A 3K7

*Corresponding Author: agarwa23@mcmaster.ca



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Abstract

Introduction: Parkinson's disease (PD) is a neurodegenerative disorder that commonly affects the basal ganglia dopaminergic signaling system, which can contribute to moderate-severe gait impairments in individuals. Many therapies have been proposed to mitigate this effect, however, there are often issues to consider such as the relative invasiveness of the procedure and other side effects. Rhythmic auditory stimulation (RAS) is a non-invasive therapeutic avenue with the potential to mitigate associated impairments in gait parameters. This review aims to evaluate the recent literature regarding the efficacy of this intervention in improving gait parameters in individuals with Parkinson's disease.

Methods: PubMed and OVID Medline databases were consulted to find nine randomized controlled trials (RCTs) written in the English language, published between 2012 and 2022 and subject to a strict inclusion criterion. Keywords included, but were not limited to, "Parkinson's disease", "rhythmic auditory stimulation", and "gait". Outcomes were critically analyzed, and their implications were evaluated in the context of existing research within this field.

Results: Many of the studies showed a strong immediate improvement in several of the gait parameters, such as speed, stride length, cadence, balance, and falls, identified across a variety of RCT designs. However, many reviewed studies included a small sample size ($n \leq 30$) and showed no significant outcomes in specific parameters, and several lacked an adequate follow-up period, limiting assessment of long-term efficacy.

Discussion: The findings showed strong implications surrounding the use of rhythmic cues to prime the motor system to facilitate gait relearning and motor rehabilitation, at least in the short term. This method can be applied in future therapeutic avenues to address gait rehabilitation in a non-invasive manner.

Conclusion: Existing literature demonstrates that RAS therapy is a promising method to incorporate into such therapeutic avenues; however, further research for the long-term efficacy of this approach is required.

Keywords: Parkinson's disease (PD); rhythmic auditory stimulation (RAS); neurologic music therapy; gait; balance; basal ganglia dopaminergic system

Introduction

The rapid growth of aging populations around the world has led to many geri-centric diseases becoming more prevalent, a trend which is predicted to continue to rise [1]. One such disease is Parkinson's disease (PD), a neurodegenerative disorder which commonly presents in middle-aged and older adults and is characterized by unintended and uncontrollable movements, such as gradually worsening shaking, tremors, prolonged muscle stiffness, and poor balance and coordination which can result in falls [2]. Other symptoms include depression, difficulty swallowing, chewing, problems with urination as well as skin-related issues. While most individuals develop PD after 60 years of age, 5-10% of cases are from early onset (<50 years), and it has been theorized that both genetic and environmental factors contribute to its onset. Given that the disease is

incurable, the need for new treatment guidelines to help reduce the symptoms for individuals with PD becomes more urgent with every passing year.

PD is commonly characterized by damage to the substantia nigra within the basal ganglia, a common site for dopaminergic signalling, which contributes to direct and indirect motor signalling pathways depicted in Figure 1 [3]. In particular, dopaminergic signalling plays a critical role in increased activation of the direct pathway and decreased activation of the indirect pathway, thereby facilitating increased movement [4]. It has therefore been theorized that many of the movement-related symptoms that individuals with PD experience are correlated with hypokinesia (restriction of movement) due to a lack of dopaminergic signaling at the basal ganglia [5].

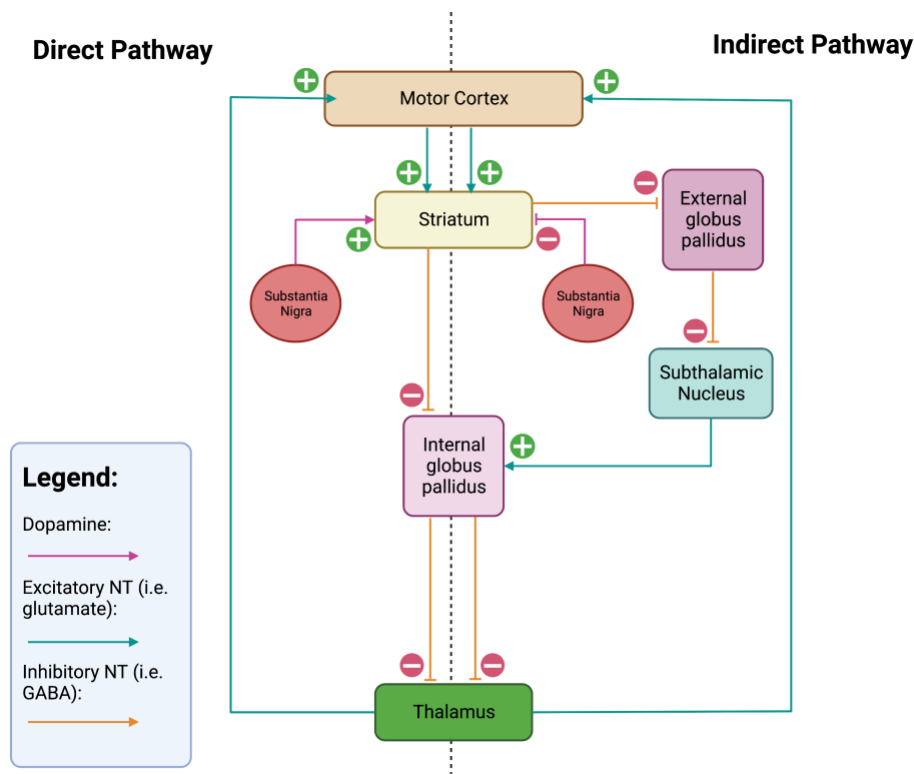


Figure 1. Schematic of the direct and indirect cascades of typical motor movement, with arrows indicating stimulation and inhibition. Direct pathway: To increase overall movement, inputs from the cortex activate the striatum, which in turn sends inhibitory signals to the internal globus pallidus and leads to fewer inhibitory signals being sent to the thalamus, which becomes distributed to various other motor processing sites within the brain. Indirect pathway: To decrease overall movement, inputs from the cortex stimulate the striatum, which sends inhibitory signals to the external globus pallidus, leading to fewer inhibitory signals being sent to the subthalamic nucleus, which then sends more excitatory signals to the internal globus pallidus; as a result, more inhibitory signals are sent back to the thalamus to decrease the amount of overall movement. Created with BioRender.com.

The primary clinical diagnosis of PD is heavily based on the presence of the cardinal motor features (“a classical triad”), which include bradykinesia (the decreased amplitude of movement), “cogwheel” rigidity (muscular stiffness of passive movement in both extension and flexion), and resting tremors, often involving the hands [6]. Additional symptoms include asymmetry of the signs of onset, postural instability, cerebellar and oculomotor disorders, and dystonia (a disorder characterized by slow repetitive movements).

Presently, many interventions have been introduced to slow the progression of symptoms of PD. These include various physiotherapy, occupational therapy, and speech and language therapy techniques [7]. However, recent evidence has demonstrated the merits of incorporating auditory stimulation treatment for individuals with PD, due to its non-invasive and purported therapeutic nature of music [8].

Rhythmic auditory stimulation (RAS) is an auditory-based cueing technique that has been largely employed as a therapy in response to acquired brain injuries to restore gait and movement [9]. It is unique in that it is a non-invasive

option that helps restore internal rhythm and motion using auditory signals, often through music, and falls under the broad classification of neurologic music therapies. Recent advances in the medical research field have revealed the role of RAS as an “internalized timekeeper for rhythmic patterned movements.” [10] Rhythm is essential to motor control and output, and as such, can prime muscle activation, providing a mechanism for motor execution and an increased readiness to move [11]. Indeed, recent research has shown that engaging in rhythmic stimulation can be beneficial to motor rehabilitation due to its involvement in premotor and cortico-basal and cortico-cerebellar networks.

While there is not yet a consensus on the exact role of audition in gait, studies have revealed through electroencephalography (EEG) that auditory cueing in healthy individuals using a frequency of approximately 120 beats per minute (bpm) was associated with strong improvements in higher frequency electroencephalogram (EEG) activity in the motor cortex of the brain [12]. This may be due to the frequency of the cues falling under the

same spectrum as neural oscillatory waves in the beta frequency (13-30Hz), leading to increased arousal and alertness in movements.

It is generally thought that RAS exerts its beneficial effects on individuals with PD through its external auditory stimulation components to improve gait-related aspects of motion (i.e., speed, stride length, balance and fall risk), but the extent of these benefits in this population are unclear. Therefore, this systematic review aims to investigate the effectiveness of RAS in improving movement parameters most affected in individuals with PD, such as speed, number of falls, balance, cadence, stride length, and gait, by examining the literature published over the past 10 years on the subject. To ensure that results obtained were process-pure, only randomized controlled trials (RCTs) were screened during data collection given their rigorous scientific nature.

Methods

Important topics related to musical therapy used as treatment for individuals with PD were first identified through preliminary research to determine the state of the literature and identify any areas requiring further study. With such a large scope, the topic of interest was then modified to focus on RAS to improve gait and motion for individuals with PD. Database searches were conducted in PubMed and OVID MedLine over a ten-year period between 2012 and 2022. The following searches were conducted (all: filtered with RCT): “(Rhythmic Auditory Stimulation OR RAS) AND (Parkinson’s disease OR PD)”. Searches were restricted to papers written in English and were selected according to the following inclusion criteria:

1. *Title and abstract must be relevant to the research question* - Both the title and the abstract of the RCT must be relevant to the subject of interest.
2. *Main body text must be relevant to the scope of the review* - Studies which addressed the use of rhythmic cueing/rhythmic auditory stimulation within

individuals diagnosed with PD were chosen as a part of this literature review.

3. *Methods must include a specific intervention relevant to research outcome* - All selected studies must apply external rhythmic cueing/rhythmic auditory stimulation explicitly.
4. *Methods must include intervention targeted to specific outcomes relevant to the research question* - RCTs which focused on gait/motion training as a primary outcome as a result of the chosen intervention within those with PD were chosen.
5. *Recruited participants must meet the inclusion criteria* - Study should adequately assess clinical diagnosis of individuals with PD using strict criteria.

Primary, peer-reviewed empirical research was included, however, reviews, meta-analyses, conference proceedings, preprints (such as from BioRxIV and MedRxIV) were excluded. Results and conclusions that were reached were critically analyzed and their clinical implications were determined.

Literature searches initially identified 25 studies from both databases. Eight studies were removed as duplicates, and abstract screening removed a further six. The full-text review resulted in two further studies being removed due to the scope of the research question and irrelevant outcome measures. Methodologies employed by nine articles were screened following full-text review. The inclusion and exclusion criteria of nine RCTs were evaluated based on scientific rigour, and the appropriate diagnosis of PD by researchers was evaluated by all authors.

Results

A summary of the methodologies and main findings for each RCT is displayed in Table 1. Many studies involved strict inclusion and exclusion criteria where a clinical primary diagnosis of PD was required according to the H&Y Parkinson's scale.

Table 1. Summary of the methodologies and main findings for each RCT.

	Authors	Methods	Eligibility Criteria	Interventions	Main Findings
1	Thaut et al., 2019 [13]	Double-blinded, cross-over	<p><u>Inclusion:</u> Primary diagnosis of idiopathic PD (H&Y 3-4), at least two falls in the past 12 months, can ambulate independently, on a stable anti-Parkinsonian medication regimen</p> <p><u>Exclusion:</u> Other neurological conditions, cognitive impairments (MMSE < 24), medically diagnosed hearing loss.</p>	<p><u>Experimental:</u> 30 min/day of home-based gait training via metronome click-embedded music for 24 weeks</p> <p><u>Control:</u> 30 min/day of home-based gait training via metronome click-embedded music for 24 weeks except for Week 8-16</p>	Speed, cadence, stride length, gait parameters improved, falls reduced in RAS/experimental group, maintained across full 24-week timeframe.

	Authors	Methods	Eligibility Criteria	Interventions	Main Findings
2	Calabro et al., 2019 [14]	Single-blinded, parallel group	<p><u>Inclusion:</u> Diagnosed with PD (H&Y 2-3), showed no cognitive impairments (MMSE > 23), on a stable antiparkinsonian treatment regimen over previous 6 months.</p> <p><u>Exclusion:</u> Other severe systemic diseases, had received NMT in the previous 3 months.</p>	<p><u>Experimental:</u> Treadmill gait training with RAS at various frequencies.</p> <p><u>Control:</u> Treadmill gait training without RAS.</p>	Gait, stride length, cadence and UPDRS improved in RAS/experimental group, reduced falls. Nonsignificant changes in speed between RAS and control conditions.
3	Capato et al., 2020 [15]	Single-blinded, parallel group	<p><u>Inclusion:</u> Diagnosed with PD (H&Y 1-3), history of falls in the past year, can walk indoors independently and continuously for 10 minutes, no cognitive impairments (MMSE ≥ 24), on a stable antiparkinsonian medication regimen, no hearing or visual problems, stable deep brain stimulator settings.</p>	<p><u>Experimental:</u> Group 1: Multimodal balance training supported by RAS. Group 2: Regular multimodal balance training without RAS.</p> <p><u>Control:</u> General education program.</p>	Balance, falls, gait, UPDRS improved in RAS-supported group, maintained to 6 month follow up. Both multimodal training groups showed improved balance, gait from control, maintained to 6-month follow-up.
4	Chang et al., 2019 [16]	Cross-over, single-blinded	<p><u>Inclusion:</u> >20 years old, diagnosed with idiopathic PD (H&Y 1-3), able to walk independently for at least 10 minutes, no hearing aids or cognitive impairments (MMSE ≥ 24)</p> <p><u>Exclusion:</u> Diagnosed with other neurological/psychological disorders, unable to follow instructions, contraindications in TMS assessments, or diagnosed with dementia.</p>	<p><u>Experimental:</u> AC: SIP training, metronome-applied auditory cueing.</p> <p><u>Control:</u> NC: SIP training, at participant speed.</p>	Nonsignificant changes in speed and stride length between AC and NC conditions. Cadence improved in AC and NC, not maintained to follow-up.
5	Song et al., 2015 [17]	Single-blinded, prospective group	<p><u>Inclusion:</u> Valid clinical diagnosis of PD, no cognitive impairment, able to walk independently following intake of conventional anti-PD drugs</p> <p><u>Exclusion:</u> Other disorders affecting the nervous system, vision and hearing impairments.</p>	<p><u>Experimental:</u> Conventional drugs alongside RVS + RAS training.</p> <p><u>Control:</u> Conventional drug treatment.</p>	Significant improvements in BBS scores, increase in stride length, reduced UPDRS score, and an improvement in cadence in the experimental group.

	Authors	Methods	Eligibility Criteria	Interventions	Main Findings
6	Braun Janzen et al., 2019 [18]	Single-blinded, parallel group (Mixed-design ANOVA)	<p><u>Inclusion:</u> Diagnosed with PD (H&Y 1-2), on a stable antiparkinsonian medication regime, and can walk independently for 14 meters.</p> <p><u>Exclusion:</u> Any other neurological/orthopedic conditions, severe perceptual and sensory deficits.</p>	<p><u>Experimental:</u> 1 - Finger Tapping: Tap with index finger of the least affected hand in synchrony with a metronome. 2 - Arm Swing: Swinging both arms in an alternating motion in synchrony with a metronome set 20% faster than pre-training walking cadence.</p> <p><u>Control:</u> No training; rested for 4 mins.</p>	<p>Finger tapping group: significant improvement within gait velocity and gait cadence post-training.</p> <p>No changes to gait cadence pre- and post-swing training for the arm swing group and in the control group.</p>
7	Uchitomi et al., 2013 [19]	Single-blinded, prospective	<p><u>Inclusion:</u> Normal hearing, regular intake of dopaminergic medications, and no prior diagnosis of dementia.</p>	<p><u>Experimental:</u> 1) interactive WalkMate, 2) fixed tempo, or 3) <i>I/f</i> fluctuating tempos.</p> <p><u>Control:</u> No cue provided.</p>	Gait fluctuation in the WalkMate group gradually increased to a healthy <i>I/f</i> level.
8	Capato et al., 2020 [20]	Single-blinded, prospective	<p><u>Inclusion:</u> PD diagnosis (H&Y 4), at least one fall in the past 12 months, no hearing, visual or cognitive impairments (MMSE \geq 15), able to walk indoors.</p> <p><u>Exclusion:</u> Unstable medication history over past 3 months, unstable deep brain stimulator settings over past year.</p>	<p><u>Experimental:</u> Multimodal balance training with RAS cues provided by metronome.</p> <p><u>Control:</u> Multimodal balance training without RAS cues.</p>	Sustained improvements in balance in those with advanced staged PD.
9	Zhao et al., 2016 [21]	Randomized crossover design	<p><u>Inclusion:</u> UK brain criteria diagnosis, minimum history of 2 FOG events per day, walk over a flat 20 m surface without walking aids.</p> <p><u>Exclusion:</u> Impaired gait, visual impairments, cognitive impairments indicated on Frontal Assessment Battery.</p>	<p>All participants underwent 4 walking courses (i) wide turn (ii) narrow turn (iii) full turn (iv) doorway.</p> <p><u>Experimental:</u> 3 audiovisual cues using Google Glass (i) metronome (ii) LED flashing light (iii) optic flow.</p> <p><u>Control:</u> No cues from Google Glass.</p>	<p>Increased stride length using metronome.</p> <p>Fewer FOG episodes per trial with metronome.</p> <p>More stable gait pattern with cues for complicated walking courses.</p>

Discussion

Results from the 9 RCTs largely demonstrated significant changes in gait-related outcome measurements between RAS/experimental and control groups. This can

likely be attributed to the use of external rhythmic cues to bypass the internal pacing mechanisms regulated by the basal ganglia that are impaired in individuals with PD [14]. In particular, functional neuroimaging has recently

identified that RAS training modulated fronto-centroparietal and fronto-temporal brain activity during certain periods of the gait cycle. In particular, rhythms within the beta wave frequency range (13-30 Hz) may contribute to stronger clinical improvements by increasing activity of auditory, motor, and associative cortex regions of the brain. However, given the current lack of conclusive evidence on this subject, more information is necessary to confirm these observations. Moreover, a better understanding of the positive effects of RAS on the motor system provides researchers with the opportunity to further investigate novel and non-invasive treatments for individuals with PD. The reported findings within this study demonstrate significant implications regarding the use of rhythmic cues to prime the motor system to facilitate gait relearning and motor rehabilitation.

The severity of PD as part of the inclusion criteria varied between studies. Many studies excluded participants based on different prior neurological or orthopedic conditions, such as severe medical perceptual impairments (hearing or visual impairments), a diagnosis of dementia and other comorbidities or inability to follow experimental instructions. The differences in the evaluation of PD in participants indicating eligibility of participation may prevent results from being analyzed holistically and the comparison of results across studies.

A major limitation of many of the reviewed studies includes a small sample size ($n \leq 30$), as was evidenced in Zhao et al., ($n = 12$) and Chang et al., ($n = 21$) [16,21]. With a limited sample size, the findings may be underpowered, hence unable to accurately detect statistical differences in outcomes and may not be representative of the general population. Additionally, many studies did not show significant outcomes in a few parameters being evaluated. This suggests that studies may need longer time periods of participant interaction with the interventions and hence require longer follow-up periods. Several studies, such as Calabro et al., Zhao et al., Song et al. and Braun Janzen et al. excluded a follow-up period during outcome measurements, effectively limiting their long-term clinical efficacy [14,17,18,21].

Furthermore, the selected studies included subtle variations in methodological design, which may have hindered the validity and generalizability of outcome analyses. Thaut et al. lacks an alternative intervention for their control group (i.e., passive control group) [13]. Calabro et al.'s participants were also receiving daily rehabilitation programs during the study period, which may have inflated improvements in overall walking parameters solely attributed to RAS [14]. Capato et al.'s earlier study only studied individuals with mild/moderate PD who were on a stable medication regime, thereby reducing the generalizability of results [15]. In addition, the activity monitors given to participants to assess gait parameters were not used to evaluate overall activity during and after the intervention was employed, which would have

strengthened conclusions about the long-term efficacy of RAS. Since the experimental group in Song et al. included both RAS and RVS training, it is difficult to determine whether the findings can be attributed to only the auditory stimulation [17]. Janzen et al. conducted their experiment in a highly controlled setting over the course of four days, limiting the generalizability of its findings [18]. Uchitomi et al., only considered the effects of one possible interactive rhythmic cue through the WalkMate system, further illustrating the need for other cues to be studied to reach a conclusion regarding the effects on intrapersonal gait relearning [19]. Capato et al.'s later study lacks a control group that receives no intervention. Both groups receive multimodal balance training (RAS and no RAS) [20]. Moreover, Zhao et al.'s use of a Google Glass intervention to provide mobile cueing resulted in both visual and auditory cues being administered, resulting in a separate point of analysis from the remaining studies analyzed [21].

Throughout the process of gathering relevant articles for a comprehensive review, the initial search parameters included only 25 articles. An additional rigorous screening process involving abstract screening, full-text review and evaluation of the methodologies employed by the authors further limited the sample size of articles reviewed. In addition, the study design was not conducive for a connection between the effects of RAS cueing on the specific auditory-motor pathways involved in participants with PD. In particular, the screening process involved an emphasis on RCTs, which limited the scope of articles selected. Expanding the scope of the review to allow for articles focusing on the theoretical implications of RAS on the auditory-motor pathways would bridge the gap between the theoretical and clinical significance of RAS in individuals with PD.

Although results from the RCTs are promising, a plethora of parameters showed no significance between the intervention and control conditions. To further evaluate these parameters, future research can incorporate a longitudinal design focusing on outcomes surrounding both the intervention and control group across an extended time period. The present results open new disciplines of research, allowing for further investigation into the underlying cross-effector coupling mechanisms across auditory and motor domains. Moreover, personalized on-demand auditory cues should be created to address individuals' diverse needs and preferences in their day-to-day living. Thus, further research and development in the personalization of cueing is required. In addition, larger studies which include various demographics can be investigated to optimize protocols. Studies emphasize the immediate improvement in individuals with PD directly after the RAS intervention compared to the control group, however, report that these improvements are not maintained at the follow-up time periods. Additional studies must be conducted to reduce the discrepancy between initial clinical improvements and long-term results. For example, current studies did not focus on the ideal frequency

of RAS-therapy for individuals with PD (continuous training, boost sessions at one-month intervals, etc.)

Conclusions

In conclusion, this review evaluated the recent evidence regarding the clinical significance of incorporating auditory stimulation treatment for individuals with PD to improve parameters such as gait, falls, speed, stride length and cadence. Given the increasing global prevalence of PD, and the need to incorporate and diversify current treatments, these findings are relevant to identify new non-invasive therapeutic avenues for this population. Existing literature demonstrates that RAS therapy seems to be a promising method to incorporate into such therapeutic avenues and demands further research.

List of Abbreviations Used

PD: Parkinson's disease
NT: neurotransmitter
RAS: rhythmic auditory stimulation
EEG: electroencephalography
RCT: randomized controlled trial
FGA: functional gait assessment
BBS: berg balance scale
10MWT: 10-minute walking test
TUG: timed up and go (TUG) rating scale
GQI: gait quality index
UPDRS - unified Parkinson's disease rating scale
H&Y: Hoehn and Yahr
MMSE: mini mental state examination
FES-1: falls efficacy scale rating scale
LED: light-emitting diode
FAB: frontal assessment battery
FOG: freezing of gait
Bpm: beats per minute

Conflicts of Interest

The author(s) declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent

Due to the nature of the proposal, ethics approval and participant consent were not required.

Authors' Contributions

AA: Made contributions to the results and discussion of this paper. AA is to be held equally accountable for all other aspects including drafting the manuscript, critically examining it for its content and collectively approving the final version to be submitted.

AM: Made contributions to the results and discussion of this paper. AM is to be held equally accountable for all other aspects including drafting the manuscript, critically examining it for its content and collectively approving the final version to be submitted.

AS: Made contributions to the results and discussion of this paper. AS is to be held equally accountable for all other aspects including drafting the manuscript, critically examining it for its content and collectively approving the final version to be submitted.

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