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Review article

Rhythmic auditory stimulation as a potential neuromodulator for Parkinson's disease

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ABSTRACT

Auditory rhythm-based therapeutic interventions such as rhythmic auditory stimulation (RAS) are effective in improving gait and balance and preventing falls in idiopathic Parkinson's disease (PD). Research showing associated neuromodulatory effects of RAS on brain oscillations is also emerging. The neuromodulation may be induced by neural entrainment and cross-frequency oscillatory coupling. Auditory rhythm and RAS based interventions are potentially effective in improving other PD symptoms and can be extended to atypical parkinsonism.

1. Introduction

In advanced Parkinson's disease (PD), recurrent falls, postural impairment, unstable balance, and freezing of gait (FOG) are often observed in addition to gait dysfunctions. As these symptoms tend to have limited responses to conventional dopaminergic therapies, multidisciplinary care including non-pharmacological interventions is suggested. One such intervention is rehabilitation training employing external auditory cueing such as rhythmic auditory stimulation (RAS). RAS is a Neurologic Music therapy (NMT) sensorimotor rehabilitation technique, specifically designed for gait. It is based on entrainment models in which the auditory cues synchronize motor responses into stable time relationships, similar to oscillatory coupling models. Beneficial effects of RAS on gait impairment were initially discovered in a series of research studies [1,2]. A seminal randomized clinical trial (RCT) for PD demonstrated that the PD group who had a three-week home-based gait training program using RAS significantly improved their gait velocity, stride length, and step cadence compared with the active control group who had an internally self-paced gait training as well as compared with the control group who did not have any training [1] and a subsequent experimental study showed an anticipatory synchronization stride pattern induced by RAS (Fig. 1) [2].

For gait training, RAS is applied in the form of regular isochronous auditory pulses such as metronome clicks, or metrical acoustical beats embedded in instrumental music (usually in 2/4 or 4/4 m). It is first matched to an individual's preferred cadence and gradually increased or decreased by 5-10% to optimize their gait parameters such as cadence, velocity, and stride length [3]. In PD, RAS training has been shown to be effective to reduce gait impairment, falls, and freezing of gait (FOG), as well as to improve balance. Carry-over effects of the interventions persisted up to six months, some of which were shown to be only observed following the RAS intervention, but not the same active intervention without RAS [3].

In addition, oscillatory changes associated with the clinical benefits were demonstrated [4–7]. These neuromodulatory effects may be induced by auditory entrainment and oscillatory coupling in distributed areas of the brain including auditory and motor associated cortical and subcortical areas and have important implications for PD as electrophysiological abnormalities are well-established characteristics of PD with clinical relevance [8].

In this paper, we explore the potential of RAS technique as a non-pharmacological, neuromodulatory therapeutic intervention to remediate PD symptoms including those resistant to dopaminergic medications. We present experimental and intervention studies employing RAS that have demonstrated neurophysiological changes associated with improvement of PD symptoms and briefly discuss some literature that suggests the potential underlying neurophysiological mechanisms of RAS. Lastly, we discuss future research directions to advance the knowledge and expand the clinical application of RAS to various PD symptoms and atypical parkinsonism.

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2. Auditory rhythm induced oscillatory changes associated with improvement of PD symptoms

One experimental study demonstrated the effect of auditory cueing on beta modulation of subthalamic nucleus (STN) and on lower-limb movement (stepping) in 16 participants with PD who had deep brain stimulation (DBS) implants in STN [4]. Beta oscillation (20–30 Hz) was suppressed at the time of ipsilateral heel strikes when the contralateral foot was raised and reappeared after contralateral heel strikes, when the contralateral foot rested on the ground. The timing of this beta modulation was alternating within each stepping cycle with the left STN aligned to the right heel strike and with the right STN alighted to the left heel strike. Auditory cueing significantly enhanced the beta modulation (max–min power) between 28 and 30 Hz and reduced step timing variability, suggesting that it assisted the participants in timing their steps more regularly. In addition, with auditory cueing, the beta rebound was higher when an interval of two consecutive steps was longer and the beta power decreased faster before the ipsilateral heel strike, which may facilitate faster lifting of the contralateral foot and help to shorten the next interval to keep up with the rhythm. This may be part of the underlying mechanisms of RAS for facilitating gait cadence.

Cortical beta modulation has also been demonstrated in multiple RAS intervention studies. In one parallel-group RCT combined with EEG, 50 participants with PD (mean H&Y 3) received an eight-week treadmill gait training with or without RAS (once a day, five days a week) [5]. The RAS training group (N = 25) showed a stronger EEG power increase in event-related deysnchronization (ERD) and event-related synchronization (ERS) in alpha and beta bands within the frontal and centro-parietal areas compared to the No-RAS training group (N = 25). These EEG findings were associated with specific periods of the gait cycle. In addition, the RAS training group showed greater fronto-centroparietal/temporal connectivity in alpha and beta bands compared to the No-RAS training group. Furthermore, the greater increase in the fronto-centroparietal and fronto-temporal beta connectivity was significantly correlated with the greater gait improvement measured using the Functional Gait Assessment.

A greater remodulation of sensorimotor beta oscillations associated with gait cycle as well as greater improvement in scores of Unified Parkinson's disease Rating Scale, timed up-and-go test, and 10-m walking test were also demonstrated in 10 PD participants with DBS compared to 10 PD participants without DBS (matched for age, sex, and disease characteristics) following a one-month RAS-assisted treadmill training (once a day, six days a week), in addition that both groups showed significant improvement in Falls efficacy scale, Berg Balance Scale, and Addenbrooke's Cognitive Examination-Revised post-training compared to pre-training [6]. This study presents the preliminary data of the combined beneficial effects of DBS and RAS training.

One pilot study demonstrated that following a five-week auditory rhythm-based therapeutic intervention - NMT on upper-limb functions (three times a week), three participants with PD (H&Y 2, 2.5 and 3) benefited in one or more areas of fine motor functions for either a dominant hand or both hands and showed increased functional coupling between primary auditory and motor cortices in the beta frequency band [7]. The beneficial functional effects and associated oscillatory modulation are further to be determined in an RCT including 100 participants with PD [9].

These studies suggest that auditory rhythm/RAS can induce enhancement of alpha and beta ERD and ERS in cortical areas and beta power in the STN, as well as alpha and beta coupling in frontal, parietal, and temporal areas, which is associated with the beneficial effects on PD motor functions. Exaggerated synchronized beta oscillatory activity and long beta bursts are hallmarks of PD [8]. More studies are warranted to investigate the effects of RAS training on the pathological beta oscillatory activity of PD.

3. Auditory entrainment and oscillatory coupling

One of the neurophysiological modulatory effects underlying regular isochronous auditory rhythms such as those used in RAS may be entrainment. Entrainment is defined as the alignment of one or more oscillating systems to the periodicity of an external rhythm [10]. External auditory rhythm can entrain brain oscillations whose frequency is the closest match to the temporal structure of the inputs [10,11] and delta frequency range (1–4 Hz) can strongly induce entrainment in the auditory cortex [12]. Both visual and auditory rhythm can entrain oscillations in the human brain [13]; however, the auditory system can

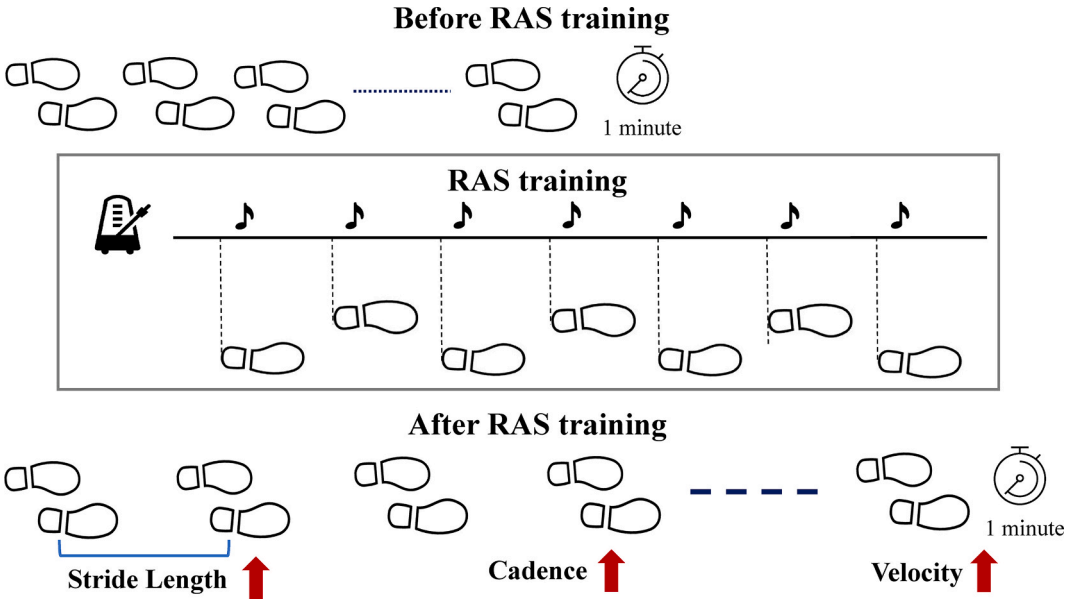

Fig. 1. Schematic illustration of RAS training and beneficial effects of RAS training on gait in Parkinson's disease. RAS: Rhythmic Auditory Stimulation. The top illustration depicts a walking pattern before RAS training, characterized by short stride as well as decreased cadence and velocity in people with Parkinson's disease. The middle illustration shows a walking pattern synchronized to RAS in which the temporal regularity of RAS generates anticipation of the timing of upcoming stimuli, leading to anticipatory motor actions. The lower illustration depicts an improved walking pattern after RAS training, characterized by faster walking with more steps and longer stride length, travelling a longer distance in people with Parkinson's disease.

process the temporal information of rhythm faster and with high temporal precision [14,15].

Slow frequency oscillations can also recruit a larger number of neurons in a broad area of the brain and can couple local faster frequency oscillations [11]. This may allow for delta coupling and cross-frequency coupling within and between auditory and non-auditory areas of the brain [16–19]. In healthy individuals, passive listening to regular isochronous auditory stimuli of delta frequency range without an intention to move induced beta power comodulation (decrease after stimulus onset and rebound just before the next stimulus that followed the periodicity of stimulus) between auditory and distributed areas of the brain including motor associated areas such as the basal ganglia/-thalamus, premotor cortex, supplementary motor area, and cerebellum [18]. This beta modulation may reflect an internal representation of temporal anticipation and/or temporal attention of events [10,12,18], facilitating action as beta oscillatory power suppression appears preceding movement in self-paced motor tasks. Therefore, beta power comodulation induced by RAS plays a significant and distinctive role in producing clinical benefits of the training.

Research on such periodic auditory rhythm and oscillatory entrainment and modulation is mostly conducted in animals and healthy individuals, but intact auditory entrainment was also reported in PD employing auditory stimuli of interstimulus interval of 1000 ms in two studies to date [20,21]. However, one of the studies reported that the effects of auditory beta entrainment did not transfer to the motor area in the PD group, suggesting that auditory-motor beta coupling is impaired in PD. Nonetheless, the PD group performed the task as well as the healthy control (HC) group in this study. It is noted that these two studies were different in the experimental task, outcome measure of entertainment, and recording areas of the brain. It is also unknown whether these studies have enrolled PD participants with similar disease characteristics.

4. Future directions

Experimental and intervention studies with neurophysiological data have revealed part of neuromodulatory effects of RAS in PD. More studies are needed to investigate RAS-induced neural entrainment, oscillatory coupling including cross-frequency coupling within and between auditory and non-auditory areas of PD brain, and relationships between neuromodulation and symptom improvement. In addition, future studies need to include HC data to determine initial pathological oscillations of PD and the brain changes observed post-intervention to compare with. Such studies would help to elucidate whether the brain changes post-intervention are compensatory for and/or modulation of PD pathophysiology.

More RAS studies are also needed in those with DBS implants as such studies can provide unique opportunities to investigate the neurophysiological activities in subcortical nuclei. In addition to DBS in STN, pedunculopontine nucleus (PPN) is one of the emerging DBS targets with demonstrated (but inconclusive) reduction of falls and FOG. In addition, PPN alpha and beta frequency band activity is associated with gait in PD [22]. Given that PPN is connected with the inferior colliculus (IC) - auditory nuclei in the midbrain, and that the IC responses became phase-locked to rhythmic auditory cues of 1.5 Hz and 2 Hz, it would be interesting to investigate whether RAS could modulate PPN oscillatory activity and associated clinical symptoms [23]. Furthermore, a neurophysiological relationship between cortical and DBS implant sites in response to RAS can provide a more comprehensive picture of neurophysiological effects of RAS. Cortico-subthalamic decoupling of a low frequency band (4–13 Hz) has been shown as a characteristic of FOG in people with PD [24].

Neurophysiological studies on RAS training may be expanded to atypical parkinsonian disorders (APD) such as progressive supranuclear palsy (PSP) and multiple system atrophy whose clinical manifestations include postural instability, falls, and gait impairment including FOG with limited levodopa response. To date, only behavioral data of RAS are available: it has been reported that supervised home-based RAS training was feasible in a small group of people with PSP, these participants showed some improvement in temporal and spatial measures of walking, and all participants enjoyed the intervention program [25]. In addition, one experimental study demonstrated immediate improvement in cadence using RAS in 46 APD [26]. Furthermore, an NMT intervention combined with transcranial direct current stimulation on upper-limb functions and brain oscillations in corticobasal syndrome awaits the results [27].

Rhythmic auditory cueing with a tempo of delta frequency range may also be applied to improve other PD symptoms, given that the delta frequency range is associated with the oscillations of various functions and behaviors. For example, an application of isochronous auditory rhythm with delta frequency range may improve visuospatial and visual processing tasks [17]. It facilitated attention measured by saccade latency during visuospatial tasks [28]and modulated alpha and beta oscillations in the occipital cortex [17], which was accompanied with the better task performance. It may be interesting to investigate the effects of rhythmic auditory cueing on visuospatial/visual processing function and/or attention in PD with the cognitive impairment. Furthermore, hypokinetic dysarthria is frequently observed in PD, but it is only partially relieved by dopaminergic medication. Prosodic information of speech has a rhythmic structure with delta frequency band [29,30]. One study showed that rhythmic cueing improved speech intelligibility in 20 PD participants with hypokinetic dysarthria [31].

Another potential application of rhythmic auditory cueing may be toward tremor. One study showed that with auditory cueing of frequency of 1.6, 3.2, and 4.8 Hz (selected within the range of frequency found during gait and PD tremor) and DBS combined, significant reduction in the number of extremities showing action tremor in seven medicated PD with bilateral STN DBS electrodes [32]. As regular isochronous auditory rhythm also modulates electrophysiological activity including beta oscillation in cerebellum [18] (suggested interventional target of tremor [8]), this may be a potential future avenue of research. In addition, the combined effect of rhythmic auditory cueing and non-invasive neuromodulation techniques on tremor and entrainment can be further investigated [33].

Lastly, there are some considerations to be taken into the future RAS research from the clinical point of view. Regarding future DBS studies, given that DBS may aggravate or develop FOG and falls [34,35], and may develop dysfunctional motor behavior such as poor interlimb coordination [36,37], gait, falls, FOG, and interlimb coordination should be assessed before and after DBS and RAS training.

More research is needed to effectively apply research findings of RAS training to clinical practice [38,39]. Factors such as training protocol as well as individual differences such as cognitive function [40,41], baseline behavioral and brain functions, rhythmic abilities and musical training, and/or genetic variants [42] can play an important role in the responsiveness to the training. As PD presents various non-motor symptoms, more detailed clinical characteristics of PD need to be collected in the studies. RCTs with large samples, allowing the stratification of participants based on the characteristics can address the research questions [39].

More generally, future studies need to address the criticisms/limitations of music-based intervention research [43]. These include a paucity of high quality RCTs including large multi-center clinical trials [38,39] and poor quality of reporting regarding providing information about theory, interventionist qualifications, treatment fidelity, setting, and intervention content across studies, making it difficult to draw conclusions on specific clinical application and benefits [44].

In addition, accessibility to music-based therapy is also important to be considered. Availability and cost of music-based therapy at a hospital and training for music therapists may vary across the country and internationally. However, as rehabilitation training provided at a hospital and a community center limits accessibility, more studies are

needed concerning home-based training with low-cost and highly available technologies including the feasibility and safety of participants [38,45].

5. Conclusions

To further advance the knowledge and application of RAS to rehabilitation programs for movement disorders as a potential oscillatory modulator and a behavioral facilitator, we have presented paucity but interesting research literature to link RAS with neuroscience and medicine and shed light on an avenue for future research. Literature suggests that RAS intervention programs have potential to be one of the neuromodulatory therapeutic interventions for movement disorders. More research studies investigating whether RAS can modulate oscillopathology of movement disorders through neural entrainment and cross-frequency oscillatory coupling in distributed areas of the brain and clinical symptoms are warranted. Furthermore, future research needs to investigate the effects of RAS rehabilitation training on motor symptoms before and after deep brain stimulation.

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Declaration of competing interest

None

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