Sing for Your Saunter:

Using Self-Generated Rhythmic Cues to Enhance Gait in Parkinson's

NCT06115382

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I. SPECIFIC AIMS

The primary objective of this study is to determine how music and singing enhance walking ability among people with Parkinson disease (PD). Participants with PD (n = 74) will be included in one of two interventions led by a music therapist and a physical therapist. The two interventions include 24 one-hour group classes (twice weekly excluding holidays) and will focus on standard elements of training in beat perception, rhythm production and synchronization of movement to a rhythm. The two interventions will be taught nearly identically, with the slight differences on the focus, including the home practice. Individuals will focus on either rhythmic movement training using external musical cues (Music) or rhythmic movement training using self-generated internal singing cues (Singing). As the classes will be taught in waves, participants will not be individually randomized but randomized as a group prior to the first date of the class. Pre- and post-intervention data collection will include assessments of mobility, gait, and inter-tap interval variability for tapping. Using tapping as a gait surrogate, participants will also undergo task-based fMRI at pre- and post-test time points to understand the neural mechanisms underpinning auditory cueing. Twelve weeks after the intervention, participants will complete a final questionnaire regarding whether and under what circumstances they continue to use cueing in their daily lives.

During the group classes (n~12), each individual will be pulled aside once per week for a ten-minute consultation with the physical therapist. During this individual consultation, the participant will practice walking using their personalized cues developed during their evaluation. Participants will be provided a recording of their personalized cues on their own personal device or a device provided by us and will be asked to practice walking with music or mental singing on their own three days a week for a total of 30 minutes per day.

Specific Aim 1: Compare the effects of training using external musical cues vs. self-generated singing cues on movement performance among people with PD.

Specific Aim 2: Compare the effects of training using external musical cues vs. self-generated singing cues on brain activity among people with PD.

Specific Aim 3: Compare the acceptability and usability of training using external musical cues vs. self-generated singing cues in people with PD.

II. HYPOTHESIS

Specific Aim 1: Compare the effects of training using external musical cues vs. self-generated singing cues on movement performance among people with PD.

> Hypothesis 1: Gait speed will improve similarly with both forms of training. Temporal variability in gait and finger tapping will improve more with mental singing training than with music training.

Specific Aim 2: Compare the effects of training using external musical cues vs. self-generated singing cues on brain activity among people with PD.

> Hypothesis 2: Following training, the music group will show increased activation in auditory cortex whereas the mental singing group will show increased activation of the putamen and cerebellum relative to baseline. Changes in movement timing variability will be related to changes in putamen activation.

Specific Aim 3: Compare the acceptability and usability of training using external musical cues vs. self-generated singing cues in people with PD.

> Hypothesis 3: Both music and mental singing training will be acceptable to participants; usability will be higher for singing.

III. BACKGROUND AND SIGNIFICANCE

Rhythmic movements such as gait are key to everyday function, and people living with Parkinson disease (PD) commonly have trouble with their gait which can lead to disability, reduced quality of life, and is highly predictive of mortality[1]. There are currently about 10 million people living with PD, with approximately 60,000 new diagnoses annually in the United States alone. Gait impairment may occur early in the disease process and is considered a harbinger of impending disability[2]. As such, much effort has been devoted to developing methods to enhance gait in PD. Gait enhancement via rhythmic sensory cues generated externally, for example by music, has been explored extensively (for reviews see[3,4]). Self-generated rhythmic cues, on the other hand, have been neglected in research in spite of many reports that patients commonly use them to aid in walking[5–7]. Our pilot work suggests use of internal, self-generated rhythmic cues in the form of singing - and in particular imagined or mental singing - holds considerable promise for gait enhancement in PD.

The studies proposed herein build on our pilot work and are among the first to compare training using external musical cues vs. self-generated singing cues. Several studies have demonstrated improvements in stride length and gait velocity with training using external rhythmic auditory cues (for a comprehensive reviews see[3,8]). Very few studies have examined the effects of external cues on variability and evidence is even scarce regarding the effects of training with cues on stride-to-stride variability. However, the literature suggests benefits to gait are substantially increased after training with external cues as compared to the acute benefits within a single session[3]. Further evidence suggest cortical activation is increased with repeated exposure to rhythmic auditory cues, though this has only been shown in older adults during treadmill walking[9]. However, we lack data on training with mental singing and we lack understanding of how cueing training interventions work in terms of neural mechanisms. This study will address multiple critical gaps in our knowledge. Overall, this work has potential to open up an entirely new approach for gait improvement in PD using a fully accessible, adaptable, and low-cost approach.

The Traditional Approach: External Rhythmic Auditory Cueing to Improve Gait in PD

For more than forty years, scientists have been exploring the impact of external rhythmic cues on movement. Early work described the link between auditory and motor systems, implicating these connections in the ability to synchronize movement to sound[15]. Numerous researchers have conducted studies across the decades since, consistently showing that rhythmic auditory stimulation can influence gait in people with PD, improving gait speed, stride length, and/or cadence[6,10–13]. Auditory stimulation is generally more effective than other types of external cues (e.g., visual, somatosensory)[14], which may relate to the shorter latency required to react to auditory as compared to visual or somatosensory cues, or to the auditory system being ideally suited to detect temporal patterns and rhythms[7]. Furthermore, musical cues are more effective at increasing gait speed than isochronous metronome beats, perhaps because of their motivating and enjoyable qualities[15]. Interestingly, recent evidence suggests that a variable external rhythmic cue that oscillated based on a model of human gait also provided greater benefit than an isochronous external cue[16]. Self-generated rhythmic cues may possess similar biological variability that may be particularly conducive to improving walking. Despite the improvements in gait that often occur with external rhythmic auditory cueing, there are several noteworthy limitations to its use. One limitation is that not all individuals benefit from external rhythmic cues, and it is not yet clear what factors account for ability to respond[17]. Another notable downside is the effects of external cues on walking typically persist only briefly once the cues are removed[18,19]. This necessitates the constant presence of an external device to provide stimulation, which could be burdensome and reduce accessibility in everyday settings. In addition, as evidenced in our pilot data, external cues may not increase temporal stability whereas internally self-generated singing does. In this study, we propose a novel approach using self-generated rhythmic cues, which are readily accessible at any time and are hypothesized to provide greater benefit as compared to external cues.

A Novel Approach: Self-Generated Rhythmic Cueing to Improve Gait in PD

Given the limitations associated with external rhythmic auditory stimulation noted above, it is surprising that studies of self-generated rhythmic cues are lacking. Several pieces of evidence suggest self-generated sung cues may be effective for enhancing movement. People with PD report using singing as a strategy to aid with initiation and maintenance of gait in challenging situations[5]. In fact, in one of the first reports of training with external musical cues, participants reported singing the music in their heads (mental singing) to recall the cue and enable them to walk at the desired pace during post-training gait evaluation[6]. Additional support for the use of vocalization to foster movement comes from work showing that self-speech enhances upper extremity movements in people with PD, resulting in faster and smoother reaching movements on trials where movement was accompanied by speech as compared to trials without speech[20]. However, speech performance may degrade over the course of PD, while ability to sing remains relatively preserved. Individuals with PD who exhibit dysprosody of speech show no decrements in singing prosody[21]. When singing, ability to maintain tempo, interval size, and interval variability is maintained in people with PD despite the fact during speech these abilities are impaired. This suggests singing could be used to facilitate linguistic prosody. In

practice, singing is increasingly used as a therapeutic technique for vocal rehabilitation in PD. While the impact of singing on motor function is largely unknown, we hypothesize that singing may have benefits that go well beyond vocalization and extend to gait. However, in some situations it may not be desirable or appropriate to sing aloud, necessitating use of mental singing as an alternative method of self-cueing. A small pilot study of eight people with PD who were taught to imagine singing while walking suggests that mental singing may enhance gait velocity and turning performance[22]. (It is worth noting this study had several limitations including small sample size, use of subjective rating of videos to determine changes in performance, and lack of comparison to other cued conditions.) Recent work also shows improvements in gait post-stroke with mental singing[23]. And, our own work suggests mental singing is as effective, if not more effective, than singing aloud for improving gait in PD[24,25] (see preliminary data section for more details). Therefore, the work proposed herein will compare mental singing (rather than singing aloud) to external musical cues through a randomized intervention. Our exciting preliminary result leaves us eager to explore this topic further to understand the differences between responses to external vs. self-generated rhythmic cues as well as the brain mechanisms that underlie these responses and the potential to enhance response to cues through personalization and training.

Understanding Mechanisms of Cueing Responses

In spite of decades of research on the effects of cues on movement, little is known about the mechanisms that underlie motor synchronization. Production of successful and stable locomotor patterns relies on precise timing mechanisms. As faulty internal timing likely contributes to gait difficulties in PD, people with PD represent a unique population in which to study the mechanisms that enable matching footfalls to cues. External rhythmic auditory cues provide a source of regular input that may facilitate movement timing through auditory-motor coupling. Movement is synchronized to the beat of the external rhythm via entrainment, as the beat creates a template for anticipation of the timing of future events[7]. Multiple pieces of evidence support the influence of the auditory system on the motor system. First, connections between the auditory and motor systems are present in a wide range of animals from fish to humans. For example, auditory system projections can modify spinal motor neuron excitability via reticulospinal pathways[26]. Brain areas involved in rhythm processing overlap substantially with those involved in motor control (e.g., premotor and supplementary motor cortices, cerebellum, basal ganglia)[27–29]. Evidence shows that coupling between auditory and premotor cortices is enhanced during rhythm processing[30,31]. The cerebellum may also play a role in monitoring ongoing rhythmic movements and adjusting to changing tempos[32,33]. The putamen, in particular, is implicated in rhythmic event sequencing and beat perception[11,31]. In individuals with PD, activity in the putamen, cerebral cortex, and corticostriatal pathways is reduced during uncued movements. However, during externally cued movements, activity is more similar to that of control participants[34]. Thus, external rhythmic cues are thought to facilitate sensorimotor network activity and may also involve executive/attentional control as evidenced by increased prefrontal cortex activity when walking with external cues[9]. Current theories suppose that external cues allow bypassing of the impaired basal ganglia to supplementary motor area (SMA) loop

via activation of cerebello-thalamo-cortical pathways. We hypothesize that external musical cues will primarily drive the cerebello-thalamo-cortical pathways whereas mental singing, which could be considered a type of internal cue, will drive basal ganglia activity and act through the cortico-striato-thalamic pathway (Figure 1).

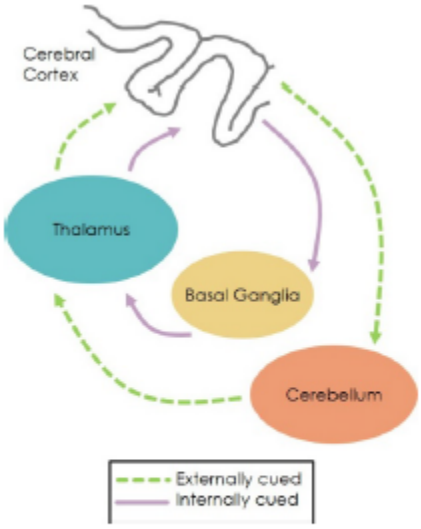

Figure 1. Schematic showing proposed pathways for externally cued (dashed green arrows) vs. internally cued (solid purple arrows) movements.

Singing is a complex, multimodal task that requires integration across multiple brain areas. Neuroimaging studies have begun to elucidate the patterns of brain activation that occur during singing and speech. Singing is distinguished by activation of Perisylvian regions of the right hemisphere that are not active during speech[35]. This activation is thought to account for the relative preservation of singing vs. speech in some neurological conditions including stuttering and aphasia following left hemisphere stroke. This distinction between neural control of singing as compared to speech may also contribute to the preservation of singing prosody in people with PD who demonstrate speech dysprosody[21].

Singing also results in activation of several areas within the frontal, parietal, and temporal cortices along with subcortical and brainstem structures including pre-SMA, SMA, dorsolateral prefrontal cortex, primary somatosensory and auditory cortices, basal ganglia, and cerebellum[35]. Evidence from imaging literature suggests that mental singing activates brain areas similar to those activated during singing aloud[36]. Furthermore, processing and producing rhythms activates areas involved in motor control including bilateral SMA, inferior frontal gyri, inferior parietal lobules, and cerebellum[37].

IV. METHODS

PARTICIPANTS RECRUITMENT

Recruitment of participants with PD will be through:

- Movement Disorders Clinic in the Department of Neurology at Washington University School of Medicine
- Flyers and newsletter blurb via the American Parkinson Disease Association St. Louis Chapter.
- Advertisements through Meta (Facebook and Instagram) that will target older adults and people with Parkinson disease. The ads will contain a link to a RedCap survey where individuals can provide their contact information to the study team.
- We will also use ads managed by the study team and the Director of Marketing for the Program in Physical Therapy or Volunteers for Health. The ads will be provided on Facebook, Instagram, Google, or Twitter. The ad will have a "learn more" link that directs potential participants to a recruitment survey. The content of the ads will be drawn from the attached ad titles and descriptions (Social Media Ads) and the attached recruitment images (Photos-Ads). An ad will be a combination of one title, one description, and one image. The ad will have a "learn more" link that directs potential participants to the recruitment survey referenced in 1.8. To maintain privacy, all ads will have the comments disabled if possible. (If it is not possible to disable the comments the Director of Marketing for the Program of Physical Therapy will continually monitor comments and hide them in a timely manner; no member of the research team or marketing department will respond to any comments on social media ads). In addition, to maintain privacy all ads will not include PHI and have any list of followers of the social media page hidden. Access to social media accounts also will be limited to the research team, the Director of Marketing for the Program in Physical Therapy, and Volunteers for Health. A disclaimer will be added to advertisements that cannot have comments disabled asking viewers to refrain from disclosing any sensitive personal information in comments.

We will also post advertisements on the Program in Physical Therapy social media homepages (twitter, facebook, and Instagram) and post flyers around Washington University campuses.

PARTICIPANT INCLUSION AND EXCLUSION CRITERIA

For inclusion in the study, participants with PD must be:

- at least 30 years of age;
- diagnosis of idiopathic, typical Parkinson disease according to the UK Brain Bank Criteria;
- Hoehn & Yahr stages 2-3 (mild to moderate disease severity);
- stable on all PD medications for at least one month prior to study entry;

- willing and able to provide informed consent;
- right-handed or ambidextrous;
- score of ≥ 1 on the MDS-UPDRS-III Item #10 indicating observable gait impairment;
- able to walk for 10 continuous minutes with or without an ambulatory device;
- a score of 1 or less on item # 7 on the New Freezing of Gait Questionnaire;
- weigh less than 250 pounds;
- no contraindications for magnetic resonance imaging (e.g., metallic implants); and
- MMSE score of >=24 to indicate no significant cognitive impairment.

Exclusion criteria:

- diagnosis of any other neurological condition;
- unstable medical or concomitant illnesses or psychiatric conditions which, in the opinion of the investigators, would preclude successful participation;
- cardiac problems that interfere with ability to safely participate (i.e., uncontrolled congestive heart failure, myocardial infarction in past 6 months, complex cardiac arrhythmias, significant left ventricular dysfunction, dyspnea on exertion, chest pain or pressure, resting tachycardia (>100 beats/min);
- orthopedic problems in the lower extremities or spine that may limit walking (i.e., severe neuropathy, spinal stenosis); or
- uncontrolled tremor or dyskinesia while on PD medications
- Inability to pass a hearing screen without hearing aids
- Using specific strategies to assist in your walking, such as rhythmic cueing or use of music to specifically regulate your walking pattern, meaning walking to the beat of a song regularly (e.g., once a day)
- Currently participating in LSVT or planning to start LSVT

Participants with PD will remain on their normal anti-PD medications throughout the study. Evaluations will be conducted in the ON medication state because this represents everyday life. All visits at pre- and post- testing will be scheduled at the same time of day as noted by that person as their optimal ON period when their medications work best.

MATERIALS

<u>Pre-assessment materials via phone</u>

- Phone screen to inform the participant about the study and ask questions to determine eligibility.
- MRI Screening Questionnaire will be administered to people with PD who are eligible to participate to ensure they can safely participate in the fMRI portion of the study.

Pre-assessment materials during pre-intervention assessment, Visit one

- Participants will complete the Mini-Mental State Exam (MMSE)[38] as a measure of cognitive performance. In order to qualify for the study people with PD must score ≥24 on the MMSE, indicating no significant cognitive impairment. In earlier phases of this project we determined that the potential risks for those with possible cognitive impairment did not outweigh the potential benefits. Therefore, were are using the MMSE to screen for low cognitive performance and will exclude these individuals.
- Participants will complete a demographic form that includes questions about mobility and fall history.
- Participants will complete the New Freezing of Gait Questionnaire to identify individuals with severe freezing.
- Pure-tone hearing test to ensure hearing abilities are proficient for the testing.
- MDS-UPDRS-III Motor Assessment (for people with PD) – to ensure participants have a Hoehn and Yahr score of 2-3 and observable gait disturbance per scoring of the gait item on this test.

Evaluation materials during pre-intervention assessment, visit one

- Six Opal inertial sensors (APDM, Inc) will be worn to provide an assessment of gait parameters. APDM sensors are worn on both feet, both wrists, chest, and posterior trunk at the level of L5 with elastic Velcro bands as the subjects perform their tasks (uncued, listening to music, and mentally singing). This will allow quick assessment of stride length during the different tempos.
- A catalog of songs that are commonly known (e.g., Row Row Row your boat), cross-cultural, age-appropriate, and have characteristics appropriate for gait training (e.g., salient beat, 4/4 timing, activating) will be available.
- Keyboard for finger tapping and finger tapping data collection sheet
- Balance test: Mini-BEST test
- Beat Alignment Test
- Additional questionnaires to take home and return at visit two: MDS-UPDRS-I, MDS-UPDRS-II, PDQ-39, Beat Alignment Test Questionnaire

Evaluation materials during pre-intervention imaging assessment, visit two

- MRI data will be collected on a new, state-of-the-art 3T Prisma scanner system, using multiband factor 4, which capitalizes on simultaneous multi-slice acquisition to improve spatial resolution without increased scan time. The scanner is located in the Neuroimaging Laboratory

Evaluation materials during intervention

- Participants will complete a weekly 10MWT with the physical therapist. Time to completion using a stopwatch and number of steps will aid in accounting for progression of pace during the 24 class intervention. General notes from the therapist on the weekly check-in can be added to this collection sheet as well.

Evaluation materials during post-intervention assessment, visit three

- Participants will complete the Mini-Mental State Exam (MMSE) as a measure of cognitive performance.
- Participants will complete the New Freezing of Gait Questionnaire to measure freezing in participants
- MDS-UPDRS-III Motor Assessment (for people with PD)
- Six Opal inertial sensors (APDM, Inc) will be worn to provide an assessment of gait parameters. APDM sensors are worn on both feet, both wrists, chest, and posterior trunk at the level of L5 with elastic Velcro bands as the subjects perform their tasks (uncued, listening to music, and mentally singing). This will allow quick assessment of stride length during the different tempos.
- Keyboard for finger tapping and finger tapping data collection sheet
- Balance test: Mini-BEST test
- Beat Alignment Test
- Additional questionnaires to take home and return at visit four: MDS-UPDRS-I, MDS-UPDRS-II, PDQ-39, Beat Alignment Test Questionnaire

Evaluation materials during post-intervention imaging assessment, visit four

- Same materials as “pre-intervention imaging assessment”: MRI data will be collected on a new, state-of-the-art 3T Prisma scanner system, using multiband factor 4, which capitalizes on simultaneous multi-slice acquisition to improve spatial resolution without increased scan time. The scanner is located in the Neuroimaging Laboratory

Evaluation materials during follow-up time point

- A survey will be sent to those who participated in the intervention at 12 weeks after the completion of the intervention. This survey will be focused on whether and under what circumstances they continue to use cueing in their daily lives

PROTOCOL

Consent

Participants will receive and sign the informed consent during the first in-person visit. We will ensure the participants have the opportunity to ask the researcher any questions they may have regarding the study and procedure.

Participants will need to provide verbal consent on the phone prior to us using their email for communications. We will explain to the participant the purpose of contacting them by email (i.e., scheduling, visit information, or completing surveys), notify them that some emails may contain health information, risks associated with using email (could be intercepted), that we will send a test email, remind the participant of their responsibilities (protect their username and password to their email account, log out, and if they share computer or cell phone with family member and want privacy then need to provide an email that only they can access), and let them know they can tell us if they want us to stop using their email as a method of communication.

Pre-intervention assessment

Pre-intervention assessment, Visit one

After the consent form is signed, a trained researcher will administer the MMSE, demographics form, hearing test, and MDS-UPDRS-III. We will also collect medical history and medications, fill out the MRI Screening Form a second time, and administer the New Freezing of Gait- Questionnaire (NFOG-Q). After this in-person screening, we will determine if the participant meets inclusion criteria.

If the participant passes the in-person screening, sensors will be put on the participant to record data during the gait assessments. All participants will be fitted with a safety belt and research team members will be close by to prevent falls during the visit.

A balance test will be conducted first. The Mini-Best is a clinically relevant balance test that is valid and reliable for individuals with PD. The test includes sections to test anticipatory balance, reactive postural control, sensory orientation, and dynamic gait.

Next, participants will complete the uncued walking and tapping assessments. Then be asked to choose from the song catalog the song that is most familiar to them.

Participants will then complete the walking and tapping assessments during the mental singing, singing out loud, and music conditions.

Six Minute Walk: This condition will be used to measure walking endurance. Participants are asked to cover as much ground as possible over the course of six minutes. This will occur with no cueing.

Baseline Uncued: This condition will be used to represent normal baseline walking and will provide a point of comparison for the other conditions. It will include three, 30-second trials. Participants will be asked to walk at their preferred walking speed. This will occur in silence, as no cueing will be provided.

The following music and mental singing conditions will be conducted at four tempos (90%, 100%, 110%, and 120%) to identify the optimal tempo to use for the finger tapping assessments.

Music: Our music condition represents traditional cueing techniques in which music will play and participants will be asked to walk to the beat. Once the song is turned on for each trial, participants will be told to take as long as needed to listen to the song, pick out the beat, and begin walking.

Sing: Participants will be asked to sing the song out loud while walking without music playing. Participants will first hear the music played and once the song is over they will be instructed to sing the song out loud at the same pace as the music they just heard while walking.

Mental Singing: Participants will be asked to mentally sing while walking without music playing. Participants will first hear the music played and once the song is over they will be instructed to mentally sing at the same pace as the music they just heard while walking.

Using output from the APDM Sensors, the tempo that elicited the longest stride length, determined by average stride lengths across the music and mental singing trials within each tempo, will be used for the finger tapping tasks. This tempo will also be used as the starting tempo for the music-walking programs.

Finger tapping tasks will next be assessed. Using the tempo selected from the walking assessments, participants will complete three, 30 second trials during both listening to music, singing out loud, and mentally singing conditions.

Pre-intervention assessment, Visit two

During this visit, participants will have 2 structural scans: a T1-weighted (T1W) sagittal, magnetization prepared rapid acquisition with gradient echo (MP-RAGE, TR=2400 ms, TI=1000 ms, TE=3.16 ms, FA=15°,1.0 mm3 voxels, 8:09 min) and a T2-weighted fast spin echo (TR=3200 ms, TE=455 ms, 1.0 mm3 voxels, 4:43 min). A midsagittal scout T1W spin-echo pulse sequence will be used for positioning. A brief fieldmap scan (54 seconds) will be used to correct for spatial distortion caused by spatial inhomogeneties inside the scanner.

Task-based fMRI will consist of two T2* echo-planar BOLD scans (EPI; MB = 4; TR=1200ms, TE=26.6ms, 3.0 mm3 voxels, FoV = 213mm, 48 slices) with whole-brain coverage including the cerebellum. During the fMRI scans, participants will view the instructions on a mirror mounted to the head coil and receive auditory input through headphones delivered via a custom made ePrime program.

Five functional scans, using the design shown in Figure 2, will consist of eight task blocks (36 sec per block) interleaved with 12 second rest blocks throughout the period of one scan, lasting approximately 6.5 minutes per fMRI scan for each of the five different conditions (uncued tapping, music with tapping, mental singing with tapping, music only, and mental singing only)

The order of task/rest block pairs will be randomized across scans and participants to avoid order and practice effects. Tapping responses and start/stop times of music listening and mental singing will be recorded using an MR-compatible response pad (Mag Design and Engineering, Redwood City, CA). Note that mental singing removes the potential motion confound induced by the act of singing aloud, to be confirmed with out-of-scanner pilot testing to assess for large differences in movement or breathing patterns between mental singing and listening to music while finger tapping. Participants will be observed throughout the scan session; scans with observable, sustained body motion (e.g, tremor, dystonia) will be excluded.

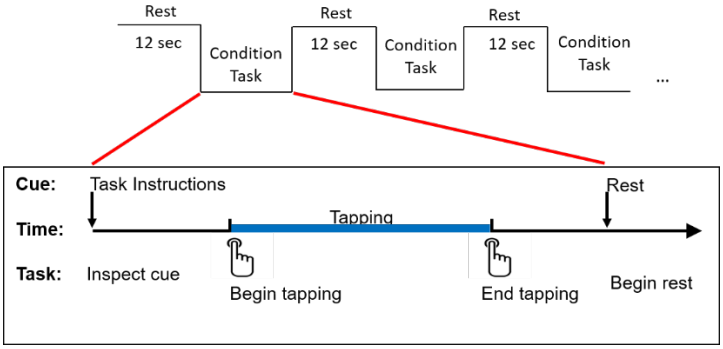

Figure 2. Boxcar design that will be used for FMRI scans.

Intervention

Participants will be assigned to either the music-based or mental singing-based intervention. Randomization will done by group so that once the first set of ~12 people are enrolled, a random number generator will select if all 12 individuals will participate in the music-based focus class or the mental singing-based focus class (Figure 3). The next class will be the opposite matching class. Class randomization will occur before the beginning of every set of classes, with a set of classes consisting of one mental singing-based class and one music-based class.

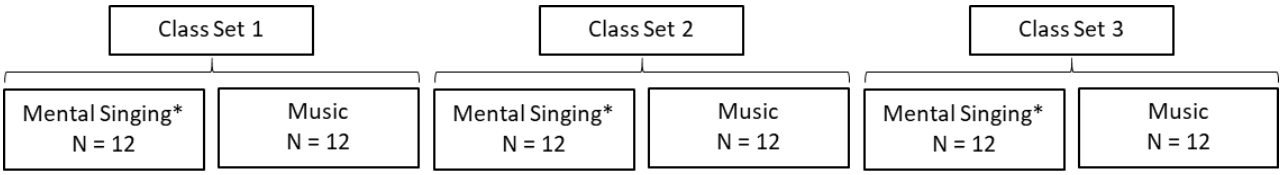

Figure 3. Randomization by class set. *indicates when randomization occurs

All participants will receive 24 classes of the intervention (Figure 4). The interventions will be delivered jointly by a music therapist and a physical therapist. Interventions will consist of twice weekly (excluding holidays), 1-hour group classes that will focus on learning how to identify a beat in music, how to make a steady rhythm, and how to match your movement to a musical rhythm. Both music-based and singing-based classes will be taught in a similar way with focus on identical elements. The key difference will be on the home practice of either musical or sung depending upon the

group. During the group work, each individual will be pulled aside once per week for a 10-minute consultation with the physical therapist. During this individual consultation, the participant will practice walking to music or walking while mentally singing using their personalized cues (developed in the pre-intervention assessment session, see following section). Participants will be provided with a recording of their personalized cue on their own personal device or a device provided by us and will be asked to practice walking with music or mental singing on their own three days a week for a total of 30 minutes per day, to be done on the days when they do not attend the group class. Participants will keep a weekly log to document their participation in the home program. Gait performance of each participant in the uncued condition will be assessed every week and their cues adjusted as necessary to match their current performance. Participants will complete a weekly 10MWT with the physical therapist. This test includes walking a distance of 10 meters at their preferred comfortable pace. Time to completion and number of steps will aid in accounting for progression of pace during the 24 class intervention. General notes from the therapist on the weekly check-in can be added to this collection sheet as well. If cadence increases by more than five steps per minute for 2 consecutive weeks, the physical therapist may choose to increase the tempo of their personalized cue to account for increases in velocity/cadence over the course of training. Ultimately any changes will be at the discretion of the therapist to encourage safe walking.

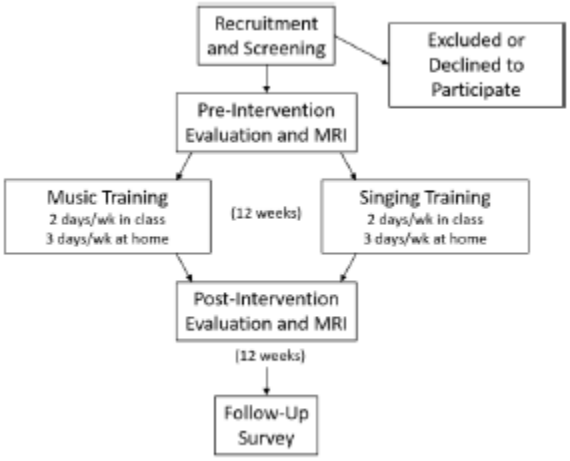

Figure 4. Consort diagram showing flow of participants through the clinical trial.

Post-intervention and Follow-up assessments

Post-intervention assessment, Visit one

All tests and procedures will be repeated after the music-based walking program as mentioned in “Pre-intervention assessment, Visit one.” This includes the MMSE, MDS-

UPDRS, medications, the New Freezing of Gait- Questionnaire (NFOG-Q), PDQ-39, beat alignment test, Mini-Best, and tapping assessments and the six-minute walk test.

After the six-minute walk test, a shortened version of the walking tests will be completed (see example diagram below; Figure 5). First, individuals will walk at their preferred, self-selected pace while no cue or instruction is provided. Participants will then complete a block of music trials and block of singing trials at the pre-evaluation or post-evaluation tempo, randomized, and with the order of music and singing blocks randomized. In total, 4 conditions will be completed: Pre-evaluation tempo Mental Singing, Pre-evaluation tempo Music, Post-evaluation tempo mental singing, and Post-evaluation tempo Music.

- Pre-evaluation tempo: At the pre-evaluation, a research team member identified the participant's "optimal percentage" (either 90%, 100%, 110%, or 120% of uncued cadence) that elicited longest stride length. This was then converted to the optimal pre-evaluation tempo, i.e. how many beats per minute rounded to the nearest 5-beat increment.

  For example, using the data from the pre-evaluation, if an individual walked uncued at 100 steps per min and the "optimal percentage" selected was 120%, than the "optimal pre-evaluation tempo" would be 120 bpm (100 steps per min x 1.20 = 120).

- Post-evaluation tempo: At post-evaluation, if the same individual noted above now walked uncued at 110 steps per min, the optimal post-evaluation tempo would be 132 beats per min (110 steps per min x 1.2 = 132). Rounding to the nearest 5, the post-evaluation optimal post-evaluation tempo is 130 bpm. Both conditions of music and mental singing will be completed while the selected song plays at 120bpm and, in two separate trials, at 130bpm.

No other tempos will be tested, and singing out loud will also not be tested.

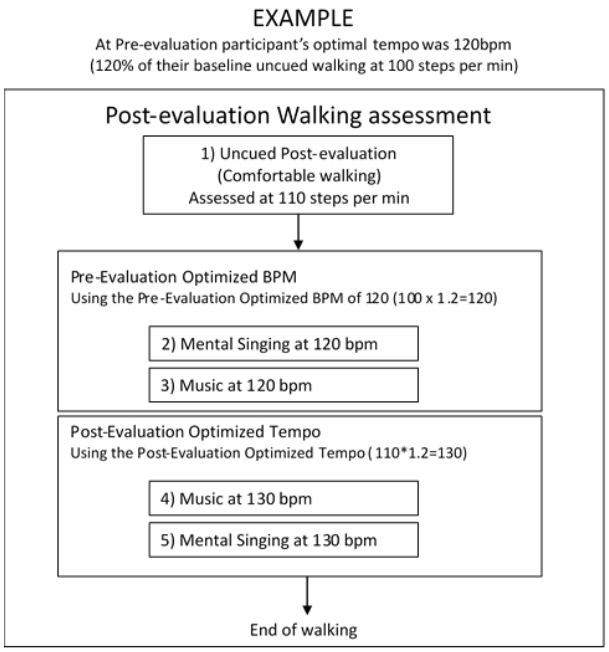

Figure 5. Example Post-test walking

Additional questionnaires will include participant experiences with the training program, continued use of the program, soliciting opinions about acceptability, usability and satisfaction (including specific questions to address use of a single song vs. a suite of songs to inform future studies).

Post-intervention assessment, Visit two

All tests and procedures will be repeated after the music-based walking program as mentioned in "Pre-intervention assessment, Visit two." The tapping rhythm will be identical to the "optimal tapping" identified in the Pre-intervention assessment.

Follow-up time point

A series of questionnaires will be mailed and/or sent via email to participants after 12 weeks have passed after the conclusion of the intervention. These questionnaires will by focused on whether and under what circumstances they continue to use cueing in their daily lives.

OUTCOME MEASURES

- Gait Speed – A measure of how quickly someone walks; this measure is a product of stride length and cadence.
- Stride Time Variability – an assessment of temporal stability of gait that indicates how consistent the duration of each stride is throughout a period of walking.

- Inter-tap interval variability – a measure of temporal stability of tapping of the finger
- MRI BOLD Beta Weights – measure of blood oxygen levels which is indicative of level of activity within different brain regions
- Beat Alignment Test – measure of ability to perceive rhythmic beats and synchronize movement to these beats
- Cueing Activity Log - Measure of frequency and duration that participants engage in for their at-home practice of either music or mental singing
- Post-intervention survey - Report of participant experiences with the training program, soliciting opinions about acceptability, usability and satisfaction (including specific questions to address use of a single song vs. a suite of songs to inform future studies)
- Six Minute Walk distance - Measure of walking endurance that tracks distance a person can cover in six minutes
- Parkinson Disease Questionnaire (PDQ-39) – Self-report measure of quality of life specific to Parkinson disease
- New Freezing of Gait Questionnaire – Self-report questionnaire that assesses frequency, duration, and circumstance of freezing of gait episodes

MDS-UPDRS – Gold standard measure of global disease severity in PD, including measures of motor signs, non-motor symptoms, and activities of daily living

V. RISKS AND BENEFITS

There are several risks associated with this protocol. In addition to the ones listed below, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

Of the Likely / Common risks, the majority are considered Mild and are related to the walking tasks during the evaluations and during the classes themselves. These include:

- Fatigue: Participants may feel tired or weak during the walking tasks or while performing the tapping tasks during the imaging session. Research staff will ask several times if a break should be taken, and participants will be encouraged to inform a member of the research team if they need a break. The research team will help participants take a break from the study or discontinue the study if necessary.
- Physical discomfort: Participants may experience physical discomfort such as muscle soreness while engaging in the walking exercises. Participants will be encouraged to not move in ways that cause discomfort.
- Discomfort during group learning experiences: Participants may experience discomfort during group learning experiences. In any group setting participants may feel uncomfortable or embarrassed while participating with others.
- Discomfort answering questions: Participants may experience some discomfort when completing some of the surveys during the pre-evaluation testing and post-

evaluation testing as they ask about their daily lives including emotion states. Participants may skip any questions they like.
- Technological burden: Participants will be asked to use a personal audio player which they may consider burdensome. The research team will provide multiple options and train individuals on how to best use the devices.

Of the Less Likely / Less Common risks, there is a chance that participants may stumble during walking tasks in the testing sessions or in the classes themselves. The research team will fit individuals with gait belts to assist if needed. We consider this a mild risk.

There is a rare risk of falling that would be considered a moderate risk. It is unlikely that individuals will fall during the walking testing or during class but, as mentioned, the research team is nearby to assist as needed.

There are multiple risks related to the MRI / imaging portion of the evaluations. Common risks include:
- Discomfort inside MRI scanner, particularly if participant has claustrophobia
- Muscle stiffness from lying still
- Muscle cramping that may be caused nerve stimulation that can occur during MRI scans
- Tissue heating causing the participant to be warm

Rare risks include:
- Hearing loss due to loud noise of MRI scanner
- Sensation of flashing lights while in the scanner
- Burns, including serious burns

If participants have devices including pacemaker, bone hardware, stents or other devices, there may be additional risks. While the research team is fully trained in accordance with the facility regulations, these risks include heating or movement of device, device malfunction, and damage of tissue surrounding the device.

There may or may not be specific benefit to participants. Generally, the research team hope that individuals may benefit by improving their walking ability and performance, but this is not known at this point. Other people (in the future) may benefit from this study as it will provide information on the benefits of music-based walking therapy for improving walking among people with Parkinson disease.

Participants will be paid, via check, for their participation. Participants can receive up to $400 for completing the entire study which will be pro-rated if they do not complete all study visits. The pro-rated payment schedule includes $50 for the first pre-testing visit and $125 for the second pre-testing visit (the first MRI). There is an additional $50 for the first, post-testing visit and $125 for the second post-testing visit (the second MRI). The participants will receive $50 for finishing the follow-up surveys. If they do not complete all the study visits they will be paid for those they do complete. Completing the first MRI visit is required prior to starting the music-based walking program.

VI. STATISICAL ANALYSES

Aim 1: Compare the effects of training using external musical cues vs. self-generated singing cues on movement performance in people with PD.

Gait speed will improve (i.e., increase) similarly with both forms of training.

- Repeated measures analysis (RM ANOVA, alpha = .05) to compare average gait speed across time (pre- vs post-) between both training groups (mental singing vs music training).

Temporal stability in gait, measured with stride time variability, will improve more (i.e., decrease) with mental singing training than with music training.

- Repeated measures analysis (RM ANOVA, alpha = .05) to compare stride time variability across time (pre- vs post-) between both training groups (mental singing vs music training).

Temporal stability in tapping, measured with inter-tap interval variability, will improve more (i.e., decrease) with mental singing training than with music training.

- Repeated measures analysis (RM ANOVA, alpha = .05) to compare inter-tap interval variability across time (pre- vs post-) between both training groups (mental singing vs music training).

Aim 2: Compare the effects of training using external musical cues vs. self-generated singing cues on movement performance in people with PD.

Following training, the music group will show increased activation in auditory cortex whereas the mental singing group will show increased activation of the putamen and cerebellum relative to baseline.

- Repeated measures analysis (RM ANOVA, alpha = .05) to compare activation in the auditory cortex across time (pre- vs post-) between both training groups (mental singing vs music training).
- Repeated measures analysis (RM ANOVA, alpha = .05) to compare activation in the putamen across time (pre- vs post-) between both training groups (mental singing vs music training).
- Repeated measures analysis (RM ANOVA, alpha = .05) to compare activation in the cerebellum across time (pre- vs post-) between both training groups (mental singing vs music training).

Changes in inter-tap interval variability will be related to changes in putamen activation.

- We will determine correlations between changes of inter-tap interval variability and changes in putamen activation in both groups (alpha = .05).

Aim 3: Compare the acceptability and usability of training using external musical cues vs. self-generated singing cues in people with PD.

Both music and mental singing training will be acceptable to participants; usability will be higher for singing.

- Program satisfaction as a minimum average rating of >1.5 on the Client Satisfaction Questionnaire (CSQ) questions 1-6.
- Program Acceptability as a minimum average rating of >1.5 on the Client Acceptability Questionnaire (SAQ) question 1 & 2
- Program Usability as a minimum average rating of >1.5 on the Client Usability Questionnaire (SUQ) questions 1-3

Feasibility Objectives

- Demonstrate that cueing with music and with mental singing can be delivered consistently in a group setting as defined by 75% of participants attending at least 75% of training sessions
- Demonstrate acceptable adherence to the intervention as defined by 75% of participants completing at least two out of three weekly home training assignments
- Demonstrate the safety and tolerability of music and mental singing to facilitate movement in the study, as defined by less than 20% of participants experiencing an adverse event related to the intervention
- Demonstrate the ability to recruit and retain subjects in the clinical study by being within 25% of our target accrual rate and having 70% of participants who initiate the study complete the full training protocol.

POWER

Aim 1: Gait velocity is our primary variable. Data from our pilot data show that cues increase gait speed significantly with an effect size of .80 for music and .72 for mental singing. Our secondary variable of stride time variability had an effect size of .78 for music and .83 for mental singing. Our secondary variable of inter-tap interval variability had an effect size of .79 for music and .96 for mental singing. Given these effect sizes, we powered Aim 1 to detect an effect size of .7 (Cohen's d) in a RM ANOVA with 2 groups (music vs. mental) and three outcomes (gait velocity, stride time variability and inter-tap interval variability). At total sample size of 37 would be needed to detect an effect size of .7 for the within factor main effect, at 80% power, correlation among repeated measures

of .30, and alpha = .017 (to account for three outcomes). To account for 20% attrition a total sample size of 41 is needed for Aim 1.

Aim 2: We powered this neuroimaging aim to detect a moderate effect size (Cohen's d = .5) in a RM ANOVA with 2 groups (music vs mental) and three outcomes (changes in auditory, putamen, cerebellum). A total sample size of 62 would be needed to detect a moderate effect size for the within factor main effect, at 80% power, correlation among repeated measures of .30, and alpha = .017 (to account for the three outcomes). To account for 20% attrition, we will recruit an additional 12 participants for a total sample size of 74 needed for Aim 2.

VII. MONITORING & STORAGE OF DATA FOR FUTURE USE

The data safety and monitoring plan includes recording all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious adverse events) or 30 days (for serious adverse events) after the last day of study participation. Unanticipated problems that are serious adverse events will be reported to the IRB, Independent Safety Monitors, and NCCIH within 7 days of the investigator being aware of the event. Any other unanticipated problem will be reported to the same entities within 14 days of the investigator becoming aware of the problem.

Study progress and safety will be checked monthly for accuracy, compliance, and completeness by the senior scientist and concerns will be discussed with the PI.

An independent monitoring committee (DSMB) not associated with the research project will receive reports semi-annually regarding progress, recruitment, retention/attrition, and adverse events. An annual report will also be compiled that will include a list and summary of adverse events and this will be sent to the Independent Monitors and forwarded to the IRB and NCCIH.

All data recorded in hard form will be stored in the laboratory in a manner compliant with all HIPAA requirements. All paper forms will be labeled with study visit data and study participant ID. All records will be kept in a secured laboratory that is locked when research team members are not present. Electronic records will be referenced by coded numbers in our databases, stored on password-protected computers in a locked office and/or on secure networks in full compliance with HIPAA guidelines for security of protected health information. Identifiable data will be destroyed when the project is closed.

The data we collect in this study may be made available for studies ongoing or for studies in the future. These studies are not limited to the researchers at Washington University, but also other research centers and institutions, or potentially private companies involved in research. Data may be shared with large data repositories for

use by others. In accordance with protecting information, all names and other identifying information will be removed before sharing. All reasonable precautions will be taken to protect participants' privacy and confidentiality. Necessary approvals will be obtained to use the data.

Participants will be provided with the option to not allow their data to be shared for other research studies. Participants who elect to not share their data will still be allowed to participant. For those participants electing to allow for future use of their data, they may change their mind at any time by contacting the research team.

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