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WASHINGTON UNIVERSITY IN ST. LOUIS
Interdisciplinary Program in Movement Science

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Singing as a Therapeutic Technique to Improve Gait for People with Parkinson Disease

by

Elinor Clare Harrison

A dissertation presented to
The Graduate School
of Washington University in
partial fulfillment of the
requirements for the degree
of Doctor of Philosophy

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List of Abbreviations

PD: Parkinson disease

OC: Healthy older adult control

YC: Healthy younger adult control

MDS-UPDRS-III: Movement Disorders Society Unified Parkinson Disease Rating Scale, motor subsection

UNCUED: Uncued condition

MUS: Music only condition

MUS+SING: Music and singing condition

SING: Singing only condition

IMAG: Imagined singing condition

DT: Verbal dual-task condition

MMSE: Mini Mental Status Examination

BQMI: Betts' Questionnaire Upon Mental Imagery

NFOG-Q: New Freezing of Gait Questionnaire

LEDD: Levodopa Equivalent Daily Dose

CV: coefficient of variation

GV: gait variability

GA: gait asymmetry

FOG: freezing of gait

FOG+: freezers, or people with PD who exhibit FOG

FOG-: non-freezers, or people with PD who do not exhibit FOG

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Elinor Harrison

Washington University in St. Louis

December 2018

Dedicated to Paul, Thomas, Marion, Peter, Mom and Dad.

Abstract of the Dissertation

Singing as a Therapeutic Technique to
Improve Gait for People with Parkinson Disease

by

Elinor Clare Harrison

Doctor of Philosophy in Movement Science

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Professor Gammon Earhart, Chair

Gait impairment is common in older adults and even more prevalent for people with Parkinson disease (PD). Gait dysfunction is often characterized by reductions in speed, step frequency, and step length. In addition, decreased ability to regulate step length and step frequency may contribute to increased gait variability, making walking less stable and increasing risk for falls. As gait deficits are often resistant to drug therapy, there is a need to find alternative therapies that improve mobility. Rhythmic cueing in the form of listening to music is effective at enhancing walking for people with PD, helping people lengthen strides and increase velocity. However, research on rhythmic facilitation of movement has been limited to external cues and it is unknown if self-generated rhythmic cues, such as singing, may provide the same or greater benefit. This projects described in this dissertation are among the first to examine the effects of singing on walking and may reveal a novel, low-cost, non-invasive, accessible and adaptable therapeutic technique to normalize gait in PD.

In order to study the effects of internal cues on movement patterns in PD, we conducted four experiments (chapters 2-5). In the first experiment (chapter 2), we tested the feasibility of singing as a cueing technique by comparing it to traditional external cueing and to dual-task walking. We showed that while a dual task slowed and destabilized gait, singing while walking did not have this detrimental effect. In fact, singing did not negatively affect velocity, cadence, or stride length, and it positively impacted measures of gait variability. These results indicated that singing is not only feasible for people with PD but that it may hold potential to improve gait stability.

Buoyed by the results of our pilot study, we then set out to examine how best to administer singing as a therapeutic technique to elicit the most benefit for people with PD. In experiment two (chapter 3), we assessed the differential effects of internal and external cueing techniques on basic walking as well as more challenging gait situations. We tested both forward walking, commonly considered an automatic motor pattern, and backward walking, which tends to reveal more pronounced gait impairment and is related to fall risk. We included people with PD and a healthy control group to provide additional insight into how the role of beat impairment in PD may differentially affect task performance. Our results showed that internal cueing was associated with improvements in gait velocity, cadence, and stride length in the backward direction, and reduced variability in both forward and backward walking. In contrast, external cues minimally benefitted gait characteristics and detrimentally affected gait variability. We also confirmed that people with PD may exhibit greater improvement than their healthy counterparts, particularly in more challenging gait situations such as backward walking.

In experiment three (chapter 4), we investigated how different cue rates might alter responses in healthy controls and people with PD. In order to test this, we assessed cued walking conditions at

tempos above, at, and below preferred gait cadence. We also added a second internal cueing condition of mental singing, in which participants sang in their heads, to determine if it could elicit the same benefits as singing aloud. The results indicated that mental singing was more effective than overt singing at eliciting gait improvement, which renders this technique more practical for everyday use. When done at rates of 10% above preferred cadence, mental singing allowed people to increase velocity while simultaneously reducing variability and gait asymmetry.

In our final experiment (chapter 5), we sought to compare the same cued conditions using motion capture technology in order to determine if rhythmic cues can improve movement quality as well as spatiotemporal gait features. In our assessment of lower extremity sagittal plane joint angles, we showed that cues may combat downregulation of movement amplitude by increasing range of motion at all lower limb joints. These increases in movement amplitude may be associated with longer strides and reduced stride-to-stride variability. We were able to distinguish some key features that may predict likelihood of responding positively to internal cueing techniques, such as freezing status, fall history, and prior musical experience. The results indicate that internal cues may benefit a range of people with PD, even those at risk of more debilitating gait impairments such as falling or freezing of gait, and that those with prior musical experience are most likely to respond.

Taken together, these results provide compelling evidence that internal cues are a promising therapeutic technique that may transform gait rehabilitation for older adults as well as people with PD. The experiments detailed herein contribute to a burgeoning field of literature concerning rhythm processing and are among the first to examine singing as a cueing technique for people with PD.

Chapter 1: Introduction

1.1 Parkinson Disease

Parkinson disease (PD) is the second most common neurodegenerative disorder in the United States affecting 1% of the population over the age of 65¹. Diagnosed prevalence exceeds one million Americans and is expected to reach 9.3 million worldwide by the year 2030². The significant social and economic burden of PD was estimated at over \$14 billion in 2010, or \$22,800 per patient per year¹, and will continue to escalate as the elderly population grows over the next few decades.

The neuropathological underpinnings of PD involve formation of α -synuclein-containing Lewy bodies and loss of dopaminergic neurons in the substantia nigra pars compacta, spreading to cortical regions as the disease progresses³. Dopaminergic depletion in PD disrupts the corticostriatal balance and leads to excessive inhibitory output from the basal ganglia and significant motor dysfunction⁴. Motor symptoms typically manifest after 30% loss of nigral dopaminergic neurons and are clinically represented by four cardinal signs: tremor, rigidity, bradykinesia, and postural instability⁵. Motor impairments in PD restrict functional independence and are a major cause of morbidity and mortality⁶⁻⁸.

As PD is a multi-system brain disease affecting various non-dopaminergic transmitter systems, concurrent non-motor, cognitive, and autonomic impairments may also develop⁹. In spite of significant interindividual heterogeneity and varied phenotypes, most people with PD experience asymmetrical onset localized to the upper extremities that eventually progresses to affect overall mobility with frequently debilitating effects on gait and balance¹⁰.

No available treatments are proven to cure or slow disease progression, so continual refinement of therapeutic techniques targeted at alleviating motor symptoms is crucial¹¹. Treatment strategies that offer to improve quality of life, functional independence, and reduce caregiver burden may have a measurable impact¹². Walking is one of the most challenging motor impairments for people with PD but also one that is highly amenable to treatment options¹³. Therefore, a common goal of rehabilitation efforts in this population is to improve locomotor function.

1.2 Gait impairment

1.2.1 Gait impairment in aging populations

Gait impairment due to aging is prevalent, affecting a third of the population over 70 years of age¹⁴, and represents a major cause of falls in the elderly¹⁵. Deteriorating walking performance may reflect diminished muscle strength, balance control, movement efficiency, and endurance¹⁶. Gait speed is an important marker of overall health, as reductions in self-selected gait speed due to aging can predict adverse events, future disability, healthcare utilization, and even mortality¹⁷. Decreased speed in older adults is often accompanied by shorter step lengths, increased step width, and prolonged double support, which are likely compensatory strategies to avoid falls and reduce the energetic cost of walking¹⁸.

1.2.2 Gait impairment in PD

Since the prevalence of PD increases with age, many people with PD may already be experiencing gait dysfunction due to aging at the time of disease diagnosis¹⁹. Gait impairment, then, may be compounded in those who also experience neurological decline. In PD, the

stereotypical short, shuffling gait is characterized by even more marked reductions in speed, step frequency, and step length, than their age-matched controls^{20,21}. Other PD-specific impairments include forward flexed posture, reduced arm swing, longer time spent in double limb support, and axial rigidity. The primary deficit to gait disturbance in PD is commonly considered to be insufficient step length generation, which is related to deficient amplitude scaling^{10,22}. Shortened strides contribute to other continuous gait disturbances such as reduced speed and increased support time, with less time spent in the swing phase of gait. In order to compensate for smaller strides, step frequency can increase leading to an abnormal stride length-cadence relationship²². Further contributing to the dysfunction is marked postural instability. While slight changes in balance are noticeable early in the disease, considerable postural instability can emerge as the disease progresses, resulting in impairments in balance and gait^{23,24}. Reduced gait speed is also a clinical marker in PD that correlates to disease severity, loss of mobility, fall risk, and mood disorder²⁵.

1.2.3 Gait variability

Though the systems that regulate gait are highly accurate and fine-tuned, natural gait fluctuations occur over time and from one stride to the next. Therefore, measurements of gait characteristics such as speed, stride length, and cadence, are inadequate to fully understand walking performance. Gait variability is a quantifiable measure of altered walking performance that is strongly indicative of overall stability. Measures of temporal gait variability, such as stride time and single support time, may provide an assay of neurodynamics²⁶ whereas measures of spatial variability, such as stride length, may reflect variability in amplitude scaling and force production²⁷. Both temporal and spatial measures of variability are associated with functional

status and clinical outcomes and are highly predictive of falls in the elderly²⁸ and people with PD⁷.

Numerous factors can influence gait variability, including neural control, muscle function, postural control, cardiovascular alterations, and mental health. In healthy older adults, multiple physiological changes may compound to increase “neuromotor noise” and, in turn, stride-to-stride variability²⁹. Healthy older adults, thus, exhibit increased gait variability independent of walking speed which may reflect diminished balance control^{30,31} and further increase the risk of falls¹⁰.

For people with PD, fluctuations between strides are even more pronounced. Multiple studies show that people with PD exhibit temporal and spatial variability up to two times higher than controls³² and that the degree of variability correlates with disease severity³³. Impaired ability to maintain a steady gait rhythm can cause decreased symmetry between sides and reduced bilateral coordination³⁴. Decreased ability to regulate step length and step frequency may contribute to increased gait variability, rendering walking less efficient and more unstable^{35,36}.

Combined, these characteristics lead to an unstable gait pattern that puts people at risk of injury. Falls occur in 40-70% of people with PD⁷. Recurrent falls are particularly disabling and may contribute to increased fear of falling, social isolation, and reduction in activity⁸. People with PD have a nine times greater risk of recurrent falls compared to their healthy counterparts³⁷ and are 3.2 times more susceptible to hip fracture³⁸. In fact, 25% of patients with PD will sustain a hip fracture within 10 years of being diagnosed³⁹, and average survival is reduced to approximately 7 years once recurrent falls are present⁴⁰. Rehabilitation programs and therapeutic interventions can provide important tools to help improve gait stability and reduce the risk of falls.

1.3 Beat impairment and gait rhythmicity in PD

The disordered gait patterns of people with PD described above are likely related to neurodegeneration of brain regions that regulate movement timing and rhythm. Basal ganglia degeneration is linked to impaired beat perception, as people with PD have difficulty discriminating beat-based rhythms⁴¹⁻⁴⁴. Beat impairment may impact movement since specific motor network regions, such as the basal ganglia, cerebellum, premotor cortex, and supplementary motor area are also responsible for rhythm processing^{45,46}. Neurodegeneration of these motor regions may disrupt the internal regulation of movement amplitude and timing in PD and lead to a loss of gait rhythmicity, or the ability to maintain a steady gait rhythm. While maintaining gait rhythmicity is an automatic and effortless process in healthy individuals, for people with PD, this may become attention-demanding and worsen during performance of unrelated secondary tasks⁴⁷. Less rhythmic gait is naturally more variable and less efficient, and may contribute to freezing of gait or falls^{48,49}.

1.4 Rhythmic auditory cueing in PD

In spite of beat impairment, people with PD are capable of using external auditory cueing to compensate for loss of internal timing mechanisms. This may be possible because sensory-motor coupling, or the ability to drive motor action by auditory information, appears to be intact in people with PD⁴⁶. Traditional auditory cueing, in which participants walk to a metronome beat or to the beat of a song, is an effective strategy to improve gait and restore gait rhythmicity^{46,50,51}. Instructing people with PD to match footfalls to external rhythms typically increases gait speed and elicits larger, more uniform steps⁵¹⁻⁵⁶. Notably, a recent meta-analysis concluded that

auditory cues are more effective at increasing velocity, cadence, and stride length than other cue types, such as visual or attentional⁵⁵.

The mechanisms by which auditory cues work are not fully understood, but one theory posits that cueing replaces the defective internal timing mechanism within the basal ganglia with an external template to which people can match their movement^{51,53,54}. The remarkable ability to time-lock movement to an external auditory pulse is known as *entrainment*. In humans, entrainment is possible across different sensory modalities, allowing information integration and facilitating complex coordination between activities⁵⁷. Matching rhythmic movement to sounds is possible via auditory-motor coupling, or the tight anatomical and functional coupling between auditory and motor cortices.

In PD, auditory-motor coupling remains possible, in spite of neurodegeneration in nearby cortical and subcortical circuits. Bypassing the areas within the brain that are affected by PD in favor of alternative unaffected pathways may reduce reliance on defective automatized basal ganglia processes and thereby enhance motor performance⁴⁶. A current popular theory supposes that enhanced activity in cerebello-thalamo-cortical circuitry during auditory cueing may compensate for malfunctioning cortico-basal ganglia circuitry^{58,59}. Increased cerebellar activations during motor tasks that are predictive⁶⁰ or coupled to external stimuli⁶¹⁻⁶³ support this theory. Alternatively, activation of brain areas involved in rhythm perception and movement may additively combine and lead to increased activation of the motor network, thereby facilitating pre-existing movement patterns by matching them to sound^{48,49}.

1.5 Limitations of external auditory cueing

While external auditory cueing through music is widely established as an effective tool to improve gait in PD, it has noteworthy limitations. One is that the benefits do not persist without the presence of a cue^{64,65} and the need for an external device to provide constant stimulation reduces accessibility in everyday situations. Another is that individuals do not all respond the same to external cues, and we do not know how much beat impairment or other factors may contribute to these differential effects^{41,66}. Furthermore, most external cues are set at a fixed tempo, whereas adaptive cueing techniques that synchronize to an individual's walking speed are more effective⁶⁷⁻⁷⁰. These limitations may explain why people with PD do not report using external cues as a strategy to improve gait⁷¹ and support the need to explore alternative cueing techniques.

1.6 Singing in PD

Using one's own voice presents one such alternative that has thus far been unexplored. This is surprising given the abundant rationale for testing such a technique. Studies of singing in aging and neurological conditions show far-ranging benefits including improved physiology, reduced pain thresholds, and increased social bonding⁷². Singing also causes endorphin release and has positive effects on cognition and mood in patient populations⁷³⁻⁷⁶. Such benefits can take effect quickly as enhancements are seen immediately after group singing of either familiar and unfamiliar songs⁷⁷. In PD, group singing can improve mood, quality of life, and emotional wellbeing^{73,77}. Participation in performing arts also provides psychosocial benefits that may counteract social isolation and reduced activity levels, common in PD^{78,79}. Considering the high

prevalence of neuropsychiatric disturbances in PD--with about 35% of patients experiencing depression⁸⁰ that correlates to cognitive impairment and quality of life⁸¹--such improvements are not to be taken lightly.

Evidence also suggests that benefits of singing may extend beyond speech to improvements in motor control⁷⁸. Self-generated vocal cues enhance upper extremity movement in people with PD, resulting in faster and smoother reaching movements⁸². Vocalizations may enhance lower body movement as well, as people with PD report using singing to aid with gait initiation and maintenance, particularly in challenging gait situations⁸³. Motor benefits conferred by active music-making (such as singing) rather than passive music listening may be related to movement “vigor” or eagerness to move⁷⁶. While synchronizing movement to music may induce an arousal effect that makes movement faster, larger, and more vigorous⁸⁴ and may lead to greater motor network activation⁸⁵, it is possible that synchronizing movement to one’s own voice may elicit an even stronger motor response.

For people with PD, singing may be a particularly promising technique because it is uniquely accessible. While an estimated 80% of people with PD will develop voice and speech problems at some point⁸⁶, singing ability may be retained much longer. In a study using blind raters to assess vocal function, raters could distinguish between controls and people with PD during speaking but not singing tasks⁸³. Thus, individuals with PD who exhibit speech dysprosody show no decrements in singing prosody⁸³. This accounts for the common use of singing in this population to target hypophonia, or vocal softness, a common PD symptom. Previous reports show that singing elicits improvements in speech intelligibility, vocal intensity, and respiratory function^{87,88}.

Given the abundant rationale for utilizing singing as a therapeutic tool to aid gait in PD and the inherent deterrents of external auditory cues, in **Aim 1**, we sought to test singing as compared to more traditional cueing techniques such as listening to music. In order to capture gait improvement in PD, we assessed primary outcome measures of gait velocity, cadence, and stride length, as well as secondary measures of gait variability, including step time, single support time, and step length.

1.7 Dual task paradigms

In **Aim 1**, we also compared singing to a verbal dual task paradigm, known to cause gait decrement. Dual task (DT) walking paradigms are commonly used as an assay of motor automaticity. Automaticity refers to the ability to perform movements without directing attention to the details. Automatic activities such as gait require minimal cognitive resources and are resistant to interference. This accounts for our ability to walk and talk on a cell phone without falling over. This activity, though automatic for healthy adults, can require significant attentional and cognitive resources for people with PD. Under dual task conditions, the secondary task consumes available resources, resulting in degradation of primary task performance. An alternative theory suggests that these detrimental dual task effects on gait are actually due to faulty task prioritization in PD^{89,90}. This suggests that healthy adults, when required to perform a cognitive task while walking, tend to increase attention allocation to gait in order to maintain upright balance, whereas people with PD divide attentional resources equally between tasks, thereby degrading performance of both⁴⁷.

The neural correlates of automaticity support the idea that automatic activities require fewer cognitive resources. Decreased activity in frontal, parietal, premotor, supplementary motor, and cerebellar areas during automatic tasks suggests more efficient processing requiring fewer attentional resources^{91,92}. Increased connectivity between motor areas such as the cingulate motor area, supplementary motor areas, putamen, and cerebellum, may reflect enhanced synaptic strength during the automatic process⁹³⁻⁹⁶.

Impaired automaticity in PD implicates dopaminergic degeneration in the basal ganglia, which likely impairs cognitive, as well as motor, circuits. Impaired executive function in PD is associated with degenerated circuits projecting to the dorsolateral prefrontal cortex, an area known to be involved in attentional set shifting ability^{97,98} and response inhibition and conflict resolution⁹⁹. Increased cortical activity during balance and gait tasks for people with PD suggest that more cognitive resources are required to compensate for deficient automatic motor control^{100,101}. Dopaminergic involvement is also confirmed by improvement in dual task conditions in patients on medication¹⁰².

Gait impairments in PD are exacerbated under DT conditions that require concurrent motor and cognitive skills. Negative effects on balance, gait, and other functional activities are well known⁹⁰. Reductions in velocity, stride length, and cadence are commonly reported¹⁰³⁻¹⁰⁵, as are detrimental effects on variability, symmetry, and rhythmicity^{103,106-108}. Auditory cues can improve dual task gait characteristics, implying that cues can reduce the attentional demands of walking and free up cognitive resources to devote to secondary task performance^{47,109}.

Given the correlation between basal ganglia degeneration and impaired automaticity, as well as known detrimental effects of secondary tasks on PD gait, we compared auditory cueing

techniques to typical dual task paradigms in **Aim 1**. The goal of this comparison was to determine if cueing would divide attentional resources, reflected in gait decrement, in the same way that a dual task condition would, or if cueing would facilitate attentional reallocation, reflected in gait improvement.

1.8 Backward walking

Whereas forward walking addresses automatic locomotor circuits, backward walking represents a more complex gait scenario that may pose particular risks for people with PD. Backward walking is characterized by slower velocity, a wider base of support, decreased cadence, shorter stride lengths, and substantial increases in variability¹¹⁰. This gait pattern is more pronounced for the elderly¹¹¹ and especially problematic for people with PD. Furthermore, moving in the backward direction is a common cause of falls and injury^{23,111,112}.

Previous reports showed that both healthy adults and people with PD reduce velocity and stride length during backward walking^{111,113}. These differences in backward as compared to forward walking are particularly pronounced in people with PD, regardless of medication status, and reflect diminished balance control and propensity to fall when perturbed in the backward direction¹¹⁴. Detrimental effects of dual-task conditions reflect the especially challenging nature of backward walking which is more negatively impacted by a secondary task than is forward walking^{111,115}. Therefore, in **Aim 2**, we addressed both forward and backward walking to determine if rhythmic cues had the same effect on more challenging, complex gait situations and those that are more automatic. We used a similar protocol to compare the effects of singing aloud and listening to music.

1.9 Optimal cue rate

Previous PD research suggests that changing cue tempo to a percentage above or below preferred cue rate can elicit greater improvements in gait velocity and stride length than cueing at preferred cadence; however, these findings are not consistent and the effects of tempo changes on gait variability are less well known and similarly mixed. Increasing cue rate to up to 125% of preferred walking cadence may elicit substantial improvements in gait velocity, cadence, and stride length^{51,116–118} while also improving variability of stride time and swing time⁵³. Decreasing cue rate, on the other hand, may be better suited to increasing stride length¹¹⁹ but may worsen step length variability¹²⁰ and stride time variability^{121,122}. This suggests that using slower cue rates to improve stride length may come at the expense of increasing gait variability. As both slow walking and increased variability are independently related to gait instability, slow gait speed may induce a qualitative change in gait control that degrades stability¹²³. Previous reports also indicate that patients respond differently to different cue rates¹¹⁹. More work is required to determine optimal rate of cueing based on what gait parameters are targeted and taking into account individual patient characteristics.

Therefore, in **Aim 3**, we explored the effects of auditory cues at tempos faster and slower than preferred cadence. We used cues of 10% above or below preferred, as these tempos have shown the most frequent benefit in studies of external cueing^{53,124}.

1.10 Mental singing

A potential criticism of singing aloud as a therapeutic technique to improve gait is that it may be embarrassing in public settings and not practical for all participants. One prior study of mental,

covert singing showed improvements in motor timing^{85,125}, but precise gait characteristics have not been measured using this technique. While this suggests that people with PD might be able to utilize covert singing as effectively as overt singing for gait entrainment, such a leap requires considering the mechanistic overlaps between auditory perception, auditory imagery, and imagined song production.

Neuropsychological studies suggest a mechanistic overlap between auditory perception and auditory imagery. Musical imagery recruits auditory cortical areas, primarily A2, even in the absence of sound¹²⁶, and cerebral blood flow increases have been recorded in the superior and middle temporal gyri¹²⁷. Hemodynamic response functions of perceived and imagined sounds overlap¹²⁸ as do alpha band response profiles¹²⁹.

Auditory imagery and perception also share an ability to engage the motor network, accounting for their shared ability to influence movement. Neuroimaging studies suggest that moving to imagined music engages the same areas of the motor network as moving to perceived music, though to differing degrees^{85,130}. This is obvious to anyone who has ever caught herself tapping to a beat when a song gets stuck in her head. Synchronization studies have shown that tapping along to imagined music improves timing accuracy of perceived rhythms^{85,131}, which may reflect the proposed benefit of mental imagery in generating anticipatory images that enable temporal precision and movement economy¹³².

Mental singing, however, goes a step beyond musical imagery to a more explicit imagining of action involving both auditory and kinesthetic forms of imagery. In the last two years, surging interest in cross-pollination between neuroscientists and artists have resulted in famous singers such as Renee Fleming and Sting undergoing fMRI scans while singing both overtly and

covertly. The results of these scans confirm that music perception and imagined vocal *production* recruit similar neural substrates and activate similar clusters of brain regions^{133,134}.

Taken together, this evidence suggests that imagined singing may activate the same processes involved in auditory perception and may facilitate sensorimotor synchronization in gait in the same way that it does in the upper extremity. Thus, in **Aim 3**, we broadened our conditions to include mental singing, in order to determine if producing sound was necessary to benefit from internal cueing techniques. This condition was also included to increase acceptability among a broader range of people.

1.11 Gait kinematics in PD

Surprisingly few studies to date report how spatiotemporal gait deficits in PD relate to movement quality as assessed by gait kinematics. Of those that do, the over-arching conclusions reveal that reduced spatiotemporal parameters correspond to reductions in lower limb joint movement relative to controls, further confirming PD as a central amplitude regulation disorder^{20,135}.

Distinctive kinematic features include flat foot contact, reduced hip extension in stance, knee flexion in swing, and plantarflexion at toe-off¹³⁶⁻¹³⁸. Sagittal plane gait kinematics are important because they predict kinetic features as well. Thus, the impact of reduced movement amplitude in PD occurs in conjunction with kinetic gait abnormalities, as people with PD exhibit reduced vertical force production during both push-off at the ankle and pull-off at the hip^{139,140}.

Reduced joint excursions persist in spite of anti-Parkinsonian medication^{21,140} but can be improved through subthalamic nucleus stimulation¹⁴¹ as well as cueing techniques. Visual¹⁴²,

auditory^{117,143}, and attentional cues¹⁴⁴ elicited improvements in PD biomechanics by increasing movement amplitudes at different points throughout the gait cycle. In order to shed light on the biomechanics underlying spatiotemporal gait changes observed in our previous three Aims, in **Aim 4**, we explored the effect of cues on gait kinematics in PD.

1.12 Freezing of Gait

Aside from the previously mentioned continuous gait disturbances in PD, freezing of gait (FOG) is an episodic gait disturbance affecting about half of people with PD. FOG has been defined as a “brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk”¹⁴⁵. Commonly described by patients as “the sensation of your feet being glued to the floor”, FOG is particularly incapacitating and can significantly affect activity level¹⁴⁶ and quality of life¹⁴⁷. These short cessations of gait are more prevalent in advanced stages of the disease and are commonly provoked during gait initiation, turning, and passing through doorways¹⁴⁷. As FOG is highly unpredictable and develops independently of the other cardinal symptoms of PD¹⁴⁸, its etiology remains a mystery¹⁴⁹.

However, people who experience FOG, or “freezers” (hereafter, FOG+), do show abnormalities in gait patterns that manifest outside of transitory freezing episodes and that may contribute to likelihood of experiencing FOG. Decreased stride length¹⁵⁰, increased step time variability¹⁵¹ and increased cadence during turns¹⁵², for instance, all correlate to greater incidence of FOG. Such correlations between FOG and gait dysfunction fit into a conceptual model of FOG suggesting that multiple seemingly independent gait impairments may interact simultaneously¹⁵³. When these combined impairments cross a critical threshold of gait deterioration, a FOG episode is

triggered. This theoretical framework would imply that improving independent elements of gait could potentially reduce the likelihood of crossing this threshold and therefore reduce risk of FOG.

An alternative theory proposes FOG as a deficit in automaticity, suggesting that freezers exhibit malfunctioning of frontostriatal circuitry causing a breakdown in automatic motor patterns to a greater extent than non-freezers¹⁵⁴. According to this theory, FOG episodes may be more likely to occur when attention is allocated elsewhere and there is increased reliance on the BG to control rhythmic movement. This theory also implies that cueing might be beneficial to people with FOG as they may help restore gait automaticity and rhythmicity^{119,155}.

In **Aim 4**, we explored differences between freezers and non-freezers to see if response to cues differed between these two subtypes of PD.

1.13 Rationale for studies

Overall, the proposed work will contribute to a burgeoning field of literature concerning beat impairment in PD, potentially shedding light on rhythmic and motor processing in healthy and diseased populations that underlie the use of auditory cueing. Our research may also provide people with gait dysfunction due to aging or neurological decline with a novel form of cueing to improve gait through the use of internally-generated cueing in the form of singing or imagined singing.

In **Aim 1**, we compared gait during singing, singing to music, listening to music, and dual-tasking, measuring basic gait features of velocity, cadence, stride length, and gait variability. We

assessed each cueing technique relative to uncued walking to determine differential effects of cue type relative to baseline. We expected that singing may provide similar benefit to gait velocity and cadence as listening to music and that it would not cause gait detriment as a verbal dual-task condition does.

In **Aim 2**, we compared gait while singing versus listening to music in forward and backward walking to assess the effects of cueing techniques on both automatic walking and more challenging gait situations. A healthy control group was tested to provide additional insight into the role of beat impairment in PD and how it may differentially affect task performance. We expected that people with PD would gain more benefit than their healthy counterparts.

In **Aim 3**, we compared internal and external cueing techniques at tempos faster and slower than preferred pace in order to learn how to optimize this tool for people with PD. Comparisons of velocity, cadence, stride length, and gait variability extend past research showing more extreme gait improvements at different tempos as compared to preferred-pace cueing. We expected increased cue tempos to elicit the most positive response. We also added a condition of mental singing, or singing in one's head, to increase acceptability and effectiveness in everyday life. We expected mental singing to provide similar benefits to singing aloud.

In **Aim 4**, we explored the effects of singing, mental singing, and listening to music, on movement quality as assessed by two-dimensional (2-D) kinematic analysis. We hoped that this different methodology might capture more qualitative aspects of walking performance and give us deeper understanding of how the internal cueing techniques affect joint motion. We expected that sagittal-plane gait kinematics would improve via cueing and that internal cueing would show greater changes in angle excursions and range of motion than external cueing.

1.14 Specific Aims

AIM 1: Determine the effects of singing, compared to traditional cueing and dual-tasking, on forward walking in people with PD.

Hypothesis 1: Singing while walking will be as effective as traditional cueing for improving gait velocity, cadence, and stride length in people with PD. In contrast, a verbal dual-task will reduce gait velocity and increase gait variability.

AIM 2: Determine the effects of singing vs. listening to music on forward and backward walking in people with and without PD.

Hypothesis 2: Singing will be more effective than listening to music at improving both forward and backward gait. Gait will improve more in people with PD while singing aloud compared to controls.

AIM 3: Determine the effects of mental singing and cue tempo on forward walking for people with and without PD.

Hypothesis 3: Increasing cue tempo to 110% of preferred cadence will increase velocity and cadence and reduce stride length and variability relative to cueing at preferred cadence. In contrast, decreasing cue tempo to 90% of preferred cadence will decrease velocity and cadence and increase stride length and variability relative to cueing at preferred cadence. Mental singing will be as effective as singing aloud at improving gait characteristics.

AIM 4: Determine the effects of singing and imagined singing on 2D gait kinematics in people with PD.

Hypothesis 4: In people with PD, ankle, knee, and hip joint angle ROM in the sagittal plane will increase during cued gait, and these increases will be greater with singing and imagined singing versus listening to music.

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Chapter 2: The feasibility of singing to improve gait in Parkinson disease

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2.1 Abstract

Brain regions important for controlling movement are also responsible for rhythmic processing.

In Parkinson disease (PD), defective internal timing within the brain has been linked to impaired beat discrimination, and may contribute to a loss of ability to maintain a steady gait rhythm. Less rhythmic gait is inherently less efficient, and this may lead to gait impairment including reduced speed, cadence, and stride length, as well as increased variability. While external rhythmic auditory stimulation (e.g. a metronome beat) is well-established as an effective tool to stabilize gait in PD, little is known about whether self-generated cues such as singing have the same beneficial effect on gait in PD. Thus, we compared gait patterns of 23 people with mild to moderate PD under five cued conditions: uncued, music only, singing only, singing with music, and a verbal dual-task condition. In our single-session study, singing while walking did not significantly alter velocity, cadence, or stride length, indicating that it was not excessively demanding for people with PD. In addition, walking was less variable when singing than during other cued conditions. This was further supported by the comparison between singing trials and a verbal dual-task condition. In contrast to singing, the verbal dual-task negatively affected gait performance. These findings suggest that singing holds promise as an effective cueing technique that may be as good as or better than traditional cueing techniques for improving gait among people with PD.

2.2 Introduction

In Parkinson disease (PD), basal ganglia degeneration has been linked to impaired beat processing, as people with PD have difficulty discriminating beat-based rhythms¹⁻³. This beat impairment may impact movement since brain regions involved in rhythm processing, such as

the basal ganglia, cerebellum, premotor cortex, and supplementary motor area, are also responsible for motor function⁴. Neurodegeneration in these motor regions may disrupt the internal regulation of movement amplitude and timing in PD and lead to a loss of gait rhythmicity (i.e., ability to maintain a steady gait rhythm). While maintaining gait rhythmicity is an automatic and effortless process in healthy individuals, for people with PD, this becomes attention-demanding and is particularly impaired during performance of secondary tasks⁵. Less rhythmic gait is naturally more variable and less efficient, and may contribute to freezing of gait or falls^{6,7}.

Music is well-established as an effective cueing technique to improve gait and restore gait rhythmicity^{4,8,9}. Traditional auditory cueing, in which participants walk to a metronome beat or to the beat of a song, typically increases gait speed and elicits larger, more uniform steps^{6,9-11}. This technique, however, is challenging to implement consistently outside of the clinic because it requires use of an external device and headphones. The burden of wearing this device may prevent patients from using it regularly, particularly during short walking bouts in the home where falls commonly occur. Singing, on the other hand, requires nothing but one's own voice. Additionally, most external cueing devices are set at a fixed tempo and incapable of adapting to a person's varying cadence, thereby reducing effectiveness in the real world. One's voice, in contrast, may be easily adapted to any circumstance, and may even help cue challenging gait situations such as step initiation, turning, or freezing. External cueing techniques have inconsistent carry-over effects, as the benefits of cueing are not always retained once the device is removed. Singing, however, is an active process that may cause melodies to get stuck in people's heads and therefore may have longer lasting effects. Although external cueing devices

may be effective at improving gait, they are not a perfect tool, and therefore, there is a need to find accessible and adaptive alternatives to traditional cueing techniques¹².

The purpose of our study was to determine if people with PD could generate their own cues through singing and if this novel cueing technique could improve gait in the same way that traditional cueing techniques do. Among the potential benefits of this technique are that it could be used at any time and in any place, without the need for a device to play music, and that it can be customized to match one's cadence. Past research on imagined singing suggests the potential of singing to improve gait in PD and confirms that internal generation of musical cues is possible in PD and other neurological disorders¹³⁻¹⁵. However, no studies to date directly measure the effects of singing on gait parameters that have typically shown improvement with external cueing. Therefore, we developed a single-session protocol to test feasibility of singing as a tool to improve gait. We hypothesized that singing would stabilize gait in the same way that music does. We expected that singing would be as effective as traditional cueing at improving velocity, cadence, and stride length in PD, and that it would decrease gait variability as traditional cueing does. To assess the attentional demands of singing while walking, we also included a dual-task condition known to divide resources and cause gait decrement. We predicted that this verbal dual-task would be detrimental to gait, whereas singing would not.

2.3 Methods

2.3.1. Participants

Twenty-three individuals with PD were recruited from a convenience sample of people who were participating in a separate study¹⁶ at Washington University School of Medicine (Table 2.1). Inclusion criteria were (1) a diagnosis of idiopathic PD, as determined by a board certified neurologist using diagnostic criteria for ‘definite PD’¹⁷, (2) ability to ambulate independently indoors for short distances without an assistive device, (3) absence of other neurologic disorder or dementia as measured by a minimum MMSE score of 24¹⁸, (4) absence of orthopedic injury or other comorbidity affecting gait, and (5) adequate vision and hearing (with or without a hearing aid). All participants gave informed consent to perform experimental procedures approved by the Human Research Protection Office at Washington University School of Medicine.

Table 2.1. Participant Demographics.

N (male)	23 (13)
Age	69.5 (7.6)
MDS-UPDRS-III	30.5 (11.8)
Hoehn & Yahr	II(10) II.5(10) III(3)
Years since Diagnosis	3.8 (4.2)
MMSE, median (range)	29 (24,30)

Values are standard deviations (SD) \pm SEM, except where noted.

2.3.2 Experimental Protocol

Participants were tested in the ‘on’ state (i.e., they had taken anti-Parkinson medication within the previous 2.5 hours) to maximize relevance to everyday walking conditions. Participants performed all walking trials on a 5m instrumented, computerized GAITRite Walkway (CIR

Systems, Inc., Franklin, NJ). For all trials, participants were instructed to begin walking prior to reaching the GAITRite and to continue walking once off the mat to minimize acceleration and deceleration effects. An initial trial where participants were instructed to walk at their comfortable speed was used to determine each participant's preferred cadence. This cadence was used to adjust song tempo to match each individual's comfortable pace. Although cueing is often assessed using cues set to 110% of preferred cadence, we chose to use preferred cadence for this feasibility study to simplify task demands. For these musically-cued conditions, the cue was administered in the form of an instrumental version of "Row, Row, Row Your Boat" via a laptop no further than 10 m from the participant at any time during walking. Song tempo was adjusted for each individual using Audacity (The Audacity Team, audacity.sourceforge.net/download/) open source audio editing software. The song was chosen for its familiarity, as singing a life-long familiar melody results in better consolidation and higher retention¹⁹ and because improvements in velocity and stride length have been seen in people with PD when synchronizing to a highly familiar song²⁰. The particular instrumental version was selected for its high beat saliency, which enabled participants to more easily find the beat and sing along²¹. Follow-up interviews confirmed that all participants were able to hear the music and knew the melody and lyrics.

Participants completed three walking trials in each of five conditions as described below and were instructed to begin each trial when ready. Dual-task data were collected first as this was required as part of the study protocol for the larger trial. All other conditions were randomized to eliminate any training effects.

1. **Uncued:** This condition was used to represent ‘normal’ walking and provided a point of comparison for the other conditions. Participants were asked to walk at their preferred walking speed when given the signal to go. This occurred in silence as no cueing was present. In instances where the UNCUED condition came after a condition in which music played, participants were instructed not to think of the previously heard song as they walked.
2. **Music only (MUS):** Our music-only condition represents traditional cueing techniques in which music was playing and participants were asked to walk to the beat. Once the song was turned on for each trial, participants were told to take as long as needed to listen to the song, pick out the beat and begin walking.
3. **Singing only (SING):** Participants were asked to sing aloud while walking *without* music playing. In the absence of an external cue, participants were required to internally generate and produce the music to cue their walking. Therefore, this condition represented the novel cueing technique in which we were most interested.
4. **Singing along with music (MUS+SING):** Participants were asked to walk to the beat of the music while singing along. Instructions for this condition were the same as for the MUS condition except that participants were now asked to sing aloud to the music. This condition was included to capture the potentially additive effect of listening to music while also singing.
5. **Verbal dual-task condition (DT):** This is a commonly used dual task in which participants were asked to walk at preferred speed while generating as many words as possible that began with different letters of the alphabet (H, L, T). Participants were given instructions on this task and a letter was given just before they began walking so they did not have time to think of words

in advance. At the end of the walkway, they turned around and repeated the protocol with the next letter.

Additional Measures: Disease severity was assessed by a trained physical therapist using the Movement Disorders Society Unified Parkinson's Disease Rating Scale Motor Subscale 3 (MDS-UPDRS III) and Hoehn and Yahr staging (H&Y), the New Freezing of Gait Questionnaire (nFOGq) was used to assess freezing, and the Mini-mental Status Exam (MMSE) was used to assess cognition. Beat processing impairment was assessed by the Beat Alignment Test (BAT).

2.3.3 Data Analysis

IBM SPSS Statistics 22 was used for all statistical analyses. For each participant, data were averaged across the three trials of each condition. Normalized velocity, cadence, stride length, and variabilities of step time, single support time, and stride length were compared across conditions using one-way repeated measures ANOVAs. Variabilities were calculated as the standard deviation of each trial and then averaged across trials. Comparisons between the single initial trial used to determine preferred cadence and the three uncued trials were not statistically significant, and therefore we used the average of uncued trials to represent baseline. Post-hoc pairwise comparisons were used as appropriate, and Bonferroni corrections were used to correct for multiple comparisons. Statistical significance was set at $p < 0.05$.

2.4 Results

2.4.1. Normalized velocity, cadence, and stride length

Cueing in the form of MUS, SING, or MUS+SING did not alter velocity, cadence, or stride length relative to UNCUEED (Figure 2.1). DT, however, elicited significant decreases in normalized velocity ($F(4,19)=16.418, p<.001$), cadence ($F(4,19)=7.04, p=.001$), and stride length ($F(4,19)=10.115, p<.001$) compared to all other conditions (Table 2.2).

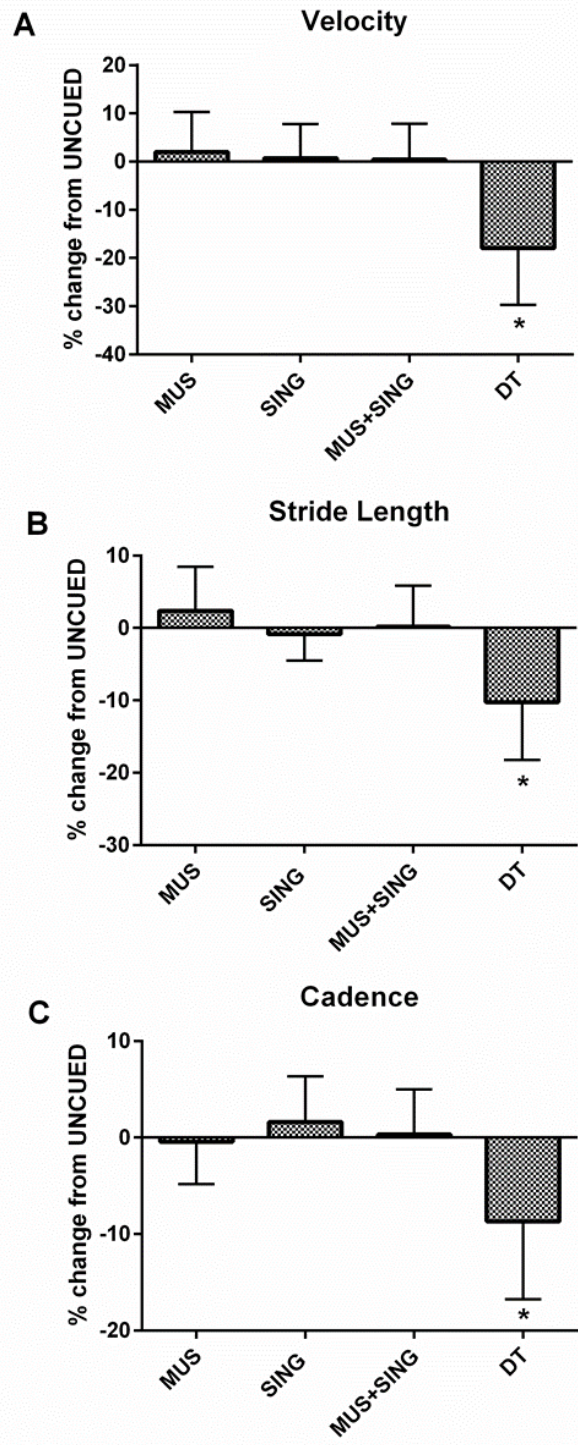


Figure 2.1. Gait characteristics across 4 conditions as percent change from UNCUEDE walking. Error bars represent \pm SEM. * denotes $p < .001$ where DT was worse than all other conditions.

Table 2.2 Measures of gait velocity, stride length, and cadence across all 5 conditions.

	UNCUED	MUS	SING	MUS+SING	DT
Velocity (<i>cm/sec</i>)	123.97 (18.99)	126.65 (23.74)	124.87 (29.92)	124.92 (24.29)	101.75 (20.77)*
Stride Length (<i>cm</i>)	131.4 (16.9)	134.7 (20.2)	130.4 (18.4)	131.9 (20.7)	118.1 (18.8)*
Cadence (<i>steps/min</i>)	113.6 (9.7)	113.1 (10.3)	115.3 (9.6)	113.9 (10.6)	104.0 (14.3)*

Values are means +/- SD. * denotes $p < .001$ where DT was worse than all other conditions.

2.4.2. Variability of step time, single support time, and step length

Variability measures revealed greater differences between cueing techniques. SING closely resembled UNCUED in that it showed minimal variability across all measures. Variability was significantly lower for SING compared to MUS+SING and DT for step time ($F(4,19)=7.172$, $p=.008$, $F(4,19)=7.172$, $p=.003$, respectively) and single support time ($F(4,19)=6.806$, $p=.031$, $F(4,19)=6.806$, $p=.004$, respectively). Step length revealed a similar but non-significant trend in which SING was less variable than other cued conditions. MUS+SING was associated with higher gait variability than all other cued conditions and this was significant for step time when compared to UNCUED ($F(4,19)=6.806$, $p=.045$) (Figure 2.2). The DT condition was the most variable of all five conditions. For step time, DT was more variable than UNCUED ($F(4,19)=7.172$, $p=.003$), MUS ($F(4,19)=7.172$, $p=.021$), and SING ($F(4,19)=7.172$, $p=.003$). For single support time, DT was more variable than UNCUED ($F(4,19)=6.806$, $p=.003$) and SING ($F(4,19)=6.806$, $p=.004$) (Table 2.3).

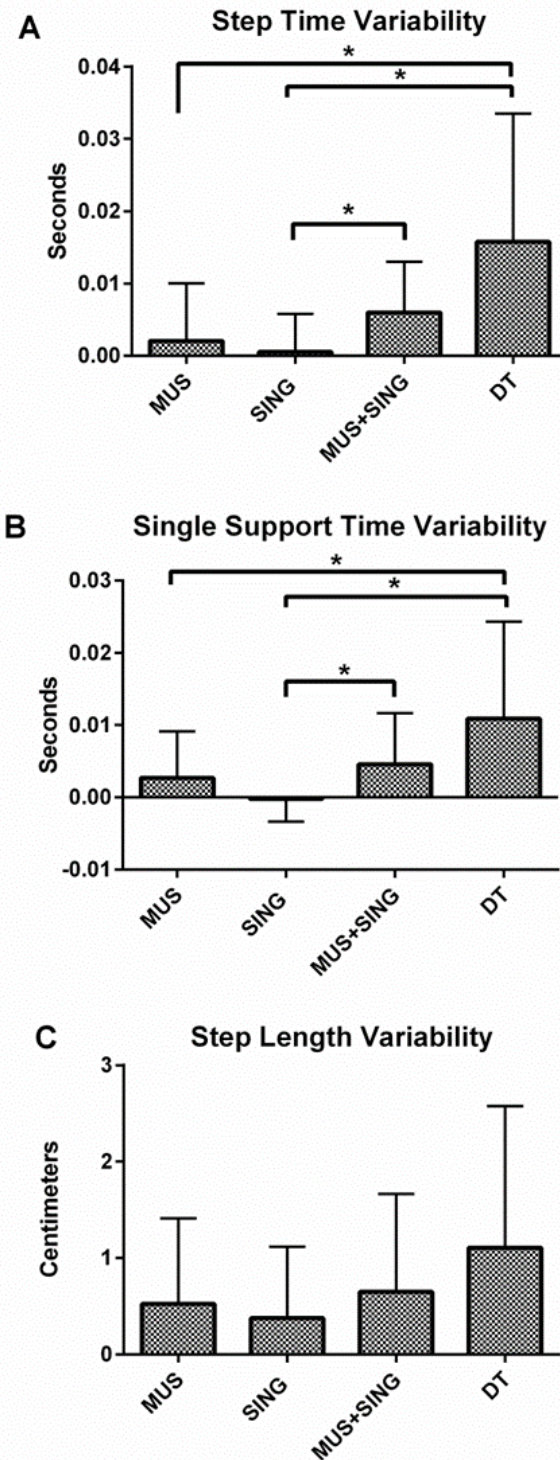


Figure 2.2. Gait variability across 4 conditions as compared to UNCUEDED walking. Data represent standard deviations \pm SEM. * denotes significance of $p < .05$.

Table 2.3. Measures of gait variability across 5 conditions.

	UNCUED	MUS	SING	MUS+SING	DT
Step time SD	0.018 (.005)*	0.020 (.008)*	0.018 (.005)*#	0.024 (.007)	.034 (.018)
Single support time SD	0.015 (.005)*	0.018 (.006)	0.015 (.003)*#	0.020 (.007)	0.026 (.013)
Step length SD	2.517 (0.548)	3.041 (0.750)	2.894 (0.953)	3.167 (1.271)	3.624 (1.130)

Values are standard deviations (SD) \pm SEM. Significance is set at $p < 0.05$. * denotes significantly better than DT. # denotes significantly better than MUS+SING.

2.5 Discussion

In this study, we explored a novel cueing technique to improve gait in PD by singing a song oneself rather than listening to a song, as in traditional cueing techniques. Our primary finding is that singing at a tempo matching comfortable gait pace may improve gait variability while not causing other gait decrements. The absence of gait decrements during singing trials indicates that singing while walking was not excessively demanding for people with PD. This was further supported by the comparison to a verbal dual-task condition which negatively affected gait performance, whereas singing did not. In addition, singing while walking produced less variability than other cueing techniques. Variability is a valuable marker of overall gait performance that reflects gait unsteadiness and dyscontrol. People with PD have increased gait variability which reflects reduced automaticity of walking²². Stride-to-stride fluctuations related to both stride time and stride width are sensitive measures that correlate more closely to fall risk than other elements of gait²³. Therefore, decreasing gait variability may be even more important than increasing gait speed or distance. Our results suggest that singing holds promise as a cueing technique that may be as beneficial as traditional cueing techniques for improving gait in PD.

Singing is already widely used as a therapeutic technique for voice rehabilitation in PD because it targets hypophonia, a common PD symptom, and elicits improvements in speech intelligibility,

vocal intensity, and respiratory function^{24,25}. However, it is not known if the benefits of singing may extend beyond speech to improvements in motor control. External auditory cueing through music is widely established as an effective tool to stabilize gait in PD^{4,9}. The musical cue may work by replacing the defective internal timing mechanism within the basal ganglia with an external template to which people can match their movement^{9,10}. By contrast, little is known about whether singing can serve the same purpose or if impaired beat processing would preclude people with PD from either creating an internal template through song or synchronizing movement to it.

We expected some of our participants would be unwilling or unable to sing aloud; however, all participants sang aloud with apparent ease. Ability to do the task was likely not attributable to musical experience, as only nine participants reported having any musical training. In addition, our participants were a subset of a larger sample that showed impaired beat processing as compared to controls²⁶, confirming past reports among people with PD²⁷. Our results support the idea that, in spite of this deficiency, people with PD can internally generate music and use it as a cue to guide movement, as was shown previously in a study in which imagined singing was used to improve motor timing in people with PD¹³.

When comparing singing trials to the verbal dual-task condition, we noted significant differences in all gait measures. Word generation created a dual-task effect that slowed and destabilized gait. This corroborated previous studies where gait impairment was exacerbated during a concurrent speaking task in people with PD^{28,29}. Dividing limited cognitive and motor resources between complex activities is known to disrupt gait automaticity and increase stride-to-stride variability⁵.

Our finding that singing did not negatively affect gait suggests that singing a rhythmic and familiar song may not divide resources in the same way as speaking.

When comparing cueing techniques, we noted that walking to music, either while listening, as in traditional cueing, or while singing along, increased variability of temporal and spatial gait parameters. These increases were not byproducts of changes in speed, cadence, or stride length, as these measures were unchanged. In the singing only condition, by contrast, no music was present so participants did not have to match their singing or footsteps to an external source. Higher variability in the musically-cued conditions may reflect the extra attentional resources required to synchronize even simple, automatic movements to sound¹⁴. Thus, participants may have had an easier time walking to the beat when they were able to generate the song themselves than when they had to synchronize to music. Another possibility is that active music-making (such as singing) may confer greater motor benefits than passive music listening³⁰ by affecting movement “vigor” or eagerness to move. While synchronizing movement to music induces an arousal effect that makes movement faster, larger, and more vigorous³¹ and can lead to greater motor network activation¹⁴, synchronizing movement to one’s own voice may elicit an even stronger motor response, or at least a more precisely timed one.

Singing may hold other benefits over external auditory cueing. Studies suggest that adaptive cues that synchronize to an individual’s walking speed are more effective than set-tempo cues, and singing, similarly, can be altered to fit any situation¹². Singing also creates a longer-lasting memory trace over spoken words, resulting in improved memory consolidation and retention³². Our participants reported that the song got “stuck in their heads”, possibly reflecting carry-over benefits and supporting the theory that singing mentally after singing aloud allows rhythm recall

and facilitates movement³³. Singing may also be useful in challenging gait situations that cause freezing, as one's voice can easily be turned on and off as needed. Six participants in our sample were identified as freezers, and some of them suggested singing might be helpful during freezing episodes. This is promising as auditory cueing has been shown to benefit freezers and non-freezers alike^{34,35}. Singing, therefore, may be feasible for a wide variety of patients in a variety of situations.

Several limitations of our study are noted. One is that our singing and dual-task paradigms were not equally demanding, as participants sang a familiar song but spoke a word-generation task that likely required higher cognitive effort. Another is that we took no explicit measures of attention, so we cannot know how division of resources differs when synchronizing movement to endogenous cues versus heard cues. Also, since we tested only one version of one song, we cannot rule out the possibility that another song, or one without lyrics, may have elicited a different response. A potential criticism of this technique is that singing aloud may not be preferred to wearing an external cueing device for people who experience gait difficulty in public settings. Therefore, future work should examine the possibility that imagined singing, or a combined training program that included both audible and mental singing, could ameliorate gait in the same way as singing aloud.

In conclusion, singing positively affected gait variability while having no detrimental effect on velocity, cadence, or stride length. Whereas traditional cueing techniques require the use of external devices that typically do not adapt to one's cadence and do not convey long-lasting benefits in their absence, singing can be easily implemented anytime, anywhere, without the need for significant training, and could therefore be translated into practice quite expeditiously.

There is a strong need for inexpensive, non-invasive, and widely accessible interventions to address gait impairments in PD. Singing holds promise as a useful alternative to traditional cueing techniques to regulate gait in PD. Further study is warranted to determine the effect of singing tempo on gait, how long the effects of singing last, and who is most likely to benefit from this novel technique.

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Chapter 3: Internal cueing improves gait more than external cueing in healthy adults and people with Parkinson disease

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3.1 Abstract

Walking can be challenging for aging individuals and people with neurological disorders such as Parkinson disease (PD). Gait impairment characterized by reduced speed and higher variability destabilizes gait and increases the risk of falls. External auditory cueing provides an effective strategy to improve gait, as matching footfalls to rhythms typically increases gait speed and elicits larger steps, but the need to synchronize to an outside source often has a detrimental effect on gait variability. Internal cueing in the form of singing may provide an alternative to conventional gait therapy. In the present study, we compare the effects of internal and external cueing techniques on forward and backward walking for both people with PD and healthy controls. Results indicate that internal cueing was associated with improvements in gait velocity, cadence, and stride length in the backward direction, and reduced variability in both forward and backward walking. In comparison, external cueing was associated with minimal improvement in gait characteristics and a decline in gait stability. People with gait impairment due to aging or neurological decline may benefit more from internal cueing techniques such as singing as compared to external cueing techniques.

3.2 Introduction

Age-related gait disorders affect a third of the population over 70 years of age¹ and cause people to walk slower with less stability. Reduced gait speed in older adults is a sensitive marker of overall health and can predict adverse events, such as falls, and future disability^{2,3}. Two-thirds of gait disorders are related to neurological decline⁴ and are exacerbated in movement disorders such as Parkinson disease (PD). PD is characterized by bradykinesia, rigidity, and postural instability, all of which contribute to walking difficulty⁵. Compared to age-matched controls, people with PD experience accelerated gait decline as evidenced by reductions in speed, step

frequency, and step length. In addition to these basic gait deficits, people with PD exhibit substantial increases in gait variability⁶ which may reflect diminished balance control⁷ and a disruption of internal timing mechanisms within the brain. Gait variability is a strong indicator of overall stability⁸⁻¹⁰, worsens with disease severity, and may lead to a loss of mobility and independence^{11,12}. When moving in the backward direction, as is common in everyday life, gait impairment is more pronounced and more likely to contribute to fall risk¹³⁻¹⁵. Hence, a major focus of gait therapy is to reduce gait variability in order to stabilize walking and reduce the risk of falls.

External auditory cueing through music is widely established as an effective tool to normalize gait disturbance¹⁶⁻¹⁸. For people with PD, matching one's footfalls to the beat of a song can restore gait to levels closer to those of healthy controls^{16,17,19,20}. Rhythmic cues allow predictable mapping of motor output onto stable auditory templates via a process called "entrainment" that enables people to anticipate the next beat and step on it. Musical cues are superior to other types of cues at increasing velocity and stride length¹⁹ though they are more effective after a period of training²¹ and for those with more severe gait impairment²².

In spite of evidence supporting the efficacy of rhythmic auditory cues for improving certain gait characteristics^{17,23-26}, recent research suggests that synchronizing footfalls to external rhythmic cues detrimentally effects gait variability²⁷. External cues require adjusting every step in order to synchronize, and this increased cognitive load may have the undesirable effect of increasing gait variability, particularly for older adults or neurological patients who are more likely to experience cognitive decline²⁸. Internal cueing through singing, on the other hand, eliminates the need to entrain to an external source. Instead, a rhythm generated and produced via the vocal system is then adopted by the locomotor system to produce rhythmic motion of the legs. This

method may allow for greater coupling between systems, potentially reducing attentional load and enhancing stability.

Singing is already used for vocal rehabilitation in PD because, in spite of speech degradation, singing ability is preserved²⁹⁻³¹. Evidence also suggests that the benefits of singing may extend beyond speech to improvements in motor control³² as singing may engage a vocal sensorimotor loop involving both perceptual and motor planning components³³. For example, self-generated vocal cues enhance upper extremity movement in people with PD, resulting in faster and smoother reaching movements³⁴. Vocalizations are also likely to enhance lower body movement, as people with PD report using singing to aid with gait initiation and maintenance, particularly during challenging gait situations such as moving backwards and turning³⁵. Despite abundant evidence supporting the use of singing to improve walking in aging and neurologic populations, previous research is mostly limited to the use of external cueing for gait rehabilitation.

In this study, we examined the effects of internal cueing, in the form of singing, versus external cueing, in the form of listening to music, on gait in people with and without PD. We addressed both forward walking, which engages automatic locomotor circuits, and backward walking, which represents a more challenging gait situation. We hypothesized that both external and internal musical cueing would improve backward walking more than forward walking in all our participants, and that internal cueing would be more effective at reducing gait variability over external cueing. We also expected to see the greatest benefit from cueing in people with PD, followed by older adults and finally younger adults.

3.3 Methods

3.3.1 Participants

A total of 90 participants, thirty (15 male) in each group (young control (YC), older control (OC), and Parkinson disease (PD)) took part in this study (Table 3.1). PD participants were recruited from the Movement Disorders Center at Washington University School of Medicine. Healthy controls were recruited via emails, social media, and flyers in and around the Washington University School of Medicine campus as well as through the Research Participant Registry through the Volunteers for Health database managed by Washington University School of Medicine. Age criteria for young controls were 18-35 whereas older controls were ≥ 50 . PD participants were ≥ 50 years of age and had a neurological diagnosis of “definite PD”, as previously described³⁶ and based upon established criteria³⁷.

Table 3.1. Participant Demographics.

	Young control (YC)	Older control (OC)	Parkinson disease (PD)
N (male)	30(15)	30(15)	30(15)
Age, yrs	25.8(\pm 2.8)	64.9(\pm 7.2)	65.8(\pm 6.5)
MDS-UPDRS-III	-	-	24.9(\pm 10.27)
MMSE, median (range)	30(28,30)	30(27,30)	29(24,30)
LEDD, mg	-	-	933(\pm 658)
Years since dx	-	-	5.77(\pm 3.79)
Musical experience, yrs	4.43(\pm 3.39)	4.42(\pm 6.02)	7.77(\pm 11.45)

Values represent mean \pm SD, except where noted. MDS-UPDRS, Movement Disorder Society Unified Parkinson Disease Rating Scale. MMSE, Mini Mental Status Examination. LEDD, Levodopa Equivalent Daily Dose.

All participants had vision corrected to 20/40 or better, were able to stand independently for at least 30 minutes, and had no evidence of dementia (MMSE \geq 26). Participants were excluded for any history of neurological deficit (aside from PD), orthostatic hypotension, or prior deep brain stimulation surgery. One participant in the OC group was excluded for cognition as evidenced by an MMSE score of below 24 and an additional participant was recruited as a replacement.

Participants provided informed consent before participating and were compensated for their time. The protocol was approved by the Human Research Protection Office at Washington University School of Medicine, and the methods were carried out in accordance with the approved guidelines. Prior to testing, participants were assessed via the following questionnaires: the New Freezing of Gait Questionnaire (nFOGq), the Fall History questionnaire, and the Betts' Questionnaire upon Mental Imagery (BQMI). The Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was used to assess disease severity. Subsections I (non-motor symptoms), II (motor aspects of daily living), and III (motor sign severity) were administered and scored by trained staff.

3.3.2. Experimental Protocol

Participants in the PD group were tested in the "on" state (i.e., they had taken their anti-Parkinson medication within the previous 2 hours) to maximize relevance to everyday walking²⁶ and to optimize gait performance³⁸. All walking trials were performed on a 5m instrumented, computerized GAITRite Walkway (CIR Systems, Inc., Franklin, NJ). Three baseline trials (UNCUED) were collected in both forward and backward walking to capture each participant's comfortable walking features. Participants then completed three walking trials in each of the conditions below in both forward and backward directions. Condition order and walking direction within each condition were randomized and counterbalanced to eliminate any training

effects. In order to control cadence across conditions, participants always heard the music immediately prior to walking.

1. MUSIC: Participants listened to one verse of the song and then began walking to the beat of the song while the song looped for the duration of the walking trial. This condition is similar to a beat-synchronization paradigm and replicates traditional external cueing techniques.

2. SING: Participants listened to one verse of the song, but then the music stopped and they began singing aloud and walking to the beat of their singing. In this condition, no external source provided a cue while they walked, so participants had to generate the cue themselves.

For all cued conditions (both MUSIC and SING), we used an instrumental version of “Row, row, row your boat” that was designed with a salient beat that participants could readily detect. All participants were familiar with the melody and lyrics and sang the song without difficulty. The musical cue was administered from a laptop connected to speakers no farther than 10 m from the participant during walking and at an audible volume. Song tempo was adjusted maintaining key consistency via Audacity open source audio editing software (The Audacity Team, audacity.sourceforge.net/) to match preferred cadence in each direction, as determined from the baseline trials. Cue rate was set to 100% of preferred cadence of each direction so as not to complicate task demands, particularly for backward walking.

Data Analysis

Statistical analyses were done using IBM SPSS Statistics 24. For each participant, data were averaged across the three trials of each condition. Gait characteristics (velocity, cadence, and stride length) and variability (coefficients of variation for stride length, stride time, and single support time) were compared in two separate analyses, one for each walking direction.

Normalized velocities were calculated as velocity/average leg length (cm/s/leg length) and coefficients of variation (CV) were calculated as the ((standard deviation/mean) x 100) for each person in each condition. As we were only interested in how cueing affected these measures, we ran analyses on each variable as it compared to the UNCUEDE condition. Hence, gait characteristics were expressed as a percent change from UNCUEDE and gait variabilities were expressed as a change in CV from UNCUEDE. Mixed model repeated measures ANOVAs with between-subject factor of group and within-subject factor of condition were used to assess differences, and Tukey-corrected post-hoc pairwise comparisons were used as appropriate. Statistical significance was set at $\alpha=.05$.

3.4 Results

3.4.1 Gait characteristics

A. Differences between conditions.

In forward walking, there was an overall effect of condition ($F(1,87)=6.978, p<.001$) with univariate tests showing a significant increase in cadence for SING versus MUSIC ($F(1,87)=15.121, p<.001$). (Figure 3.1, Table 3.2).

In backward walking, there was an overall effect of condition ($F(1,87)=8.396, p<.001$) with univariate tests showing that participants walked faster ($F(1,87)=10.868, p=.001$) with higher cadence ($F(1,87)= 22.523, p<.001$) in SING as compared to MUSIC.

B. Differences between groups.

There were no significant differences between groups in forward walking gait characteristics.

In backward walking, there was a significant between-subject effect of group for velocity ($F(2,87)=3.552$, $p=.033$) and stride length ($F(2,87)=5.744$, $p=.005$). Regardless of condition, pairwise comparisons indicated that the PD group showed a more robust response to cueing than the YC group as evidenced by their greater percent change in velocity ($p=.010$) and their greater percent change in stride length ($p=.001$). The OC group also showed a greater percent change in stride length as compared to the YC group ($p=.028$). There were no significant interactions, indicating that all groups responded similarly to cueing.

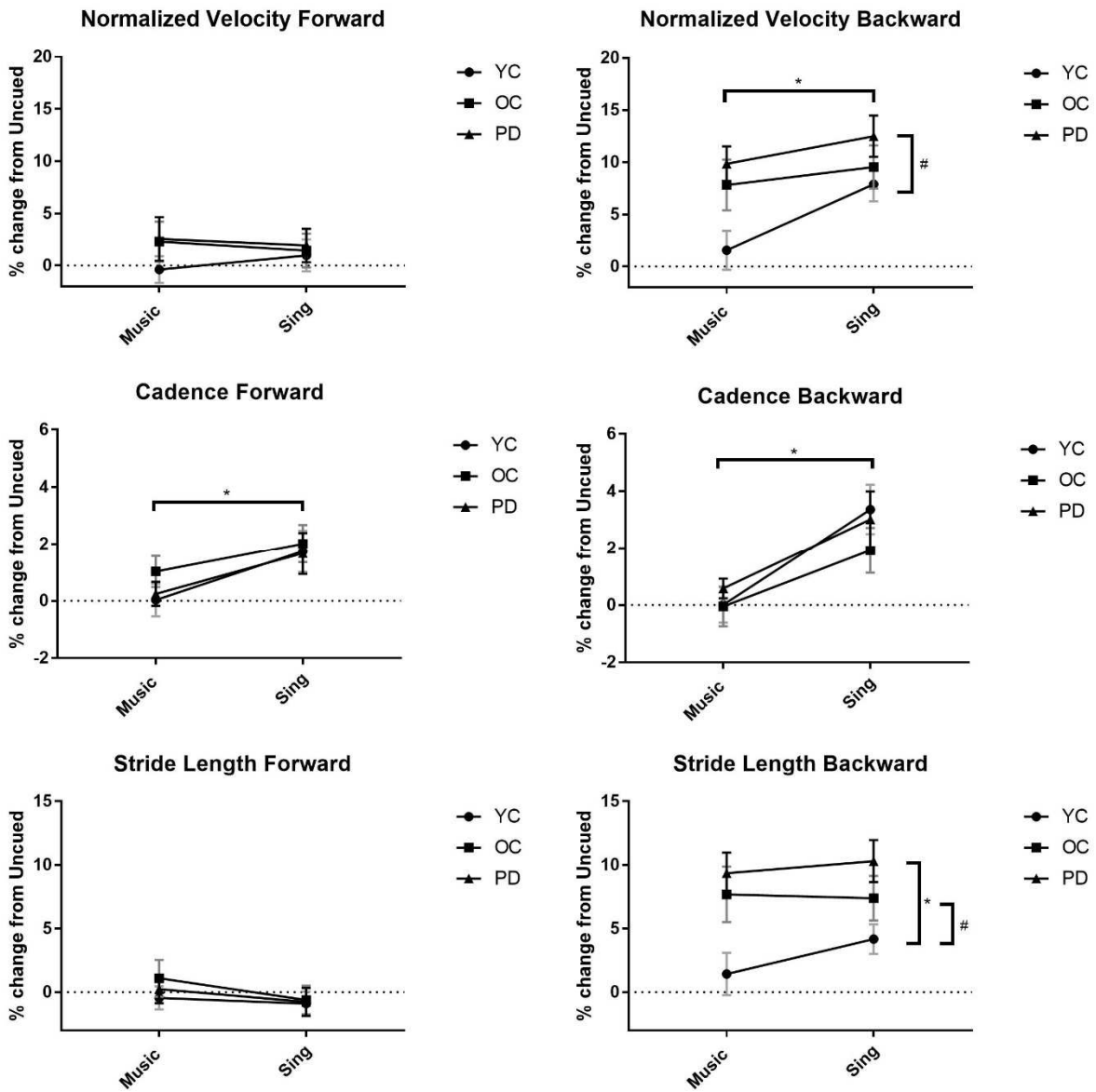


Figure 3.1. Gait characteristics shown as a percent change from Uncued walking compared across groups for forward and backward walking. All bars represent means \pm SEM. Horizontal significance bars indicate an overall effect of condition whereas vertical significance bars indicate an overall effect of group. * indicates $p < .01$. # indicates $p < .05$

	Normalized Velocity (cm/s/leg length)			Cadence (steps/min)			Stride Length (cm)			
	YC	OC	PD	YC	OC	PD	YC	OC	PD	
Forward	Uncued	1.71 (0.21)	1.66 (0.16)	1.53 (0.21)	110.58 (6.74)	112.14 (6.02)	110.90 (7.84)	149.47 (10.31)	143.51 (15.28)	134.08 (15.58)
	Music	1.70 (0.20)	1.69 (0.16)	1.56 (0.20)	110.60 (7.31)	113.28 (6.66)	111.13 (7.71)	148.58 (9.29)	144.34 (12.10)	134.16 (15.66)
	Sing	1.73 (0.22)	1.68 (0.17)	1.56 (0.26)	112.49 (7.89)	114.43 (7.62)	112.72 (8.63)	147.93 (10.16)	142.15 (13.22)	133.02 (17.23)
Backward	Uncued	1.32 (0.22)	1.17 (0.19)	0.99 (0.23)	107.29 (9.19)	110.86 (9.46)	112.30 (9.93)	118.72 (13.36)	102.77 (16.47)	83.48 (21.55)
	Music	1.33 (0.21)	1.26 (0.21)	1.07 (0.22)	107.24 (9.12)	110.72 (9.44)	112.96 (10.43)	119.83 (12.33)	109.67 (15.88)	90.45 (20.35)
	Sing	1.41 (0.21)	1.28 (0.21)	1.10 (0.22)	110.71 (8.68)	112.89 (9.54)	115.54 (10.02)	123.38 (13.14)	109.86 (17.04)	91.15 (20.90)

	Stride Length CV			Stride Time CV			Single Support Time CV			
	YC	OC	PD	YC	OC	PD	YC	OC	PD	
Forward	Uncued	1.83 (0.77)	2.18 (0.67)	2.73 (1.43)	1.73 (0.59)	2.19 (0.82)	2.24 (0.71)	2.55 (0.75)	3.19 (1.07)	3.78 (1.09)
	Music	2.77 (1.19)	2.79 (1.32)	4.07 (2.59)	2.25 (0.85)	2.32 (1.05)	2.45 (0.77)	3.43 (1.17)	3.78 (1.77)	4.32 (1.58)
	Sing	2.04 (0.84)	2.35 (1.04)	2.52 (0.93)	1.65 (0.61)	1.86 (0.57)	2.02 (0.66)	3.02 (0.79)	3.18 (0.71)	3.82 (1.25)
Backward	Uncued	4.33 (1.44)	6.11 (2.38)	7.77 (2.99)	3.11 (0.97)	3.84 (1.28)	4.15 (1.54)	5.03 (1.18)	5.97 (1.68)	7.14 (2.70)
	Music	5.35 (2.14)	6.18 (2.35)	7.59 (2.54)	3.27 (1.89)	3.01 (0.86)	3.63 (1.89)	5.29 (2.36)	5.44 (1.79)	6.63 (2.83)
	Sing	4.19 (1.42)	5.65 (2.03)	7.12 (2.97)	2.81 (0.71)	2.64 (0.86)	3.25 (1.19)	4.56 (1.12)	4.99 (1.45)	5.99 (1.98)

Table 3.2. Means and standard deviations of gait characteristics and variabilities for different cueing conditions, averaged across participants for each group.

3.4.2 Gait variability

A. Differences between conditions.

In forward walking, all participants walked with less variability in SING than in MUSIC, as evidenced by a significant main effect of condition ($F(1,87)=14.564, p<.001$) (Figure 3.2). This was significant for CVs of stride length ($F(1,87)=20.039, p<.001$), stride time ($F(1,87)=27.623, p<.001$), and single support time ($F(1, 87)=10.673, p=.002$).

For backward walking, participants walked with less variability in SING than in MUSIC, as there was a main effect of condition ($F(1, 87)=3.035, p=.034$). This was significant for CVs of stride length ($F(1,87)=5.498, p=.021$), stride time ($F(1,87)=5.793, p=.018$), and single support time ($F(1,87)=6.825, p=.011$).

B. Differences between groups.

There were no significant differences between groups in forward walking variability.

In backward walking, there was a significant main effect of group for stride time ($F(2, 87)=4.525, p=.014$). Pairwise comparisons revealed that the OC group ($p=.004$) and the PD group ($p=.05$) had significantly less variability regardless of condition than the YC group. There were no significant interactions.

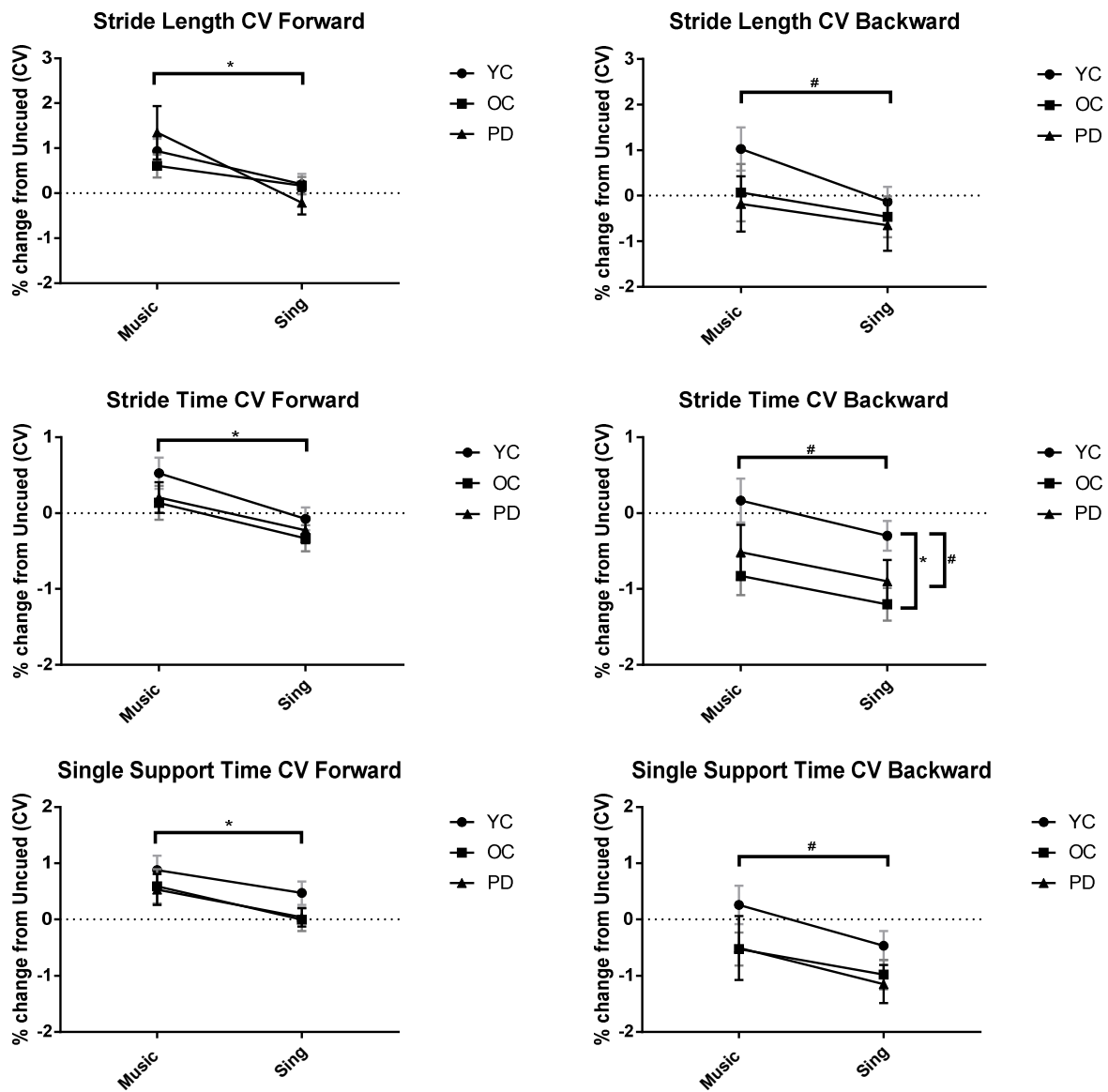


Figure 3.2. Coefficients of variation compared across groups for forward and backward walking. All bars represent means \pm SEM. Horizontal significance bars indicate an overall effect of condition, whereas vertical significance bars indicate an overall effect of group. * indicates $p < .01$. # indicates $p < .05$.

3.5 Discussion

In this study, we examined the effects of internal versus external cues on forward and backward walking in three groups of people: healthy young, healthy older, and people with PD. The results support our hypotheses, that internal cueing in the form of singing may be more beneficial to gait than external cueing. The results also confirm that people with PD exhibit greater improvement than their healthy counterparts³⁹ and may stand to gain the most benefit from internal cueing techniques, particularly in challenging gait situations such as moving in the backward direction.

One of our primary results was that singing increased cadence in both walking directions. In backward walking, this increase in cadence led to higher velocity as well. External cues, in contrast, did not have a significant effect on gait speed, cadence, or stride length on forward walking and had a lesser effect than internal cues on backward walking. This is in accordance with previous studies of forward walking showing only small effects of external cues at preferred walking tempos^{40,41} and with a recent review revealing generalized small effects on velocity and cadence in cueing without training²⁰. During MUSIC, the cadence was set by the cue, and as we explicitly told participants to synchronize to it, they did not stray far from baseline. In SING, by contrast, with no outside source dictating the song tempo, participants tended to increase their cadence as they sang.

One possible explanation for this is that active music-making (such as singing) may confer greater motor benefits than passive music listening⁴² by tapping into reward circuitry and affecting movement “vigor,” both of which are compromised in PD. Endorphin and oxytocin release during singing has positive effects on motivation and may translate into higher motor output⁴²⁻⁴⁵. Singing is also known to activate motor regions in the brain including the primary

motor cortex, the basal ganglia, thalamus, and cerebellum^{46,47}, which may additively combine with motor activation during locomotion. While synchronizing movement to music may induce an arousal effect that makes movement faster, larger, and more vigorous⁴⁸, synchronizing movement to one's own voice may lead to even greater overall motor network activation and, hence, higher cadence⁴⁹.

We also noted that, in relation to baseline, external cues had a detrimental effect on forward-walking variability. This supports previous work showing that, for healthy young adults with low baseline variability, external cues tend to perturb normally-functioning internal cueing mechanisms and interfere with gait stability⁵⁰⁻⁵³. Similarly, older adults do not benefit when constrained by external cues, as gait variability is either unaffected¹⁹ or increased with cues at preferred cadence^{51,53,54}. Cues at tempos below⁵⁵ or above³⁹ preferred cadence also increase gait variability^{24,51}.

For people with PD, preferred cadence cues have shown no effect^{24,54} or increases in variability⁵⁵, even after training²². Reductions in variability have been reported, but only for faster tempos and after a brief period of training⁵⁶. The sum of these studies shows that isochronous external cues lend only a minor benefit to gait characteristics and may come at the price of sacrificing temporal stability, particularly for those with more impaired baseline gait.

In contrast, singing did not negatively affect gait variability. In forward walking, internal cues did not cause gait decrement, and in backward walking, internal cues elicited greater reductions in variability than external cues. The effectiveness of internal cues over external cues in decreasing gait variability may be partially explained through several speculations detailed below.

While external rhythms rely on auditory-motor coupling within the brain to perceive sensory stimuli and match body movement to them, internal rhythms utilize what we will refer to as *vocal-motor coupling*. As humans are capable of entrainment within both the vocal and motor systems, it is possible that matching one system's output to that of another through self-generated cues allows for greater stability. Entrainment of one system to another within the same body may reduce attentional load and facilitate motor synchronization. Additively combining motor output from two effectors within one individual may reduce variability in a central timing process that results in lower movement variability. For instance, a bimanual advantage makes tapping with two hands less variable than tapping with only one⁵⁷.

A similar mechanism may be at play when a motor effector matches a vocal effector. Skills in motor synchronization and singing are strongly linked, as the neuronal networks that support sensorimotor translation in both partly overlap⁵⁸. Aligning speech to movement enhances verbal processing and facilitates temporal predictions, as information at expected times is processed more efficiently⁵⁹. Furthermore, concurrent rhythmic vocalizations can reduce variability of whole-body movement, which suggests that moving and vocalizing as a coordinative structure causes mutual stabilization between systems⁶⁰. As seen through the lens of an internal model, feedforward control during singing masks auditory feedback and allows singers to continuously phonate without processing each note before continuing. By canceling out reafferent signals to the auditory cortex, singing may reduce reliance on real-time auditory feedback that is necessary with external cues, thereby increasing predictability and decreasing motor variability⁶¹.

Better synchronization when singing may also be related to our bias for hearing the human voice, or a "vocal advantage." This postulates that it is easier to match stimuli to personal motor representations that are recognized as biologically possible. The voice is a highly salient stimulus

that causes enhanced arousal⁶², greater pupil dilation⁶³, and greater activation in the sensorimotor cortex⁶⁴ in listeners as compared to non-vocal melody perception. The dorsal auditory stream, which connects the auditory and motor cortices, has stronger connectivity when participants listen to singing-voice versus non-vocal music, facilitating matching between perceived sounds and motor representations⁶⁵, and sung melodies are better encoded than instrumental melodies, resulting in faster auditory processing⁶⁶. Faster processing and stronger dorsal stream connectivity may enable motor improvement during vocally-*produced* sounds as well.

Notably, the PD group exhibited the largest response from internal cueing. This implies that, in spite of basal ganglia degeneration linked to internal timing deficiencies⁶⁷⁻⁷⁰, people with PD were not only capable of internally generating rhythms through singing but were also able to match their movement to it. Beat impairment in PD is thought to impact movement as specific motor network regions, such as the basal ganglia, cerebellum, premotor cortex, and supplementary motor areas, are also responsible for rhythm processing^{16,71}. Neurodegeneration of these motor regions may disrupt the internal regulation of movement amplitude and timing in PD and lead to an inability to control automatic locomotor rhythm⁷⁰. For people with PD, for whom disease-related decreases in striatal dopamine affect excitatory input to the putamen, external cues are thought to reduce reliance on putamen activity by compensating for impaired internal timing mechanisms⁷². Singing may achieve the same end by rerouting temporal sequencing from the impaired basal-ganglia-thalamocortical network to other brain areas, such as the spared cerebellar-thalamocortical network, which regulates perceptual and motor timing, or the premotor cortex (PMC), an area known to upregulate its activity during explicit cues to synchronize to a beat^{73,74}.

Furthermore, the same features of singing that underscore its therapeutic benefit to dysarthric speech may also explain the motor benefit we witnessed. In continuous voicing that occurs when singing, increases in phonation time and syllable lengthening lead to greater connectedness between words. This fluency-enhancing effect on speech may translate to motor impairments as well. As people with PD who experience vocal softness, hoarseness, and slurring when they speak are able to maintain tempo and interval variability when they sing⁷⁵, increased vocal fluency during singing may similarly encourage motor fluidity and reduce movement variability³¹.

One limitation of this study is that we only tested one version of one song, and other musical choices might affect gait parameters differently^{48,52}. Our participants had only mild-moderate disease severity, and, as external cues tend to improve gait variability for patients with greater disease progression⁵⁴ or freezing of gait⁷⁶, our technique should be tested on a broader spectrum of individuals. Another limitation is that all walking trials were tested on a short walkway, and some research suggests that older adults require several steps to attune to acoustic stimuli⁷⁷ and choose different speed strategies over longer distances⁷⁸. Although habitual walking tends to occur in short spurts, future work should explore this technique over longer distances. Lastly, as participants were never required to begin singing without hearing the song first, we do not know how this technique would translate to everyday life in which people would self-initiate their own singing. Future work should address internal cueing techniques using both beat-continuation and beat-initiation paradigms.

This study is the first to our knowledge to compare internal and external cues on walking performance in healthy adults and people with PD and to explore the effects of cueing on backward walking. While effective in laboratory settings¹⁶⁻¹⁸, external cueing has limitations that

reduce its applicability to the real world. Carry-over effects are limited, so a device is required to provide constant stimulation^{17,79}. Fixed-tempo rhythmic cues do not readily adapt to ever-changing environmental surroundings and are less effective than variable cues that oscillate in accordance with human gait⁸⁰⁻⁸². Perhaps most importantly, people with PD do not report using external cues in their daily lives³⁵.

Our results indicate that internal cueing through singing may be more useful than external cueing techniques for people who experience gait dysfunction from aging or neurological decline. Future work should examine different cue rates to potentially elicit stronger responses and explore rhythmic ability and musical training to elucidate who best responds to this technique. Mental singing, or singing in one's head, should also be tested to discover if it is necessary to produce sound in order to gain benefit from singing as a cue. As external cueing is useful to a wide range of people with health conditions, from Alzheimer's to multiple sclerosis to cerebral palsy, internal cueing may also hold benefit for myriad populations. Ultimately, a singing intervention study should be undertaken to begin to transfer this technique into a clinical setting to make it accessible to patients and carry-over effects should be tested to explore whether vocalizations enhance motor memory⁶⁴.

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**Chapter 4: Mental singing reduces gait
variability more than music listening for
healthy adults and people with Parkinson
disease**

4.1 Abstract

Background and Purpose: Previously, we showed that internal cues (such as singing) produce similar motor benefits as external cues (such as listening to music) for people with Parkinson disease (PD). This study takes that research further by exploring how singing—either aloud or mentally—at different tempos can ameliorate gait, and it offers insight into how internal cueing techniques may enhance motor performance for older adults and people with PD.

Methods: 60 participants (30 female) were recruited; half had PD and half were healthy age-matched controls. Participants completed walking trials involving external and internal cueing techniques at 90, 100, and 110% of preferred cadence. The effects of different cue types and rates were assessed in a repeated-measures cross-sectional study by comparing gait characteristics (velocity, cadence, stride length) and variabilities (coefficients of variation of stride length, stride time, single support time).

Results: All participants modified their cadence and stride length during cued conditions, resulting in changes in gait velocity closely reflecting expected changes based upon cue rate. External cueing resulted in increased gait variability, whereas internal cueing decreased gait variability relative to uncued walking. Variability decreases were most significant during mental singing at tempos at or above preferred cadence.

Discussion and Conclusions: Matching movement to one's own voice improves gait characteristics while reducing gait variability for older adults and people with PD. Optimizing the use of internal cues to facilitate movement is an important step towards more effectively meeting the needs of people with gait disorders related to aging or neurological disease.

4.2 Introduction

Parkinson disease (PD), the second most common neurodegenerative disorder, can cause debilitating effects on gait that may contribute to increased falls and decreased quality of life¹. Dopamine depletion within the substantia nigra of the basal ganglia leads to malfunctioning of temporal control mechanisms, which disrupts both movement timing and amplitude^{2,3}. This affects walking ability; people with PD tend to walk slower and with less stability. Reductions in gait speed are typically attributed to a combination of shorter step lengths and decreased step frequency and indicate a decline in overall health in both aging and patient populations⁴. Increased gait variability, characterized by inconsistent step timing and reduced step symmetry, is considered a measure of dyscontrol, arrhythmicity, and instability⁵. Hence, slower, more variable gait in PD may contribute to diminished stability and increase the risk of falls⁶.

External auditory cueing through music can normalize gait speed for people with PD. By creating an external template to which people can align their footfalls, auditory cues impose a walking cadence that, presumably, reduces reliance on defective internal timing mechanisms and increases motivation, thereby increasing walking speed⁷. However, the need to synchronize to an external source can have detrimental effects on gait variability that may outweigh any benefits. Furthermore, some researchers have discouraged the use of external cueing devices in everyday life as they distract from other environmental stimuli and impose unnatural rhythms on inherently adaptable gait patterns^{8,9}.

Our previous work showed that overt singing improve gait in PD and healthy controls more than passively listening to music. Singing constitutes an internal cue that utilizes *vocal-motor coupling* to match one's movement to one's own voice. We saw that this form of internal cueing particularly aids gait variability, reducing the need to synchronize to an outside source¹⁰. As

singing ability is preserved in PD, this technique is easily accessible to this population¹¹.

However, singing aloud may be embarrassing in public settings and not practical for all participants. In this study, we extended our past research to explore the use of mental singing, or singing in one's head, which has improved motor timing in one prior study, though precise gait characteristics were not measured¹².

Here, we also sought to optimize internal cueing techniques by determining what cue rates are most effective. Previous research suggests that cues administered at tempos above or below preferred walking cadence may either improve or degrade measures of gait, but inconsistent methods and results leave this an open source of debate^{13–22}. We hypothesized that mental singing would be as effective as singing aloud at improving gait for all participants and that greater effects would be seen with increased cue tempos. We included both people with PD and healthy controls to better understand how disrupted rhythmic processing in PD might hinder the efficacy of internal cueing techniques.

4.3 Methods

4.3.1 Participants

A total of 60 participants, thirty (15 male) in each of two groups – healthy controls and people with Parkinson disease (PD) – took part in this study (Table 4.1). Group size was determined by power analysis based on preliminary data¹⁰. Participants with PD were recruited from the Movement Disorders Center at Washington University School of Medicine. Healthy controls were recruited via the Research Participant Registry through the Volunteers for Health database managed by Washington University School of Medicine and via emails, social media, and flyers in and around the Washington University School of Medicine campus. All participants were ≥ 50

years of age, and participants with PD had a neurological diagnosis of “definite PD”, as previously described and based upon established criteria^{23,24}.

Table 4.1. Participant Demographics.

	Controls	PD
N (male)	30(15)	30(15)
Age, yrs	64.9(±7.2)	65.8(±6.5)
MDS-UPDRS-III	-	24.9(±10.27)
MMSE, median (range)	30(27,30)	29(24,30)
Years since dx	-	5.77(±3.79)
LEDD, mg	-	933(±658)
Musical experience, yrs	4.42(6.02)	7.77(11.45)
BQMI	1.68(0.57)	2.12(0.68)

Values represent mean ±SD, except where noted.

MDS-UPDRS, Movement Disorder Society Unified Parkinson Disease Rating Scale. MMSE, Mini Mental Status Examination. LEDD, Levodopa Equivalent Daily Dose. BQMI, Betts’ Questionnaire upon Mental Imagery (auditory portion only).

All participants were able to stand independently for at least 30 minutes and had no evidence of dementia (MMSE \geq 26). We excluded people with history of neurological deficit (aside from PD), orthostatic hypotension, or deep brain stimulation surgery. One healthy control was excluded for cognition (MMSE < 26) and an additional participant was recruited.

All participants provided informed consent prior to testing and were compensated for their time. The protocol was approved by the Human Research Protection Office at Washington University School of Medicine. The Movement Disorders Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) was used to assess disease severity. Sub-sections I (non-motor symptoms), II (motor aspects of daily living), and III (motor sign severity) were administered and scored by

certified staff. Additional questionnaires included the New Freezing of Gait Questionnaire (nFOGq) and the Fall History questionnaire. Auditory imagery was assessed using the Betts' Questionnaire upon Mental Imagery (BQMI), which uses a 7-point vividness scale, with 1 indicating high imagery ability and 7 indicating low imagery ability²⁵. We collected only the auditory imagery portion of the test and calculated an average for each participant. Information on past musical experience was recorded.

4.3.2 Experimental Protocol

Participants with PD were tested in the “on” state as determined by self-report during the MDS-UPDRS Part III evaluation to capture their normal walking condition. A 5 m instrumented, computerized GAITRite Walkway (CIR Systems, Inc., Franklin, NJ) recorded walking trials. Three baseline trials (UNCUED) were used to assess each participant's comfortable walking characteristics. All participants then completed three blocks of cued trials trials at 90%, 100% and 110% of preferred walking cadence. The block of trials cued at 100% of preferred cadence was always completed first followed by blocks at either 90% or 110% of preferred cadence, the order of which was randomized and counterbalanced. Within each block, the randomized conditions were:

1. **MUSIC:** Music was playing and participants were asked to walk to the beat of the song. This represents typical external cueing techniques. Participants listened to one verse of the song and began walking when they were ready, similar to a beat-synchronization paradigm. The song looped throughout the duration of the trial.

2. **SING:** Participants were asked to sing aloud while walking. In this condition, no external source provided a cue while they walked, so participants generated the cue themselves.

Participants listened to one verse of the song and then began walking as soon as the music stopped.

3. **MENTAL:** Participants were asked to sing in their heads without moving their lips or producing overt sound. As in the SING condition, participants listened to one verse of the song and then began walking when the music stopped.

All conditions were cued using an instrumental version of “Row, Row, Row your Boat” designed with a salient beat that could be readily detected by participants. Everyone was familiar with the lyrics and melody of the song and able to sing it without difficulty. The musical cue was administered from a laptop connected to speakers no farther than 10 m from the participant during walking and at an audible volume. Song tempo was adjusted based upon each individual’s preferred walking cadence while maintaining key consistency using Audacity open source audio editing software (The Audacity Team, audacity.sourceforge.net/).

4.3.4. Statistical Analysis

Statistical analyses were done using IBM SPSS Statistics 24. For each participant, data were averaged across the three trials of each condition. Gait characteristics (velocity, cadence, and stride length) and variability (coefficients of variation for stride length, stride time, and single support time) were compared in three separate analyses, one for each cue tempo. Coefficients of variation (CV) were calculated as the $((\text{standard deviation}/\text{mean}) \times 100)$ for each person in each

condition. As we were only interested in how cueing affected these measures, we ran analyses on each variable as it compared to the UNCUEd condition. Hence, gait characteristics were expressed as a percent change from UNCUEd and gait variabilities were expressed as a change in CV from UNCUEd. Gait asymmetry (GA) was calculated for each condition at each tempo based on previous reports as: $GA = 100 \times \ln(\text{swing ratio})^{26}$. Swing ratio was defined as the ratio of the mean left and right swing times with the larger value in the numerator. Mixed model repeated measures ANOVAs with between-subject factor of group and within-subject factor of condition were used to assess differences, and Tukey-corrected post-hoc pairwise comparisons were used as appropriate. Differences between groups in auditory imagery ability were assessed via independent t-test. Statistical significance was set at $\alpha = .05$.

4.4 Results

4.4.1 Gait Characteristics

Cueing at 90% of preferred cadence: Mauchley's test of sphericity was not met, thus, adjusted multivariate and univariate (Greenhouse-Geisser) statistics are reported (Figure 4.1, Table 4.2). There was a within-subject effect of condition ($F(6,230) = 4.754, p < .001$) with univariate tests showing an effect of condition on cadence ($F(1.74, 100.67) = 6.348, p = .004$) and stride length ($F(1.76, 102.09) = 5.179, p = .01$). Pairwise comparisons indicated cadence was higher for SING than MUSIC ($p = .022$) or MENTAL ($p = .006$), and stride length was higher for MUSIC than for SING ($p = .027$).

Cueing at 100% of preferred cadence: There was a within-subject effect of condition ($F(6,53)=4.025, p=.002$) with univariate tests showing an effect of condition on cadence ($F(2,58)=7.927, p=.001$). Pairwise comparisons indicated cadence was higher for SING than for MUSIC ($p=.031$) or MENTAL ($p=.002$).

Cueing at 110% of preferred cadence: Mauchley's test of sphericity was not met for stride length, thus, adjusted multivariate and univariate (Greenhouse-Geisser) stats are reported. In the multivariate model, there was a main effect of condition ($F(6,230)=6.882, p<.001$). Univariate tests showed an effect of condition on cadence ($F(1.93,111.89)=19.952, p<.001$) and stride length ($F(1.73, 100.32)=7.428, p=.002$). Pairwise comparisons, corrected for multiple comparisons, showed cadence was higher for MUSIC ($p<.001$) and SING ($p=.001$) than for MENTAL, and stride length was higher in MENTAL than MUSIC ($p=.001$).

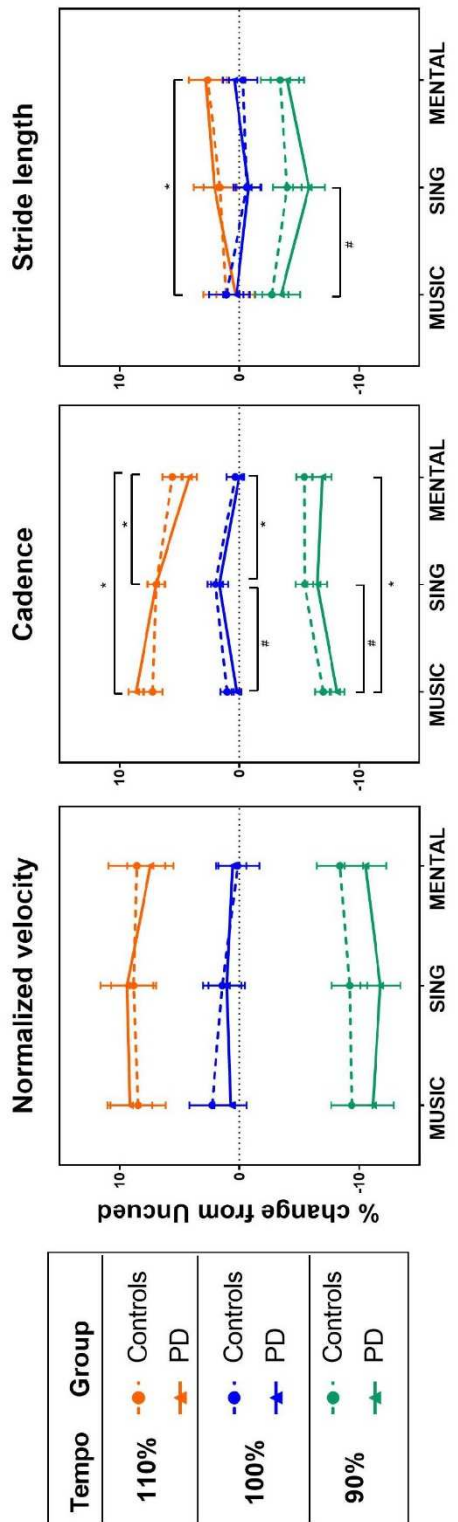


Figure 4.1. Gait characteristics shown as a percent change from Uncued walking compared across groups for three tempos: 90%, 100%, and 110% of preferred walking cadence. All bars represent means \pm SEM. Horizontal significance bars indicate an overall effect of condition * indicates $n < 01$ # indicates $n < 05$

4.4.2. Gait Variabilities

Cueing at 90% of preferred cadence: Mauchley's test of sphericity was not met for cadence, thus, adjusted multivariate and univariate (Greenhouse-Geisser) stats are reported (Figure 4.2.). In the multivariate model, there was a main effect of condition ($F(6, 230) = 6.096, p < .001$). Univariate tests showed an effect of condition on stride length CV ($F(1.790, 103.846) = 12.981, p < .001$), stride time CV ($F(1.732, 100.48) = 12.165, p < .001$), and single support CV ($F(1.882, 109.16) = 14.85, p < .001$). Pairwise comparisons, corrected for multiple comparisons, showed stride length variability was higher for MUSIC compared to SING ($p = .024$) and MENTAL ($p < .001$), stride time variability was higher for MUSIC compared to SING ($p = .005$) and MENTAL ($p < .001$), and single support time variability was higher for MUSIC compared to SING ($p = .001$) and MENTAL ($p < .001$).

Cueing at 100% of preferred cadence: Mauchley's test of sphericity was not met, thus adjusted multivariate and univariate (Greenhouse-Geisser) stats are reported. In the multivariate model, there was a main effect of condition ($F(6,230) = 7.805, p < .001$). Univariate tests showed an effect of condition on stride length variability ($F(1.56, 90.34) = 9.250, p = .001$), stride time variability ($F(1.69, 98.04) = 16.76, p < .001$), and single support time variability ($F(1.62, 93.86) = 15.14, p < .001$). Pairwise comparisons, corrected for multiple comparisons, showed stride length variability was higher for MUSIC compared to SING ($p = .002$) and MENTAL ($p = .01$), stride time variability was higher for MUSIC compared to SING ($p = .002$) and MENTAL ($p < .001$), and single support time variability was higher for MUSIC compared to SING ($p = .032$) and MENTAL ($p < .001$) and for SING compared to MENTAL ($p = .002$).

Cueing at 110% of preferred cadence: The multivariate test showed a main effect of condition ($F(6,230)=4.179$ ($p=.001$)). Univariate tests showed an effect of condition on stride length CV ($F(2,116)=5.525$, $p=.005$), on stride time CV ($F(2,116)=8.185$, $p<.001$), and on single support time CV ($F(2,116)=5.856$, $p=.004$). Pairwise comparisons showed stride length variability was higher for MUSIC compared to MENTAL ($p=.003$), stride time variability was higher for MUSIC compared to SING ($p=.015$) and MENTAL ($p<.001$), and single support time variability was higher for MUSIC ($p=.006$) and SING ($p=.019$) compared to MENTAL. The multivariate test also showed an interaction between group and condition ($F(6,230)=2.302$, $p=.035$). Univariate tests showed this interaction was significant for stride length ($F(2,116)=5.19$, $p=.007$) indicating that people with PD lowered their stride length variability during MENTAL more than controls.

4.4.3 Gait Asymmetry

Univariate tests showed a main effect of group at each tempo: 90% ($F(1,58)=26.42$, $p<.001$), at 100% ($F(1,58)=15.59$, $p<.001$), and at 110% ($F(1,58)=20.00$, $p<.001$) (Table 4.2). There were no differences between conditions at any tempo.

4.4.4 Auditory Imagery Ability

Controls ranked their auditory imagery abilities lower (better) than PD participants ($F(2,58)=2.579$, $p=.013$) (Table 4.1). Bivariate correlations of auditory imagery and changes in gait variabilities during MENTAL were not significant.

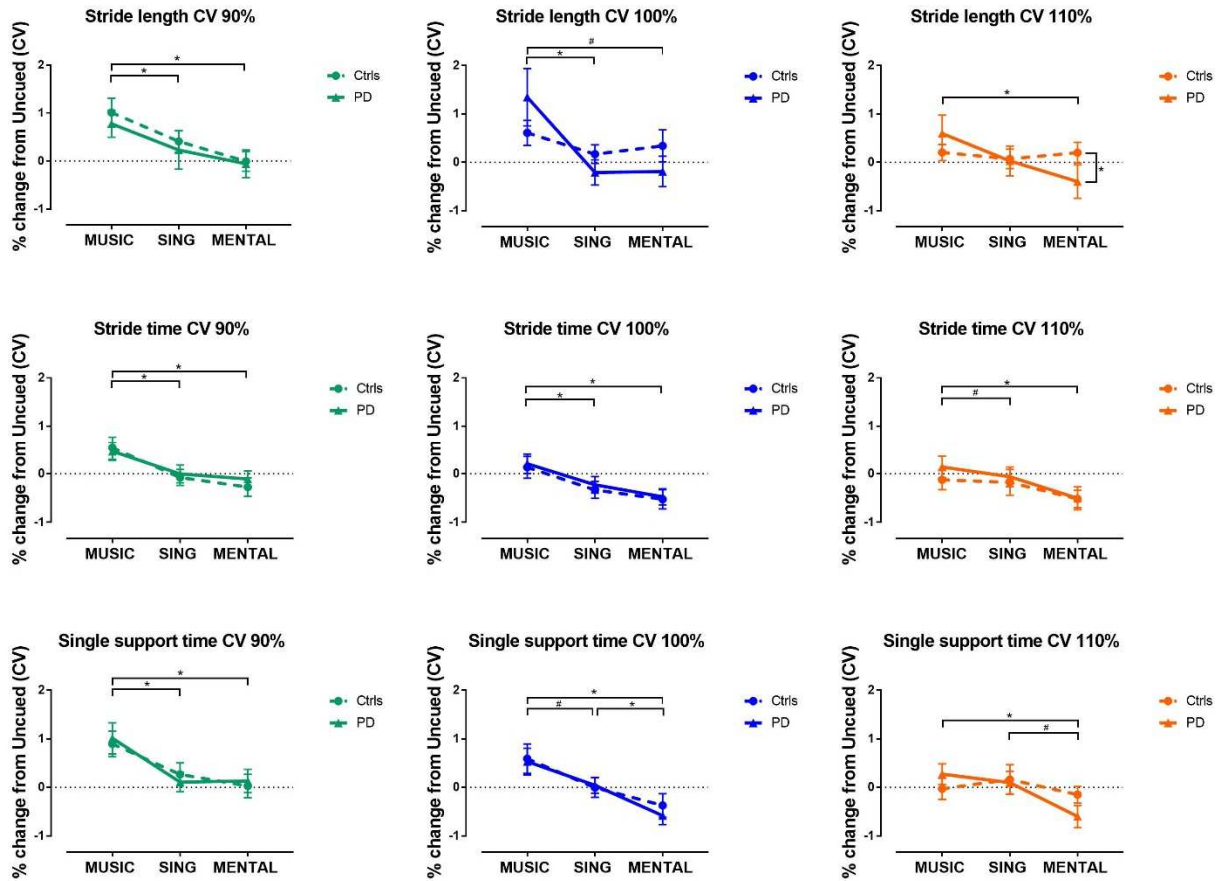


Figure 4.2. Gait Variabilities. Coefficients of variation compared across groups for three tempos: 90%, 100%, and 110% of preferred walking cadence. All bars represent means \pm SEM. Horizontal significance bars indicate an overall effect of condition, whereas vertical significance bars indicate an overall effect of group. * indicates $p < .01$. # indicates $p < .05$.

Table 4.2. Means and standard deviations of gait characteristics and variabilities by condition and cue rate, averaged across participants for each group.

GAIT CHARACTERISTICS	<i>Control baseline</i>	TEMPO	90%	100%	110%
Velocity (cm/s)	<i>133.9 (15.0)</i>	music	120.9 (15.2)	136.1 (13.3)	144.6 (18.0)
		sing	121.6 (16.5)	135.3 (14.5)	145.3 (18.2)
		mental	122.4 (17.9)	133.8 (16.8)	144.9 (18.7)
Cadence (steps/min)	<i>112.1 (6.0)</i>	music	104.3 (6.9)	113.3 (6.7)	120.2 (7.4)
		sing	106.0 (6.8)	114.4 (7.6)	120.0 (8.2)
		mental	106.1 (7.4)	112.6 (7.7)	118.4 (8.0)
Stride length (cm)	<i>143.5 (15.3)</i>	music	139.0 (13.3)	144.3 (12.1)	144.3 (15.3)
		sing	137.4 (14.0)	142.1 (13.2)	145.3 (14.6)
		mental	138.0 (14.7)	142.7 (13.9)	146.6 (14.3)
GAIT VARIABILITIES	-	TEMPO	90%	100%	110%
Stride length SD	<i>3.1 (0.9)</i>	music	4.4 (1.7)	3.9 (1.7)	3.3 (1.2)
		sing	3.5 (1.5)	3.3 (1.3)	3.3 (1.3)
		mental	2.9 (1.1)	3.5 (2.0)	3.4 (1.3)
Stride time SD	<i>0.02 (0.01)</i>	music	0.03 (0.02)	0.02 (0.01)	0.02 (0.008)
		sing	0.02 (0.01)	0.02 (0.01)	0.02 (0.001)
		mental	0.02 (0.01)	0.02 (0.01)	0.02 (0.005)
Single support time SD	<i>0.01 (0.004)</i>	music	0.02 (0.01)	0.02 (0.007)	0.01 (0.004)
		sing	0.01 (0.004)	0.01 (0.003)	0.01 (0.005)
		mental	0.01 (0.005)	0.01 (0.004)	0.01 (0.003)
Gait Asymmetry	<i>1.81 (1.7)</i>	music	1.74 (1.1)	1.81 (1.3)	1.67 (1.3)
		sing	1.87 (1.6)	1.56 (1.2)	1.24 (1.0)
		mental	1.59 (1.3)	1.58 (1.4)	1.62 (0.9)
GAIT CHARACTERISTICS	<i>PD baseline</i>	TEMPO	90%	100%	110%
Velocity (cm/s)	<i>123.6 (15.1)</i>	music	109.7 (18.3)	124.1 (16.2)	134.5 (19.5)
		sing	109.0 (18.0)	124.9 (20.4)	135.2 (23.4)
		mental	110.6 (18.4)	124.1 (16.6)	132.5 (20.4)
Cadence (steps/min)	<i>110.9 (7.8)</i>	music	101.9 (8.9)	111.1 (7.7)	120.4 (8.5)
		sing	103.8 (9.8)	112.7 (8.6)	118.6 (9.1)
		mental	103.3 (9.3)	110.9 (7.6)	115.5 (8.9)
Stride length (cm)	<i>134.1 (15.6)</i>	music	129.0 (16.3)	134.2 (15.7)	134.2 (17.0)
		sing	126.1 (15.8)	133.0 (17.2)	136.6 (18.7)
		mental	128.4 (15.9)	134.5 (16.1)	137.5 (16.6)
GAIT VARIABILITIES		TEMPO	90%	100%	110%
Stride length SD	<i>3.6 (1.7)</i>	music	4.5 (1.6)	5.3 (3.1)	4.3 (1.8)
		sing	3.7 (1.6)	3.3 (1.2)	3.7 (1.2)
		mental	3.4 (1.2)	3.4 (1.7)	3.1 (1.4)
Stride time SD	<i>0.02 (0.01)</i>	music	0.03 (0.01)	0.03 (0.01)	0.02 (0.01)
		sing	0.03 (0.01)	0.02 (0.01)	0.02 (0.01)
		mental	0.03 (0.01)	0.02 (0.01)	0.02 (0.01)
Single support time SD	<i>0.01 (0.004)</i>	music	0.02 (0.01)	0.02 (0.007)	0.01 (0.01)
		sing	0.02 (0.01)	0.01 (0.005)	0.01 (0.004)
		mental	0.02 (0.01)	0.01 (0.004)	0.01 (0.004)
Gait Asymmetry	<i>3.87 (2.8)</i>	music	3.45 (2.2)	2.85 (2.1)	3.53 (2.2)
		sing	3.73 (2.2)	3.12 (2.3)	3.22 (2.8)
		mental	3.57 (2.5)	3.13 (2.4)	3.04 (2.5)

4.5 Discussion

In this study, we expanded our past research on internal cueing to explore the effects of both overt and covert singing as well as different cue rates on gait in healthy controls and participants with PD. The primary objectives of this research were to determine if mental singing could elicit similar gait improvement as singing aloud and if changing tempo from preferred walking cadence might generate greater benefits. Our results supported our hypotheses that mental singing was as effective, if not more so, as overt singing at improving gait for all participants. This renders this technique more clinically relevant for people who would not be comfortable walking down the street while singing aloud. Our results also support the use of cues at faster tempos than preferred as they increased velocity, cadence, and stride length while also decreasing gait variability.

Our primary result is that internal cues were superior to external cues at reducing gait variability (GV). Whereas external cues increased nearly all measures of GV from baseline, internal cues generally decreased GV, particularly at tempos at or above preferred cadence. Adverse effects on GV when synchronizing to isochronous external cues have been reported previously in both healthy older adults and people with PD^{13,14,16,27,28}. Here, internal cues reduced GV more than external cues for all participants, which we partially attribute to eliminating the need to synchronize to an external source. Without the need to constantly adjust footfalls to match external cues, coordinating steps to one's own vocal cues via a mechanism of *vocal-motor coupling* may reduce motor variability.

Counter to our expectation that people with PD would gain more benefit from internal cues than controls, both groups responded similarly across conditions. The efficacy of internal cueing techniques for people with PD may relate to the remarkable preservation of singing ability in

spite of speech degradation, as people with PD who experience speech dysprosody show no similar decrements in singing¹¹. Ability to maintain song tempo, rhythm, interval variability, and overall fluency, may relate to greater bilateral activation, especially in the right superior temporal gyrus, during overt singing compared to speaking²⁹.

While singing reduced GV more than external cues, mental singing elicited even greater improvements in gait. Perhaps, by eliminating the need to create and monitor sound, participants were able to direct more attentional resources to walking¹⁴. Elements of vocalization such as respiratory kinematics, word formation, and monitoring aural feedback, unnecessary when mental singing, potentially simplified task demands and enabled more efficient movement.

The benefit of mental singing may also relate to the multimodal nature of the task, which requires integration of motor, kinesthetic, and auditory imagery capabilities. Even in the absence of sound, imagined music recruits auditory areas of the brain and broad regions of the motor network. Motor regions implicated in auditory imagery, such as the premotor cortices and supplementary motor areas, enable motor anticipation by facilitating action preplanning, movement selection, and sequencing³⁰⁻³². As auditory imagery alone can improve amplitude and timing of hand taps, it may not be necessary to produce sound in order to utilize *vocal-motor coupling*, as evidenced by GV reductions seen in our participants³³. Movement, thus, may benefit from being entrained to vocalizations regardless of if they are produced overtly or simply imagined.

Sensorimotor synchronization ability likely relies on auditory imagery skill, and, while motor imagery vividness and accuracy is generally well-preserved in PD and can improve with cueing, less is known about auditory imagery ability^{34,35}. In our sample, PD participants reported higher

(worse) auditory imagery vividness than controls, though both groups reported better than normative averages. Gait improvement in the PD group in spite of lower auditory imagery capabilities is likely not related to their overall higher musical experience, which was driven primarily by two people with extensive experience and not statistically different. Instead, it may reflect increased activation of cortical and subcortical structures implicated in PD during anticipatory auditory imagery³⁶.

Another possibility is that internal cues may bypass rhythmic centers of the brain typically affected by neurodegeneration, thereby allowing patients to reroute through unaffected areas. Internal cues may bypass a dysfunctional subcortical loop connecting the basal ganglia, SMA and thalamus in favor of a cerebellar-thalamo-cortical loop that serves as a compensatory network known to be more active during self-paced rather than external movements^{37,38}.

As loss of gait rhythmicity is associated with impaired rhythmic processing in the basal ganglia, we wondered if gait asymmetry (GA) showed similar improvements as GV. GA in our sample was higher in our participants with PD than in our controls, which was expected because maintaining symmetric interlimb coordination is less automatic in pathological gait disorders and indicative of increased instability and higher risk of freezing of gait³⁹. Whereas GA typically worsens with cognitive loading, auditory cues in our study caused no decrement to GA. Some conditions, in fact, elicited small improvements in GA, the largest being for the PD group while mental singing. Though non-significant, evidence suggests that this reduction (from 3.87 to 3.04) may be sufficient to reduce risk of freezing of gait and falls^{26,39}.

In terms of tempo differences, our results suggest that increased cue rates provide more benefit to gait than cues at or below preferred cadence¹⁷⁻²¹. External musical cues at 110% of preferred

cadence elicited near 10% changes in velocity and cadence, which were expected as they were set by the cue. Internal cues did not elicit the same change in cadence. Without a cue present, participants may have reverted back to a pace that more closely matched their preferred walking cadence or to a tempo of song that was more natural to sing. The latter may reflect a propensity to retrieve familiar songs at previously-encoded absolute tempos when singing aloud or imagining well-known songs^{40,41}.

In spite of less substantial changes in cadence during internal versus external cues, we observed no significant differences in velocity between cueing conditions. This indicates that participants achieved velocity changes during internal cueing by altering both stride length and cadence. Particularly while mental singing at 110%, participants achieved higher gait speeds by taking longer strides, which may be useful in PD to counteract tendencies to shorten strides and festinate.⁴²

Faster cue rates also benefitted GV, which may relate to an overall increase in stability when moving faster or to improved synchronization due to a preference for neural entrainment at certain beat frequencies^{16,43,44}. Optimal frequencies of neural entrainment (2Hz) for movement synchronization accuracy correspond closely to cadence rates in our study of approximately 120 steps/min in both groups at the faster cue rate⁴⁵. In contrast to research suggesting that reducing speed may allow for longer stride lengths or improved variability due to a speed-stride length trade-off, we saw no benefit from the slower cue rate²². Slower walking speeds may constitute a more challenging gait condition that results in increased variability and worsened bilateral coordination^{43,46}.

In an effort to assess the impact of gait improvement elicited by internal cueing, we compared our mental singing condition at 110%, the condition in which we saw the greatest benefit to GV, to recent research addressing meaningful gait changes in older adults⁴⁷. The changes in velocity that we saw (8.9 cm/s for PD and 11.0 cm/s for controls) are similar to meaningful change values seen in older adults (10.4 cm/s) and between moderate and large effect sizes (6 and 10 cm/s, respectively) in PD (Table 4.2)^{47,48}. Measures of variability, too, compare to values deemed meaningful in older adults, as we saw a reduction in stride length standard deviation of 0.5 cm in PD, which falls within the range of small to substantial changes for step length standard deviations (0.24-0.61 cm). These comparisons lead us to believe that the increases in gait speed and reductions in variability seen during internal cueing are clinically meaningful and could contribute to decreases in fall risk.

A few limitations should be considered. During the mental singing condition, we monitored lip movement and audible vocalizations but not laryngeal movements, so small sub-glottal movements may have contributed to motor output. Also, the auditory imagery scale we used only covers environmental sounds and alternative tests may be better-suited to assess musical imagery ability in the future⁴⁹. Lastly, up to 40 footfalls may be necessary to capture reliable estimates of GV, so future studies should assess gait over longer periods of time⁴⁴.

4.5.1 Conclusions

The results of this research indicate that older adults and people with PD may gain greater benefit from internal versus external cueing techniques, the latter of which are commonly prescribed and seemingly detrimental to gait variability. In contrast, internal cues allow people to increase gait velocity while simultaneously reducing stride-to-stride variability, which may

ultimately contribute to overall gait stability and reduction of fall risk. Internal cues may also be useful for reducing gait asymmetry in other populations, as a recent study showed improvements in velocity, cadence, and stride length after a single session of mental singing in patients with post-stroke hemiplegia⁵⁰. Here, we showed that mental singing provides more benefit to gait variability than singing aloud which makes internal cueing more practical for everyday use.

4.6 References

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Chapter 5: Internal and external auditory cues enhance gait kinematics for people with Parkinson Disease

5.1 Abstract

Internal cueing techniques, such as singing or mental singing, may provide greater benefit to gait for people with Parkinson disease than external cueing techniques, such as listening to music, by eliminating the need to match an external source. Mental singing, in particular, can improve spatiotemporal features such as gait variability, but the effects on gait kinematics are unknown. In this study, we sought to compare the effects of different rhythmic cued conditions on lower limb movement trajectories. Using motion capture, we assessed sagittal plane joint angles at the hip, knee, and ankle across 35 participants with PD. We also explored differences between participants who responded positively and those that received less benefit from cued conditions. Our results indicate that rhythmic cues can improve range of motion and that people with PD who experience falls or freezing of gait are generally able to utilize internal cueing techniques to improve their walking. Furthermore, previous musical experience may influence likelihood of response. These results provide important insight into how novel internal cueing techniques may benefit gait stability in PD, potentially reducing the risk of debilitating incidents, such as freezing of gait or falls.

5.2 Introduction

Parkinson disease (PD) is a neurological disorder caused by progressive loss of dopaminergic neurons within the basal ganglia, a region of the brain known to help regulate movement size and timing. Overall reductions in movement amplitude and generalized slowness of movement contribute to gait impairment, which typically consists of reduced speed, shorter stride lengths, and increased cadence and double support time. Neurodegeneration of the rhythm processing centers within the basal ganglia can further disrupt the rhythmic nature of walking, leading to

more variable gait timing and increasing the risk of falls^{1,2}. Nearly 50% of people with PD will develop a debilitating phenomenon known as freezing of gait (FOG) as the disease progresses, which can further exacerbate gait variability and unsteadiness³. Since people with PD report walking difficulty as a primary concern⁴, rehabilitation efforts commonly focus on improving gait.

Pharmacological and surgical treatments do not adequately address gait impairments in PD, but targeted interventions such as rhythmic auditory stimulation (RAS), in which participants match steps to external cues, can be effective. Myriad studies of external cueing effects on spatiotemporal gait parameters have shown consistent improvement in gait velocity and stride length⁵; however, growing evidence shows that these improvements may come at the expense of increasing stride-to-stride variability⁶⁻⁸. Recent research from our lab showed that internal cueing in the form of singing or mental singing may convey similar benefits as external cues while also improving gait variability for people with PD⁹. The natural extension of this research was to explore the effects of internal cueing on gait kinematics to determine if movement quality may also benefit from this technique.

Kinematic studies of PD gait verified that reduced spatiotemporal parameters correspond to reductions in lower limb joint movement relative to controls and persist in spite of anti-Parkinsonian medication^{10,11}. Distinctive kinematic features include flat foot contact, reduced hip extension in stance, knee flexion in swing, and plantarflexion at toe-off¹²⁻¹⁴. Normalization of movement trajectories with the use of visual cues suggests that cues can alter motor strategies¹², but few studies to date have explored the effects of auditory cues on gait kinematics, in spite of their superiority to other cue types¹⁵. While metronome cues induce increases in lower limb

movement trajectories^{16,17} no studies that we know of report the effects of musical cues, which provide additional motivation and are considered optimal for gait training¹⁸. Furthermore, people with PD exhibit varied responses to external cues¹⁹, but little information presently exists regarding what factors contribute to likelihood of a positive response to internal cues. While some have suggested that internal cues may be particularly suited to people with PD who experience more profound gait impairments such as freezing of gait (FOG), the use of internal cues has not been explored in this population²⁰.

The purpose of this study was to compare gait kinematic profiles during different rhythmic cueing techniques for people with PD. We analyzed sagittal plane movement during gait while walking to music, constituting an external cue, and while walking and singing or mentally singing, constituting an internal cue. We showed previously that internal cues elicited greater benefit to spatiotemporal gait parameters. Thus, we hypothesized that internal cues, and particularly mental singing, would also improve kinematic measures, resulting in overall increases in lower limb joint trajectories over externally cued conditions. Additionally, we sought to assess qualitative differences between responders and non-responders during internally cued conditions to determine who may be more likely to respond. We hypothesized that people who experience more impaired gait, as evidenced by a history of freezing episodes or falls, and those with some degree of musical experience might respond more positively to internal cues than others.

5.3 Methods

5.3.1 Participants

All participants had diagnosed idiopathic PD with mild-moderate disease severity as evidenced by Hoehn & Yahr (H&Y) scores of 2-3 (Table 5.1). Inclusion criteria were: a) able to stand independently for at least 30 minutes, b) normal peripheral neurological function, c) no history of vestibular disease, d) no evidence of dementia (Mini Mental State Examination (MMSE) ≥ 24). Participants were excluded if they had any of the following: a) any serious medical problem aside from PD, b) previous abnormal brain scan, c) deep brain stimulation surgery, d) diagnosis of peripheral neuropathy, or e) use of dopamine-blocking medication. All participants were recruited as part of a larger study, and only those with a body mass index (BMI) < 30 who were naïve to the cued conditions were included in the present analysis. Of 56 participants in the larger study, 35 met all inclusion criteria for this analysis.

Participants were recruited through the Movement Disorders Clinic at Washington University School of Medicine in St. Louis, Missouri and from the local chapter of the American Parkinson Disease Association. The study was approved by the Human Research Protection Office at Washington University School of Medicine, and all participants provided written informed consent prior to data collection and were compensated for their time.

Table 5.1. Participant demographics.

	All	Non-freezer (FOG-)	Freezer (FOG+)
N (male)	35 (21)	24 (14)	11 (7)
Age, yrs	67.17 (9.04)	67.92 (9.81)	65.55 (7.24)
Years Since Diagnosis	4.92 (4.82)	3.57 (3.34)	7.86 (6.30)
MDS-UPDRS-III	28.69 (11.21)	27.33 (11.62)	31.64 (10.14)
MMSE, median (range)	29 (25,30)	29 (25,30)	29 (27,30)
Baseline Velocity, m/s	1.15 (0.18)	1.19 (0.17)	1.06 (0.17)
Musical Experience, yrs	9.24 (13.94)	11.18 (16.95)	5.67 (4.84)
BQMI, median (range)	4 (2,7)	4 (0,5)	3.5 (0,5)
NFOG-Q, median (range)	12 (0, 26)	0 (0)	12 (4,26)
Fall Status (fallers, nonfallers)	11, 24	6, 18	5, 6

Values represent mean \pm SD, except where noted. MDS-UPDRS, Movement Disorder Society Unified Parkinson Disease Rating Scale. MMSE, Mini Mental Status Examination. BQMI, Betts' Questionnaire Upon Mental Imagery. NFOG-Q, New Freezing of Gait Questionnaire.

5.3.2 Experimental Protocol

Participants were tested in the 'ON' state of their anti-Parkinson medication in order to increase relevance of assessment conditions to daily walking in everyday life. All participants completed a behavioral assessment prior to kinematic assessment. Questionnaires included the New Freezing of Gait Questionnaire (NFOG-Q), the Fall History Questionnaire, the auditory portion of the Betts' Questionnaire Upon Mental Imagery (BQMI), and questions about prior musical experience. Disease severity was assessed using the Movement Disorder Society Unified Parkinson Disease Rating Scale (MDS-UPDRS III)²¹. Three initial walking trials, measured on a 5-meter instrumented walkway (GAITRite, CIR Systems, NJ), were used to assess self-selected walking cadence in order to tailor the cue tempo to each individual.

5.3.3 2D Motion Capture

Sagittal-plane kinematic data were collected using an 8-camera Hawk Digital RealTime system by Motion Analysis (Motion Analysis Corporation, Santa Rosa, CA) with a 100Hz sampling rate. Participants were provided form-fitting clothing to wear along with their own shoes. Fifty-

three reflective markers (20mm diameter) were placed on bony prominences including: T12, L5, bilateral PSIS, ASIS, iliac crests, greater trochanters, medial and lateral femoral condyles, tibial tuberosities, medial and lateral tibial malleoli, 1st and 5th metatarsophalangeal joints, first toe, and 1” above the floor on the heel. The thigh and shank were tracked using plates with four evenly-spaced markers mounted 3.5” above the lateral condyle of the femur and 6” above the lateral condyle of the tibia.

5.3.4 Procedure

An initial static trial was collected in order to design a model for each individual. Six medial markers were removed prior to the walking trials. For each condition, participants walked diagonally across a 10’x10’x10’ capture volume. The cue was administered from a laptop connected to speakers no farther than 10m from the participant during walking to ensure audibility. The song “Row, row, row your boat” was used for cueing so that participants would be familiar with the melody and lyrics and able to sing it without difficulty. This particular instrumental version was designed with an easily detectable, salient beat⁹. The song tempo was adjusted to 110% of each participant’s self-selected walking cadence while maintaining key consistency using Audacity open source audio editing software (The Audacity Team, audacity.sourceforge.net/).

An *UNCUED* condition occurred first in which participants walked at their comfortable pace in silence. Three randomized cued conditions followed:

1. *MUSIC*: Participants were instructed to walk to the beat of the musical cue.

Participants were asked to listen to the song one time through and begin walking on the second round. The music was playing during walking.

2. *SING*: Participants were instructed to listen to the musical cue one time and then begin walking while singing out loud at the tempo they just heard. The music was not playing during walking.
3. *MENTAL*: Participants were instructed to listen to the musical cue one time and then begin walking in silence while singing in their heads. They were not allowed to move their lips or produce overt sound. The music was not playing during walking.

5.3.5. Data Processing

Motion capture data were pre-processed in Cortex (version 1.1.4, Motional Analysis Corporation, CA) and imported into Visual3D (version 6, C-Motion, MD). Three gait trials in each condition were processed for analysis. A low-pass Butterworth 6Hz filter was used to smooth the kinematic data, and hip, knee, and ankle joint angles and spatiotemporal measures were extracted. Gait cycles were defined by heel strikes, which were calculated by the velocity of the toe marker in relation to the pelvis using a previously validated method²². No differences were noted between sides, so left and right gait cycles were combined and a minimum of six cycles was used for each participant within each condition. Joint trajectories were normalized to percent of gait cycle, and range of motion for each joint was calculated as the difference between maximum and minimum values during the gait cycle.

5.3.6 Statistical Analysis

IBM SPSS (version 24, IBM, NY) was used for all analyses. Differences between conditions for gait characteristics (velocity, cadence, stride length; stride time, double limb support time (DLST), stride width), gait variabilities (stride time, stride length, and single support time coefficients of variation (CV) calculated as the $((\text{standard deviation}/\text{mean}) \times 100)$ for each

participant in each condition), joint range of motion (ROM) and angle at initial contact (IC) (for the hip, knee, and ankle) were analysed using repeated measures MANOVAs. Sphericity was assessed with Mauchly's test of sphericity, and Greenhouse-Geisser corrections were used when necessary. Tukey-corrected post-hoc pairwise comparisons were used as appropriate. Extreme outliers (≥ 3 interquartile ranges from mean) were winsorized. Participants were classified as "fallers" if they self-reported one or more falls in the six months prior to testing. The first question of the NFOG-Q, "Did you experience freezing episodes in the past month?" was used to divide participants into freezers and non-freezers. We based likelihood of responding to internal cues on the MENTAL condition because it showed the greatest mean increase in hip ROM. Participants who improved by more than 1 standard deviation (SD) above the mean change ($> 2.1^\circ$) were classified as "responders" and everyone else was classified as a "non-responder". Pearson Chi-Square tests assessed demographic differences between responders and non-responders. Statistical significance was set at $\alpha=.05$.

5.4 Results

5.4.1 Basic Spatiotemporal Gait Features

There was a within-subject effect of condition ($F(9, 306)=7.328, p<.001$) with univariate tests showing an effect of condition on velocity ($F(1.84, 62.72)=10.876, p<.001$), cadence ($F(3, 102)=31.551, p<.001$), and stride length ($F(1.989, 67.623)=3.753, p=.029$) (Table 5.2). Pairwise comparisons indicate that velocity (all $p<.015$) and cadence (all $p<.001$) were higher for all cued conditions over UNCUEDED, and stride length showed a similar trend, with strides being longer for MENTAL ($p=.062$) and SING ($p=.071$) over UNCUEDED. There was a within-subject effect of condition ($F(9,306)=7.94, p<.001$) with univariate tests showing an effect of condition on stride

time ($F(3,102)=33.686$, $p<.001$), double limb support time (DLST, $F(3,102)=13.933$, $p<.001$), and stride width ($F(3,102)=2.861$, $p=.041$). Pairwise comparisons indicate that stride time ($p<.001$) and DLST (all $p<.002$) were lower for all cued conditions over UNCUEDED, and stride width showed a similar trend, with strides being narrower for MUSIC ($p=.088$) and SING ($p=.10$).

Table 5.2. Spatiotemporal and Kinematic Gait Variables.

	Uncued	Music	Sing	Mental
Gait Characteristics				
Speed (m/s)	1.15(0.18)	1.26 (0.24)*	1.25 (0.21)*	1.26 (0.23)*
Cadence (steps/min)	110.05 (7.81)	117.35 (11.37)*	115.53 (10.49)*	115.74 (10.13)*
Stride Time (s)	1.1 (0.08)	1.03 (0.10)*	1.05 (0.09)*	1.04 (0.09)*
Stride Length (m)	1.26 (0.19)	1.30 (0.20)	1.30 (0.18)*	1.31 (0.19)*
DLST (%GC)	33.6 (2.42)	32.34 (2.77)*	32.52 (2.45)*	32.78 (2.59)*
Stance Time (%GC)	66.84 (1.19)	66.19 (1.36)*	66.31 (1.25)*	66.39 (1.19)*
Swing Time (%GC)	33.16 (1.19)	33.81 (1.36)	33.69 (1.25)	33.61 (1.19)
Stride Width (m)	0.14 (0.02)	0.13 (0.02)	0.13 (.03)	0.13 (0.03)
Gait Variabilities				
Stride Time CV	1.90 (0.86)	2.30 (1.31)	2.06 (0.84)	1.57 (0.49)*#
Stride Length CV	1.51 (0.78)	1.65 (0.90)	1.57 (0.66)	1.52 (0.60)
Single Support Time CV	2.70 (1.03)	3.13 (1.48)	2.82 (0.96)	2.59 (0.76)
Stride Width CV	11.82 (5.16)	11.05 (5.81)	12.84 (5.70)	11.01 (5.96)
Hip				
Flexion at IC (°)	32.68 (7.63)	33.98 (8.05)*	33.69 (7.70)*	33.90 (7.89)*
Peak Hip Extension (°)	-4.6 (8.97)	-5.20 (9.13)*	-5.38 (9.11)*	-5.48 (9.00)*
Peak Hip Flexion (°)	32.68 (7.63)	33.98 (8.05)*	33.69 (7.70)*	33.90 (7.89)*
Mean ROM Sagittal Plane (°)	37.27 (5.76)	39.18 (6.13)*	39.07 (6.29)*	39.38 (6.56)*
Knee				
Flexion at IC (°)	8.42 (5.33)	9.91 (5.49)*	9.62 (6.30)	9.72 (5.73)*
Peak Knee Extension (°)	7.71 (5.14)	8.84 (5.10)*	8.32 (5.29)	8.42 (4.85)
Peak Knee Flexion (°)	70.42 (5.18)	71.28 (5.63)*	71.25 (5.24)*	71.45 (5.11)*
ROM Sagittal Plane (°)	62.71 (5.83)	62.44 (5.17)	62.93 (5.31)	63.02 (5.02)
Ankle				
Dorsiflexion at IC (°)	7.79 (3.15)	8.52 (3.24)*	8.19 (3.17)	8.47 (3.19)*
Peak Dorsiflexion (°)	21.67 (3.67)	21.52 (4.25)	21.52 (3.99)	21.53 (4.04)
Peak Plantarflexion (°)	-6.28 (5.59)	-6.81 (6.93)	-6.69 (6.54)	-7.19 (6.28)
ROM Sagittal Plane (°)	27.95 (4.69)	28.34 (5.00)	28.20 (4.96)	28.72 (4.93)

Values represent mean \pm SD across all participants. * indicates significant difference from UNCUEd. # indicates significant difference from MUSIC and SING. DSLT, double limb support time. CV, coefficient of variation. IC, initial contact. ROM, range of motion.

5.4.2 Gait Variability

There was a within-subject effect of condition ($F(9, 306)=2.223, p<.001$). Univariate tests showed an effect of condition on stride time variability ($F(3, 102)=5.04, p=.003$) with similar trends showing an effect of condition on single support time variability ($F(3, 102)=2.509, p=.063$) and on stride width variability ($F(3, 102)=2.602, p=.056$). Pairwise comparisons indicate that stride time variability in MENTAL was lower than MUS ($p=.005$) and SING ($p=.013$).

5.4.3 Ranges of Motion

There was a within-subject effect of condition ($F(9, 306)=4.188, p<.001$) for total joint ROM (Figure 5.1). Univariate tests showed an effect of condition on total hip ROM ($F(3, 102)=11.647, p<.001$). Pairwise comparisons indicated increased ROM in all cued conditions compared to UNCUEDED (all $p<.003$).

5.4.4 Joint Angles at Initial Contact

There was a within-subject effect of condition ($F(9, 306)=4.847, p<.001$)(Figure 5.1). Univariate tests showed an effect of condition on hip flexion ($F(2.387, 81.168)=9.612, p<.001$), knee flexion ($F(1.882, 63.973)=6.212, p=.004$), and ankle dorsiflexion ($F(2.392, 81.313)=5.497, p=.004$) at initial contact (IC). Pairwise comparisons indicated that hip flexion at IC was higher for all cued conditions than UNCUEDED (all $p<.004$), knee flexion at IC was higher for MUS ($p=.035$) and MENT ($p=.039$) than UNCUEDED, and ankle dorsiflexion was higher for MUS ($p=.044$) and MENT ($p=.019$) than UNCUEDED. In SING, knee flexion at IC showed a trend towards being higher than UNCUEDED ($p=.085$).

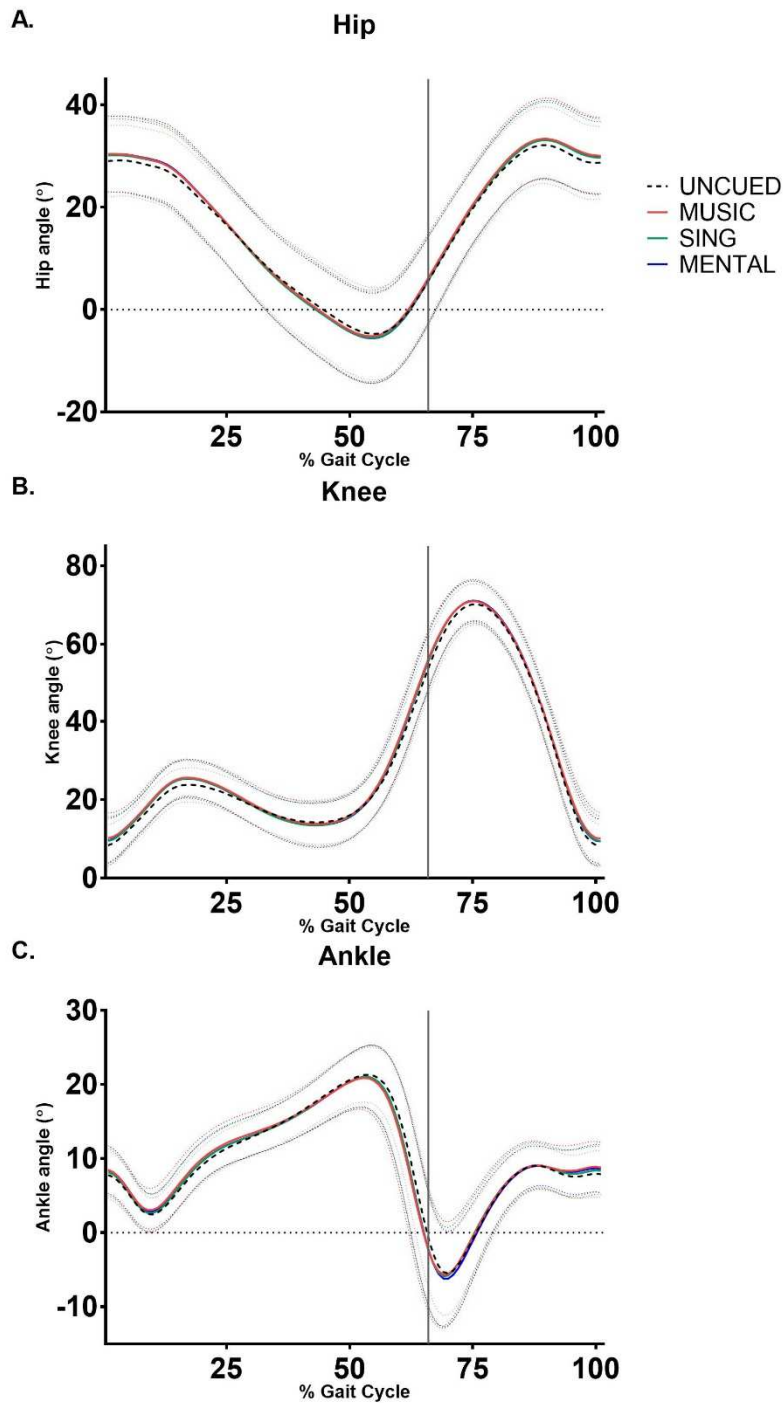


Figure 5.1. Joint angle trajectories for the hip, knee, and ankle show data averaged across 35 participants and normalized to the gait cycle. Fine dotted lines represent \pm standard deviation. Dotted lines represent joint excursions during UNCUEW walking. All cued conditions show similar patterns of slight expansion in both directions revealing increases in overall range of motion (ROM) and greater flexion/dorsiflexion at initial contact (IC) at the start of the gait cycle.

5.4.5 Responders and non-responders

From our sample of 35 participants, 16 were classified as “responders” based on improvement in hip ROM in MENTAL. “Non-responders” included 17 participants who showed minimal change, falling within ± 1 SD of the mean change, and 2 participants who substantially decreased their hip ROM more than 1 SD from the mean change. Ten of 15 participants with some musical experience were “responders” as opposed to only 6 of 20 participants with no musical experience ($p=.031$). Based on this parameter, 7 of 11 freezers and 7 of 11 fallers (not all the same participants) responded positively.

5.4.6 Effects of Cueing in People with and without FOG

A sub-analysis comparing FOG+ to FOG- revealed some differences based on freezing status (Figure 5.2). There was an interaction between condition and freezing status ($F(9, 297)=1.67$, $p=.096$) with univariate tests showing an effect on velocity ($F(1.928, 63.609)=2.437$, $p=.097$) and on stride length ($F(2.155, 71.123)=4.363$, $p=.014$). Pairwise comparisons showed that FOG- increased velocity more in SING ($p=.043$) and MENTAL ($p=.028$) than UNCUEDED, whereas FOG+ increased velocity in all cued conditions (all $<.004$) over UNCUEDED and in MUS over SING ($p=.022$). Only FOG+ showed a differential effect of condition on stride length with strides being longer in all cued conditions (all $p<.006$) than in UNCUEDED.

The multivariate test showed a between-subject effect of freezing status on joint angles at initial contact ($F(3,31)=3.697$, $p=.022$) with univariate tests showing an interaction between condition and freezing status on hip flexion at initial contact ($F(3,99)=2.769$, $p=.046$) and knee flexion at initial contact ($F(1.976, 65.201)=3.234$, $p=.046$). Pairwise comparisons showed that FOG- increased hip flexion at initial contact in MENTAL ($p=.03$) over UNCUEDED, whereas FOG+ increased hip flexion at initial contact in all cued conditions (all $p<.039$) over UNCUEDED.

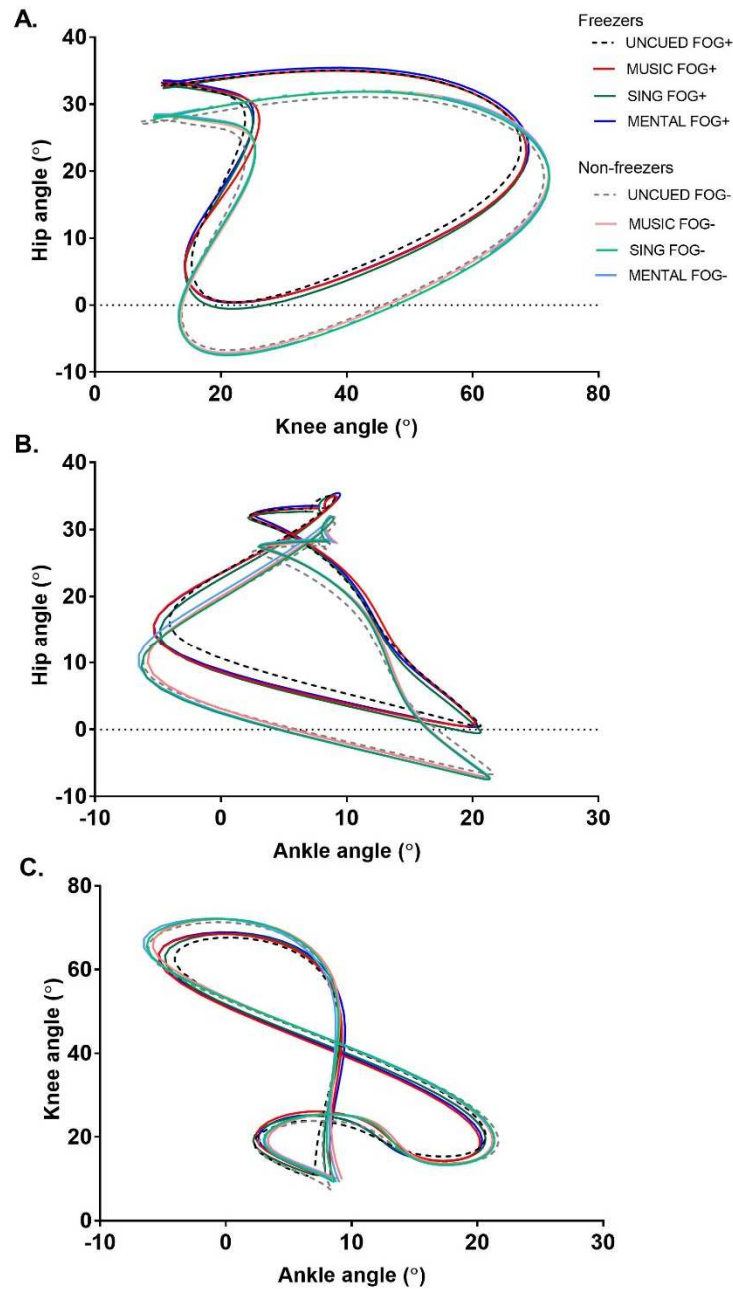


Figure 5.2. Angle-angle plots representing mean joint trajectories for the hip, knee, and ankle plotted against one another. Dotted lines represent joint excursions during UNCUED walking and solid lines represent joint excursions during cued conditions. Bright colored lines represent FOG+ (n=11) and lighter colored lines represent FOG- (n=24). Shifted plots in A and B reveal disparate hip angles at initial contact, with freezers exhibiting higher hip flexion than non-freezers. Greater divergence from UNCUED walking among FOG+ indicates more robust responses to cueing for freezers.

5.5 Discussion

In this study, we explored the effects of internal and external auditory cues on gait kinematics of people with PD. The motion capture data we collected largely mirror recent spatiotemporal data from our lab showing a greater benefit of internal cues, such as singing or mental singing, than external cues, such as listening to music, on PD gait. We observed that all rhythmic cues examined can effectively increase gait speed, cadence, and stride length, but only internal cues reduce gait variability as well. Here, we additionally show beneficial effects of cues on multi-joint limb excursions. Although we were surprised to see no significant differences in gait kinematics between cued conditions, we were encouraged that all auditory cues increased joint angle trajectories from uncued walking. These results indicate that people with PD can use both external and internal auditory cues to enhance spatiotemporal and kinematic movement parameters.

The stereotypical shuffling gait pattern commonly seen in PD can be traced to several key impairments throughout the gait cycle. At the outset, an absence of heel rocker at foot strike causes initial contact to occur closer to the forefoot than the heel²³. Impaired foot strike angle and abnormal foot loading can reduce force generation¹³, stride length²⁴, and gait speed²³. Inability to properly execute heel-to-toe roll further decreases time spent in stance, and therefore, gait stability¹⁴. During toe-off, reduced ankle plantarflexion and reduced hip extension can also contribute to shortened strides²⁵.

Previous work showed that various cueing techniques can improve these impairments.

Attentional strategies to focus on heel strike can cause an immediate increase in ankle dorsiflexion²⁶. Visual cues that require participants to step over floor markers can increase ROM

and step length¹. Auditory cues improve step preparation²⁷ and improve spatiotemporal gait parameters largely due to increases in hip flexion^{16,17}, similar to improvements we observed here.

Similarly, we saw the largest changes in ROM at the hip, but cues increased ROM at all joints. Increased ankle dorsiflexion at initial contact may indicate a more effective stepping strategy that could reduce shuffling and improve stability at the beginning of the gait cycle. Cueing also increased ankle plantarflexion at toe-off. Improved foot lift during the swing phase has been shown to increase clearance of toes from the ground which may enable longer strides²⁵ and reduce the risk of tripping⁴. In our study, peak ankle plantarflexion was highest in the MENTAL singing condition and accompanied by the greatest amount of knee flexion during the swing phase. Such alterations to joint trajectories, though slight, may help elongate swing times, increase push-off, and improve forward propulsion.

Our results support the use of cueing to improve two other markers of postural instability and fall risk in PD: stride width and double support time. Increased width in base of support is associated with poor balance control and fear of falling²⁸ and prolonged time spent in double support is considered a compensatory strategy for gait instability²⁹. The decreased time spent in stance observed here supports past work showing that auditory cueing may normalize the subdivision between stance and swing phases¹⁶.

Increases in spatiotemporal and kinematic variability are well-documented in neuropathic gait and sensitively predict fall risk in people with PD³⁰. Gait variability in PD may relate to inconsistent muscle activation³¹, deficient neuromuscular patterning¹², or loss of rhythmicity in automatic movements⁶. Corroborating other studies^{9,16}, MUSIC increased (worsened) nearly all measures of gait variability while MENTAL singing improved temporal variability measures. In

contrast to our past work showing a minor benefit of singing aloud, in this study, SING increased variability, suggesting that singing aloud may be less beneficial than singing in one's head.

Although we previously showed improvements in spatial variability with internal cues, here we found no benefit to stride length variability. However, all measures of variability reported herein should be considered in light of limitations to calculating variability from so few strides³².

The improvements we saw in ROM were less substantial than some previously reports (increased hip ROM of 6-10°, for instance^{12,16,17}), although some individuals within our sample did respond to this extent. Smaller mean effects may be attributed to the mild disease severity of our sample, leaving less room for improvement. We may also have seen greater effects had we offered more instruction or training, and future studies should include an intervention to train participants on how to effectively utilize internal cueing techniques. Higher cadences in externally versus internally cued conditions suggest that, while participants were capable of matching footfalls to imposed tempos, they tended to revert back to preferred cadence once the external signals were removed.

As people with PD greatly differ in their response to auditory cues, we sought to determine who was more likely to respond³¹. It is noteworthy that, from our sample of 35 participants, 16 were classified as “responders”, displaying increases in hip ROM between 2-9°, while 18 showed minimal response to cueing. For these “non-responders”, cueing did not significantly alter joint motion nor spatiotemporal gait variables. Only 1 participant substantially *decreased* hip ROM in MENTAL, which corresponded to a decrease in stride length and an increase in cadence. This participant appeared to significantly shorten strides—and thereby reduce hip movement—in order to match the song tempo, which supports recommendations to individually tailor cue rates

in order to optimize stride length³¹. Analyses of responders and non-responders suggest that internal cueing techniques, even when done without training, are unlikely to cause significant gait detriment and have a near 50% chance of improving overall movement trajectories.

Our observation that participants with musical experience responded better to internal cueing corroborates previous reports that some degree of musical training or rhythmic skill may improve the likelihood of responding to musical cues³¹. This may be particularly useful in mental singing as it requires maintaining a beat in silence. We also noted that a majority freezers and fallers, who typically exhibit higher gait impairment³³, responded positively to internal cues. While both FOG+ and FOG- successfully increased their cadence, only FOG+ also lengthened strides, increased ROM, and reduced variability to a greater extent than FOG-. Though these enhancements in FOG+ may merely reflect lower baseline values with more room for improvement, they suggest, in contrast to past work, that cueing may hold an immediate benefit for people with PD who experience FOG+³⁴. Hence, internal cues hold promise to improve movement for people at risk of FOG and falls, and future studies may explore this more in depth.

In this study, we showed that people with PD can utilize both external and internal musical cueing techniques to gain immediate benefit to movement quality and that mental singing may be more effective than other cued conditions. While cues can improve both spatiotemporal and kinematic gait parameters, as evidenced by increases in velocity, cadence, stride length, and joint angle trajectories, only mental singing can also decrease gait variability, which is an important marker of overall gait stability. Previous musical experience may improve the likelihood of benefitting from internal cues, and people with PD who experience freezing of gait may receive even greater benefit than those who do not. Mental singing holds promise as an effective

alternative to external rhythmic cueing that may improve movement quality and increase stability for people with PD.

5.6 References

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Chapter 6: Conclusion

“Every disease is a musical problem; every cure is a musical solution.” –Novalis

These words of the early Romantic German poet Novalis reflect the long-held belief, documented in nearly every culture across time, that science and art combined hold the power to heal. For brain diseases such as Parkinson disease (PD), no cure currently exists, but music can indeed serve as a solution of sorts. While pharmacological and surgical treatments fall short at addressing the motor, cognitive, and emotional needs of people with PD, music-based interventions can facilitate motor function and promote wellbeing and quality of life. External rhythmic stimulation in PD is well known to improve gait dysfunction in a research laboratory setting, but these techniques are difficult to use in everyday life. The studies reported in this dissertation are among the first to elucidate the benefits of internal cueing techniques such as singing, which may provide a similar benefit and are highly accessible and cost-effective.

6.1 Summary of main findings

In this dissertation, we tested a novel technique of internal cueing to facilitate movement in healthy adults and people with PD. Though several others have suggested that singing or mental singing may provide benefit to motor impairments in neurological disorders, we are among the first to quantitatively assess specific gait characteristics while using this technique. To this end, we assessed: 1) the feasibility of internal cueing for people with PD by comparing it to external cues and a verbal dual task, 2) the effects of internal versus external cueing on forward and backward walking in healthy adults and people with PD, 3) the effects of internal cueing in the

form of singing and mental singing on forward gait at different cue rates in healthy adults and people with PD, and 4) the effects of internal cues on gait kinematics in people with PD. A summary of the main findings of our experiments follows.

6.1.1 Aim 1

In **Aim 1**, our objective was to determine if internal cueing was feasible for people with PD and if it could elicit improvement in gait parameters comparable to external cueing. Therefore, we tested four conditions, including both external and internal cue types, with all cues given at preferred cadence, and a dual task (DT) condition. The first notable finding of **Aim 1** was that singing did not degrade gait in the same way that a verbal dual task did. Whereas the DT condition slowed and destabilized gait, internal cueing did not negatively affect gait characteristics or variabilities. Verbal word generation tasks done concurrently with walking disrupt gait automaticity in PD by dividing attentional resources between the motor and cognitive task, causing degradation of one or both¹⁻³. Even though our participants were susceptible to DT effects, as evidenced by gait degradation in the DT condition, singing did not induce similar negative effects. This suggests that singing is not as cognitively challenging as other dual tasks and does not utilize significant attentional resources that might detract from concurrent motor tasks.

Furthermore, in our comparison of internal versus external cues in **Aim 1**, we showed that internal cues were actually more beneficial than external cues at reducing gait variability. In both of our external cueing conditions, MUS and MUS+SING, variability measures increased from baseline. Increased temporal and spatial variability with external cues occurred independent of measures of speed, cadence, or stride length, which were unchanged. Internal cueing did not

have this same effect and was slightly beneficial to measures of spatiotemporal variability. The results of this Aim countered the common assertion that external cues are beneficial to both gait characteristics and variability, and warranted further study in our other Aims.

6.1.2 Aim 2

Backward gait

In **Aim 2**, we addressed the suitability of internal cues in more challenging gait situations such as backwards walking. Backwards walking causes slower, more variable steps and is a common cause of falls and injury^{4,5}. Moving in the backward direction occurs commonly in everyday life, as transitional movements such as turning often require backward steps^{6,7}. Backward and forward walking, while similar, are worth studying independently as they do have some distinct kinematic properties⁸⁻¹⁰ and may be controlled by different neuromuscular control networks¹¹. Though no previous studies had explored the use of cues on backward walking, we expected that this less automatic form of gait would be more impaired at baseline and thus more amenable to improvement through cueing.

The major conclusion of this experiment was that internal cues provided more benefit to gait than external cues in both walking directions, and that backward walking characteristics improved more than forward characteristics. Internal cueing was associated with improvements in velocity, stride length, and cadence in the backward direction, as well as reductions in variability in both forward and backward walking. This suggests that synchronizing movement to one's own singing induces more stability in motor output, in both automatic and challenging gait situations.

Detrimental effects of external cues for PD and controls

In **Aim 2**, we also included two control groups so that we could compare PD participants with healthy older and healthy younger controls. Confirming the results of **Aim 1**, we saw detrimental effects of external cues on gait variability in all three groups. Similar negative effects from external cues were reported previously in healthy young adults¹²⁻¹⁴, healthy older adults^{12,15-20}, and in people with PD^{16,21-25}. Theories suggest that for people with low baseline variability, cues may compete with intact internal timing mechanisms and perturb gait rhythmicity¹⁹. They may also require additional neural engagement that divides attentional demands²⁰. Directing attention to motor performance may make people overcorrect or increase deviations due to discrepancies between feedforward and feedback control^{26,27}.

Reports of gait decrement from external cues for people with low baseline variability suggest that external cues are only beneficial for people with sufficiently impaired baseline gait. Our results do not fully support this, as we saw detrimental effects with external cues for all three groups even though baseline gait measurements and motor severity ratings show that our PD sample was, in fact, more impaired than the other groups. Instead, we suggest that synchronizing to an external source requires extra attentional resources that can cause gait decrement for a broad range of people. With internal cues, on the other hand, we observed that people with PD exhibit greater improvement than healthy adults, especially in the backward direction. This could reflect more impaired backward gait with more room for improvement or to a greater reduction in reliance on impaired internal timing mechanisms.

6.1.3 Aim 3

In **Aim 3**, we tested the effects of two internal cue types—singing and mental singing—on gait in people with PD and healthy age-matched controls. We explored the effects of different cue rates, as well, to optimize the benefits of internal cues. Here, we found that participants were able to match their footfalls to an externally imposed cadence at varied cue rates, reflecting the suitability of auditory cues in this population. Internal cues, again, showed a more marked benefit than external cues on gait variability, and these improvements were most significant during mental singing at tempos at or above preferred cadence.

Mental singing

Our condition of mental, covert singing was included primarily to improve accessibility of internal cueing techniques for people who would not be comfortable singing aloud and enhance ability to use internal cueing across a variety of situations. We expected mental singing to be possible, based on earlier reports of motor benefits in PD²⁸, and to provide similar benefit as singing aloud, based on similarities in covert and overt singing^{29,30}. The inclusion of mental singing, a skill that combines elements of auditory perception, auditory imagery, and vocal production, contributes to a burgeoning field of research on the auditory-motor network, and improves usability of this technique in real world situations.

Cue rate

The rate of cueing is a common source of debate in the PD literature. In our assessment of rhythmic cueing at different tempos in **Aim 3**, we observed the greatest gait benefit at tempos at

or above preferred cadence. This supports past work showing that external cues at increased rates from preferred can improve gait velocity, cadence, and stride length^{31–34} as well as measures of variability³⁵. We saw little discernable benefit from decreasing the cue rate, as the 90% cue slowed and destabilized gait for all participants. This supports past studies showing worsened step length variability²¹ and stride time variability¹ at slower cue rates. We did not see a previously hypothesized speed-accuracy trade-off, which allows accuracy to improve as speed decreases³⁶. Rather, increased variability at slower speeds may compromise postural stability and detrimentally affect balance and gait variability³⁷. In contrast to reports of increased stride lengths at slower rates³⁸—when given more time to swing the leg through—we did not see a benefit to stride length at this tempo. Thus, these results support the use of preferred-tempo or above preferred-tempo cue rates, in order to most benefit gait characteristics and variabilities for the majority of people.

6.1.4 Aim 4

In **Aim 4**, we explored the effects of the same cued conditions on gait kinematics and movement quality. As no studies that we know of report the effects of musical cues on PD gait kinematics, we sought to test the effects of external and internal cues on lower limb movement trajectories, known to be impaired in PD^{39–41}. Although metronome cues can improve PD gait kinematic features^{32,42}, no studies we know of report the effects of musical cues or internal cues. We expected that internal cueing improvements in stride length and variability seen in Aims 1-3 would likely be reflected in joint angle trajectories. The results, however, did not reveal significant differences between conditions. While measures of spatiotemporal variability did decrease in MENTAL singing more than in other conditions, overall, we saw that all cued

conditions, regardless of cue type, improved gait kinematics to approximately the same extent. The improvements during cueing corroborate previous reports of improved ROM, particularly at the hip and ankle at initial contact. The results also confirm that singing is as suitable a cueing technique as music listening, in that both improve kinematic gait features, while singing additionally benefits spatiotemporal variability.

Differential response to internal cues

Though the grouped data reveal minimal differences between conditions, we noticed that a large number of people did improve gait kinematics in MENTAL singing more than other conditions, as we had hypothesized. In order to better understand any contributing factors to likelihood of response in **Aim 4**, we sought to parse out differences between “responders” and “non-responders” based on increases in hip ROM in the MENTAL condition, as it was the joint in which we saw the greatest change. In doing so, we addressed the potential use of internal cues for people with more profound gait impairments such as freezing of gait (FOG) or recurrent falls. In our comparison of non-freezers (FOG-) to freezers (FOG+), we found that FOG+ increased ROM, elongated strides, and reduced variability more than FOG-. We also noted that a majority of fallers responded positively to internal cues by increasing ROM in the hip.

We also observed that musical experience contributed to likelihood of response, as the majority of people with musical training improved gait features with internal cues. These enhancements were expected based on extensive research suggesting that musical training induces plastic changes in the brain and enhances musical processing and entrainment capabilities^{25,43-47}.

6.2 Significance and Common Themes

Over the course of developing and researching the studies reported in this dissertation, we found several recommendations in the literature to either sing or mentally sing in order to improve motor patterns for people with PD⁴⁸⁻⁵¹. We found anecdotal reports of people who were already using this technique^{52,53}. We found implorations to researchers to study it^{54,55}. To our surprise, however, no reports evaluating precise gait characteristics existed. While one decade-old study showed motor benefits in PD after a month of training in covert singing, no follow-up studies were conducted²⁸. Thus, the studies listed herein are among the first to specifically evaluate the effects of internal cues. Taken together, the results from Chapters 2-5 suggest that internal cueing can provide benefit to gait impairment that can exceed that of external cues.

We also found abundant evidence that external cues are an imperfect tool. They require a device and are difficult to use in short walking bouts common in daily life. Others have warned against using them because they may distract from environmental disturbances in the real world, such as oncoming traffic¹⁶. Furthermore, several reports suggest that isochronous external cues degrade biological gait variability that is crucial for adapting gait to meet the needs of the moment⁵⁶⁻⁵⁸. They are impractical to use for reducing motor blocks, which are unpredictable^{59,60}. As such, external cues are infrequently prescribed and not commonly used by people with gait impairment. Below, we review multiple factors that must be considered in the use of internal cueing for people with gait impairment.

6.2.1 Comparison of singing versus speech

Throughout these studies, we showed that, in spite of the complex nature of singing, vocal production of a familiar song does not divide attention and cause gait impairment in PD as a typical dual task. Singing is a complex, multimodal process that requires integrating components of both music (e.g., melody, harmony, etc.) and speech (e.g., semantics, syntax, phonological constraints). Efficient use of the vocal apparatus involves accurate representation of pitch, rhythm, timbre, and other features, as well as implementing motor plans and actively monitoring feedback⁶¹. Singing, then, might be considered a more complex process than speech.

However, several pieces of evidence suggest that singing may not be excessively attention demanding. Singing, like speech, is a nearly universal skill that is widespread in the population. The majority of the population is proficient in singing and can carry a tune when asked to sing a well-known song⁶². The ability to sing is evident in infancy, and does not require formal training but can be enhanced with practice⁴⁸. Studies show that singing actually develops before speech, in the form of sung exchanges in parent-infant interactions⁵². This evidence suggests that singing, though complex, is an innate and easily-accessed skill that is not overly challenging for most people.

Furthermore, the inherent complexity of singing, involving high levels of integration, may subserve motor synchronization more than detract from it. While speech lacks fundamental rhythmic properties like predictable regular beats and metrical structure⁶³, music, including sung lyrics, are more regular in rhythm and allow for better synchronization⁶⁴. This distinction may explain why spontaneous motor synchronization to spoken words does not occur the way it does for music⁶³. Singing also requires multiple neural circuits to work in tandem. A theorized “vocal

sensorimotor loop” (VSL) supposes that extensive brain activations underlie singing ability that involves perception, auditory-motor mapping, motor control, and memory processes⁶⁵.

Neuroanatomically, hemispheric lateralization distinctions reveal that speech production is primarily left hemispheric dominant, activating the left sensorimotor cortex, cerebellum, and insula, while singing activates homologous brain regions on the right^{66,67}. In addition to hemispheric differences, the circuitry underlying melodic production may simply be more diffuse and therefore more likely to engage alternate pathways⁶⁸. Singing is more likely to engage the dorsolateral premotor cortex (PMd) and the supplementary motor areas (SMA), which may enhance movement pre-planning and sequencing^{69,70}. These areas are also implicated in processing amodal, or non domain specific, imagery that enhances sensory-cognitive processing and may play a role in sequencing movement to match self-generated sounds^{71,72}. Singing also activates reward centers in the brain, such as the nucleus accumbens, posterior cingulate, and parahippocampal gyrus, more than speaking, which suggests a greater emotional and motivational component, potentially underlying motor enhancements during synchronization to song²⁹.

In comparing speech to singing, we must also address task differences as our verbal DT and the singing task were not directly comparable. One required active word generation, known in linguistic circles as “propositional” speech, and the other required repetition of a highly familiar phrase (which includes familiar songs), or “automatic” speech. Whereas the former requires new generation of internal models of motor performance, “automatic” or recited speech engages memorized internal models without the burden of internal planning⁷³. Singing a familiar song, then, may provide a template that requires minimal attentional planning. This would suggest that

internal cueing, or singing, fills the same hypothesized role as an external cue, providing a scaffolding to which people can align their movement. The comparison between external versus internal cues was the second main comparison addressed in **Aim 1**.

6.2.2 Comparison of external and internal cueing techniques

The widely accepted explanation for the use of external cueing techniques in PD, which has been advanced for over forty years, is that external cues compensate for impaired basal ganglia function by providing a regularizing temporal input to align movement^{31,34,74}. External cues generate temporal expectations via a process called “entrainment”, which enables time-locking between the auditory and motor systems and facilitates motor prediction⁷⁵. Synchronizing actions to an externally-imposed template may optimize anticipation and improve the subsequent response by reducing reliance on impaired internal timing mechanisms⁷⁶. By reducing the need to internally plan and prepare movement, external cues may decrease cognitive load and therefore facilitate gait prioritization⁶⁰. Cues may also enable re-routing through the less affected cerebellar-cortical loops in order to bypass areas of neurodegeneration. The cerebellum, which influences regulation of timing, rate, and force of muscle activity necessary for gait consistency⁷⁷, is also more often activated during motor than perceptual explicit timing tasks⁷⁸ and may optimize motor execution by recalibrating predictions with sensory consequences^{79,80}.

For people with PD, impaired internal timing mechanisms have been tested using synchronization-continuation paradigms consisting of two phases: first, a synchronization phase, in which participants must find the beat and tap in synchrony with it, and second, a continuation phase, in which they continue tapping at the previous rate without the auditory cue. While

finding the beat requires searching for a structure, continuing the beat requires making predictions and internally generating the beat based on detected structure. Here, an externally-triggered cue gives way to an internally-generated beat based on the template provided. Our protocol used a similar paradigm by setting up an external template, turning off the music once it was established in the mind of the listener, and requiring participants to continue the song in silence. Reports of increased putamen activation during beat continuation than during beat finding suggest that people with PD might exhibit deficiencies in continuing the song in silence^{76,81,82}. However, we observed that people with PD were able to continue the beat in silence when singing and match footfalls to their own internal cues. This raises the possibility that internal cueing through singing can allow for accurate beat continuation, even in people with basal ganglia degeneration.

6.2.3 Vocal-motor coupling improves motor variability

The major finding of **Aim 2** was that internal cues reduced variability not only in automatic gait, but also in challenging gait situations. This suggests that synchronizing movement to one's own singing induces more stability in motor output. In order to explain the reduced attentional load that likely underlies this phenomenon, we put forth a theory of *vocal-motor coupling*, in which a motor effector matches a vocal effector. Coupling between two systems in one body allows for matching between the body's internal oscillatory systems. Such locking between systems has previously been noted in respiration (when matching inhalations during jogging or swimming, for instance), heart rhythms⁸³, gestures between different body parts⁸⁴, or during vocalizations matched to gestures⁸⁵. Directly linking physical oscillators may improve temporal stability.

According to the “multiple timer theory”, every motor effector is independently controlled by a timer, but the timing mechanisms are gated so that it is difficult to separate them⁸⁶. As humans are capable of entrainment in both the vocal and the motor system, matching one to the other via *vocal-motor coupling* may facilitate motor synchronization and reduce attentional load, thereby accounting for reductions in gait variability.

6.2.4 Internal cueing facilitates motor prediction via an internal model

One way to examine our results is through the lens of an internal model, which can provide a theoretical framework for understanding the integration of action-based effects on music perception and embodiment. Internal models that differentiate action and perception enable us to discriminate between those of the external world (when we listen to music) and our own actions (when we sing). Accordingly, an inverse model allows us to translate perceived sensory states into motor commands, such as when an auditory stimulus induces body movement⁸⁷. Forward models, in contrast, allow us to predict the sensory outcomes of our planned actions⁸⁸. In a forward model, the central nervous system makes a copy of the motor command (an “efference copy”) which it then compares to actual sensory feedback⁸⁹. When the sensory consequence of an action matches the predicted outcome, the sensory response is suppressed so that it does not have to be attended to twice. In other words, we do not have to react to our own actions because we already know that we did them.

Forward models play a functional role in the auditory and vocal systems as well. Self-produced key presses that generate auditory tones evoke smaller brain responses and are perceived as quieter than externally-generated sounds⁹⁰. Auditory attenuation to self-produced vocalizations

allows us to speak without auditorily processing every word we say. When humans vocalize, the vocal motor system produces a motor speech template that can be used to compare the sound that is heard to what is produced. If the stimulus matches the intended outcome, the resulting brain activity will be suppressed⁹¹. Not only do self-initiated actions cause stronger predictions for action consequences, they also result in smaller delays than passive actions which happen to the body⁸⁹. Information that occurs at expected times is processed more quickly and efficiently than at unexpected times⁹², which may explain why both speech and hand movements have reduced reaction times for temporally-predictable stimuli⁹³. This may also account for more accurate timing and reduced variability measures during self-generated vocalizations as opposed to externally-imposed cues.

6.2.5 Mental singing and auditory imagery

In **Aim 3**, we showed that mental singing improved gait measures over both music listening and singing aloud. These results not only help optimize this technique but also contribute to a spectrum of recent research on auditory imagery in both healthy and patient populations.

Although most imagery literature has focused on the visual domain, recent research suggests that the visual system is not unique in its ability to activate sensory processing areas in the absence of external stimulation. As in the visual system, in which objects are internally represented in the same way whether visible or imagined⁹⁴, in the auditory system, melodies can be conjured endogenously whether they are heard or imagined. The ability to imagine music, like singing ability, is fairly ubiquitous among humans, whether musically trained or not, as many people report being able to imagine music or musical attributes⁹⁵. Many features of music, including

pitch, tempo, melody, and timbre can be represented through images. Whereas an action observation network is known to mediate motor responses to observed actions, mental singing activates vocal-related areas of the sensorimotor cortex corresponding with tongue movement⁹⁶ as well bilateral fronto-parietal areas³⁰.

Mental singing is highly conducive to synchronization-continuation paradigms, such as we used in all of our studies. In our protocol, an external cue establishes the structure, and the participant must then continue it in silence. Auditory cues can enable continuation of a pattern in silence once it is established within the mind of the listener through musical imagery mechanisms⁸¹. Musical imagery is obvious in earworm, a phenomenon that occurs when a tune gets stuck in one's head, or in the ability of composers who have lost their hearing to continue to write music, as Beethoven did when writing his violin concerto in D-major⁹⁷. Furthermore, mental imagery of musical passages may actually improve motor performance by reducing the need to perceive or match auditory feedback. The violinist Vladimir Horowitz reportedly practiced mentally before his concerts so as not to disturb his motor skills with aural feedback⁹⁸. He may have been onto something. In our exploration of mental singing, we found that this condition elicited the largest reductions in variability. When singing overtly, eliminating the need to synchronize to an external cue minimized aural feedback and improved gait, but when singing covertly, taking away the need to vocalize the cue aloud improved it even more. While we thought that mental singing would work similarly to singing aloud, the discovery that it would actually elicit greater gait improvement was unexpected.

6.2.6 Freezing of gait and cueing

Previous reports suggest that freezers might be particularly amenable to auditory cues³⁸, particularly during turns⁶ or gait initiation⁵⁹, which are challenging situations likely to induce FOG. Externally-imposed cues have successfully improved temporal characteristics of gait in freezers and simultaneously reduced occurrence of FOG⁶. This would be in accordance with the theory that improving gait characteristics overall can lessen the likelihood of passing below a critical threshold in which FOG is induced⁹⁹. FOG episodes are more likely to occur in complex gait situations such as turning or backwards walking, and, as we showed in Aim 2, internal cueing can significantly improve gait features during backward walking. Taken together, this evidence suggests that internal cues may be an especially useful tool for people who experience freezing of gait or motor blocks. Furthermore, internal cues may be particularly beneficial because of their ease of use. Self-generated cue strategies such as “3-2-1-GO” are effective at recovering from FOG during continuous gait or gait initiation^{59,100-102}. Singing, which similarly can be enacted quickly by the individual without the need for any device, may be similarly accessible at a moment’s notice and has the potential to reduce FOG rather than simply assisting with recovery from FOG, though this remains to be tested.

6.2.7 Musical experience and entrainment ability

In **Aim 4**, we observed differences in responsiveness to cues based on musical experience. Musicians’ brains have been used as a model of neuroplasticity with the realization that musical training has a pervasive impact on brain structure, function, and development⁴³⁻⁴⁷. Musical training can strengthen top-down auditory mechanisms¹⁰³ and the strength of neuronal activation

during music perception correlates to the number of years of training¹⁰⁴. Structural brain changes from musical training in early childhood suggest that training-induced brain plasticity can correlate to musically relevant motor and auditory skills that remain into adulthood⁴⁷. Active music-making can specifically induce changes in the arcuate fasciculus, the fiber tract connecting the auditory and motor cortices^{45,105}, and people with musical training exhibit increased connectivity between these areas during rhythm perception⁸². Musicians have more robust subcortical representations of acoustic stimuli, with faster neural timing¹⁰⁶. They also exhibit differences in basic synchronization skills, evidenced by smaller asynchronies, lower tapping variability, and better perception skills than non-musicians¹⁰⁷. Musical and entrainment skills may play facilitate cued gait, as patients with PD who are stronger beat perceivers are more likely to improve gait with musical cues¹³. Our results contribute to the overarching conclusions of these studies that musical training may be predictive of responsiveness to cueing techniques.

6.3 Clinical applications

The preliminary evidence we have provided here suggests that internal cueing may benefit gait for people with PD, but more work is needed to optimize the internal cueing techniques we have described. Future studies should assess optimal cue rates and song choices. We believe that both may be subject to highly individualized needs and preferences in order to gain the most benefit. Here, we consider some potential future avenues of research.

6.3.1 Cue Rate

In all of our experiments, we based the cue rates on each individual's preferred walking cadence. As we expected based on the literature, in Aim 3 we saw the greatest benefit to gait when we raised the cue rate to 110% of preferred cadence, and therefore, we used that same rate in Aim 4. Using external cues at this rate, participants came close to achieving a 10% increase in cadence and velocity, potentially indicating good synchronization to the imposed cadence. In MENTAL, however, these increases were less substantial, indicating that people tended to regress toward their preferred walking cadence. A similar pattern was observed in **Aim 4**. As velocity and stride length increases were still substantial, lower cadences during mental singing are probably not detrimental and may even be optimal, as lengthening strides while reducing cadence is a common goal of gait therapy in PD^{60,108}.

While the combined results of our experiments support the use of cue rates above preferred cadence cues, we recommend this with the caveat that optimal cue rates should likely be individualized based on the specific gait deficits and risks a person exhibits. As an example, in **Aim 4**, we discussed one participant who significantly shortened strides during cueing in order to match the increased cadence of 110%. This individual's response may reflect a breakdown in the linear relationship between stride length and cadence, which has previously been shown to occur at cues over 120% of preferred cadence³⁸ or over 120-130 steps/min¹⁰⁹. This indicates that there may be a ceiling effect of velocity for patients, a limit beyond which they can no longer increase speed while maintaining normal stride lengths. As a result, external cues, even in a research setting, are sometimes determined on an individual basis, for instance, at a rate that induces the longest strides^{42,110}. Other risks should also be taken into account. For people with FOG, for

instance, increased cue frequency may actually provoke FOG events¹¹¹, so such risks should be considered when determining optimal, safe cue rates.

6.3.2 Song choice

A notable limitation of these studies is that we always used the same song for cueing. We chose the song because it was imperative that people knew the lyrics and melody, and songs with life-long familiar melodies are most suitable to entrainment^{49,50}. Song familiarity is undoubtedly an important factor for reducing attentional demands during internal cueing, and repeated musical exposure increases walking speed and enjoyment of music¹⁴. However, different musical choices may encourage different expressive aspects of movement¹¹² as activating music makes movement more vigorous⁸⁷ and may give a “boost effect” to the motor system. Individual preferences for song choice and elements of groove, a feature of music that enhances motor synchronization, may be important factors to consider in future studies^{13,113,114}. For those with weaker beat perception abilities, well selected musical cues can increase velocity, even if no appreciable beat synchronization occurs^{25,110,112}.

6.4 Limitations

6.4.1 Gait Measurement

Quantitative assessments of gait using instrumented walkway mats and motion capture technology, such as we used in these studies, are useful and reliable¹¹⁵ but imperfect tools for assessing the complexity of gait biomechanics and motor control¹¹⁶. Spatiotemporal measures are

inadequate to fully understand movement patterns in healthy or neurological pathology, and motion capture technology leaves room for error¹¹⁷. They also collect a limited amount of information.

Thus, one limitation to the data we have presented here is that we tested our participants in only short bouts of walking, which is representative of how daily walking often occurs but fails to capture gait consistency over more prolonged walking. This limits our ability to make conclusions on the effects of cues over longer distances. While cadence, for instance, reverted slightly back towards preferred over the course of a few trials, we do not know if it would stay at that rate or continue to decline over longer periods. An inherent risk of internal cues is that no pacemaker resets the tempo if the participant deviates too far from “optimal” which could potentially worsen over time.

Another inherent risk of testing only short distances is that gait variability measurement accuracy, in particular, may suffer from this study design. Unlike other features of gait, inter-stride variability measures have lower test-retest reliability, and measurement accuracy may improve over longer distances^{118,119}. As no standardized technique to measure variability exists, motion capture techniques, instrumentation, and analyses are inconsistent and difficult to compare between studies¹²⁰. With these limitations in mind, discriminative and predictive validity are established insofar as they relate to older adults and people living with PD^{26,27,35,121,122}.

6.4.2 Biological variability in gait

Testing only short bouts of walking comes with another consideration concerning variability measurements. Variability exists in all biological systems, and while some of this variability remains adaptive and functional, the summary metrics of variability reported here are widely considered maladaptive and dysfunctional¹²³. The measurements of gait variability that we have reported are known markers of pathological gait and strongly indicative of poor locomotor control and instability. However, at longer time scales, variability can be a sign of health, as healthy individuals display increased variability over longer stretches of time¹²¹. Some recent work suggested that, rather than focusing on restoring linear measures of gait, gait therapy should focus on optimizing movement variability. Based on observations from biological systems such as the cardio-respiratory system, this theory suggests that the goal of gait therapy should be to find balance between predictability and complexity¹²⁴. The optimal state of a physiological system may involve effective cooperation between subsystems and enhanced adaptability to changing environments¹²¹.

Training people with PD, who may exhibit suboptimal gait patterns, to walk to an isochronous beat may run contrary to the natural stride fluctuations that exist in human gait. Eliminating this variability may diminish interactive adaptability and intrinsic stability¹²⁴. Fixed-tempo external cues may not be most effective because they may disrupt the local dynamic stability by altering natural neuromuscular rhythms¹²². Walking to a beat may impose unnatural neuromuscular rhythms on the highly fractal dynamics of gait, and lower functional adaptability⁵⁶. Therefore, adaptive cueing techniques that synchronize to an individual's walking speed may be more effective^{56,113}. Recent evidence suggests that variable external rhythmic cues that oscillate in accordance with human gait are more beneficial than isochronous cues, which are ill-suited to

match the inherent biological variability of walking⁵⁷. Like external cues, these biologically variable cueing paradigms are complex and require technical expertise and equipment, so they are limited in their applicability and accessibility. They suggest, however, a potential benefit of singing in that it might allow for greater adaptability than external cues. Thus, assessing the effects of internal cues on the fractal properties of gait over longer distances may be another avenue for future research.

6.4.3 Freezing status

As FOG episodes are notoriously difficult to provoke in a research setting, freezing status is determined by self-report questionnaires. The NFOG-Q¹²⁵, though the current gold standard, relies on broad questions that may not capture the full spectrum and variability in freezing status. A dichotomous division between freezers and non-freezers may be overly simplistic and future work should address freezing more comprehensively.

6.5 Conclusion

As the world's population ages, increasing numbers of people experience age-related brain diseases. These diseases come with substantial social and economic burden which raise the need to pursue cost-effective, easily accessible rehabilitative strategies that can complement traditional therapeutic methods such as physical therapy.

The studies herein provide preliminary evidence as to the potential usefulness of internal cueing techniques for people with gait impairment due to aging or neurological decline. We have

expounded on theories, both old and new, that may explain these results. We have also provided recommendations for clinical applications and future research studies. The next steps should include an intervention to train individuals with PD to optimize use of this technique. The neuromechanisms underlying internal cueing are elusive and should be further explored using mental singing, which would be particularly conducive to currently available imaging techniques. Considering the widespread availability of singing among neurological patients, other populations, such as patients with hemiplegia or Alzheimer's, may also benefit from vocal-motor coupling techniques.

6.6 References

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