Dynamic Corticomuscular Coherence during Cyclical Ankle Movements: Effects of Aging and Parkinson's Disease

by

Takashi Yoshida

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Institute of Biomaterials and Biomedical Engineering
University of Toronto

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disease with diverse motor and non-motor symptoms. Although the primary neuropathology and symptoms of PD have been well established, the physiological mechanisms behind specific kinematic abnormalities are not well understood. Many such abnormalities (e.g., gait disturbances) can significantly impact a person's quality of life. One way that PD may affect movement is through its connection with the motor cortex. In a series of experimental studies, I have examined whether the communication between the cortex and active muscles (corticomuscular communication) is affected by PD during anti-phasic cyclical ankle movements. To quantify such communication, coherence was calculated between cortical and muscle activities (corticomuscular coherence). The results from these studies suggest that *i*) the midline cortical areas are functionally involved in the cyclical ankle movements, *ii*) the corticomuscular communication may be affected by compensation against aging-related neuromuscular changes, and *iii*) the performance of the cyclical ankle movements is impaired by PD although the kinematic abnormalities were not accompanied by changes in the corticomuscular communication. To better understand how aging and PD affect the corticomuscular communication, future studies should examine the relevant neural correlates of movement in a more comprehensive manner (i.e., including subcortical structures). To my

knowledge, these studies are the first to demonstrate that simple cyclical ankle movements are accompanied by dynamic changes in corticomuscular coherence and to examine how such coherence is affected by aging and PD.

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Chapter 1

1 Introduction

1.1 Thesis roadmap

This thesis consists of seven chapters and six appendices. In this chapter, I describe the motivation and scope of my work. In Chapter 2, I discuss five concepts that are central to my work: *i*) corticomuscular coherence, *ii*) neural correlates of bilateral, cyclical movements, *iii*) normal aging, *iv*) Parkinson's disease (PD), and *v*) neuronal network for locomotor control. In Chapter 3, I present the justification, objectives, and hypotheses for the experimental studies, which are discussed in the body of the thesis. The body of the thesis consists of three chapters, each of which presents an experimental study. All three studies examine corticomuscular communication during simple cyclical movements of the ankles with bilateral coordination, but they differ in their target population. In the first study (Chapter 4), I examine the aforementioned corticomuscular communication in healthy young participants. In the second study (Chapter 5), I examine the effects of aging on the corticomuscular communication by comparing healthy elderly participants against the young participants from the first study. In the third study (Chapter 6), I examine the effects of PD on the corticomuscular communication by comparing participants with PD against the age-matched, elderly participants from the second study. In Chapter 7, I conclude the thesis with my scientific contributions and possible directions for future research on this topic. In Appendices, I present supplementary analysis for Chapters 4 through 6.

1.2 Motivation

My work dealt with how PD affects corticomuscular communication during simple cyclical ankle movements. Here, I briefly describe the rationale for doing so. More detailed justification of the three experimental studies and their objectives are stated in Chapter 3.

1.2.1 Effects of PD on walking

PD is a neurodegenerative disorder with diverse motor and non-motor symptoms. One of the consequences of the disease is the disturbance of gait. Compared to similarly-aged healthy individuals, individuals with PD show greater asymmetry or variability in various aspects of walking. For example, increased asymmetry has been observed in swing durations [1], [2], and increased variability has been observed in the timing of toe-offs [1], step length [3], and the durations of strides [1], [4], [5], steps [6], swing phase [1], [4], [5], and double-support phase [1]. Furthermore, as the disease progresses, many individuals with PD will develop freezing of gait (FOG), which is an episodic inability to generate effective steps (e.g., shuffling or trembling in place [7], [8]). In PD, the prevalence of FOG may be less than 10% for two to three years after the symptomatic onset [9]. However, in approximately two more years, the prevalence can more than double [9]; ten years after the symptomatic onset, the prevalence of FOG can exceed 50% [10]. Although FOG is observed as brief episodes [11], individuals who experience FOG also exhibit abnormalities during steady-state walking. Specifically, individuals who experience FOG show gait abnormalities that are similar to, but worse than, those observed in PD without FOG (e.g., increased variability, asymmetry, and incoordination of various gait parameters [12]-[17]).

1.2.2 Burden of gait disturbances in PD

The aforementioned gait disturbances may contribute to falls. Indeed, it has been reported that 45% of falls in PD occur during ambulation while the remainder of falls occur during standing or postural change between standing and sitting [18]. Also, impaired walking has been identified as a risk factor for falls in PD [19], [20], and increased gait variability is correlated with the frequency of falls in PD [21]. FOG is implicated in falls, with the prevalence of falls increasing proportionally to the frequency of freezing episodes [22].

The consequences of falls are significant. Of the individuals with PD that fall, 13 to 22% may experience fractures in their upper and lower bodies [20], [23]. FOG-related falls can also lead to injuries, possibly as frequently as 50% of the time [22]. Furthermore, individuals with previous falls are likely to fall again [24], [25], making them more vulnerable to injuries. Even if a fall

does not cause a serious injury, it can make an individual fearful of walking [20]. This fear of future falls can lead to reduced mobility and eventual co-morbidities such as cardiovascular deterioration and cognitive decline [7].

1.2.2.1 Prevalence of Falls in PD

Falls are prevalent in PD. Generally, the susceptibility to falls increases over the course of PD [25], [26], and individuals who fall tend to have more advanced disease [19], [20], [25], [27]. A meta-analysis of six prospective studies calculated that 46% of participants with PD fell during a 3-month period [24]. In one study in the meta-analysis, the prevalence rose to 68% by the end of a one-year observation period [28]. Similar prevalence has been reported by retrospective studies, ranging from 38 to 64% [20], [23], [25], [27], [29], [30]. Such prevalence is probably higher than that of similarly aged healthy individuals (e.g., 27% [31]).

1.2.3 Understanding gait disturbances in PD

It has been shown that walking is associated with under- and over-activation of various cortical and cerebellar regions in PD [32]. However, the pathophysiology of gait disturbances in PD is not fully understood. Consequently, there is no single treatment that can universally normalize walking in PD (see the sub-section, *Effects of current treatments*, below) [33]. Given the impairment of walking in PD and its potential impact on the quality of life, understanding how PD affects locomotor control is an important pursuit.

1.2.3.1 Effects of current treatments

Despite being considered the most effective pharmacological treatment for PD [34], [35], levodopa does not comprehensively address the gait disturbances in PD. For walking, the most consistent benefit of levodopa appears to be the increase in step length and, consequently, walking speed [17], [36]-[40]. On other gait parameters, however, the effects of levodopa are inconsistent [41]. For example, some studies indicate that gait variability worsens or does not

improve on levodopa [13], [17], [36], [40], [42] while others report improvement [17], [43], [44]. Levodopa can significantly improve the severity of freezing of gait [45], reduce the number and duration of its episodes [11], [17], [46], and may even delay its onset [47]. However, levodopa cannot eliminate freezing [11], [17], [45], [46], [48], and the prevalence of freezing increases as PD progresses [9]. Furthermore, some individuals with PD experience freezing specifically in the on-medication state [49]-[52]. Levodopa cannot eliminate falls [48], and individuals with PD who experience falls, compared to those that do not, are typically treated with higher doses of levodopa [25], [53].

For addressing gait disturbances, common target nuclei of deep brain stimulation are the internal globus pallidus, subthalamic nucleus, and pedunculopontine nucleus. The effects of stimulation on gait can be inconsistent: the potential benefits are offset by adverse effects and inter-individual variability of outcome. Stimulation of the internal globus pallidus can improve visually-inspected gait [54]-[56] although there is also evidence that pallidal stimulation does not affect parameters of gait [57]. The benefit of pallidal stimulation may be diminished in the on-medication condition [55], [56]. In some individuals, freezing of gait can emerge post-operatively [58]. Pallidal stimulation does not eliminate falls, gait disturbances, or freezing of gait [59]. Stimulation of the subthalamic nucleus can improve visually-inspected gait [60]-[65], self-reported frequencies of falls and freezing [61], [63], self-perceived difficulty with walking [61], gait variability [57], self-reported frequency and prevalence of freezing of gait [62], [66], [67], and the number of individuals that can complete the Stand Walk Sit Test [67]. Similar to pallidal stimulation, the benefit of stimulating the subthalamic nucleus may be diminished in the on-medication condition [63], [65]. Stimulation of the subthalamic nucleus can worsen self-perceived gait in both the on- and off-medication conditions, and the prevalence of such worsening can increase over time [68]. The gradual worsening has also been observed for self-reported frequency of freezing and visually-inspected gait [63]. Some individuals can newly develop freezing or become unable to complete the Stand Walk Sit Test post-operatively [67]. Stimulation of the subthalamic nucleus does not eliminate falls, gait disturbances, or freezing of gait [59]. Stimulation of the pedunculopontine nucleus can improve visually-inspected gait [60], reduce self-reported severity of freezing [69], and increase walking velocity and stride length [70]. However, there is also evidence that pedunculopontine stimulation largely does not affect

self-reported frequencies of falls and freezing, self-perceived difficulty with walking, and visually-inspected gait [71]. Pedunculopontine stimulation does not eliminate falls [72].

Among different forms of gait rehabilitation, there is no single treatment that definitively normalizes walking. Training on a treadmill can significantly reduce the fear of falling [73], increase the speed of walking and stride length [74], increase the maximum tolerable speed of walking [73], and increase the distance that an individual can walk [73]. Treadmill training may not affect gait variability [74]. Individually customized physical therapy, which is designed to improve "balance, postural control, and walking" as well as to learn how to overcome episodes of freezing, can increase the stride length and walking speed [75]. Furthermore, this benefit may be retained in the long term [75]. With somatosensory, visual, and aural pacing at the preferred cadence, actual cadence can decrease [76], slowing down the speed of walking [76], [77]. If applied at a faster pace than the preferred cadence, aural pacing can decrease gait variability [5] and the number and duration of freezing episodes [78]. If applied at a slower pace than the preferred cadence, aural pacing may increase gait variability in the on-medication condition [42]. Training with a preferred modality of pacing (somatosensory, visual, or aural) can increase the step length and speed of walking and improve the severity of freezing [79]. Aural pacing does not eliminate freezing of gait [77], [78]. Visual spatial cues, which is intended to facilitate movement with adequate amplitude, can improve the walking speed [80] but does not eliminate freezing [80], [81].

1.2.3.2 Relevance of cortical participation

How the motor cortex participates in locomotor control and how such participation is affected in PD are of particular interest for several reasons. The basal ganglia, which is affected by degeneration of dopaminergic neurons in PD [82]-[84], is reciprocally connected with the motor cortices [34], [85]-[87], and abnormal interactions between the motor cortex and basal ganglia have been observed in rat models of PD [88], [89] and individuals with PD [90], [91]. Also, several functional neuroimaging studies have found that steady-state walking significantly activates the midline primary sensorimotor cortex [32], [92], [93]. More recent studies have

shown that, within the gait cycle, the midline primary sensorimotor cortex cyclically increases its activity [94]-[98] as well as its coherence with the contracting tibialis anterior muscle [99]. These findings suggest that the primary sensorimotor cortex participates in the control of normal steady-state locomotion. Thus, examining how the motor cortex participates in walking may provide a new insight into how PD impairs locomotion.

1.2.3.3 Selecting the tool to examine cortical participation

Because PD is a neurodegenerative disease that affects movement, the tool for examining the aforementioned cortical participation should treat the cortical and muscle activities respectively as the input and output of the relevant neuromuscular correlates. Of the methods that satisfy this requirement, the following have been used to study corticomuscular communication: corticomuscular coherence (e.g., [99]-[101]), directed transfer function (e.g., [102]), and partial directed coherence (e.g., [103]). Among these methods, I chose corticomuscular coherence for its greater temporal resolution, which was critical for examining the dynamic changes in cortical participation within movement cycles. The proposed physiological mechanisms of corticomuscular coherence are discussed in Chapter 2.

1.2.3.4 Concerns with walking

Although my primary interest is the corticomuscular communication in walking, walking poses two problems. The first problem is that the measurements of cortical electrical activities are vulnerable to motion artifacts. Electroencephalographic (EEG) signals can contain motion artifacts at the stepping frequency and its harmonics, which increase with the speed of locomotion [104]. At 4.5 km/h, which is a normal walking speed, the number of harmonics ranges approximately from 5 to 10, and there can be as many as 15 harmonics [104]. Such evidence casts doubt on the validity of previous studies that used EEG signals to show that the primary sensorimotor cortex is involved in locomotor control (e.g., [94]-[98]). The second problem is the complexity of bipedal locomotion, which requires, among others, balance with full weight bearing, visuomotor integration, and coordination of multi-joint movements. Because

of these requirements, it is difficult to deduce the exact aspect of locomotor control, to which cortical activities contribute.

These two problems can be circumvented by studying a simpler movement that does not pose a significant risk of motion artifacts. For example, studying a stationary movement during sitting would *i*) substantially reduce the risk of motion artifacts and *ii*) eliminate many of the functional requirements in bipedal locomotion. Thus, the scope of my thesis was to examine how PD affected cortical participation in bilateral, cyclical movements of the ankles during sitting. This task isolated some essential requirements for locomotion: maintaining a specific movement frequency and bilaterally coordinating the feet in an anti-phasic manner. If individuals with and without PD differed in the task performance and corticomuscular communication, this would suggest that *i*) the primary sensorimotor cortex contributes to the isolated functional requirements of locomotion via corticomuscular communication and *ii*) the impairment of such communication may lead to certain gait disturbances (i.e., greater variability and asymmetry of gait).

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Chapter 2

2 Background

This chapter discusses five concepts that are central to my thesis: *i*) corticomuscular coherence, *ii*) neural correlates of bilateral, cyclical movements, *iii*) normal aging, *iv*) Parkinson's disease (PD), and *v*) neuronal network for locomotor control.

2.1 Corticomuscular coherence

I have chosen corticomuscular coherence as the tool to examine neuromuscular communication between the cortex and activated muscles. Here, I briefly define coherence and the assumed physiology of corticomuscular coherence.

2.1.1 Definition of coherence

In signal processing, coherence quantifies similarity between the frequency contents of two signals [1]. Coherence is calculated by normalizing the cross spectrum of the two signals by their auto spectra [1]. Because of this normalization, the value of coherence ranges from zero to one, and the unity value indicates that the two signals can be related through a linear, time-invariant system. Thus, statistically significant coherence suggests that the two signals are functionally related as input and output of a particular process. Furthermore, by applying wavelet analysis, coherence can be expressed as a frequency-time distribution. Figure 2.1 shows examples of wavelet coherence between two sinusoids at 30 Hz. In a single segment of wavelet coherence (left plot in Figure 2.1), strong coherence is observed at 30 Hz. However, other areas within the distribution also show high coherence. Coherence in these areas is substantially reduced when multiple segments of wavelet coherence are averaged (right plot in Figure 2.1).

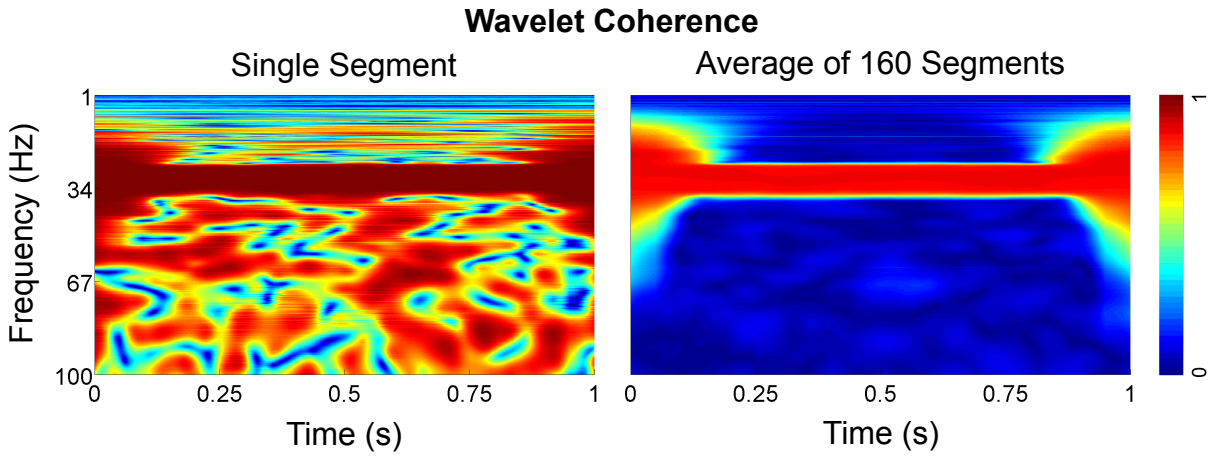

Figure 2.1. The amplitude of wavelet coherence between two signals. Each signal is a sum of *i*) a sinusoid at 30 Hz and *ii*) a normally-distributed random signal with a peak-to-peak amplitude of approximately one. The left plot shows a single segment of wavelet coherence. The right plot shows an average of 160 such segments. For each segment, the phase offset between the two signals was selected from a pre-determined set. This set comprised of normally distributed random numbers within [-π, π].

Wavelet coherence between time series, $x(t)$ and $y(t)$, is calculated using the following equation:

$$\frac{\left|S\left(C_x^*(a,b)C_y(a,b)\right)\right|^2}{S\left(\left|C_x(a,b)\right|^2\right)S\left(\left|C_y(a,b)\right|^2\right)},$$

where $C_x(a,b)$ and $C_y(a,b)$ are respectively the continuous wavelet transforms of $x(t)$ and $y(t)$, the asterisk indicates a complex conjugate, and S is a moving average filter with a specified window size in time. The continuous wavelet transform of a time series, $x(t)$, is calculated by the following equation:

$$C_x(a,b) = \int_{-\infty}^{\infty} x(t)\frac{1}{\sqrt{a}}\psi^*(\frac{t-b}{a})dt \quad ,$$

where ψ is the analyzing wavelet, and a is the scale of the analyzing wavelet at position, b, in time. The scale, a, is related to frequency, f, by the following equation:

$$f = \frac{F_c}{a\Delta t} \quad ,$$

where F_c is the center frequency of the analyzing wavelet and Δt is the sampling interval.

2.1.2 Physiological mechanism of corticomuscular coherence

Coherence can be applied to studies on motor control by treating neural and muscle activities as the input and output of the relevant neuromuscular correlates. Indeed, many studies have used coherence to quantify cortical participation in the volitional control of various upper- and lower-limb muscles [2]-[33]. In these studies, coherence was calculated between the active muscle and the corresponding area of the primary sensorimotor cortex to quantify corticomuscular communication. Below, I describe the physiological events that can lead to such corticomuscular coherence and the underlying assumptions. The descriptions pertain specifically to coherence between a surface electromyographic (EMG) signal from an active muscle and a surface electroencephalographic (EEG) signal from cortical areas that include the primary motor cortex, where the neurons that connect monosynaptically to the α motor neurons are concentrated [34], [35]. Because it is more likely for a linear relationship to exist between monosynaptically connected locations compared to polysynaptically connected ones, one of the physiological phenomena that corticomuscular coherence could indicate is the monosynaptic motor unit recruitment via the corticospinal tract.

2.1.2.1 Synchronous input to the primary motor cortex

A scalp EEG signal is the sum of all electrical field potentials in the vicinity of the measuring electrode. The most significant and physiologically relevant source of the signal is the extracellular potentials caused by post-synaptic potentials [36], [37]. Furthermore, for the signal to be measurable, a large group of neurons needs to receive synchronous input. Thus, a scalp EEG signal contains information about synchronous input to a large group of neurons near the electrode. Although EEG signals can contain sub-threshold activities, I assume that neuronal groups communicate through coherence [38]. In other words, excitabilities are phase-locked between the source of the synchronous input and its recipient to ensure that the recipient fires.

2.1.2.2 Motor unit recruitment by common supraspinal input

A surface EMG signal is the sum of all motor unit action potentials in the vicinity of the measuring electrode. In corticospinal activation of muscles, it is assumed that the motor units are recruited by common supraspinal, excitatory input. This notion is supported by experimental evidence. Common excitatory input to two motor neurons may be inferred from the cross-correlation between their spike trains [39]. If two motor neurons receive input from a single presynaptic neuron, the cross-correlation of their spike trains can show a narrow peak with a few milliseconds of delay [40]. In order to attribute such phenomenon exclusively to common pre-synaptic input from a single neuron, the temporal width of peak cross-correlation must be less than 6 ms [41]. Cross-correlation with a few milliseconds of delay has been observed for motoneuronal pairs of the tibialis anterior muscle during isometric contractions although the peak cross-correlation is slightly broader than the 6-ms threshold (approximately 10 ms) [41]-[44]. In this case, the cross-correlation may also be caused by separate interneurons that are synchronized by common input [40], [41]. Short-delay, peaked cross-correlation is absent in individuals that have experienced stroke on the contralateral side of contraction or acquired rostral cervical spinal cord injury [44], [45]. In stroke, the cross-correlation is preserved on the unaffected side [45]. These impairments (or lack thereof) suggest the supraspinal origin of the common input to cross-correlated motor units.

In most studies, corticomuscular coherence is observed within the beta band (i.e., 13 to 30 Hz) [2]-[33]. Some studies have observed coherence at higher frequencies, but these frequencies were associated with multisensory integration [23] or near-maximal voluntary contractions [16], [30]. Therefore, most studies suggest that the active motor neurons receive common supraspinal input in the beta band. This notion is supported by experimental evidence: e.g., intramuscular beta coherence between surface EMG signals from the tibialis anterior muscle during the swing phase of treadmill walking [46], [47]. Furthermore, the absence of intramuscular beta coherence in individuals with incomplete spinal cord injury suggests the supraspinal origin of the motor unit recruitment [47]. The frequencies in the beta band (13 to 30 Hz) are higher than the firing rates of individual motor units [48], [49]. This is because individual motor units do not necessarily fire at the recruitment frequency. Rather, the recruitment frequency is reflected in the sum of individual spike trains [50].

2.1.2.3 Linear transmission of motoneuronal recruitment frequency to EMG signals

I assume that the frequency, at which the motor units are recruited, is linearly transmitted from the presynaptic input to the EMG signal. The linear transmission of the corticomotoneuronal recruitment frequency has been demonstrated experimentally [51] and by computational modeling [51]-[53]. Experimentally, it has been shown that motor unit action potentials and the somatotopically corresponding EEG signal are coherent, with the coherence increasing as more motor units are used to calculate the coherence [51]. In computational modeling, the summed firing patterns of a motoneuronal group can carry the mean frequency of common presynaptic input [51]-[53], and the effectiveness of linear transmission is proportional to the size of the motoneuronal group that receive common input [51], [53]. Recently, De Luca and Kline have criticized previous studies for overestimating the percentage of motor units that are synchronized by common input [54]. With a more statistically rigorous method, De Luca and Kline found that only 50% of the motor units are synchronized by common input [54]. However, it is likely that enough motor units are synchronized to show corticomuscular coherence during muscle contractions. For example, the tibialis anterior muscle is innervated by more than 400 α motor neurons, and the medial gastrocnemius muscle is innervated by more than 500 α motor neurons

[55]. It has been shown experimentally that less than ten motor units are needed for corticomuscular coherence to reach statistical significance [51].

2.1.3 Role of corticomuscular coherence during cyclical movements

In humans, the exact contribution of the motor cortex to cyclical movements is unknown. Several studies have examined such contributions in cats during locomotion. In cats, the motor cortex is thought to modify the basic patterns of locomotion via the corticospinal tracts [56]. This notion is supported by the existence of pyramidal tract neurons in the motor cortex that increase their activity in synchrony with stepping over various obstacles during locomotion [57] or in inverse proportion to the distance between barriers that have to be stepped over during locomotion [58]. Furthermore, the patterns of leg muscle activities can be augmented during locomotion by electrically stimulating the pyramidal tract [59] or the motor cortex [60], and this augmentation is phase dependent within the gait cycle [59], [60]. However, due to the absence of monosynaptic corticomotoneuronal connections in cats [61], the aforementioned gait augmentation is likely mediated by interneurons, which are affected by the pattern-generating circuit in the spinal cord [56]. Such polysynaptic process may be non-linear and not reflected in corticomuscular coherence. It is unknown whether skillful gait modification involves monosynaptic corticomotoneuronal connections in humans. However, during movements that do not require significant adaptation to obstacles, the motor cortex may contribute to functional requirements other than ongoing modification of the movement kinematics.

2.2 Neural correlates of movement

Corticomuscular coherence does not specify where the synchronous input to the primary motor cortex originates. However, it is likely that the source of input is one of the neural correlates of movement, which can be identified by functional neuroimaging. To my knowledge, the exact neural correlates of bilateral, cyclical, anti-phasic ankle movements are unknown. However, previous studies have examined the neural correlates of similar movements. For example, Toyomura et al. examined bilateral, cyclical, anti-phasic flexion and extension of the knees at 2 Hz [62]. This movement activated the midline primary sensorimotor cortex and supplementary

motor area regardless of whether the movement was self-paced or externally paced by aural stimuli [62]. Externally-paced movements also activated the anterior lobe of the cerebellum [62]. Furthermore, between the two types of pacing, self-pacing induced greater activity in the left putamen while external pacing induced greater activity in the superior temporal gyrus bilaterally [62]. Wu et al. examined self-paced, bilateral, cyclical, anti-phasic extension and flexion of the index fingers at 0.5 Hz [63]. This movement resulted in bilateral activation of the primary sensorimotor cortex, supplementary motor area, thalamus, basal ganglia, and cerebellum [63]. Although the movement activated other brain areas, the aforementioned areas are recurrently mentioned in other studies that examined unilateral finger tapping. Unilateral finger tapping frequently activates the contralateral primary motor or sensorimotor cortex [64]-[75], medial or contralateral supplementary motor area [64], [65], [68]-[72], [74], [76], contralateral premotor cortex [65], [66], [71], [74], contralateral thalamus [66], [68], [69], [72], contralateral or bilateral basal ganglia [66], [69], [72], [73], and ipsilateral cerebellum [65]-[71], [73], [74]. The involvement of motor cortices is intuitive for the execution of voluntary movements, as is the involvement of the thalamus, which gates the output of the cerebellum and basal ganglia to the motor cortex [77]. The cerebellum is thought to correct an ongoing movement by comparing an internal model of the movement against afferent feedback (i.e., intended movement against actual movement) [78], [79]. The cerebellum is also thought to aid in executing successive movements with appropriate timing [78], [79]. Indeed, cerebellar lesions can result in dysdiadochokinesia: an inability to produce rapid alternating movements [78], [79]. The basal ganglia may aid in appropriate spatio-temporal scaling of movement [79], [80]; and the putamen increases its activity bilaterally when the periodicity of aural pacing has been internalized [81]. All of the above functions are vital in performing cyclical movements.

2.3 Aging

Individuals with PD tend to be older, with the majority between 60 and 80 years of age [82]. Because aging itself is associated with physiological changes that can affect motor control and performance, these changes need to be identified to delineate the effects of PD.

2.3.1 Effects on the nervous system

2.3.1.1 Macroscopic changes

Many effects of aging have been observed on the neuromuscular system. Macroscopically, aging is associated with diminished volumes of both white and gray matter [83]-[85]. Generally, gray matter volume declines steadily from the age of 20 years while white matter volume changes non-linearly [83]-[92]: white matter volume may peak around the age of 40 years [83], [85], [88], [90], [91], after which it decreases at an accelerating rate, especially past the age of 70 years [84], [92]. These time courses may indicate cortical maturation up to the fifth decade of life [90]. In other words, the decrease in gray matter volume represents neuronal pruning and the parallel increase in white matter volume represents continued myelination.

Many studies have attempted to identify brain region that are particularly vulnerable to age-related volumetric decline in white and gray matter. Although these studies can disagree on the relative loss between regions, a substantial volumetric decline in gray matter has been observed in the primary motor cortex [85], [88]-[91], primary somatosensory cortex [85], [88]-[91], and cerebellum [84], [88]. The relevance of these regions to the performance of cyclical movements was mentioned above. As for white matter, myelinated fibers within the anterior brain [88], [93]-[95], genu of the corpus callosum [93]-[96] (although posterior regions may also be affected [96]), and posterior limbs of the internal capsule [88], [93] may be particularly vulnerable to age-related deterioration. The frontal region of the brain and the corpus callosum may be relevant for cognition involved in bilateral coordination of movement [97], and the posterior limbs of the internal capsule contain the corticospinal tracts [77], [98].

2.3.1.2 Effects on neural correlates of movement

The above macroscopic deteriorations suggest that aging may change the neural correlates of cyclical movements. Generally, compared to young individuals, elderly individuals show greater activation of the brain (i.e., recruitment of additional brain regions or increased activation of the same neural correlates) [69], [99]-[104]. For some muscles, their somatotopic representation over

the motor cortex may become broader with age [105]. A few studies have suggested a specific pattern for how aging changes the activation of the brain. Such patterns include decreased laterality during unilateral movements [99] and less distinct patterns of activation between different motor tasks [106]. Increased brain activation may be a form of compensation for age-related deteriorations. In some cases, greater activation of neural correlates is associated with better task performance in elderly individuals [101], [107], and elderly individuals with greater activation show comparable performance to young individuals [69], [104].

2.3.1.3 Microscopic changes

Aging is also associated with microscopic changes that contribute to synaptic dysfunction and impaired transmission of action potentials. In mice, aging is associated with structural abnormalities of the neuromuscular junctions, including partial or complete denervation of the post-synaptic sites with acetylcholine receptors [108]. In humans or non-human primates, microscopic changes include degeneration of myelin sheaths and reduced conduction velocity along the affected axons [109]-[112], regression of the dendritic arbors [113], [114], fewer synapses per neuron [109], lowered density of dendritic spines on pyramidal neurons [113], [114], fewer large neocortical neurons [115], and reduced synthesis of certain neurotransmitters (e.g., dopamine, serotonin, norepinephrine, and acetylcholine) [109], [110], [116].

2.3.2 Effects on the musculoskeletal system

2.3.2.1 Sarcopenia

In the musculoskeletal system, a prominent effect of aging is sarcopenia, which is the loss of skeletal muscle mass and strength with aging [117]. Here, I focus on the effects of aging on the leg muscles. Age-related decrease in muscle mass is often reported as the discrepancy in the cross-sectional area of a muscle between young and older individuals. Smaller cross-sectional areas for older individuals have been reported for the quadriceps femoris muscle [118]-[121], hamstrings muscle group [121], and plantarflexors [122] and dorsiflexors [123] of the foot. Some studies have used computed tomography to estimate muscle volumes, which is smaller for older

individuals compared to young individuals [121], [122]. Decrease in strength is measured during maximum voluntary contractions of various muscle groups. During knee extension [118]-[120], [124], [125], foot dorsiflexion [123], [126]-[130], and foot plantarflexion [127], [131], [132], older individuals generate weaker forces than young individuals. The reduced strength may be attributed to reduced muscle mass or decrease in the intrinsic muscle strength. The latter can be measured by specific tension, which is a quotient of voluntary or electrically-evoked maximum force divided by the cross-sectional area of a muscle. Although the reports on reduced muscle mass are consistent, those on specific tension are contradictory. Some studies have reported that aging lowered the specific tension [120], [133] while others have reported no age-related difference [118], [123].

2.3.2.2 Muscle fiber composition

Several studies have used biopsies or post-mortem sampling to analyze how aging affects the composition of slow- and fast-twitch muscle fibers. Most of these studies have focused on the vastus lateralis muscle [134]-[139], but experimental evidence also comes from the lateral gastrocnemius [140] and tibialis anterior [141] muscles. Although small samples may not always represent the effects of aging on the entire muscle [142], the above studies have suggested some trends in how aging affects the fiber composition of muscles. First, with aging, both the combined number and cross-sectional area of slow- and fast-twitch fibers decreases [135], [136], [138], [139]. Second, with aging, the proportion of fast-twitch (i.e., type II) fibers can decrease [134], [138]-[141] although there is also evidence against this notion [135], [136], [140]. Third, the cross-sectional area of slow-twitch fibers may be relatively unaffected by aging [141]. These trends suggest that slow-twitch fibers become more dominant in an aging muscle.

The notion that slow-twitch fibers become more dominant in an aging muscle is also supported by age-related discrepancies in the time to peak tension for electrically-evoked contractions and muscle fiber conduction velocity of a surface EMG signal. In older individuals, the time to peak tension is longer and the conduction velocity is slower. The longer time to peak tension is a characteristic of slow-twitch fibers [55], and the conduction velocity correlates linearly with the

proportion of a muscle's cross-sectional area that is occupied by fast-twitch fibers [143]. The longer time to peak tension has been observed in the triceps surae [130], [131], [133], tibialis anterior [129], [144], and gastrocnemius [132] muscles; the slower conduction velocity has been observed in the tibialis anterior muscle [128].

2.3.3 Effects on motor units

Using the method described in [145] or its variants, several studies have estimated that older individuals have fewer functioning motor units. This trend has been shown for the extensor digitorum brevis muscle [146], biceps brachii and brachialis muscles [147], and thenar and hypothenar muscles [148]. The decrease in motor units with age is also supported by histological studies of the spinal cord in the lumbar [149], [150] or lumbosacral regions [151]. These studies have shown decrease in the number of motoneurons with aging. Age-related decrease in the number of motor units or motoneurons may be non-linear, with very little decrease until around the age of 60 years and the rate of decrease accelerating henceforth [146], [148], [151]. Furthermore, age-related decrease in motoneurons may re-organize the motor units to include more fibers per neuron, possibly impairing the ability to finely control force output [55]. The re-organization is suggested by the increased amplitude of individual motor unit activities, which has been observed in the vastus lateralis [125], [152] and tibialis anterior [152], [153] muscles. Again, the re-organization may progress non-linearly and accelerate around the age of 60 years [125], [152].

2.3.4 Effects on motor performance

As described above, aging may reduce strength and impair fine control of force output. Ankle movements without resistance are unlikely to require near-maximal strength, but impaired ability to finely control force output may affect cyclical, bilateral movements. Other effects of aging that could affect the performance of cyclical, bilateral movements include reduced range of motion, increased movement variability, impaired bilateral coordination, and reduced proprioception. Age-related reduction in the range of motion has been observed at the hip [154], [155], knee [155], and ankle [126], [156], [157]. At the ankle, the magnitude of change can range

from 3 to 10 degrees [126], [156], [157]. Increased movement variability has been observed in the cycle duration of overground walking and aurally-paced stepping during sitting [158]. Impaired bilateral coordination has been observed in the phase offset between steps of overground walking [159] and between two limbs during aurally-paced, anti-phasic upper body movements [160], [161]. At higher movement frequencies, impaired bilateral coordination becomes more pronounced [160], [161], and older individuals are more prone to transitioning from anti-phasic to in-phasic movements [161]. Finally, aging seems to reduce proprioception. Many studies have examined the effects of aging on proprioception by testing the joint position sense of the knee. The tests are typically performed by measuring either the threshold angle for detecting a slow passive joint movement [162]-[164] or the accuracy of reproducing or estimating a joint angle [162], [163], [165]-[168]. By both measures, older individuals show reduced proprioception. Similar tests have been performed for the ankle: estimating an angle of passive dorsiflexion [169], detecting slow passive dorsi- and plantarflexion [170], and detecting a specified magnitude of passive plantarflexion [171], [172]. These tests also show reduced proprioception for older individuals. Proprioception is important especially if a movement cannot be monitored via visual feedback. The effects of reduced proprioception, however, may lessen quickly with practice [167], [172].

2.3.5 Effects on corticomuscular coherence

Although many studies have used coherence to examine corticomuscular communication, only a few have examined how it is affected by aging [31]-[33], [173]. Furthermore, these studies were limited to sustained contractions. Aging has been shown to both decrease [32], [33] and increase [31], [173] the amplitude of coherence. Aging has also been shown to affect the frequency of peak coherence. The frequency of peak coherence is usually in the beta band (i.e., between 13 and 30 Hz), but aging may lower the frequency [173], increase the frequency's inter-individual variability [33], or generate multiple peaks in coherence [33]. Lastly, aging may broaden the cortical distribution of coherence. In other words, cortical activities from a broader area are coherent with a muscle activity [33].

2.4 PD

PD is a neurodegenerative disease with motor and non-motor symptoms. Here, I discuss the basics of the disease and how it affects the control and performance of cyclical movements.

2.4.1 Brief epidemiology of PD

The epidemiology of PD appears to vary between different geographical locations [174]. Therefore, I have focused on the statistics of North American populations. Incidence of PD has been reported as 13.4 per 100,000 [82], but it can be substantially higher among elderly individuals. In one study, only 13% of the new cases were under 60 years of age [82]. Another study reported that incidence was almost 4 times higher among individuals between 75 and 79 years of age, compared to individuals between 55 and 59 years of age [175]. Prevalence of PD has been estimated as 135 per 100,000 [176]. Prevalence of PD can also increase with age, especially after 60 years of age. For example, estimated prevalence in one study was almost 9 times higher among individuals between 75 and 79 years of age, compared to individuals between 55 and 59 years of age [176]. Epidemiology of PD may show sex difference, with men being more vulnerable. In one study, incidence was 1.9 times higher for men [82]. In another study, prevalence was 1.2 times higher for men [176]. Compared to healthy individuals, individuals with PD show increased mortality rate: the mortality rate ratio may vary between 1.75 and 2.7 [177], [178], and it can increase with age [175] or dementia [178]. A previous study has reported the medical burdens on a cohort of 15,304 individuals with parkinsonism, 75% of which had been diagnosed with PD, with the remainder been prescribed medications for PD [179]. Compared to an age- and sex-matched control group, the cohort of individuals with parkinsonism showed higher physician and drug costs, more frequent hospital admissions, and longer length of stay [179].

2.4.2 Neuropathology of PD

2.4.2.1 Neuronal loss

PD is associated with neuronal loss in the substantia nigra pars compacta within the basal ganglia [180]-[182]. Although the neuronal loss is also observed in normal aging, the loss is substantially greater in PD [181], [182]. Furthermore, normal aging shows a linear rate of loss while the rate is nonlinear in PD, with almost 50% of the loss occurring in the first decade after the onset of symptoms [181]. A previous study has estimated that the neuronal loss begins approximately 5 years before the onset of symptoms [181]. The neuronal loss can vary within different regions of the substantia nigra pars compacta [180], [181], [183]. Furthermore, different regions are associated with different symptoms of PD. For example, greater neuronal loss in the lateral region of the substantia nigra pars compacta is associated with hypokinesia and rigidity [180], [184] while greater neuronal loss in the medial region is associated with dementia [180], [184].

2.4.2.2 Dopamine-related changes

Compared to healthy individuals, the concentrations of dopamine and its metabolite (homovanillic acid) are substantially reduced in the striatum of individuals with idiopathic PD [185]. In other words, both the availability and metabolism of dopamine are diminished within the striatum of individuals with PD [185]. Furthermore, the striatal concentrations of both dopamine and homovanillic acid are negatively correlated with the degree of neuronal loss in the substantia nigra pars compacta [185]. The availability of dopamine at the presynaptic terminals of dopaminergic neurons can also be reduced in the striatum (especially the putamen) of individuals with PD, compared to healthy individuals [186], [187]. Reduced availability of dopamine at the presynaptic terminals is proportional to the disease severity [187].

PD is also associated with changes that affect the synaptic transmission from dopaminergic neurons. Compared to similarly-aged, neurologically normal individuals, individuals with PD show reduced expression of messenger ribonucleic acid that encodes the dopamine transporters in the substantia nigra pars compacta [188]. Because the transporters re-absorb dopamine into the

dopaminergic neurons, decrease in the number of transporters would impair the regulation of dopamine levels in the synaptic cleft. This finding is supported by functional neuroimaging studies: compared to healthy individuals, dopamine transporters on the presynaptic dopaminergic neurons are reduced in the striatum (especially in the putamen) of individuals with PD [186], [189], [190]. Even in early stages of the disease, when the symptoms occur unilaterally, the dopamine transporters are diminished bilaterally, and the extent of decrease is proportional to the severity of the disease [189]-[191].

2.4.2.3 Alpha-synuclein protein accumulation

In addition to the neuronal loss, PD is associated with inclusions of abnormally accumulated alpha-synuclein protein inside the surviving neurons [192], [193]. Such accumulation is called Lewy bodies and Lewy neurites, which are found in the substantia nigra of most, if not all, cases of PD [193]-[195]. The appearance of Lewy bodies and neurites can vary. Lewy bodies can be "sharply contoured, spherical, ovoid, plum or paddle-shaped" whereas Lewy neurites can be "slender or swollen, short or long, serpentine or chaplet-like, elongated, flagelliform, spiral or club-shaped" [193]. Lewy bodies are considered as a marker for neuronal loss [192]: among healthy, non-demented individuals, those with Lewy bodies show greater neuronal loss in the substantia nigra pars compacta [181]. Assuming that the topography of Lewy bodies and neurites indicates the progress of PD, Braak et al. have proposed six stages of PD, with the Lewy bodies and neurites being confined to the medulla oblongata in the first stage, reaching the substantia nigra pars compact in the third stage, and eventually spreading to the neocortex in the final stages [196]. The validity of this model is disputed. For example, the Braak stages of individuals with PD are unrelated to their disease severity [197]. Also, elderly individuals that die without dementia or parkinsonism can be classified as any of the six Braak stages, with the stages being unrelated to the age at death [197].

2.4.3 Clinical manifestations of PD

2.4.3.1 Asymmetry

The classic signs of PD are resting tremor, rigidity, akinesia, and bradykinesia [80]. At the onset of PD, motor symptoms occur unilaterally [190], [198], but as the disease progresses, the symptoms occur bilaterally [190]. Despite the bilateral occurrence, the severity of symptoms [199] and neuropathology [186], [189]-[191], [200] can remain asymmetrical. Symmetrical presentation may indicate more advanced stages of the disease, as the asymmetry in both the severity of symptoms [201] and neuropathology [202] tends to be reduced over time.

2.4.3.2 Non-motor symptoms

PD presents with motor and non-motor symptoms. In their review, Chaudhuri et al. classify non-motor symptoms into neuropsychiatric symptoms (e.g., depression and dementia), sleep disorders, autonomic symptoms (e.g., orthostatic hypotension and sexual dysfunction), gastrointestinal symptoms (e.g., dribbling and constipation), sensory symptoms (e.g., pain and hyposmia), and others such as fatigue [203]. Among these symptoms, rapid eye movement sleep behavior disorder [204], [205], depression [206], constipation [207], and hyposmia [208] may emerge before motor symptoms (i.e., as pre-clinical symptoms) of PD.

2.4.3.3 Heterogeneity

PD is heterogeneous in its manifestation. This is illustrated by the diversity of clinical subtypes. Several studies have identified clinical subtypes by characterizing the groups that arise from cluster analysis. For example, Graham and Sagar have identified three clinical subtypes (in the order of prevalence): *i*) individuals with motor symptoms and no cognitive impairment, *ii*) individuals with both motor and cognitive impairments, and *iii*) individuals that are older at onset and experience rapid progression of both motor and cognitive impairments [209]. Similarly, Erro et al. have identified *i*) individuals with both motor and non-motor symptoms, *ii*) individuals with predominantly non-motor symptoms, *iii*) individuals with almost exclusively motor symptoms, and *iv*) individuals with predominantly motor symptoms (in the order of prevalence)

[210]. Furthermore, all of the above groups showed relatively preserved cognitive abilities [210]. Although different subtypes can emerge in each study, some studies have reported very similar classifications [211]-[213]. These studies have identified four clinical subtypes: *i*) individuals with an early onset with signs of levodopa complications; *ii*) individuals with tremor as the dominant symptoms; *iii*) individuals with predominantly non-motor symptoms, cognitive impairment, and signs of depression; and *iv*) individuals that are older at onset and experience rapid disease progression. All but the group with predominantly non-motor symptoms show relatively preserved cognitive abilities [211]-[213] although the group with rapid disease progression may show some cognitive deficits [212]. The relative prevalence of the above subtypes varies among the studies. However, they agree that the group with rapid disease progression represents the smallest subtype while the group with an early onset or tremor-dominant phenotype represents the largest subtype [211]-[213].

2.4.4 Basal ganglia

As described above, PD affects the basal ganglia, which is a subcortical structure that has been implicated in many aspects of movement, including motor learning and automatization of movement [80]. Here, I discuss the classic model of the basal ganglia and PD, as well as the motor functions of the basal ganglia.

2.4.4.1 Classic model of basal ganglia

The basal ganglia comprises several inter-connected nuclei, which are mirrored about the sagittal plane. On each side, the nuclei consist of the caudate nucleus, putamen, substantia nigra pars reticulata and pars compacta, internal and external segments of globus pallidus, and subthalamic nucleus. The caudate nucleus and putamen comprise the striatum, which is the main recipient of excitatory input from the cerebral cortex and thalamus. The substantia nigra pars reticulata and internal segment of globus pallidus are the main output nuclei of the basal ganglia. Their inhibitory output projects to the brainstem and cerebral cortices via the thalamus, thus forming thalamocortical loops. These loops are not completely closed, as the basal ganglia receives cortical input from both pre- and post-central areas but its output projects only to the pre-central

areas [79], [80], [214]. Furthermore, considerable convergence occurs as the cortical input projects to the striatum and passes through the basal ganglia [80], [214].

It is thought that the thalamocortical loops comprise segregated circuits that serve distinct functions. These functions, which are implied by where the cerebral input arises, include motor, oculomotor, associative and executive, and limbic functions [80], [214], [215]. The aforementioned convergence of cortical input is thought to occur within (and not across) functional circuits [80], [214]. The notion of segregated functional circuits is supported by the differential association between the lateral and medial regions of the substantia nigra pars compacta. Greater neuronal loss in the lateral region is associated with hypokinesia and rigidity [180], [184] while greater neuronal loss in the medial region is associated with dementia [180], [184]. Because the lateral region projects more to the putamen and the medial region projects more to the caudate nucleus, it is likely that the former participates in the motor circuits while the latter participates in the executive and associative circuit [180].

Figure 2.2 shows the classic model of the motor circuit, which is the most studied [80] and most relevant circuit to the experimental studies in Chapters 4 through 6. The motor circuit is organized somatotopically: leg and orofacial movements are respectively represented in the dorsolateral and ventromedial regions of the putamen, and arm movements are represented in the region between the leg and orofacial regions [80], [215]. Such somatotopic organization is thought to be maintained throughout the thalamocortical loops [215]. The motor circuit may also be topographically organized, such that projections that arise from different motor cortices remain segregated throughout the circuit [80], [215]. According to the model in Figure 2.2, the inhibitory output of the basal ganglia is modulated by the dopaminergic neurons in the substantia nigra pars compacta. The modulation is achieved through the monosynaptic and polysynaptic connections between the putamen and the output nuclei (i.e., direct and indirect pathways). The dopaminergic neurons facilitate the direct pathway and inhibit the indirect pathway. Thus, increased input from the dopaminergic neurons results in the disinhibition of the thalamus and brainstem. Although it is intuitive to predict that such disinhibition may facilitate movement, the model does not explain how specific aspects of motor control are affected by PD.

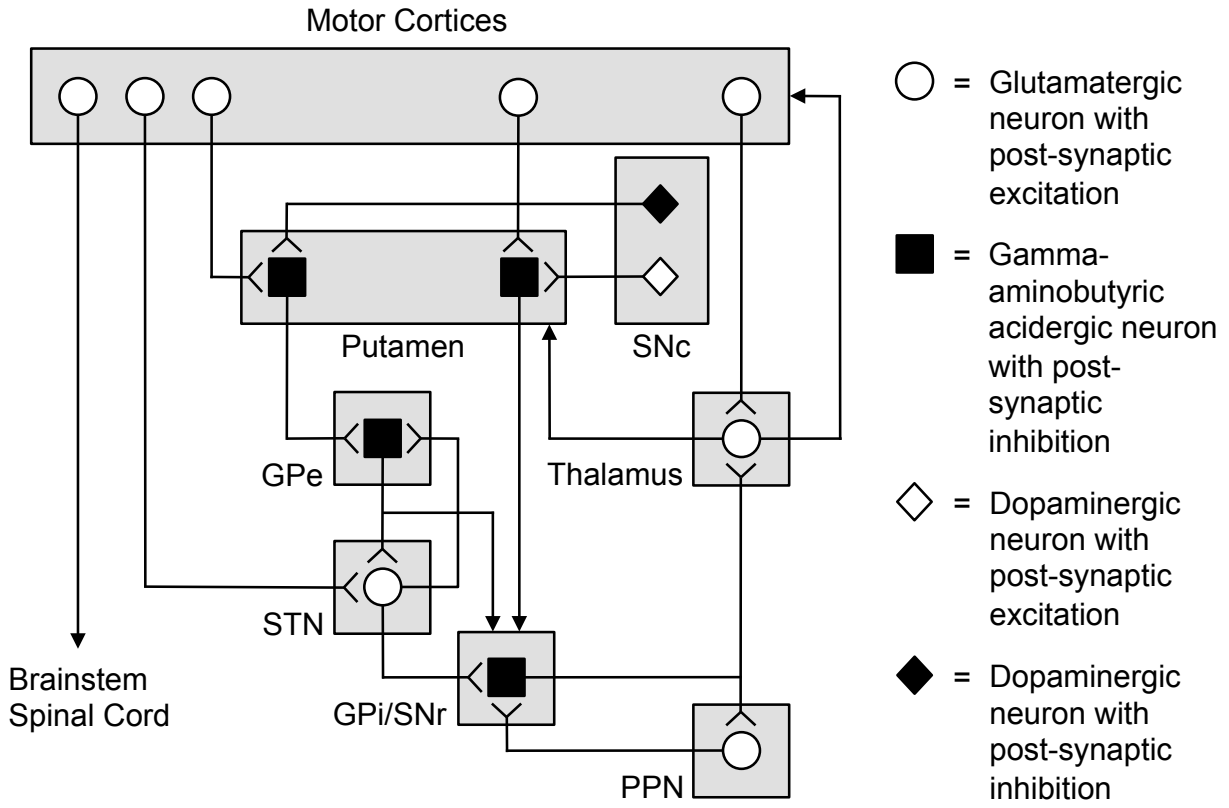

Figure 2.2. Schematic representation of the basal ganglia with emphasis on motor functions. The schematic has been adopted from [80], [215]-[217]. GPi and GPe are the internal and external segments of the globus pallidus, respectively. SNc and SNr are the pars compacta and pars reticulata of the substantia nigra, respectively. STN is the subthalamic nucleus, and PPN is the pedunculopontine nucleus.

2.4.4.2 Classic model of PD

A hallmark of PD is the gradual loss of dopaminergic neurons in the substantia nigra pars compacta. According to the classic model of the basal ganglia, reduced dopaminergic output will result in increased inhibition of the motor regions of the thalamus and brainstem [216], [217]. The increased inhibition may contribute to hypokinetic symptoms of PD. However, such a general description does not explain the diverse motor symptoms of PD. Furthermore, the classic model accounts for neither the complex anatomy of the basal ganglia [216] nor the dynamic interactions between the nuclei. I will not compare alternative models of the basal ganglia here

(e.g., [216]). Despite these shortcomings, some findings from electrophysiological studies support the classic model. For example, in individuals with PD, the internal segment of the globus pallidus shows greater neuronal firing rates than the external segment [218]. Also, the neuronal firing rate within the subthalamic nucleus is greater for individuals with more progressed PD [219]. According to the classic model of the basal ganglia, increased firing rate in the internal segment of the globus pallidus and the subthalamic nucleus is an expected consequence of dopamine deficiency.

The model is also somewhat corroborated (albeit a few contradictions) by studies on monkeys that have been rendered parkinsonian by administering 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which is a neurotoxin that selectively destroys the dopaminergic neurons in the substantia nigra pars compacta [220]. Compared to intact monkeys, monkeys with MPTP-induced parkinsonism show a substantial decrease in the dopamine levels within the striatum [221]; increased neuronal firing rate, neuronal activity, and elevated metabolism in the internal segment of the globus pallidus [222]-[224]; increased neuronal activity in the substantia nigra pars reticulata [223]; decreased neuronal firing rate in the external segment of the globus pallidus [222], [224], [225]; and increased neuronal firing rate and activity in the subthalamic nucleus [223], [225]. Increased excitation of the output nuclei, increased inhibition of the external segment of the globus pallidus, and increased excitation of the subthalamic nucleus are all predicted by the classic model of PD. However, studies of MPTP-treated monkeys have also reported lack of increase in the neuronal firing rate in the internal segment of the globus pallidus [225], elevated metabolisms in the external segment [221], and relatively unchanged metabolism in the substantia nigra pars reticulata [221]. These observations contradict the classic model.

2.4.4.2.1 Effects of levodopa

Despite some complications later in the course of treatment, levodopa (i.e., a precursor of dopamine) is considered the most effective treatment for PD [217]. Complications related to levodopa include motor fluctuations (i.e., alternation between periods of levodopa in effect and

obvious return of motor and non-motor symptoms as levodopa wears off), dyskinesia (i.e., abnormal involuntary movements), and psychiatric complications [217].

According to the classic model of the basal ganglia (Figure 2.2), increased concentration of dopamine within the striatum would mitigate the over-inhibition of the thalamus and brainstem in PD [217]. This prediction is partially supported by experimental evidence. In one study, levodopa reversed the MPTP-induced increase in the neuronal firing rate of the internal segment of the globus pallidus [224]. Another study reported that levodopa reduced the neuronal activity of the output nuclei of the basal ganglia, which had been increased by MPTP [223]. The classic model also predicts that dopamine could cause dyskinesia by excessively inhibiting the output nuclei of basal ganglia via the direct and indirect pathways [216].

2.4.4.3 Motor functions of basal ganglia

Here, I discuss motor functions of the basal ganglia that may be relevant to the experimental studies in Chapter 4 through 6. These functions include motor learning and automatization of movement. Any unfamiliar task has to be learned by study participants; once learned, the participants may be able to perform the task automatically with improved efficiency.

2.4.4.3.1 Motor Learning

Several studies have examined the neural activities of monkeys and humans learning unfamiliar visuomotor tasks. The findings from these studies suggest that the basal ganglia work with the supplementary motor area in learning new movements. This is consistent with the thalamocortical loop that the basal ganglia forms with the supplementary motor area. Single-cell recordings in monkeys have shown that neurons in the supplementary motor area are preferentially active during motor learning: some neurons decrease their activity as a task becomes well learned, while others are preferentially active during the execution of a well-learned task [226]. The same behaviors are observed in the striatal neurons [227]. When the pre-supplementary motor area is inhibited in monkeys by a pharmacological injection, motor

learning becomes impaired [228]. However, the same inhibition does not affect the performance of well-learned visuomotor tasks [228]. Similarly, motor learning is impaired by inhibition of the anterior striatum, and the execution of learned movements is impaired by inhibition of the middle and posterior putamen [229]. Also, drug-induced, unilateral dopamine depletion in the striatum can impair motor learning that involves the contralateral limb [230]. In humans, functional neuroimaging has shown that the pre-supplementary motor area is active during motor learning and that this activity gradually decreases as a movement becomes learned [231]. Motor learning also activates the striatum and globus pallidus [232].

2.4.4.3.2 Motor Automaticity

According to a theoretical model by Doyon and Benali, motor learning eventually leads to automaticity [233], which is defined by minimal conscious effort or cognitive resources to perform a certain task. The degree of automaticity is often assessed using a dual-task paradigm (e.g., a primary motor task and a secondary cognitive task) [234]. Such assessment assumes that two tasks are performed using the same limited cognitive resource. Therefore, if the primary task has been automatized, its execution should require minimal cognition and the cognitive demand by the secondary task would not exceed the capacity of the shared resource [234]. Inability to dual-task is not necessarily mutually exclusive with automaticity, as observed impairment to perform the primary task may be specific to dual-tasking. Indeed, additional brain areas are activated when two tasks are performed simultaneously, compared to each task being performed separately [235]. Also, the interference between the primary and secondary tasks may be task-dependent (i.e., some combinations of tasks may be more difficult than others). Nonetheless, dual-tasking is frequently used to assess motor automaticity. In a series of functional neuroimaging studies that used sequential finger tapping as the primary task, Wu et al. characterized motor automaticity with decreased brain activation [236]-[239] and reduced functional connectivity of the dorsolateral prefrontal cortex to other brain areas [239]. Generally, the activation of the dorsolateral prefrontal cortex is proportional to the apparent cognition required by a motor task [232]. Thus, both characteristics support the notion of more efficient cognition after automatization.

Experimental evidence, which suggest that the basal ganglia is involved in the automatization of movement, comes from both humans and monkeys. In humans, the involvement of the basal ganglia is implied by the impaired automaticity in individuals with PD. In several studies, some individuals with PD failed to dual-task while healthy individuals could perform the tasks [104], [235], [239]. Also, individuals with PD that could dual-task were characterized by greater activation of several brain areas, compared to healthy individuals [104], [235], and relatively preserved functional connectivity of the dorsolateral prefrontal cortex to the rostral supplementary motor areas and bilateral premotor cortices [239]. In monkeys, the involvement of the basal ganglia is suggested by movement-related neuronal activities in the pallidal segments [240]. In one study, monkeys were trained to perform various wrist movements, and the movements that had been practiced longer were associated with better-defined pallidal activities [240]. The above experimental findings suggest that the basal ganglia is involved in motor learning and subsequent automatization of movement. Therefore, individuals with PD may activate neural correlates that differ from those of healthy individuals even if their motor performance is equivalent.

2.4.5 Effects on motor performance

Here, I focus on the effects of PD on movements that are cyclical or require bilateral coordination. A typical example of such movements is walking. Classic parkinsonian gait is characterized by reduced range of motion, which is observed throughout the body: the extension of the hip, actuation of the knee, plantarflexion of the foot, flexion of the shoulder, and extension of the elbow are reduced [241]. Consequently, individuals with PD walk slower, have shorter strides, and walk with diminished vertical displacements of the heel and toe [241]. In other words, the speed and amplitude of movement are diminished. Furthermore, these abnormalities can worsen with disease progression [241]. PD is also associated with increased variability and asymmetry in various phases of walking [242]-[245]. These abnormalities are worse in individuals with freezing of gait [246]-[249]. Gait asymmetry may be particularly linked to lesions in the putamen [250].

Although walking is impaired in PD, it is a complicated task with requirements other than maintaining periodicity with bilateral coordination. Several studies have used unilateral, self-paced finger tapping to show that the ability to perform cyclical movements may be relatively preserved in PD [75], [251]-[253]. In these studies, individuals with PD performed the finger tapping with longer and more variable movement cycle durations than healthy individuals [75], [251]-[253]. However, these differences were not statistically significant [75], [251]-[253]; in some cases, the movement frequency was faster for individuals with PD [253]. Furthermore, the performance of individuals with PD was not affected by their on- or off-medication condition [251], [253]. Unlike the movement frequency, the amplitude of movement was significantly reduced in individuals with PD [251]. Therefore, the ability to maintain periodicity may not be critically impaired by the disease albeit smaller movements.

Bilateral coordination of even simple tasks can be more complex than performing the individual tasks unilaterally [254]. Furthermore, anti-phasic movements are less stable than in-phasic ones, and it becomes easier for anti-phasic movements to spontaneously become in-phasic as the movement frequency increases [255], [256]. Impaired performance of anti-phasic movements has been observed in PD during various tasks at frequencies around 1 to 3 Hz. Compared to healthy individuals, anti-phasic movements of individuals with PD are characterized by lower frequencies, at which the movements spontaneously shift from anti-phasic to in-phasic [63], [256], abnormal bilateral coordination (i.e., deviation of the phase offset from the expected value of 180°) [159], [257]-[259], or episodes of freezing [259]. Furthermore, depending on the task, individuals with PD may simply fail to perform the movement out of phase [260], [261].

2.4.6 Effects of PD on neural correlates of cyclical movements

PD affects the cortical participation in steady-state locomotion. Compared to similarly-aged healthy individuals, individuals with PD show under- and over-activation in various brain areas during treadmill walking [262]. To my knowledge, no study has examined such discrepancies for cyclical, anti-phasic ankle movements. During a cyclical, anti-phasic bimanual task, compared to healthy individuals, individuals with PD in the off-medication condition show less activation of

the basal ganglia despite greater activation of many other brain areas [63]. During unilateral, self-paced finger tapping, individuals with PD in the off-medication condition show greater activation of bilateral thalamus and ipsilateral cerebellum compared to healthy individuals [75]. There is also evidence that various brain areas, which are active in healthy individuals during self- or externally-paced cyclical unimanual tasks, are less active in individuals with PD in the off-medication condition [263]-[265]. Furthermore, the diminished activation can be normalized by external pacing [263] or administration of levodopa [265]. However, levodopa has also been shown to reduce brain activation during a unimanual task [266].

Thus, PD is associated with observable changes in the neural correlates of cyclical movements. However, there are some contradictions in the existing evidence. For example, PD is associated with greater brain activation in bimanual tasks and diminished brain activation in unimanual tasks. Although this discrepancy can be partially attributed to the additional requirement of anti-phasic bilateral coordination, it is difficult to fully reconcile the contradiction. Greater activation is compatible with the notion that PD makes cognition less efficient while diminished activation may indicate greater inter-individual variability in the brain activation patterns due to the heterogeneity of PD.

2.4.7 Effects on corticomuscular coherence

Experimental evidence is limited on how PD affects corticomuscular coherence during voluntary movements. Although there are several studies on the effects of deep brain stimulation on corticomuscular coherence in PD (e.g., [267]), such studies do not compare normal and impaired coherence. Salenius et al. showed that, during sustained isometric extension of the wrist, individuals with PD on levodopa showed higher coherence than healthy individuals between 3 and 12 Hz and similar coherence to healthy individuals between 15 and 30 Hz [268]. After withdrawal from levodopa, individuals with PD showed further increase in coherence between 3 and 12 Hz and decrease in coherence between 15 and 30 Hz [268]. Salenius et al. also showed that coherence varied substantially among individuals with PD in both on- and off-medication conditions. On levodopa, some individuals showed a clear peak in coherence across the beta

band, which was substantially reduced by withdrawal from levodopa [268]. Other individuals lacked a clear peak on levodopa, but withdrawal induced clear peaks in coherence across the theta and alpha bands [268]. Pollok et al. also compared healthy individuals and individuals with PD during sustained isometric contraction of the forearm [269]. In their study, individuals with PD consisted of chronic users of anti-parkinsonian drugs, who were examined on-medication, and drug-naïve individuals. Although corticomuscular coherence in the beta band did not significantly differ between healthy individuals and those with PD, the drug-naïve individuals showed lower average coherence than healthy individuals [269]. Because the drug-naïve individuals had relatively shorter disease durations [269], their off-medication coherence may gradually worsen if PD degrades corticomuscular communication.

2.4.8 Pathological entrainment of basal ganglia

PD may affect corticomuscular coherence anywhere between the origin of synchronous input to the primary motor cortex and the activated muscles. Previous studies found that the central motor conduction time did not differ significantly between healthy individuals and individuals with PD in the off-medication condition [270], [271], suggesting that corticospinal connections are normal in PD. One study found that, compared to healthy individuals, individuals with PD in the off-medication condition showed shorter central motor conduction time during relaxation [272]. However, such PD-related discrepancy was not observed during muscle contraction [272]. Thus, during muscle activation, it is possible that any PD-related discrepancies in corticomuscular coherence would be caused by cortical or subcortical activities, outside the corticospinal connections.

A rat model of PD has shown that the motor cortex and substantia nigra pars reticulata are coherent around 30 to 35 Hz during treadmill walking while such corticonigral coherence is absent in control rats [273]. Furthermore, the coherence is abolished by L-dopa and restored by an antagonist of dopamine D2 receptors [273]. If L-dopa and the D2 receptor antagonist respectively restores and inhibits the normal function of the indirect pathway, it is possible that the corticonigral coherence results from the pathological entrainment between the motor cortex

and the substantia nigra pars reticulata. Similar coherence has been observed between the motor cortex and the subthalamic nucleus in a rat model of PD during sustained exploratory movement [274]. This coherence is also abolished by a dopamine receptor agonist, suggesting the pathological nature of the coherence and supporting the notion of pathological corticonigral entrainment [274].

PD-related coherence between the motor cortex and basal ganglia has also been observed in humans. In individuals with PD, the motor cortex is coherent with the subthalamic nucleus and internal segment of the globus pallidus during rest or tonic wrist extension in the off-medication condition [275], [276]. Such coherence exists within high-beta to low-gamma bands, with the peak frequency around 20 to 30 Hz [275], [276]. Furthermore, information appears to flow from the motor cortex to the basal ganglia. One study found that the motor cortex led the subthalamic nucleus and internal segment of the basal ganglia in beta oscillations [275]. Similarly, another study found that beta oscillations in the motor cortex Granger-caused the beta oscillations in the subthalamic nucleus and that such causality was significantly greater than the causality for the reverse scenario [276]. Beta coherence has also been observed within the basal ganglia, between the subthalamic nucleus and internal segment of the globus pallidus, in individuals with PD during rest or tonic wrist extension in the off-medication condition [277]. Similar to the rat model, the above coherence in individuals with PD appears to be pathological. The pathological nature of the coherence is suggested by its dopamine dependence. In the on-medication condition, the beta coherence can diminish and coherence in the high-gamma band (70 to 85 Hz) can emerge instead [275], [277]. Also, the functional connectivity between the motor cortex and the subthalamic nucleus appears to increase in PD: compared to healthy individuals, the activities of the two sites are more correlated in individuals with PD in the off-medication condition [278]. Based on the above experimental findings, it seems likely that PD affects the interaction between the motor cortex and basal ganglia. This may contribute to abnormal corticomuscular coherence via the thalamocortical pathway [80], [279], [280].

2.5 Neuronal network for locomotor control

The experimental studies in the subsequent chapters deal with seated ankle movements, which were designed to include specific functional requirements that are common to bipedal walking. Thus, the neural control of the basic patterns of locomotion (i.e., steady-state gait without any additional tasks) is discussed below, as it is relevant for interpreting the results from the experimental studies. Figure 2.3 shows a commonly used model of the locomotor network for basic patterns of locomotion in vertebrates [281], [282].

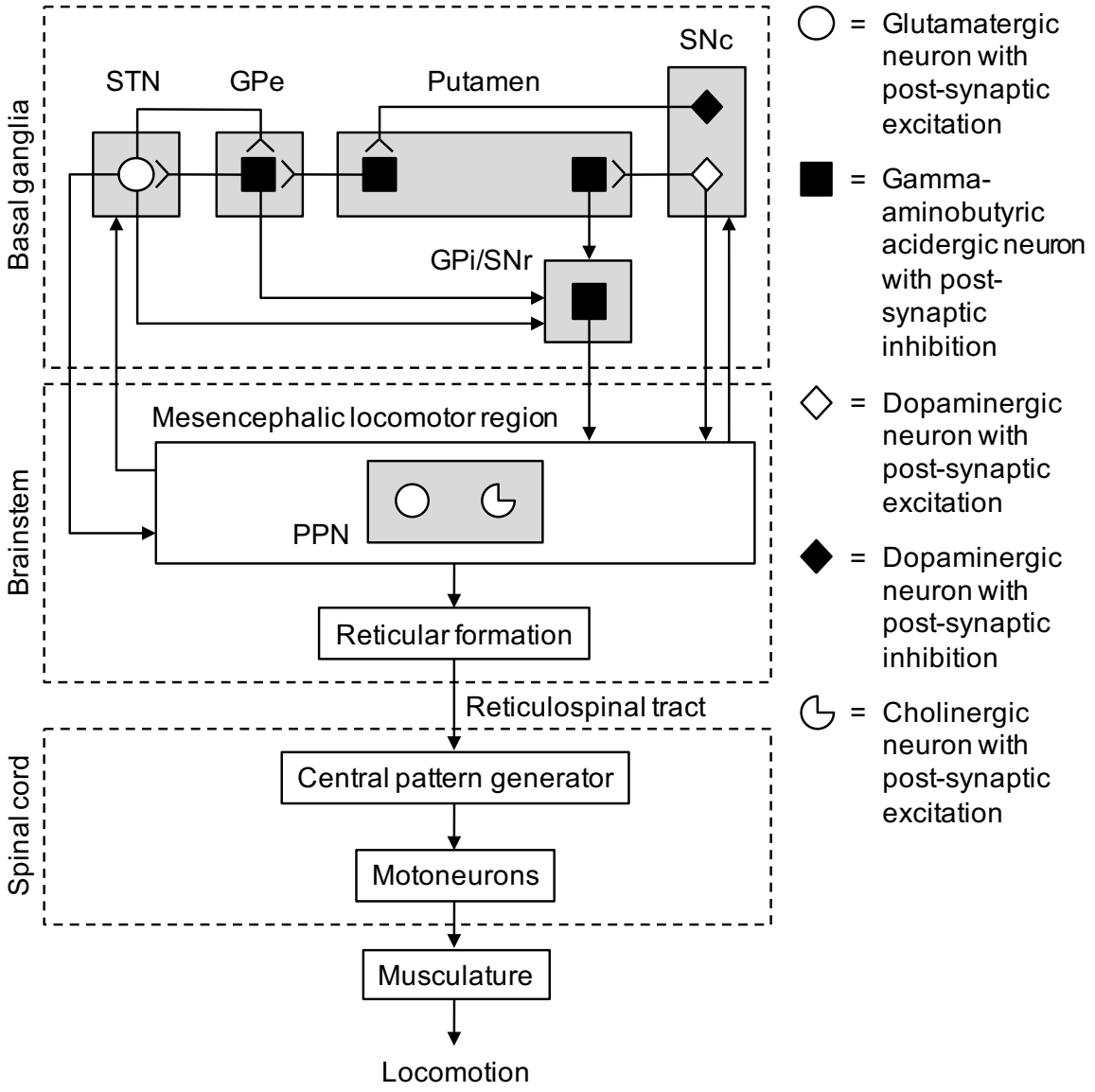

Figure 2.3. Schematic representation of the locomotor network. GPi and GPe are the internal and external segments of the globus pallidus, respectively. SNc and SNr are the pars compacta and pars reticulata of the substantia nigra, respectively. STN is the subthalamic nucleus, and PPN is the pedunculopontine nucleus.

2.5.1 Mesencephalic locomotor region (MLR)

The MLR is a physiologically defined location that is putatively involved in initiating and sustaining locomotor activities. Reported MLRs often comprise parts of the pedunculopontine

nucleus (PPN) and the cuneiform nucleus [283]-[287]. Such locations have been identified in a variety of vertebrates [282], including cats [283] and monkeys [285], [288]. In the premammillary decerebrate preparation of cats, in which the brainstem is transected from the rostral margin of the superior colliculus to a point immediately rostral to the mammillary bodies [289], spontaneous locomotor activities are accompanied by rhythmic activation of the MLR that correlates with the activation of the limb muscles [290]. In the same preparation, rhythmic activation of the MLR cannot be induced by phasic somatosensory input [290]. In the postmammillary decerebrate preparation of cats, in which the brainstem is transected from the aforementioned precollicular point to a point immediately caudal to the mammillary bodies [289], locomotor activity can be induced by tonic electrical stimulation of the MLR [289], [291]. As the stimulation is intensified, the speed of locomotion increases with corresponding gait changes from walking, trotting, to galloping [289]. Locomotor activities can also be induced by the electrical stimulation of the MLR in decerebrate monkeys [285].

There is no direct evidence of MLR in humans. However, gait disturbances have been linked to neuronal degeneration in areas that typically form the MLR in other animals. Previous studies have reported abnormal posture or gait in individuals with PD that underwent substantial neuronal loss in the PPN [292], abnormal parameters of gait initiation in individuals exhibiting reduced grey matter density in the PPN and cuneiform nucleus [293], freezing of gait in an individual with pathology in bilateral PPN [294], and astasia in an individual with a recent hemorrhage in the PPN [295].

2.5.2 Basal ganglia

2.5.2.1 Main output nuclei

It has been suggested that the basal ganglia, through its inhibitory output, regulates the activation of the MLR [296]. Chemical stimulation of the MLR with antagonists of γ-aminobutyric acid (GABA) receptors induces locomotor activity, whereas administering GABA or GABA agonists into the MLR ceases the electrically- or chemically-induced locomotor activity [291]. Because the main output nuclei of the basal ganglia send GABAergic projections to the PPN [80], [215],

[217], the aforementioned findings suggest that MLR-induced locomotion is regulated by GABAergic projections from the basal ganglia. More directly, electrically stimulating the substantia nigra pars reticulata has the following effects on MLR-induced locomotion: decreased cadence and increased stance phase, delayed gait initiation, and suppressed locomotor activities at higher stimulation intensities [296]. Furthermore, these effects are blocked by administering GABA antagonists into the MLR [296].

2.5.2.2 Subthalamic nucleus and substantia nigra pars compacta

In addition to the main output nuclei of the basal ganglia, the subthalamic nucleus and substantia nigra pars compacta also appear to contribute to the regulation of the MLR activation. Although the strength of connection may be substantially weaker than subthalamonigral or subthalamopallidal connections [297], findings from animals studies suggest that the subthalamic nucleus sends excitatory monosynaptic projections to the PPN [298]-[300]. These excitatory projections are most likely glutamatergic [301], [302]. Furthermore, the PPN sends reciprocal connections to the subthalamic nucleus [300], [303], [304]. By electrically stimulating the subthalamic nucleus, locomotor activities can be induced in cats and monkeys [285], [305].

In salamanders and rats, dopaminergic neurons project to the cholinergic neurons of the MLR from areas that are homologous to the human substantia nigra pars compacta [306]. Similarly, in humans, the cholinergic neurons of the PPN are innervated by dopaminergic neurons [306]. In salamanders, stimulating the dopaminergic projections to the MLR leads to increased activation of the reticulospinal neurons, indicating the excitatory nature of these projections [306]. The connection between the PPN and substantia nigra pars compacta is reciprocal [307], [308], with the afferent connections to the substantia nigra being cholinergic and glutamatergic [309].

2.5.3 Reticulospinal tracts

The locomotor signals from the MLR are transmitted via the reticulospinal tracts [310]-[313]. In the postmammillary decerebrate preparation of cats, locomotor activities can be induced by

electrically or chemically stimulating the reticulospinal neurons that receive projections from the MLR [314], [315]. Also, in the same preparation, transecting the ventrolateral portion of the spinal cord, where the pontine and medullary reticulospinal tracts pass [316], [317], disables the locomotor activity induced by the electrical stimulation of the MLR [318]. Conversely, cats with partially transected spinal cord, but spared reticulospinal tracts, can eventually regain locomotor function [319]. This effect of sparing the reticulospinal tracts has also been reported in monkeys [285].

The transmission of locomotor signals from the MLR appears to be mediated by glutamatergic and cholinergic neurons. This is supported by the presence of both glutamatergic and cholinergic neurons in the PPN [320]. In lampreys, administering glutamatergic antagonists into the reticulospinal neurons increases the required intensity for inducing locomotor activities by electrically stimulating the MLR and decreases the cadence of MLR-induced locomotion [313]. In salamanders, glutamatergic neurons from the MLR project to reticulospinal neurons [321]. Furthermore, administering glutamatergic antagonists into the reticulospinal neurons diminishes their response to electrically stimulating the MLR [321]. Conversely, administering glutamate into the reticulospinal neurons evokes a response, whose amplitude is proportional to the amount of administered glutamate [321]. In the postmammillary decerebrate preparation of cats, administering cholinergic agonists to the area that receive MLR projections can induce locomotor activities [314], [315]. Conversely, administering cholinergic antagonists to the same area suppresses locomotor activities that are otherwise induced by electrically stimulating the MLR [314]. Similar cholinergic induction of locomotor activities has been observed in lampreys [311].

Although both glutamatergic and cholinergic projections from the MLR have been implicated in locomotor control, their exact roles are yet unclear. One study found that glutamatergic projections alone were sufficient to initiate locomotion in mice while cholinergic projections did not initiate locomotion but increased the speed of ongoing locomotion [287]. Another study identified a neuronal circuit, which received cholinergic input from the MLR and projected glutamatergic output to reticulospinal neurons in lampreys [322]. This circuit sustained MLR-

induced excitation of the reticulospinal neurons, and administering cholinergic antagonist to the circuit noticeably reduced the cadence of MLR-included locomotion [322]. These experimental findings suggest that, despite examples of MLR-induced locomotor activities with cholinergic agonists, cholinergic neurons may modulate ongoing locomotion, which is initiated and sustained by glutamatergic projections from the MLR.

2.5.4 Central pattern generators

At the spinal level, the central pattern generators (CPGs) activate motoneurons that innervate the musculature for locomotion. By definition, CPGs are neuronal circuits that can generate rhythmical movements without phasic peripheral sensory feedback [289]. Although CPGs have been studied extensively in lampreys [281], there is little direct evidence of CPGs in human locomotion. In the supine position, epidural stimulation at the L2 segment of the spinal cord can induce rhythmical knee flexion and extension in individuals with chronic thoracic or cervical spinal cord injury [323]. Also, spontaneous episodes of rhythmic lower limb movements have been observed in an individual with chronic and complete transection of the spinal cord at T5-T6 level [324]. As indirect evidence, the cyclical EMG signals of the trunk and leg muscles during walking can be decomposed into five common temporal components, which can collectively account for approximately 60 to over 90% of the variance in the EMG signals [325]-[327]. Furthermore, these components can be obtained from the trunk and leg EMG signals of individuals with complete and incomplete spinal cord injury that have undergone body-weight-supported treadmill training [328]. Such evidence suggests the existence of a neuronal circuit at the spinal level that generates the activation patterns of the musculature during locomotion.

2.5.5 Degradation of the locomotor network in PD

In addition to the neuronal loss in the substantia nigra pars compacta, PD is associated with degeneration in the MLR. Decreased grey matter volume has been observed in the PPN and cuneiform nucleus [329]. Approximately 40% or more of the cholinergic neurons can be lost from the PPN [292], [330]-[334] although the loss is not limited to cholinergic neurons [333], [334]. Similar loss of PPN cholinergic neurons has been observed in the monkey and rat models

of PD [292], [335]. In addition to the neuronal loss, the remaining neurons in the PPN are diminished in size [333]-[335] and contain inclusions of abnormally accumulated alpha-synuclein protein, such as Lewy bodies [193]. In the monkey model of PD, approximately 90% of the dopaminergic innervation of the PPN and cuneiform nucleus is lost [336]. It is possible that these abnormalities can lead to altered activation of the locomotor network (Figure 2.3). Indeed, previous studies have also linked freezing of gait in PD to the atrophy of the grey matter in the PPN and cuneiform nucleus [337], increased resting-state functional connectivity between the MLR and supplementary motor area [338], diminished metabolism in the PPN [339], and white matter abnormalities of the PPN [340], [341].

Furthermore, deterioration in one part of the locomotor network may trigger subsequent deterioration in the remainder of the network via anterograde or retrograde transneuronal degeneration [342]. In rats, lesioning of the cholinergic PPN neurons is accompanied by decrease in the number of dopaminergic neurons in the substantia nigra pars compacta [343]. Conversely, lesioning of the nigral dopaminergic neurons is accompanied by decrease in the number of cholinergic PPN neurons [343]. Furthermore, during ongoing degeneration of the nigral dopaminergic neurons, loss of the cholinergic PPN neurons from lesioning is intensified [343]. It is unclear how exactly neuronal deterioration spreads across the locomotor network in PD. However, it appears likely that degeneration does not remain confined to one location over the course of the disease.

2.6 Reference

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Chapter 3

3 Justification, Objectives, and Hypotheses

3.1 Study 1: young healthy individuals

The overall objective was to examine how PD affected the cortical participation in the control of bilateral, cyclical ankle movements. This objective was pursued last in the third experimental study (Chapter 6). Before doing so, it was necessary to examine whether corticomuscular coherence could be observed during the ankle movements. Corticomuscular coherence has been reported almost exclusively for sustained contractions (e.g., [1]-[3]). There have been a few studies that reported coherence during dynamic movements, but the movements were either discrete and ballistic [4], [5] or cyclical but performed at a substantially slower frequency than normal cadence of walking [6]. Thus, the objective of the first experimental study (Chapter 4) was to examine and validate corticomuscular coherence during the ankle movements. Furthermore, by examining corticomuscular coherence during a simple task with a few isolated functional requirements, I aimed to better understand how the primary sensorimotor cortex participated in locomotor control.

For this study, I hypothesized that increase in corticomuscular coherence would coincide with increase in muscle activation of the foot dorsiflexor, as similar patterns have been observed during treadmill walking [7]. Because the foot plantarflexor was the antagonist of the movement and received weaker corticospinal connections [8], I hypothesized that corticomuscular coherence would not be observed for the foot plantarflexor. I further hypothesized that the observed corticomuscular coherence would exhibit some of the same characteristics as the corticomuscular coherence during sustained contractions: reaching maximum amplitude within the beta band and showing somatotopy [1]-[3], [6], [9]-[23]. Lastly, I hypothesized that aural pacing would increase the magnitude of corticomuscular coherence, as previous studies have reported increased coherence with greater attention or effort for performing a task [3], [9], [12], [14], [15], [17], [18], [20], [24].

3.2 Study 2: young vs. older individuals

In the first study, corticomuscular coherence was examined and validated in healthy young participants because normal aging is associated with various neuromuscular deteriorations that can affect corticomuscular communication as well as deficits in the performance of walking and other bilateral cyclical movements. Because individuals with PD are generally 60 years or older [25], it was necessary to examine the effects of aging on corticomuscular coherence and motor performance during the ankle movements. This was the objective of the second experimental study (Chapter 5).

The effects of aging on corticomuscular coherence have been examined by several studies, but the experimental evidence is limited to sustained contractions [26]-[29]. Furthermore, their results have been contradictory, with some studies reporting age-related increase in the magnitude of coherence [26], [29] while others reporting the opposite [27], [28]. Based on the neuromuscular deteriorations and deficits in the performance of bilateral cyclical movements that are associated with aging, I hypothesized that the magnitude of corticomuscular coherence would decrease with aging.

3.3 Study 3: older healthy individuals vs. individuals with Parkinson's disease

The objective of the third experimental study was to examine how PD affected the corticomuscular coherence during the cyclical ankle movements (Chapter 6). There are only a handful of studies that have examined how PD affects corticomuscular coherence. Furthermore, their findings are limited to sustained contractions of upper limb muscles [30], [31]. In one study, individuals with PD on levodopa showed similar magnitudes of coherence to healthy individuals [30]. However, in the off-medication condition, individuals with PD showed decreased coherence [30], suggesting that dopamine deficiency within the basal ganglia impairs corticomuscular communication. Based on this evidence, as well as known abnormal interactions between the basal ganglia and the motor cortex in PD [32]-[35], I hypothesized that diminished

corticomuscular coherence would be observed in individuals with PD in the off-medication condition during the ankle movements.

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Chapter 4

4 Dynamic increase in corticomuscular coherence during bilateral, cyclical ankle movements

Note: *This chapter of the thesis has been published as a journal paper: T. Yoshida, K. Masani, K. Zabjek, R. Chen, and M. R. Popovic, "Dynamic increase in corticomuscular coherence during bilateral, cyclical ankle movements," Frontiers in Human Neuroscience, vol. 11, article: 155, 2017. DOI: 10.3389/fnhum.2017.00155. The text presented in this chapter is identical to the one available in the journal except that it has been formatted according to the University of Toronto PhD thesis formatting requirements.*

4.1 Abstract

In humans, the midline primary motor cortex is active during walking. However, the exact role of such cortical participation is unknown. To delineate the role of the primary motor cortex in walking, we examined whether the primary motor cortex would activate leg muscles during movements that retained specific requirements of walking (i.e., locomotive actions). We recorded electroencephalographic and electromyographic signals from 15 healthy, young men while they sat and performed bilateral, cyclical ankle movements. During dorsiflexion, near-20-Hz coherence increased cyclically between the midline primary motor cortex and the co-contracting antagonistic pair (i.e., tibialis anterior and medial gastrocnemius muscles) in both legs. Thus, we have shown that dynamic increase in corticomuscular coherence, which has been observed during walking, also occurs during simple bilateral cyclical movements of the feet. A possible mechanism for such coherence is corticomuscular communication, in which the primary motor cortex participates in the control of movement. Furthermore, because our experimental task isolated certain locomotive actions, the observed coherence suggests that the human primary motor cortex may participate in these actions (i.e., maintaining a specified movement frequency, bilaterally coordinating the feet, and stabilizing the posture of the feet). Additional studies are needed to identify the exact cortical and subcortical interactions that cause corticomuscular

coherence and to further delineate the functional role of the primary motor cortex during bilateral cyclical movements such as walking.

4.2 Introduction

Traditionally, it is thought that basic patterns of locomotion are controlled primarily by subcortical and spinal networks [1], [2]. However, recent functional neuroimaging studies in humans have shown that the midline (i.e., the most medial) primary sensorimotor cortex is significantly active during steady-state walking [3]-[10]. Specifically, within the gait cycle, the midline primary sensorimotor cortex cyclically increases its activity approximately between mid-beta and low-gamma frequencies [6]-[10]. Furthermore, Petersen et al. [11] have reported that, during treadmill walking, the activities of the midline primary motor cortex and the foot dorsiflexor become cyclically coherent, with similar timing and frequency range as the aforementioned increase in the midline sensorimotor activity. Such coherence (i.e., corticomuscular coherence) may indicate corticospinal activation of the muscle [12]. Thus, the above findings suggest that the human primary motor cortex participates in steady-state locomotion, perhaps cyclically via the corticospinal tract.

To our knowledge, the study by Petersen et al. [11] is the only one that investigated corticomuscular coherence during bipedal locomotion. However, bipedal locomotion is a complex task that requires maintenance of a specific movement frequency, balance with full weight bearing, visuomotor integration, and coordination of multi-joint movements. Therefore, during bipedal locomotion, it is uncertain which aspect of locomotor control is represented by corticomuscular coherence.

The purpose of this study was to investigate whether bilateral, cyclical ankle movements involved corticospinal activation of muscles, assuming that such activation could be quantified by corticomuscular coherence. Simplifying the movement eliminated many requirements of bipedal locomotion and increased the probability that the observed coherence was relevant to

specific locomotive actions (i.e., maintenance of rhythm and bilateral coordination of the feet). The simplicity of the movement also reduced the risk of motion artifacts. By examining corticomuscular coherence during simple movements, we aimed to better elucidate how the primary motor cortex participates in the control of bipedal locomotion. To our knowledge, there is no study that describes dynamic changes in corticomuscular coherence during simple cyclical leg movements, as previous studies have overwhelmingly focused on sustained contractions of various upper- and lower-limb muscles [12]-[31]. A few studies have examined dynamic movements, but the movements were discrete and ballistic [32] or phasic but much slower than walking [13].

In previous studies that reported corticomuscular coherence during sustained muscle contractions, the maximum increase in coherence was usually observed around 13 to 30 Hz (i.e., near the β band) [12]-[30]. Also, such coherence showed somatotopy: the maximum coherence was observed between the contracting muscle and the corresponding area of the primary motor cortex [13], [15], [16], [18], [26]. In walking, coherence increased dynamically within the movement cycle, coinciding with increased muscle activity [11]. Therefore, we hypothesized that, during cyclical ankle movements, corticomuscular coherence would *i*) occur near the β band; *ii*) show somatotopy; and *iii*) increase dynamically within the movement cycle, coinciding with increased muscle activity. We further hypothesized that, between the tibialis anterior and medial gastrocnemius muscles, corticomuscular coherence would be observed only for the tibialis anterior muscle, as it was the agonist of the movement and had a stronger corticospinal connection [33]. Finally, we hypothesized that rhythmic aural pacing would increase the participant's attention to the movement, resulting in corticomuscular coherence with greater magnitude. This hypothesis was based on the findings of previous studies that increased attention or effort increased corticomuscular coherence [14], [19], [21], [22], [24], [25], [27], [28], [34]. Therefore, the cyclical movements were performed under two conditions: *i*) self-paced and *ii*) externally paced by the sound of a metronome.

4.3 Materials and Methods

4.3.1 Participants

Fifteen men were recruited by convenience sampling. They were 26.7±7.4 years old, 177±7 cm tall, and 74.9±11.0 kg in weight. All participants were able to walk unassisted and reported no history of neurological disorders. The participants were not screened for the presence of corticomuscular coherence before the experiment. Before participating in this study, all participants provided their written informed consent. The experimental protocol had been approved by the University Health Network Research Ethics Board, Toronto, Canada, and they were performed according to the relevant guidelines.

4.3.2 Experimental Task

Each participant sat in a chair with a backrest and placed their feet on a footrest (Figure 4.1). In this position, the participants performed six runs of cyclical ankle movements. Each run lasted approximately one minute and preceded a rest. The ankle movements were performed under two conditions: *i*) self-paced and *ii*) externally paced by the sound of a metronome. Each run alternated between self-paced and externally-paced movements, with the first run always being externally paced. The alternation between the two types of pacing was similar to the design of previous studies, which examined the ability to perform self-paced cyclical movements [35], [36]. We did not randomize the order of self- and externally-paced runs because the resultant inter-run and inter-individual variabilities of movement cycle duration could have been too large to ensemble average the runs for each participant or compare the ensemble averages between participants. When the movements were externally paced, the participants were instructed to maximally dorsiflex one foot and maximally plantarflex the other foot at each beat of the metronome. Thus, the instances of maximum and minimum dorsiflexion alternated between the two feet. The metronome was set to 108 beats per minute, which was comparable to the cadence of normal overground locomotion [37]. For self-paced movements, the participants were instructed to maintain the same rhythm as the externally-paced movements. Because the participants' feet were elevated (Figure 4.1), the soles of their feet largely did not come in contact with any surface during the movements.

To perform the ankle movements, the participants were instructed to flex or extend their entire foot at the ankle without flexing or extending their toes. The participants were also instructed to maintain a consistent rhythm and to focus their gaze on a bullseye, which was placed in their line of sight as they sat upright and gazed forward. To minimize the source of artifacts in EEG signals, the participants were instructed to relax their upper body and to refrain from moving their head, talking, swallowing, coughing, clenching their jaw, and blinking excessively. While the participants performed the cyclical ankle movements, their EEG signals, EMG signals, and kinematic data were recorded.

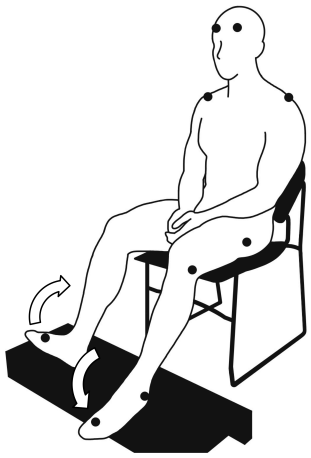

Figure 4.1. Posture assumed by the participants to perform cyclical ankle movements. The symbol, ●, indicates the placement of the markers for the motion capture system (where visible). The arrows indicate the anti-phasic ankle movements.

4.3.3 Data Collection

All signals were recorded in one-minute epochs. Each epoch began after the experimenter visually confirmed that the participant had started the movement in rhythm. The participant was told to stop the movement after the recording had stopped.

4.3.3.1 Kinematic Data

We used an optical motion capture system to track the participants' movements. The system comprised a data acquisition device (MX Giganet, Vicon Motion Systems Ltd., Oxford, United Kingdom), nine optical cameras (Bonita, Vicon Motion Systems Ltd., Oxford, United Kingdom), and data acquisition software (Nexus 1.8.5, Vicon Motion Systems Ltd., Oxford, United Kingdom). Using double-sided adhesive tape, we placed 14-mm retroreflective markers over various bony landmarks, which were identified by manual palpation (Figure 4.1). The participants wore socks and a tight-fitting outfit, which reduced the movements of the markers with respect to their skin and minimally obscured the markers. The markers over the spinous process of the seventh cervical vertebra and acromio-clavicular joints were placed on the skin. The markers over the greater trochanters, lateral epicondyles of the femur, lateral malleoli, and second metatarsal heads were placed on the outfit. To track head movements, markers were placed over the EEG electrode locations, AF_7 and AF_8 [38]. Except for the one over the cervical vertebra, markers were placed bilaterally. The instantaneous positions of the markers were sampled at 100 Hz.

4.3.3.2 EMG Signals

We used a wireless EMG system to record the EMG signals (Trigno™ Wireless EMG System, Delsys Inc., Natick, MA). Each EMG sensor used 99.9%-silver parallel-bar electrodes, which were 1 mm in diameter, 5 mm in length, and spaced at 10 mm. Before placing the EMG sensors, we removed hair from the target location and exfoliated the skin. Then, we used double-sided adhesive tape to place the EMG sensors bilaterally over the bellies of the tibialis anterior and medial gastrocnemius muscles. EMG signals were sampled at 2 kHz, with a bandwidth of 20 to 450 Hz and the common mode rejection ratio of over 80 dB. EMG signals were sampled by the same software as the motion capture system.

4.3.3.3 EEG Signals

We used an active electrode system to record the EEG signals (g.GAMMAsys, g.tec medical engineering GmbH, Schiedlberg, Austria) with compatible signal amplifiers (g.USBamp, g.tec medical engineering GmbH, Schiedlberg, Austria) and recording software (g.Recorder, g.tec medical engineering GmbH, Schiedlberg, Austria). We used a cap (g.GAMMAcap^2, g.tec medical engineering GmbH, Schiedlberg, Austria) to record EEG signals from 20 locations: AF_z, F_z, F_1, F_2, F_3, F_4, FC_z, FC_1, FC_2, FC_3, FC_4, C_z, C_1, C_2, C_3, C_4, CP_z, CP_1, CP_2, and P_z, according to the 10-10 system [38]. This configuration of electrodes covered the midline sensorimotor cortices and their vicinity. We used conductive gel to establish skin-to-electrode contact. The signals were recorded using a monopolar montage with the reference electrode on the left ear lobe and the ground electrode over the right zygomatic process of the temporal bone. EEG signals were sampled at 1.2 kHz without filtering. We used an analog switch to timestamp the EEG signal, and the same switch triggered the sampling by the motion capture system, which also collected EMG signals.

4.3.4 Data Analysis

All calculations were performed in a commercial numerical computing environment (MATLAB R2014b, The MathWorks, Inc., Natick, MA).

4.3.4.1 Motor Performance

Performance of the ankle movements was evaluated using the intra-individual mean and standard deviation of the movement cycle duration and range of motion at the ankle. For each participant, the mean and standard deviation were calculated across all movement cycles, with each cycle defined by two consecutive local maxima in the vertical elevation of the motion-capture marker over the second metatarsal head of the right foot. In other words, dorsiflexion on the right was maximal at the beginning and end of each cycle. The ankle angle was calculated between the shank and the foot. The shank was defined as a line between the markers over the lateral epicondyle of the femur and the lateral malleolus, and the foot was defined as a line between the

markers over the lateral malleolus and the second metatarsal head. To measure head movements within each movement cycle, we calculated the linear movements of the markers at the EEG electrode locations, AF_7 and AF_8.

4.3.4.2 EMG and EEG Signals

For both EMG and EEG signals, each one-minute recording was processed separately. The EMG signals were centered and then full-wave rectified. The EEG signals were first filtered by *i*) a second-order infinite impulse response notch filter with a center frequency of 60 Hz and bandwidth of 1 Hz and *ii*) a fourth-order Butterworth infinite impulse response filter with a passband between 0.5 Hz and 100 Hz. For both processes, zero-phase digital filtering was used. After filtering, the EEG signals were decomposed by independent component analysis using the algorithm by Hyvärinen and Oja [39], [40]. This decomposition isolated artifacts to one or a few independent components. The filtered EEG signals and their independent components were visually inspected for artifacts. During the visual inspection, artifacts were identified based on two characteristics: *i*) waveform and *ii*) biological plausibility [41]. Some artifacts were identified based on their waveforms. Such artifacts included electrooculographic artifacts, EMG artifacts, and ECG artifacts. Other artifacts were identified by their biological implausibility. For any deflection in an EEG signal, its biological plausibility can be determined based on topography and polarity [41]. Topography describes how the amplitude of a deflection changes over the scalp: if the deflection is caused by a biological event, its amplitude should be maximum at a certain point on the scalp and decay with various gradients away from that point. Also, the polarity of such a deflection should not change over the scalp. Based on these principles, any biologically implausible deflection was considered an artifact. The contributions of independent components that contained artifacts were subtracted from the filtered EEG signals to produce noise-reduced EEG signals. This subtraction was restricted to the observed duration of the artifactual waveform to minimize the loss of information.

4.3.4.3 EEG-EMG Coherence

EEG-EMG coherence was calculated for both the tibialis anterior and medial gastrocnemius muscles using wavelet analysis. Wavelet analysis enabled us to study dynamic changes in EEG-EMG coherence over specific frequency bands (i.e., as three-dimensional data). EEG-EMG coherence was calculated separately for each one-minute recording. First, the noise-reduced EEG signals and rectified EMG signals were down-sampled at 400 Hz, and their wavelet coherence was calculated using the following equation (wcoher, Wavelet Toolbox):

$$\frac{\left|S\left(C_x^*(a,b)C_y(a,b)\right)\right|^2}{S\left(\left|C_x(a,b)\right|^2\right)S\left(\left|C_y(a,b)\right|^2\right)},$$

where x and y are two one-dimensional time series, S is the smoothing operator in time, the asterisk indicates a complex conjugate, and $C_x(a,b)$ and $C_y(a,b)$ are respectively the continuous wavelet transforms of x and y. Smoothing was applied using a moving average filter with the window length of 200 data points. The continuous wavelet transform calculated by the following equation:

$$C_x(a,b) = \int_{-\infty}^{\infty} x(t)\frac{1}{\sqrt{a}}\psi^*\left(\frac{t-b}{a}\right)dt,$$

where $x(t)$ is the time series, whose transform is calculated; ψ is the analyzing wavelet; and a is the scale of the analyzing wavelet at position, b, in time. The scale, a, is related to frequency, f, by the following equation:

$$f = \frac{F_c}{a\Delta t},$$

where F_c is the center frequency of the analyzing wavelet and Δt is the sampling interval. For the analyzing wavelet, the complex Morlet wavelet was used:

$$\psi(t) = F_b \pi^{-0.5} e^{j2\pi F_c t} e^{-\frac{t^2}{F_b}},$$

where j is the imaginary unit, F_b is a bandwidth parameter, and F_c is the center frequency of the wavelet in Hz. The bandwidth parameter and center frequency were set to 10 and 1, respectively. For each participant, an ensemble average of EEG-EMG coherence was calculated by segmenting the coherence into individual movement cycles. The ensemble average was calculated for all EEG electrode locations.

4.3.4.4 Magnitude and Frequency of EEG-EMG Coherence

We quantified the magnitude and frequency of coherence as the volume of significant EEG-EMG coherence and its center frequency, respectively, on the frequency-time plane (Figure 4.2). Previous studies have typically quantified coherence without temporal resolution (i.e., as two-dimensional data) [13], [17], [21], [25], [34]. This approach is appropriate for quantitative analysis of coherence during sustained muscle contractions because the cortical participation can be assumed as relatively steady. However, for cyclical movements, it is more intuitive to consider the temporal modulation of coherence within each movement cycle. Thus, we quantified EEG-EMG coherence by its volume above the threshold of significance on the frequency-time plane. A similar approach has been used by Kilner et al. [19].

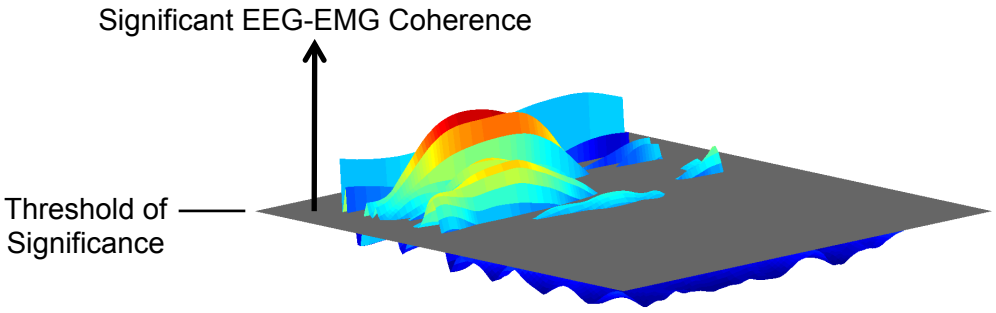

Figure 4.2. Illustration of the volume of EEG-EMG coherence above the threshold of significance on the frequency-time plane.

Before evaluating significance, each ensemble average of EEG-EMG coherence was binned across frequency and time: binning across frequency resulted in one pixel per Hz between 1 and 100 Hz; binning across time resulted in effective sample frequency of 100 Hz. The threshold of significance, *SL*, was calculated using the following equation [29]:

$$SL = 1 - \left[\frac{1}{N}\left(1 - \frac{\alpha}{100}\right)\right]^{\frac{1}{L-1}},$$

where α is the confidence level in percent, L is the number of disjoint segments that are used to estimate the cross spectra of the EEG and EMG signals, and N is the number of observations (i.e., the number of pixels in the binned coherence). The above equation accounts for the multiple observations across frequency and time by using the Bonferroni correction. Our confidence level was 95%. For L, we used the number of movement cycles that each participant completed. Using the above threshold, we calculated the volume of significant coherence at each EEG electrode location of each participant. The volume was measured in Hz multiplied by the percentage of movement cycle (Hz·%$_{Movement\ Cycle}$) and calculated above 6 Hz to exclude the low-

frequency coherence that could not be validated (see *Validation of EEG-EMG Coherence* below). The center frequency (f_c) was calculated as the geometric centroid of the volume of significant coherence along frequency:

$$f_c = \frac{\sum_{i=1}^{N} V_i f_i}{\sum_{i=1}^{N} f_i},$$

where V_i is a voxel of significant coherence at frequency, f_i, and N is the total number of V_i within the binned ensemble average of EEG-EMG coherence.

4.3.4.5 Statistical Analysis

For each measure of motor performance, we performed 2-way analysis of variance (ANOVA) with *i*) the type of pacing (i.e., self- or external pacing) and *ii*) the sides of the body (i.e., left or right) as factors. For the volume and center frequency of significant coherence, we performed 3-way ANOVA on the coherence between the EEG signal from C_z and EMG signals of the tibialis anterior and medial gastrocnemius muscles. For the 3-way ANOVA, the factors were *i*) the type of pacing, *ii*) muscle (i.e., tibialis anterior or medial gastrocnemius muscles), and *iii*) the side of the body. To compare the volume of significant coherence among all EEG electrode locations, we performed 4-way ANOVA with *i*) EEG electrode location, *ii*) the type of pacing, *iii*) muscle, and *iv*) the side of the body as factors. If any factor showed a significant main effect in the aforementioned ANOVA, we performed *post hoc* analysis with Tukey's honestly significant difference procedure. The significant level was set to 5% for all tests.

4.3.4.6 Validation of EEG-EMG Coherence

We used surrogate coherence to validate the experimental coherence at C_z. For each participant, an ensemble average of coherence was calculated with shuffled pairing between EEG and EMG

signals: the i^{th} cycle of an EEG signal was paired with the j^{th} cycle of an EMG signal, such that $i \neq j$ and none of the original pairing was preserved. To match the durations of paired segments of EEG and EMG signals, all segments were re-sampled to the average cycle duration. The re-sampling was performed with margins of fifty data points on either side of each segment. For each participant, 100 such ensemble averages were calculated with differently permutated pairing of EEG and EMG signals, and the average magnitude of the 100 ensemble averages was used as the surrogate coherence. To validate the experimental coherence, we examined how the shuffled pairing of signals affected the volume of significant coherence at C_z. For each pair of experimental and surrogate coherence, their significance was determined by the same threshold value. The effects of shuffled pairing were examined using 4-way ANOVA with *i*) the type of pacing, *ii*) muscle, *iii*) the side of the body, and *iv*) shuffling (i.e., pre- or post-shuffling) as factors. From preliminary analysis, we observed that shuffling the pairing between EEG and EMG signals resulted in residual, relatively high coherence at lower frequencies (generally up to 6 Hz). Therefore, the above ANOVA was performed separately above and below 6 Hz.

4.3.4.7 Group Average of EEG-EMG Coherence

At each EEG electrode location, the magnitude of cyclical coherence was averaged among participants to yield a group average. For the group average, the threshold of significance was calculated using the average number of movement cycles completed among participants. The surrogate coherence was also averaged among participants to yield a group average.

4.4 Results

4.4.1 Kinematic Data

Figure 4.3 shows the time course of ankle angles within a movement cycle. During each one-minute run, the participants completed 56.6±3.0 cycles. After each run, the participants rested 94.8±58.8 seconds. The cycle duration was 1.11±0.03 seconds. The range of motion at the ankle was 38.0±6.9°, with maximum and minimum angles of 122±7° and 83.8±8.0°, respectively.

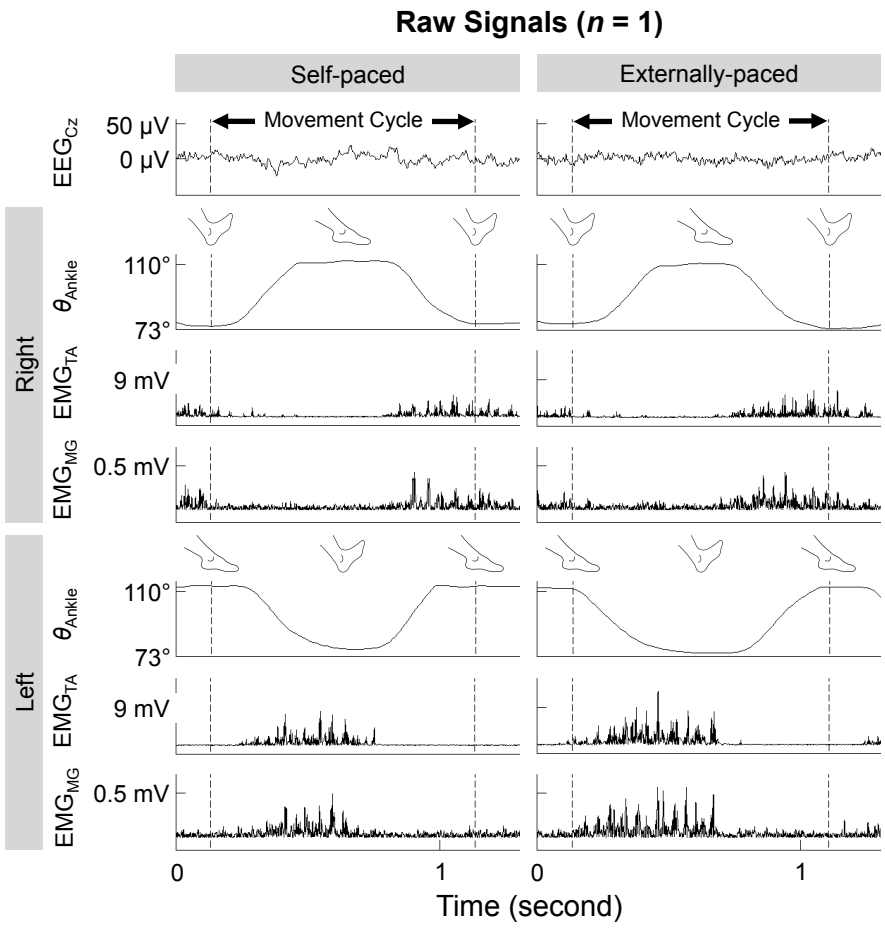

Figure 4.3. Ankle angles (θ_{Ankle}), EMG signals from the tibialis anterior and medial gastrocnemius muscles (EMG_{TA} and EMG_{MG}), and noise-reduced EEG signal from C_z (EEG_{Cz}) during self- and externally-paced movements. All signals are from the same representative participant.

Neither the type of pacing nor the side of the body significantly affected the mean and standard deviation of the cycle duration and range of motion (Table 4.1). The effect of the type of pacing was relatively large on the standard deviation of the movement cycle duration, but the effect did not reach significance ($F_{1,54} = 3.66$, $p = .0611$). In other words, motor performance did not differ significantly between self- and external pacing and between left and right feet. Also, there were no significant interactions between the type of pacing and side of the body for the parameters of motor performance (Table 4.1).

Table 4.1. Results of 2-way ANOVA on the intra-individual mean (μ) and standard deviation (σ) of cycle duration and range of motion.

Dependent Variable		Main Effects		Interaction
		Side of Body	Type of Pacing	Side of Body×Type of Pacing
Cycle Duration	μ	$F_{1,54} < 0.01$, $p = .981$	$F_{1,54} = 1.47$, $p = .231$	$F_{1,54} = 0.00140$, $p = .970$
	σ	$F_{1,54} = 1.49$, $p = .228$	$F_{1,54} = 3.66$, $p = .0611$	$F_{1,54} = 0.113$, $p = .738$
Range of Motion	μ	$F_{1,54} < 0.01$, $p = .981$	$F_{1,54} = 0.0119$, $p = .914$	$F_{1,54} = 0.00714$, $p = .933$
	σ	$F_{1,54} = 0.0401$, $p = .842$	$F_{1,54} = 0.424$, $p = .518$	$F_{1,54} = 0.206$, $p = .652$

Regardless of the type of pacing, the motion-capture markers on the head were within a volume of approximately 1 cm^3 during each movement cycle. The average cyclic linear head movements were no more than 7 mm, 6 mm, and 4 mm, in the anteroposterior, mediolateral, and longitudinal directions, respectively.

4.4.2 EEG-EMG Coherence during Cyclical Ankle Movements

Figure 4.3 shows the time courses of the EEG signals from C_z and EMG signals from the tibialis anterior and medial gastrocnemius muscles of a representative participant. On both sides of the body, the two muscles co-contracted during dorsiflexion of the ipsilateral foot. This pattern was observed for both types of pacing.

Figure 4.4 shows the cyclical frequency-time distributions of the EEG signal from C_z, EMG signals from the tibialis anterior muscle, and their wavelet coherence for a representative participant. The coherence increased cyclically below 50 Hz and approximately during dorsiflexion (cf. Figure 4.3).

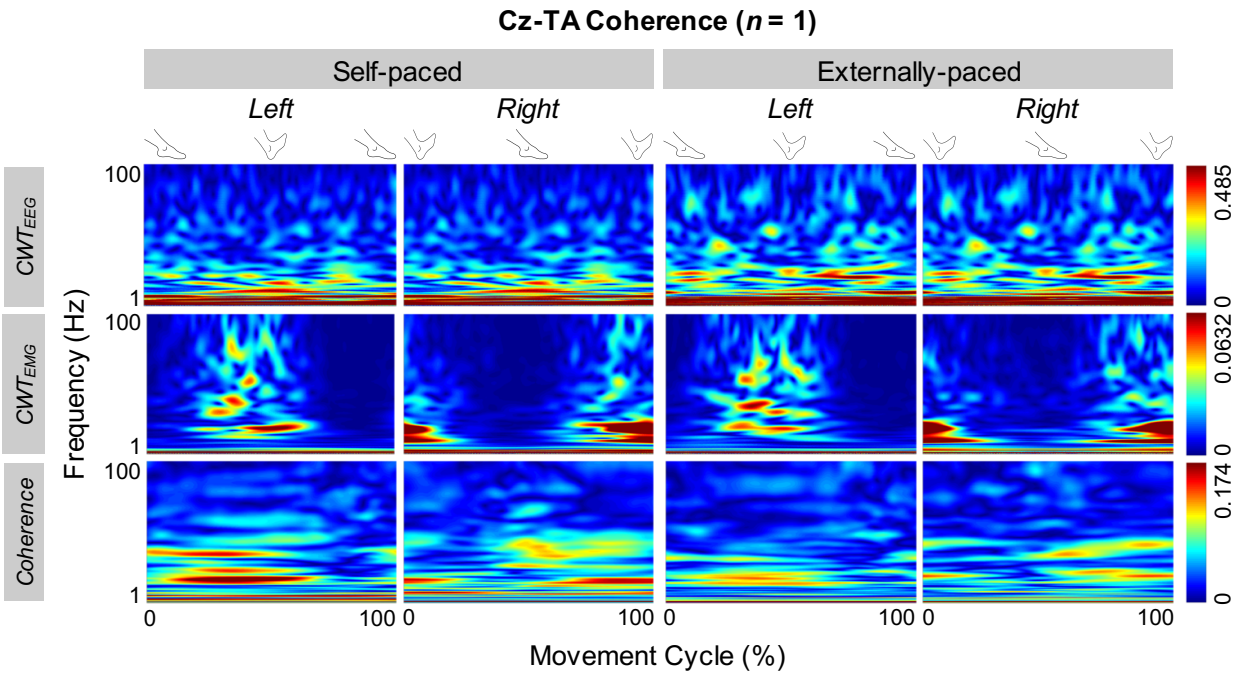

Figure 4.4. Wavelet coherence between EEG signal from C_z and EMG signal from the tibialis anterior (TA) muscle of a representative participant. The top two rows show continuous wavelet transforms (*CWT*) of the EEG and EMG signals, and the bottom row shows their coherence.

Figure 4.5 shows the significant portions of the cyclical wavelet coherence between C_z and the two muscles of a representative participant. For both types of pacing and muscles, the cyclical increase in coherence was significant. For this participant, the threshold values for significant coherence were 0.0697 and 0.0705 for self-paced and externally-paced movements, respectively, with 170 and 168 movement cycles. For the group, the thresholds of significance were 0.0705±0.0031 and 0.0697±0.0022 for self-paced and externally-paced movements, respectively, with 170±8 and 171±6 movement cycles.

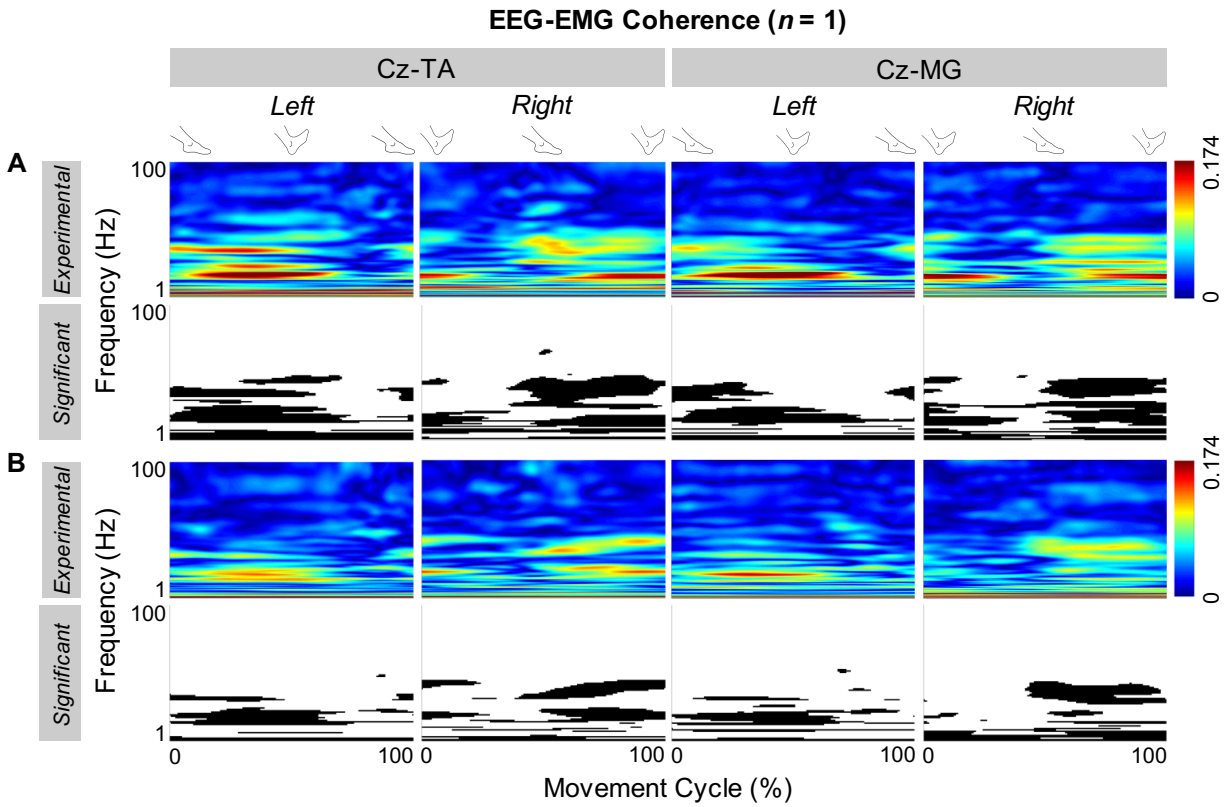

Figure 4.5. Cyclical EEG-EMG coherence of a representative participant. Coherence is calculated between Cz and the tibialis anterior (TA) and medial gastrocnemius (MG) muscles. Panels A and B respectively show coherence for self- and externally-paced movements. For each type of pacing, the black and white patterns in the bottom row indicate the significant portions of the patterns in the top row.

Figure 4.6 shows the volume and center frequency of significant EEG-EMG coherence between C_z and the two muscles. The volume of coherence was not significantly affected by the type of pacing ($F_{1,109} = 0.0299$, $p = .863$), muscle ($F_{1,109} = 0.123$, $p = .726$), or the side of the body ($F_{1,109} = 0.398$, $p = .529$). The center frequency was significantly affected by the type of pacing ($F_{1,109} = 6.48$, $p = .0123$), but not by the muscle ($F_{1,109} = 0.251$, $p = .618$) or the side of the body ($F_{1,109} = 0.0689$, $p = .793$). A *post hoc* test revealed that the center frequency was higher with external pacing. None of the factors of 3-way ANOVA (i.e., type of pacing, muscle, and side of the body) interacted significantly for the volume and center frequency of significant EEG-EMG coherence (Table 4.2).

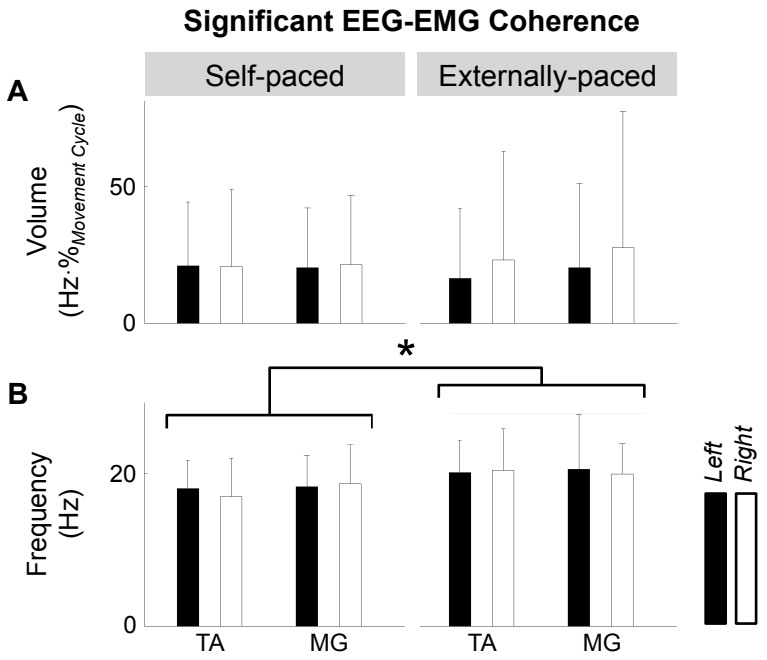

Figure 4.6. Volume (Panel A) and center frequency (Panel B) of significant coherence between EEG signal from C_z and EMG signals from the tibialis anterior (TA) and medial gastrocnemius (MG) muscles. The asterisk indicates a significant difference with a significant level of 5%.

Table 4.2. Interactions between the factors of 3-way ANOVA on the volume and center frequency of significant EEG-EMG coherence.

Dependent Variable	Interaction		
	Type of Pacing×Muscle	Type of Pacing×Side of Body	Muscle×Side of Body
Volume	$F_{1,09} = 0.125$, $p = .724$	$F_{1,09} = 0.310$, $p = .579$	$F_{1,09} = 0.00707$, $p = .933$
Center Frequency	$F_{1,09} = 0.288$, $p = .593$	$F_{1,09} = 0.00693$, $p = .934$	$F_{1,09} = 0.0220$, $p = .882$

Figure 4.7 shows the group average of the cyclical EEG-EMG coherence. The thresholds of significance for the group average were 0.0694 and 0.0693 for self-paced and externally-paced movements, respectively. In the group average, only the coherence near the β band became cyclically significant, indicating that these patterns were most common among the participants regardless of the muscle or type of pacing.

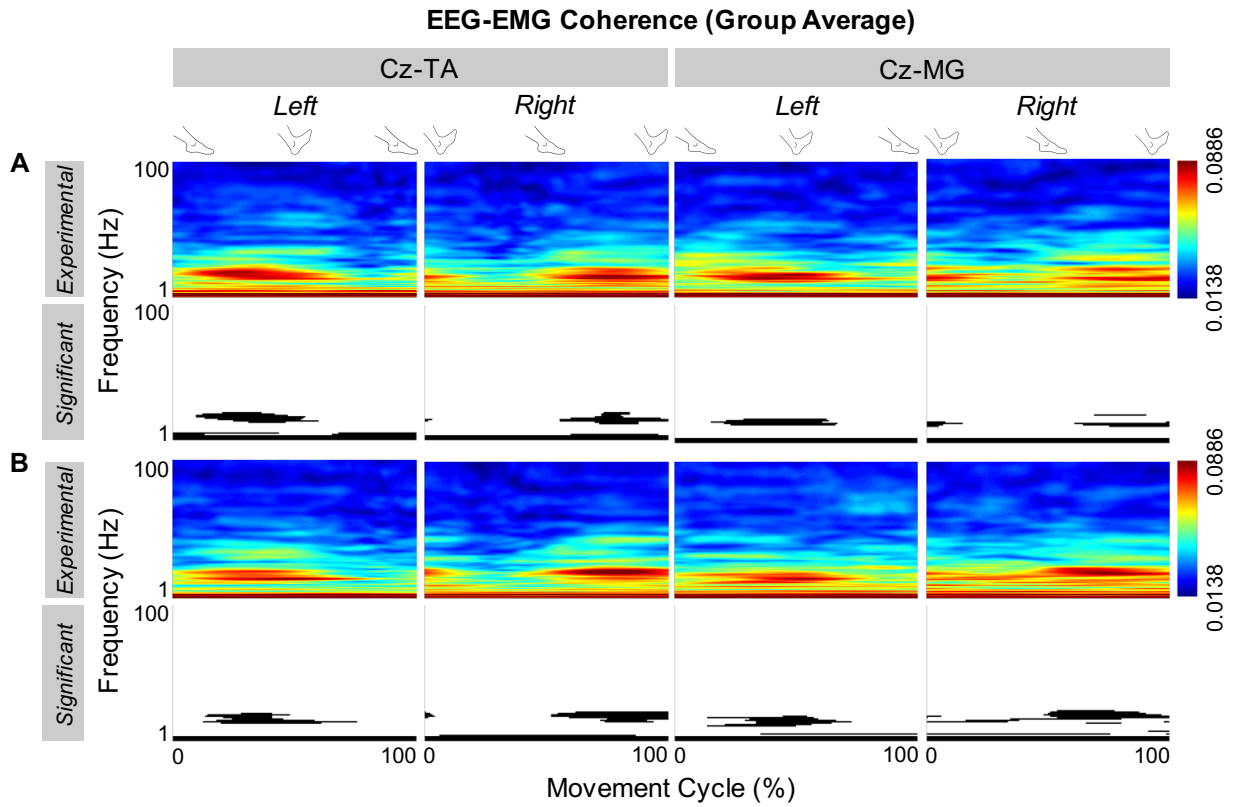

Figure 4.7. Group average of cyclical EEG-EMG coherence. Coherence is calculated between C_z and the tibialis anterior (TA) and medial gastrocnemius (MG) muscles. Panels A and B respectively show coherence for self- and externally-paced movements. For each type of pacing, the black and white patterns in the bottom row indicate the significant portions of the patterns in the top row.

Figure 4.8 and Figure 4.9 show the cortical distributions of the volume of significant coherence for group data and group average, respectively. The average volume of significant coherence was largest at C_z regardless of the muscle or the type of pacing. Based on 4-way ANOVA, the volume of significant EEG-EMG coherence was significantly affected by the EEG electrode location ($F_{19,2237} = 5.36$, $p < .001$). A *post hoc* test showed that the volume at C_z was significantly larger than those at all other electrode locations, except for C_1, C_2, and CP_z. The volumes did not differ significantly among other electrode locations. The volume was also significantly affected by the type of pacing ($F_{1,2237} = 11.9$, $p < .001$) and side of the body ($F_{1,2237} = 5.90$, $p = .0152$). *Post hoc* tests showed that the volumes were significantly larger with external

pacing and for the right side. The volume was not significantly affected by the muscle ($F_{1,2237}$ = 2.24, p = .135).

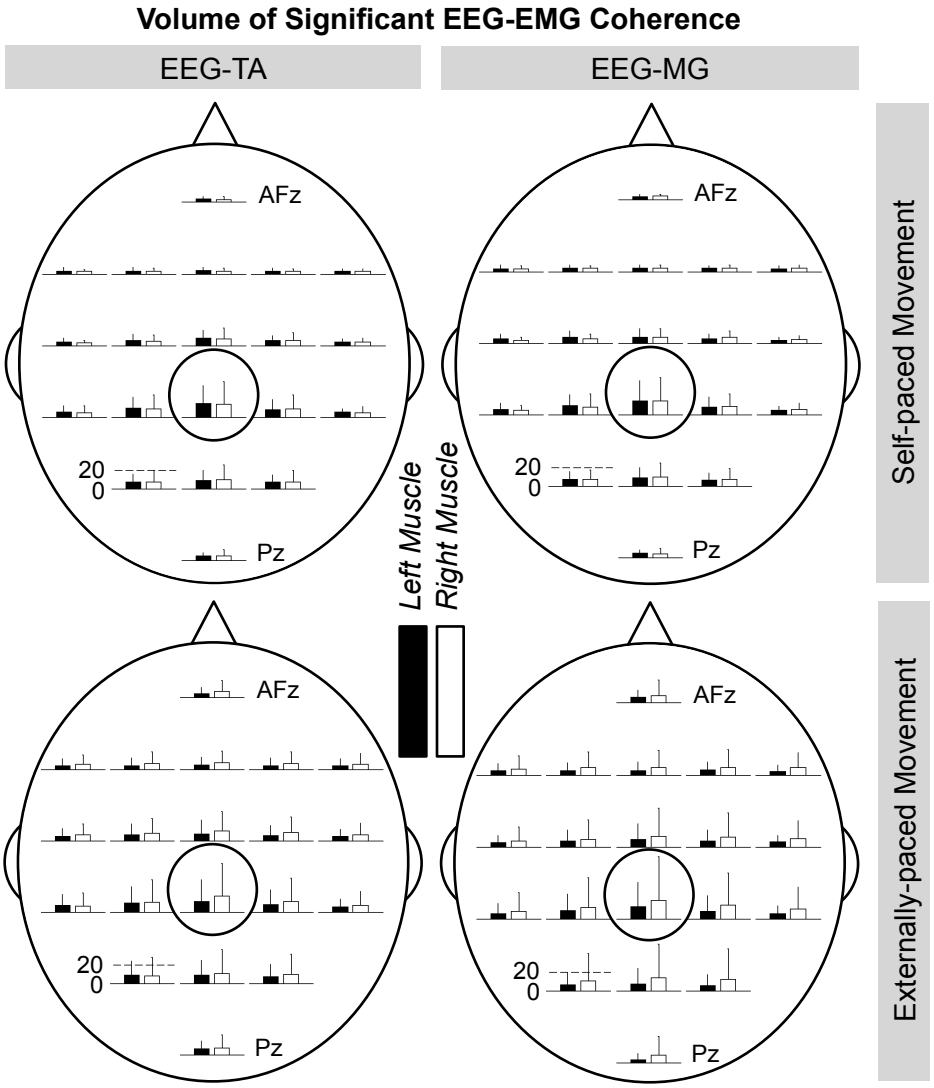

Figure 4.8. Cortical distributions of significant coherence between EEG signals and EMG signals from the tibialis anterior (TA) and medial gastrocnemius (MG) muscles. C_z is circled. At each electrode location, the bar indicates the volume of significant coherence, measured in Hz multiplied by the percentage of movement cycle (Hz·%$_{Movement\ Cycle}$). The scale of the vertical axis is the same for all distributions. Error bars indicate inter-individual standard deviations.

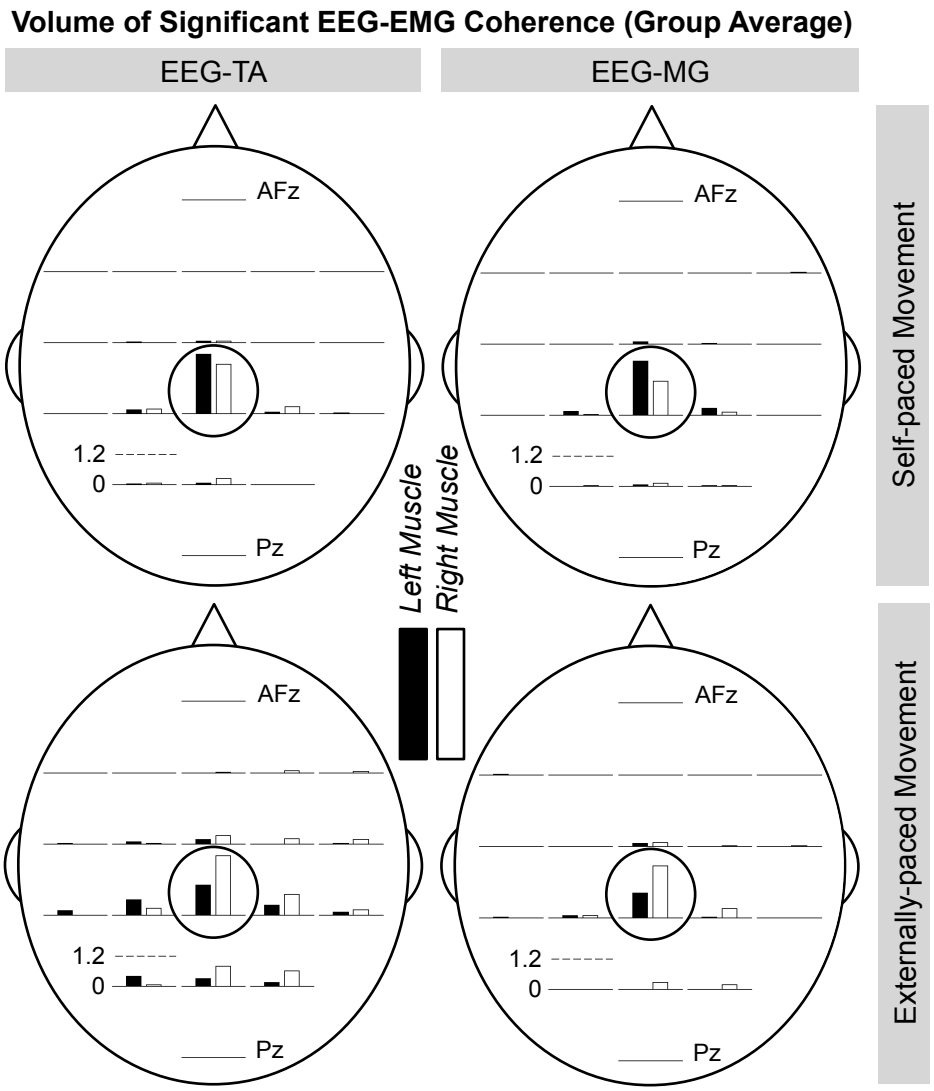

Figure 4.9. Cortical distributions of significant EEG-EMG coherence (group average) between EEG signals and EMG signals from the tibialis anterior (TA) and medial gastrocnemius (MG) muscles. C_z is circled. At each electrode location, the bar indicates the volume of significant coherence, measured in Hz multiplied by the percentage of movement cycle (Hz·%$_{Movement\ Cycle}$). The scale of the vertical axis is the same for all distributions.

4.4.3 Validation of EEG-EMG Coherence

Figure 4.10 shows the significant portions of the experimental and surrogate EEG-EMG coherence (top and bottom rows, respectively) for a representative participant (left two columns)

and group average (right two columns). For the representative participant, the surrogate coherence was only significant at lower frequencies, and shuffled pairing of EEG and EMG signals abolished the cyclical patterns of significant coherence that were observed in the experimental coherence. This phenomenon was also observed in the group average. The low-frequency coherence and the absence of cyclical coherence at higher frequencies were observed in the surrogate coherence for both muscles and types of pacing (Figure 4.11).

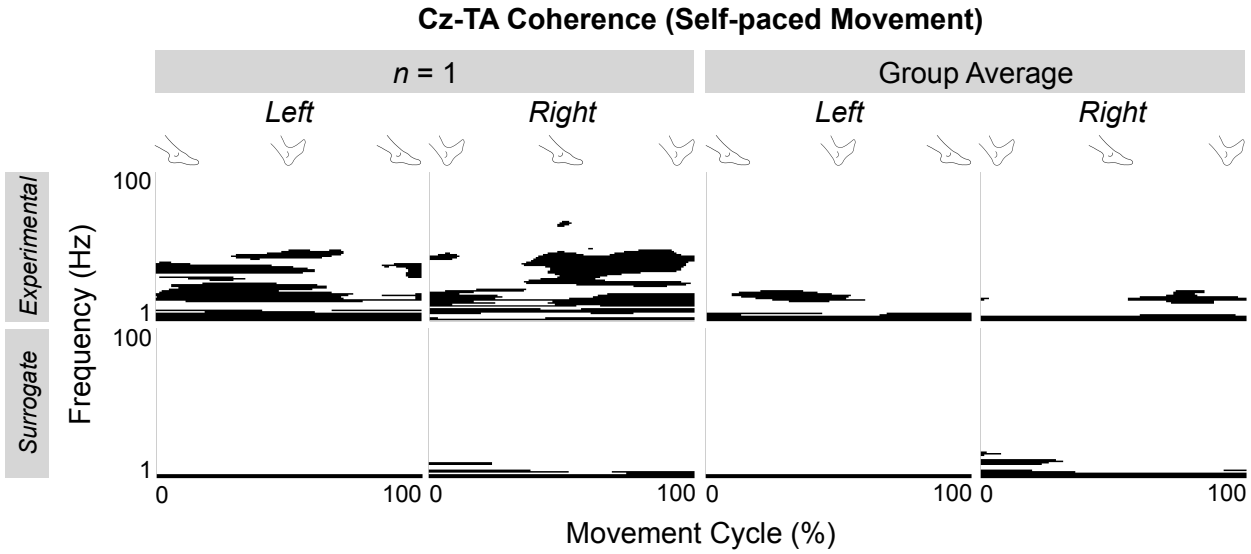

Figure 4.10. Significant portions of experimental and surrogate EEG-EMG coherence of a representative participant and group average. Coherence is calculated between C_z and the tibialis anterior (TA) muscles during self-paced ankle movements.

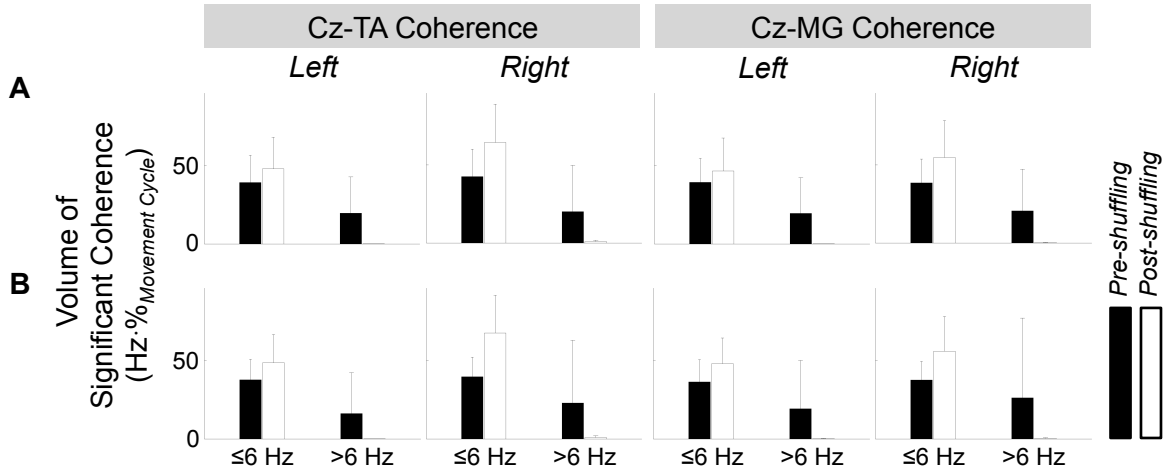

Figure 4.11. Effects of shuffled pairing between EEG signal at C_z and EMG signals from the tibialis anterior (TA) and medial gastrocnemius (MG) muscles. Panels A and B respectively show volumes of significant coherence for self- and externally-paced movements. The error bars indicate inter-individual standard deviations.

Figure 4.11 shows how the volume of significant coherence changes above and below 6 Hz due to shuffled pairing of EEG at C_z and EMG signals. Above 6 Hz, the volume of significant coherence was significantly affected by shuffling ($F_{1,221} = 45.3$, $p < .001$) but not by the muscle ($F_{1,221} = 0.0539$, $p = .817$), side of the body ($F_{1,221} = 0.531$, $p = .467$), or type of pacing ($F_{1,221} = 0.0458$, $p = .831$). A *post hoc* test revealed that the volume above 6 Hz became smaller (and almost negligible) after shuffling. These results validate that, above 6 Hz, the cyclical increase in experimental coherence was not due to the cyclical increase in either EEG or EMG signal alone.

Below 6 Hz, the volume was significantly affected by shuffling and the side of the body ($F_{1,221} = 41.3$, $p < .001$ and $F_{1,221} = 9.06$, $p = .00292$, respectively) but not by the muscle ($F_{1,221} = 2.56$, $p = .111$) or type of pacing ($F_{1,221} = 0.0100$, $p = .920$). *Post hoc* tests revealed that the volume was larger after shuffling and for the right limb.

Above 6 Hz, none of the factors of 4-way ANOVA interacted significantly. Below 6 Hz, only shuffling and the side of the body interacted significantly ($F_{1,221} = 5.82$, $p = .0166$), probably indicating that the post-shuffle increase was greater on the right side.

4.5 Discussion

4.5.1 EEG-EMG Coherence during Bilateral, Cyclical Ankle Movements

During the ankle movements, we observed a cyclical increase in the EEG-EMG coherence that approximately coincided with the co-contraction of the tibialis anterior and medial gastrocnemius muscles (Figure 4.5 and Figure 4.7). We also found that the EEG-EMG coherence occurred near the β band and was largest over C_z regardless of the muscle, side of the body, or type of pacing (Figure 4.8 and Figure 4.9). Furthermore, the cyclical increase in coherence was validated using surrogate coherence (Figure 4.10 and Figure 4.11).

Most previous studies have reported corticomuscular coherence during sustained, weak muscle contractions [12]-[14], [17], [20]-[24], [27], [30]. Furthermore, a few studies have shown that, corticomuscular coherence occurs consistently throughout sustained, weak isometric or isotonic contractions [18], [21]. These findings suggest that corticomuscular coherence occurs during periods of increased muscle activation. Indeed, we observed a cyclical increase in EEG-EMG coherence that approximately coincided with the co-contraction of two leg muscles. Such a pattern is similar to the cyclical increase in coherence that occurs during treadmill walking [11] as well as the cyclical increase in the activity of the sensorimotor cortex during robot-assisted walking [6]-[10], pedaling on a stationary bike [10], and rhythmic finger movements [42].

Some studies have shown that corticomuscular coherence disappears between two periods of sustained contractions (i.e., while the level of contraction is increased from one period to the next) [19], [21], [25]. Such findings may suggest that corticomuscular coherence does not occur during movements. However, multiple studies have observed corticomuscular coherence during various movements: treadmill walking [11], slowly increasing dorsiflexion of the foot [21], slow

self-paced wrist extension and flexion around 0.2 Hz [13], and index finger flexion against dynamic forces [14], [27]. Thus, the absence of coherence between periods of sustained contractions may be task-specific.

4.5.2 Possible Mechanism of EEG-EMG Coherence

Coherence quantifies whether two signals can be the input and output of a linear system. In this study, we assumed that an input-output relationship existed between surface EEG and EMG signals. We further assumed that the EEG signal from C_z primarily reflected the postsynaptic potentials on the apical dendritic tufts of the pyramidal neurons in the primary motor cortex [43]-[46] and that these pyramidal neurons received predominantly excitatory input [47]. Lastly, because pyramidal neurons that connect monosynaptically to the α motor neurons are concentrated in the primary motor cortex [48], [49], the most appropriate scenario for EEG-EMG coherence may be monosynaptic corticomotoneuronal recruitment via the corticospinal tracts. If more complex circuits are involved, it becomes less likely that the system between the primary motor cortex and the activated muscle is linear.

The cyclical increase in C_z-EMG coherence near the β band suggests that the motor units had been recruited at these frequencies. The motor unit recruitment in the β band has been suggested by the intramuscular coherence in the tibialis anterior muscle that occurs during the swing phase of treadmill walking [50], [51]. Furthermore, the absence of such intramuscular coherence in individuals with incomplete spinal cord injury implies the supraspinal origin of the recruitment [51]. Lastly, it has been demonstrated experimentally [52] and computationally [52]-[54] that the frequency of recruitment can be linearly transmitted from presynaptic input to the motoneuronal group that receives the input. There has been some criticism against overestimating the percentage of motor units that are synchronized by common input. With a more statistically rigorous method, De Luca and Kline [55] found that only 50% of the motor units are synchronized by common input. However, the tibialis anterior and medial gastrocnemius muscles are innervated by over 400 and 500 α motor neurons, respectively [56], and less than 10 motor units are necessary to show clear corticomuscular coherence [52]. Thus, it is likely that

enough motor units will be synchronized by common input to show corticomuscular coherence during weak muscle contractions.

Although corticomuscular coherence suggests corticospinal muscle activation, it does not specify the source of the synchronous input to the primary motor cortex. Witham et al. [57] have suggested that, during a precision grip task, afferent feedback may be involved in corticomuscular coherence. However, the origin of the synchronous input could not be determined definitively for this study.

Regardless of where the synchronous input originates, the observed EEG-EMG coherence suggests that the primary motor cortex contributes to the control of simple cyclical ankle movements. In cats, corticospinal contribution appears to modify the basic patterns of locomotion for skillful movements (e.g., obstacle avoidance) [58]. However, the skillful gait modifications are thought to occur through the integration of cortical signals into the pattern-generating (probably spinal) circuit [58]. Because such processing may be complex (and possibly less linear), the corticospinal contribution that is reflected in EEG-EMG coherence is probably less relevant to the ongoing skillful modification of cyclical movements but more relevant to specific requirements of the movement: maintaining a constant frequency and bilaterally coordinating the feet. The role of the human primary motor cortex may be similar in bipedal locomotion, during which the above requirements also apply.

4.5.3 EEG-EMG Coherence in Medial Gastrocnemius Muscles

We hypothesized that EEG-EMG coherence would be observed for the tibialis anterior muscles but not for the medial gastrocnemius muscles. This hypothesis was unsubstantiated: C_z-EMG coherence was similarly observed in both muscles (Figure 4.5 and Figure 4.7) during their co-contraction (Figure 4.3). This finding suggests that the primary motor cortex participates in the control of both agonist and antagonist muscles during cyclical ankle movements.

In the adopted posture (Figure 4.1), we expected the ankle movements to require predominantly the tibialis anterior muscles, as dorsiflexion had to be performed against gravity. Conversely, we did not expect the movements to require much contraction of the medial gastrocnemius muscles, as plantarflexion was aided by gravity and could be achieved partially through relaxing the dorsiflexors. Indeed, the amplitude of EMG signals was much smaller for the medial gastrocnemius muscles than for the tibialis anterior muscles (Figure 4.3). However, we did not expect the medial gastrocnemius muscles to weakly co-contract with the tibialis anterior muscles during dorsiflexion and show coherence with the primary motor cortex.

Corticomuscular coherence has been observed for co-contracting agonist and antagonist muscles during sustained isometric elbow flexion [59]. During elbow flexion, the antagonist shows lower magnitude of corticomuscular coherence compared to the agonists [59]. In this study, we found that the co-contracting agonist and antagonist (i.e., the tibialis anterior and medial gastrocnemius muscles, respectively) showed EEG-EMG coherence of comparable magnitude. The co-contraction of the medial gastrocnemius muscle may contribute to the postural control of the foot. If so, our findings suggest that the primary motor cortex dynamically participates in the postural control of the foot as well as locomotive actions.

4.5.4 Effect of Aural Pacing on EEG-EMG Coherence

Previous studies suggest that corticomuscular coherence is affected by the attention or effort in performing a precise motor task. For example, coherence is greater during isotonic contraction than isometric contraction [21], with better performance to match a target force during isometric contraction [34], when greater effort is required to transition into isometric contraction [24], during isometric contraction of a fatigued muscle [28], when a dynamic force has to be counteracted by a finger to maintain its position static [14], [27], when a greater digit displacement is required during a precision grip task [19], [25], and when isometric contraction is mechanically perturbed [22]. Conversely, corticomuscular coherence decreases during isometric contraction when the effort or attention is reduced by a concurrent cognitive task [17],

[20] or when the required precision of contraction is reduced [20]. Thus, corticomuscular coherence may be linked to the degree of effort or attention in achieving specified performance.

Based on the assumption that rhythmic aural pacing would increase the participants' attention to the movement, we hypothesized that external pacing would increase the magnitude of EEG-EMG coherence. Additional evidence also supported this hypothesis, as rhythmic aural pacing can *i*) make individual movement cycles more consistent through auditory entrainment [60], [61] and *ii*) increase the contributions of cortical activities to motor control by evoking periodic fields in the primary auditory cortex [62]. However, our findings did not support the above hypothesis, as the type of pacing did not significantly affect the magnitude of coherence at C_z (Figure 4.6). Therefore, in the case of simple cyclical movements, rhythmic aural pacing may not significantly improve attention to the task and increase the degree of corticospinal muscle activation. However, the lack of task-dependence may be attributed to the particular sequence of external and self-pacing that we used (i.e., externally- and self-paced movements alternated with external pacing always being performed first). This sequence may have affected the self-paced movements, as participants could remember the rhythm of the aural pacing from the previous run. The magnitude of coherence may have differed had the participants first performed the ankle movements at a self-selected pace and external pacing was applied at the self-selected pace.

Although the magnitude of coherence was unaffected, its frequency was slightly but significantly increased by external pacing for both muscles (Figure 4.6). Omlor et al. [23] have reported an increase in the frequency of peak coherence due to multisensory integration. In their study, participants were asked to maintain the position of a manipulandum static against sinusoidal mechanical perturbation while visually monitoring the performance [23]. For this task, the frequency of peak coherence was higher than the frequency for isometric contractions: a shift from 15 to 30 Hz to 30 to 45 Hz [23]. In this study, the shift in frequency was smaller than what Omlor et al. reported, but the degree of sensorimotor integration was also arguably less. Therefore, the observed increase in frequency with external pacing may have some physiological

relevance if we assume that the magnitude of shift in frequency is proportional to the degree of sensorimotor integration.

4.5.5 Conclusion

We have shown that cyclical increase in corticomuscular coherence, which has been observed during walking, also occurs during simple bilateral, cyclical ankle movements. One possible mechanism for such coherence is corticomuscular communication, in which the primary motor cortex participates in the control of movement. However, additional studies are needed to identify what cortical and subcortical interactions cause corticomuscular coherence. Additional studies are also needed to delineate the functional role of the primary motor cortex during bilateral cyclical movements such as walking. However, for the ankle movements, with fewer functional requirements than walking, the observed coherence suggests that the primary motor cortex may participate in *i*) maintaining a constant movement frequency, *ii*) bilaterally coordinating the feet, or *iii*) stabilizing the posture of the foot through weak co-contraction of the antagonist muscle.

4.6 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

4.7 Author Contributions

TY, KM, and KZ designed the experiment. KZ also provided technical consulting. TY performed the experiments and analyzed the data. TY, KM, RC, and MRP interpreted the data. TY drafted the manuscript. KZ, RC, and MRP edited the manuscript. TY and KM revised the manuscript.

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4.9 Acknowledgments

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Chapter 5

5 Dynamic cortical participation during bilateral, cyclical ankle movements: effects of aging

Note: *This chapter of the thesis has been published as a journal paper: T. Yoshida, K. Masani, K. Zabjek, R. Chen, and M. R. Popovic, "Dynamic cortical participation during bilateral, cyclical ankle movements: effects of aging," Scientific Reports, vol. 7, article: 44658, 2017. DOI: 10.1038/srep44658. The text presented in this chapter is identical to the one available in the journal except that it has been formatted according to the University of Toronto PhD thesis formatting requirements.*

5.1 Abstract

The precise role of the human primary motor cortex in walking is unknown. Our previous study showed that the primary motor cortex may contribute to specific requirements of walking (i.e., maintaining a constant movement frequency and bilaterally coordinating the feet). Because aging can impair *i*) the ability to fulfill the aforementioned requirements and *ii*) corticomuscular communication, we hypothesized that aging would impair the motoneuronal recruitment by the primary motor cortex during bilateral cyclical movements. Here, we used corticomuscular coherence (i.e., coherence between the primary motor cortex and the active muscles) to examine whether corticomuscular communication is affected in older individuals during cyclical movements that shared some functional requirements with walking. Fifteen young men and 9 older men performed cyclical, anti-phasic dorsiflexion and plantarflexion of the feet while seated. Coherence between the midline primary motor cortex and contracting leg muscles cyclically increased in both age groups. However, the coherence of older participants was characterized by *i*) lower magnitude and *ii*) mediolaterally broader and more rostrally centered cortical distributions. These characteristics suggest that aging changes how the primary motor cortex participates in the cyclical movements, and such change may extend to walking.

5.2 Introduction

In humans, the primary motor cortex participates in the control of the basic patterns of walking [1]-[4]. However, the precise nature of its participation is not yet known. In our previous study (unpublished), we had observed that coherence between the midline primary motor cortex and the active leg muscles (i.e., corticomuscular coherence) increased dynamically during bilateral cyclical ankle movements. This finding suggested that the primary motor cortex contributed to maintaining a constant cyclical movement frequency and bilaterally coordinating the feet: functional requirements that are also present in walking.

Aging is associated with deficits in meeting the above requirements (i.e., increased movement variability and impaired bilateral coordination) during walking and other bilateral cyclical movements [5]-[8]. Aging is also associated with neuromuscular changes that can impair corticomuscular communication. These changes include decrease in the gray matter volume of the primary motor cortex [9]-[13]; decrease in the white matter volume of the posterior limbs of the internal capsule [13], [14], which contain the corticospinal tracts [15], [16]; decrease in the number of motor neurons [17]-[19]; structural abnormalities of the neuromuscular junctions [20]; and re-organization of motor units that results in more fibers per neuron [21]-[23]. Indeed, previous studies have reported age-related reduction in *i*) the amplitude of motor evoked potentials (i.e., corticospinal excitability) [24] and *ii*) corticomuscular coherence during sustained contractions of upper limb muscles [25], [26].

The purpose of this study was to examine how aging affected corticomuscular communication during movements that shared specific functional requirements with walking (i.e., bilateral cyclical ankle movements). In this study, corticomuscular communication was quantified by corticomuscular coherence. Based on the age-related impairment of motor performance and alteration of corticomuscular communication, we hypothesized that aging would be associated with lower magnitudes of corticomuscular coherence. To our knowledge, no study has examined how aging affects corticomuscular coherence during cyclical, anti-phasic movements. Several

studies have examined the effects of aging on corticomuscular coherence [25]-[28], but these studies are limited to sustained contractions.

5.3 Methods

5.3.1 Participants

By convenience sampling, we recruited 16 young men and 11 older men. One young participant and two older participants were excluded from data analysis because artifacts could not be removed sufficiently from their EEG signals. The remaining 15 young participants were 27±7 years old, 177±7 cm tall, and 75±11 kg in weight. The remaining 9 older participants were 66±7 years old, 176±6 cm tall, and 86±8 kg in weight. All participants were able to walk unassisted and reported no neurological disorders or dementia. Before participating in this study, all participants provided their written informed consent. All experimental protocols, which were performed according to the relevant guidelines, had been approved by the University Health Network Research Ethics Board, Toronto, Canada.

5.3.2 Experimental task

Each participant performed 6 one-minute runs of cyclical ankle movements while sitting. The first run was always externally paced by the sound of a metronome, and subsequent runs alternated between self- and externally-paced movements. Between runs, the participants rested briefly. The self- and externally-paced conditions have been included because age-related discrepancies have been observed with both types of pacing [5], [6], [29]-[32]. During externally-paced runs, the participants were instructed to dorsiflex and plantarflex their feet in an anti-phasic manner: at each beat of the metronome, which had been set to 108 beats per minute, one foot was maximally dorsiflexed and the other foot was maximally plantarflexed. During self-paced runs, the participants were instructed to maintain the same rhythm as the externally-paced runs. Before the first run, the participants practiced the movement until they felt comfortable with the rhythm and anti-phasic coordination of the limbs. During each run, the participants were instructed to gaze forward and look at a bullseye. They were also instructed to relax their upper

body and to refrain from moving their head, talking, swallowing, coughing, clenching their jaw, and excessively blinking. Given the simplicity of movement, we assumed that it was easy to retain the necessary motor skills during inter-run rests.

5.3.3 Data collection

All signals were recorded in one-minute epochs. Each epoch *i*) began several cycles after the participant had started the movement and *ii*) ended after approximately one minute, before the participant was told to stop the movement. The sampling of kinematic data, EEG signals, and EMG signals were synchronized by an analogic switch.

To record kinematic data, we used an optical motion capture system. The system comprised a data acquisition device (MX Giganet, Vicon Motion Systems Ltd., United Kingdom), nine optical cameras (Bonita, Vicon Motion Systems Ltd., United Kingdom), data acquisition software (Nexus 1.8.5, Vicon Motion Systems Ltd., United Kingdom), and 14-mm retroreflective markers. The participants wore socks and a tight-fitting outfit. To track head movements, markers were placed over the EEG electrode locations, AF_7 and AF_8. To track lower body movements, markers were placed bilaterally over the greater trochanters, lateral epicondyles of the femur, lateral malleoli, and second metatarsal heads. The marker positions were sampled at 100 Hz.

To record EEG signals, we used an active electrode system (g.GAMMAsys, g.tec medical engineering GmbH, Austria) with signal amplifiers (g.USBamp, g.tec medical engineering GmbH, Austria) and recording software (g.Recorder, g.tec medical engineering GmbH, Austria). We used a monopolar montage to record EEG signals from 20 locations, which covered the midline primary motor cortex (C_z) and its vicinity: AF_z, F_z, F_1, F_2, F_3, F_4, FC_z, FC_1, FC_2, FC_3, FC_4, C_z, C_1, C_2, C_3, C_4, CP_z, CP_1, CP_2, and P_z [33]. The reference electrode was placed on the left ear lobe and the ground electrode over the right zygomatic process of the temporal bone. The signals were sampled at 1.2 kHz without filtering.

To record EMG signals from the tibialis anterior muscle and the medial head of the gastrocnemius muscle on both sides, we measured the muscle activities using a wireless EMG system (Trigno™ Wireless EMG System, Delsys Inc., United States), which had a bandwidth of 20 to 450 Hz and the common mode rejection ratio of over 80 dB. All EMG signals were sampled at 2 kHz.

5.3.4 Data analysis

All calculations were performed in a commercial numerical computing environment (MATLAB R2014b, The MathWorks, Inc., United States).

For each participant, we calculated three measures of performance: the range of motion at the ankle, movement cycle durations, and the relative phase between the left and right ankles. For each measure, the intra-individual mean and standard deviation were calculated across all movement cycles. Each cycle was defined by two consecutive local maxima in the vertical elevation of the motion-capture marker over the second metatarsal head of the right foot. The relative phase was calculated according to the method described by Abe et al. [34]. On the intra-individual mean and standard deviation of cycle durations and range of motion, we performed 3-way ANOVA with *i*) aging (i.e., young or older), *ii*) type of pacing (i.e., self- or externally-paced), and *iii*) sides of the body (i.e., left or right) as factors. On the intra-individual mean and standard deviation of relative phase (with right dorsiflexion leading the cycle), we performed 2-way ANOVA with *i*) aging and *ii*) type of pacing as factors.

Using zero-phase digital filtering, the EEG signals were notch-filtered at 60 Hz and band-pass filtered between 0.5 and 100 Hz. Then, the filtered EEG signals were decomposed by independent component analysis [35], [36]. According to the principles described by Libenson [37], the filtered EEG signals and their independent components were visually inspected for artifacts. The contributions of independent components that contained an artifact were subtracted from the filtered EEG signals to produce noise-reduced EEG signals. This subtraction was

restricted to the observed duration of the artifactual waveform. The EMG signals were centered and then full-wave rectified. In corticomuscular coherence, the assumption is that rectification would enhance the power spectral density of the EMG signal at the frequency of common input that recruits the constituent motor units. This assumption is supported by experimental evidence [38] and computational modeling [39].

For each participant, corticomuscular coherence was calculated between all EEG electrode locations and the two muscles on both sides. The noise-reduced EEG signals and rectified EMG signals were synchronized by down-sampling them at 400 Hz, and their wavelet coherence was calculated using the complex Morlet wavelet. The resultant corticomuscular coherence (i.e., approximately one-minute long) was segmented into individual movement cycles and ensemble-averaged to yield a pattern of corticomuscular coherence over one movement cycle).

For each participant, the magnitude of cyclical coherence was examined at all EEG electrode locations. Cyclical corticomuscular coherence was binned across frequency and time: binning across frequency resulted in one pixel per Hz between 1 and 100 Hz; binning across time resulted in one pixel per percent of the movement cycle. Then, above 6 Hz, we calculated the integral of coherence with all pixels that exceeded the threshold of significance (i.e., the volume of significant coherence). The volume of significant coherence was calculated in units of Hz multiplied by the percent of movement cycle duration ($Hz{\cdot}\%_{Movement\ Cycle}$). The threshold of significance was calculated for the range of 1 to 100 Hz, using the equation by Ushiyama et al. [40]. At the EEG electrode position, C_z, we also calculated the center frequency (f_c) for the volume of significant coherence (i.e., geometric centroid along frequency). On the volume and center frequency of significant coherence at C_z, we performed 4-way ANOVA with *i*) aging, *ii*) type of pacing, *iii*) side of the body, and *iv*) muscle (i.e., tibialis anterior or medial gastrocnemius muscles) as factors. All of these factors were relevant to aging and corticomuscular communication: both types of pacing have been associated with age-related discrepancies in motor performance and brain activation [5], [6], [29]-[32], aging is known to affect bilateral coordination [6]-[8], and corticospinal connection differs between the tibialis anterior and gastrocnemius muscles [41]. The number of movement cycles could affect the magnitude of

coherence in an ensemble average. Therefore, for the above ANOVA, the ensemble average for each participant was calculated with the minimum number of cycles completed among the participants.

For each participant, a cortical distribution was formed with volumes of significant coherence between 13 and 30 Hz (i.e., the β band). These cortical distributions were quantified using surface fitting: we fitted a bivariate normal distribution to each participant's cortical distribution of the volume of significant coherence. To compare the cortical distributions, 4-way ANOVA was performed on the following parameters of surface fitting: the mean (i.e., location of peak value) and standard deviation of the fitted normal distribution, root-mean-square deviation, and coefficient of determination. The factors of the 4-way ANOVA were *i*) aging, *ii*) type of pacing, *iii*) side of the body, and *iv*) muscle. The fitted distributions, whose coefficient of determination was below 0.5 or whose peak was located outside the studied cortical area, were excluded from the analysis.

If any factor in ANOVA showed a significant main effect, we performed *post hoc* analysis with Tukey's honestly significant difference procedure. The significant level was set to 5% for all tests.

To validate the cyclical patterns of corticomuscular coherence, we calculated surrogate coherence at C_z. For each participant, an ensemble average of coherence was calculated by pairing the i^{th} cycle of an EEG signal with the j^{th} cycle of an EMG signal, such that $i \neq j$ and none of the original pairing was preserved. For each participant, 100 such ensemble averages were calculated with differently permutated pairing of EEG and EMG signals, and the average magnitude of the 100 ensemble averages was used as surrogate coherence. In preliminary analysis, we observed that surrogate coherence generally showed relatively high magnitude below 6 Hz. Thus, we also examined how surrogate and experimental coherence at C_z differed in magnitude above and below 6 Hz. This comparison was performed by 2-way ANOVA with *i*)

aging and *ii*) type of coherence as factors. The ANOVA was performed separately above and below 6 Hz.

5.4 Results

5.4.1 Motor performance

On average, young participants completed 170±8 and 171±6 cycles of self-paced and externally-paced movements, respectively. Older participants completed 165±10 and 170±2 cycles of self-paced and externally-paced movements, respectively. Among the participants, the minimum number of movement cycles was 139. Thus, for each participant, the first 139 of the recorded cycles were used to calculate the ensemble average of corticomuscular coherence. The inter-run rests ranged from 61 to 154 seconds for young participants and 60 to 156 seconds for older participants.

Table 5.1 summarizes the kinematics of the ankle movements. The mean cycle duration was significantly affected by aging ($F_{1,87} = 4.66$, $p = .336\times10^{-1}$) and the type of pacing ($F_{1,87} = 6.44$, $p = .129\times10^{-1}$), but not by the side of the body ($F_{1,87} = 1.54\times10^{-5}$, $p = .997$). *Post hoc* analysis showed that the mean cycle duration was significantly longer for older participants with self-pacing, compared to young participants with external pacing. The standard deviation of cycle durations was significantly affected by the type of pacing ($F_{1,87} = 7.73$, $p = .666\times10^{-2}$), but not by aging ($F_{1,87} = 1.67$, $p = .200$) or the side of the body ($F_{1,87} = 2.86$, $p = .945\times10^{-1}$). *Post hoc* analysis showed that, for both groups, the standard deviation was significantly greater with self-pacing. On the mean range of motion, the effects of aging ($F_{1,87} = 3.90$, $p = .516\times10^{-1}$), type of pacing ($F_{1,87} = 0.0255$, $p = .873$), and side of the body ($F_{1,87} = 0.107$, $p = .744$) were insignificant. On the standard deviation of the range of motion, the effects of aging ($F_{1,87} = 0.312$, $p = .578$), type of pacing ($F_{1,87} = 1.63$, $p = .206$), and side of the body ($F_{1,87} = 0.253$, $p = .616$) were also insignificant. The mean relative phase (x of ϕ in Table 5.1), which indicated the bilateral coordination of limbs, was significantly affected by aging ($F_{1,43} = 4.24$, $p = .0456$) but not by the type of pacing ($F_{1,43} = 0.282$, $p = .598$). *Post hoc* analysis showed that, although the movements were asymmetrical for both groups (with left dorsiflexion occurring slightly earlier

than it should), young participants showed greater asymmetry than older participants. The standard deviation of the relative phase (s of ϕ in Table 5.1) was not significantly affected by aging ($F_{1,43} = 1.19$, $p = .281$) or the type of pacing ($F_{1,43} = 0.537$, $p = .468$). None of the parameters of motor performance was associated with a significant interaction between the factors (Table 5.2).

Table 5.1. Kinematics of cyclical ankle movements for young and older participants.

Measurement	Group		Self-paced Movements		Externally-paced Movements	
			Left Ankle	Right Ankle	Left Ankle	Right Ankle
Cycle Duration (Seconds)	Young	x	1.11±0.05	1.11±0.05	1.10±0.02	1.10±0.02
		s	0.072±0.019	0.0657±0.0163	0.063±0.014	0.0589±0.0159
	Older	x	1.15±0.08	1.15±0.08	1.11±0.00	1.11±0.00
		s	0.0681±0.0193	0.0636±0.0167	0.0592±0.0137	0.0512±0.0108
Range of Motion (Degrees)	Young	x	38.2±8.0	38.1±5.8	37.8±8.5	38.0±5.8
		s	2.55±1.09	2.62±1.30	2.86±0.99	2.68±0.76
	Older	x	40.5±9.2	41.3±9.3	41.0±8.3	42.2±8.3
		s	2.58±0.80	2.66±0.50	3.16±1.07	2.77±1.00
ϕ (Degrees)	Young	x	185±6	175±6	185±5	175±5
		s	12.3±3.9	12.7±4.2	12.9±4.3	13.1±4.3
	Older	x	182±6	178±6	181±5	179±5
		s	10.7±4.7	10.8±4.1	11.6±3.9	12.3±3.6

Each entry shows the mean±standard deviation among participants. x and s indicate the intra-participant mean and standard deviation, respectively. ϕ is the relative phase that indicates the bilateral coordination of the limbs ($\phi = 180°$ for symmetrical coordination).

Table 5.2. Interactions between the factors of ANOVA on the parameters of motor performance.

Parameters		Interactions		
		Aging×Type of Pacing	Aging×Side of Body	Type of Pacing×Side of Body
Cycle Duration (Seconds)	x	$F_{1,87} = 1.75$, $p = .189$	$F_{1,87} = 7.45\times10^{-4}$, $p = .978$	$F_{1,87} = 7.54\times10^{-4}$, $p = .978$
	s	$F_{1,87} = 0.118$, $p = .732$	$F_{1,87} = 0.0224$, $p = .881$	$F_{1,87} = 0.00425$, $p = .948$
Range of Motion (Degrees)	x	$F_{1,87} = 0.0808$, $p = .777$	$F_{1,87} = 0.0903$, $p = .765$	$F_{1,87} = 0.00864$, $p = .926$
	s	$F_{1,87} = 0.170$, $p = .681$	$F_{1,87} = 0.0599$, $p = .807$	$F_{1,87} = 679$, $p = .412$
ϕ (Degrees)	x	$F_{1,43} = 0.0724$, $p = .789$		
	s	$F_{1,43} = 0.208$, $p = .651$		

x and s indicate the intra-participant mean and standard deviation, respectively. ϕ is the relative phase that indicates the bilateral coordination of the limbs ($\phi = 180°$ for symmetrical coordination).

To examine the effects of motion artifacts due to head movements, we quantified the cyclical linear movements of the markers at the electroencephalographic (EEG) electrode locations, AF_7 and AF_8. For both groups of participants, regardless of the type of pacing, the markers were within a volume of approximately 1 cm^3 during each movement cycle. For young participants, the average cyclical linear head movements were no more than 7 mm, 6 mm, and 4 mm, in the rostrocaudal, mediolateral, and longitudinal directions, respectively. This was true for both self-paced and externally-paced movements. The equivalent measures for the older participants were no more than 8 mm, 7 mm, and 4 mm. Because the head movements were small, we assumed that the effects of motion artifacts due to head movements on EEG signals were negligible.

5.4.2 Cyclical patterns of corticomuscular coherence

Figure 5.1 shows brief time courses of all collected signals from representative young and older participants during externally-paced movements. During dorsiflexion, both participants showed increased activation of the tibialis anterior muscle, with no obvious discrepancy in the electroencephalographic (EMG) patterns. However, the young participant also showed co-contractions of the medial gastrocnemius muscles during dorsiflexion while such co-contraction was indiscernible in the older participant (Figure 5.1). The above observations were also true for self-paced movements (Figure 5.2).

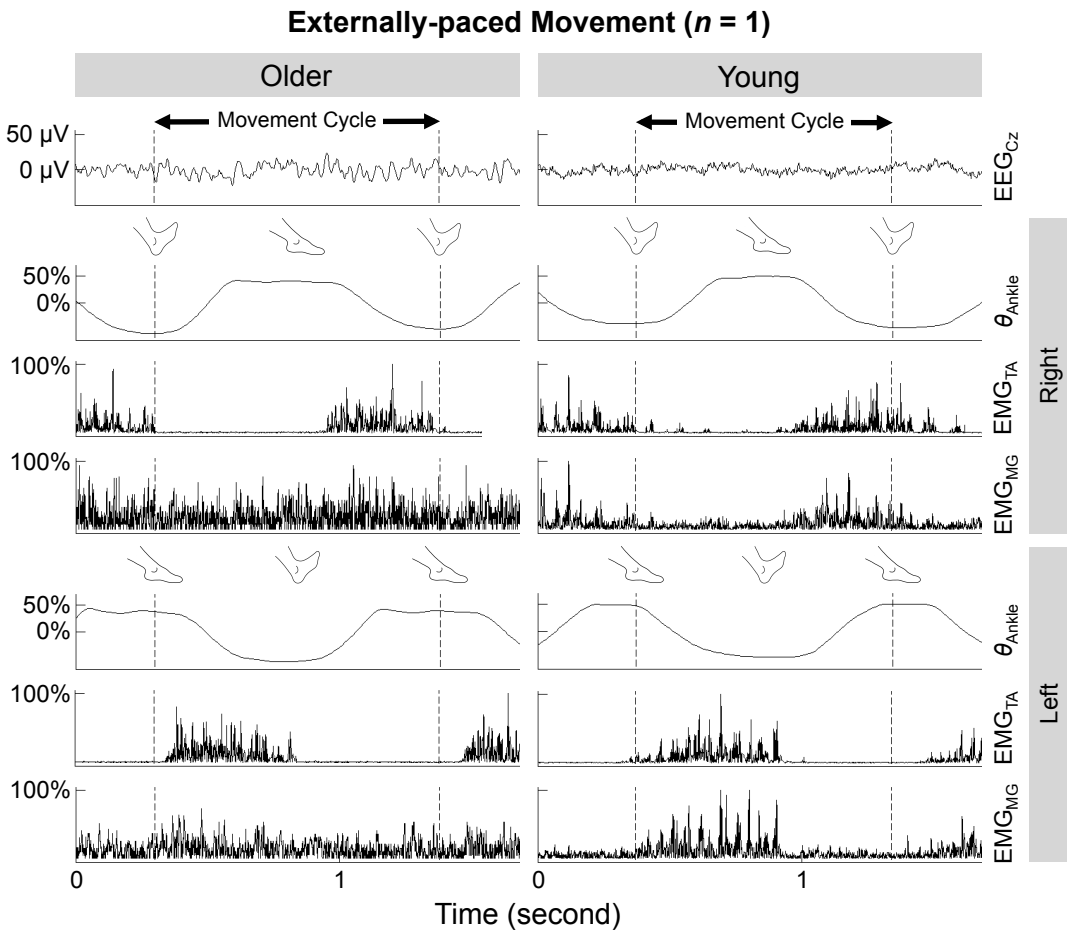

Figure 5.1. Ankle angles (θ_{Ankle}), full-wave rectified EMG signals from the tibialis anterior (TA) and medial gastrocnemius (MG) muscles, and noise-reduced EEG signal from C_z of representative older and young participants during externally-paced ankle movements. Ankle angles have been centered and normalized to its range. EMG signals have also been normalized to its range. For the older participant, the maximum values of the shown EMG signals were 0.482 and 0.277 mV for the right and left TA muscles, respectively, and 0.0112 and 0.0138 mV for the right and left MG muscles, respectively. For the young participant, the maximum values of the shown EMG signals were 0.738 and 1.26 mV for the right and left TA muscles, respectively, and 0.0512 and 0.0569 mV for the right and left MG muscles, respectively.

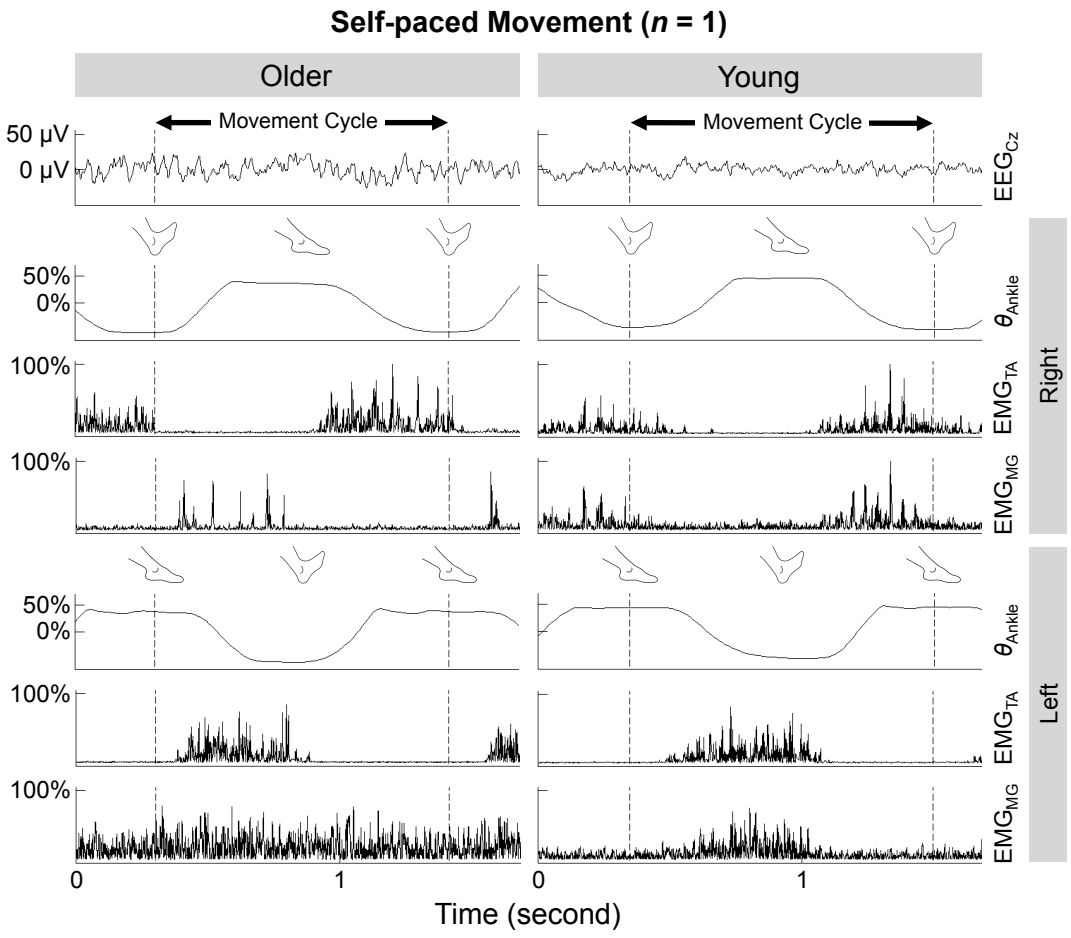

Figure 5.2. Ankle angles (θ_{Ankle}), full-wave rectified EMG signals from the tibialis anterior (TA) and medial gastrocnemius (MG) muscles, and noise-reduced EEG signal from C_z of representative older and young participants during self-paced ankle movements. Ankle angles have been centered and normalized to its range. EMG signals have also been normalized to its range. For the older participant, the maximum values of the shown EMG signals were 0.406 and 0.245 mV for the right and left TA muscles, respectively, and 0.0988 and 0.0100 mV for the right and left MG muscles, respectively. For the young participant, the maximum values of the shown EMG signals were 0.902 and 0.812 mV for the right and left TA muscles, respectively, and 0.0588 and 0.0353 mV for the right and left MG muscles, respectively.

Figure 5.3 shows the cyclical corticomuscular coherence of the representative young and older participants during externally-paced movements. For both participants, the coherence between C_z

and the tibialis anterior muscles increased cyclically, approximately coinciding with dorsiflexion (cf. Figure 5.1). Furthermore, the cyclical increase occurred below 50 Hz, particularly between β to low-γ range, and exceeded the threshold of significance. The two participants differed in their coherence between C_z and the medial gastrocnemius muscles: the young participant showed a cyclical increase in coherence during dorsiflexion while the older participant showed no such pattern (Figure 5.3). The above observations were also true for the self-paced movements (Figure 5.4).

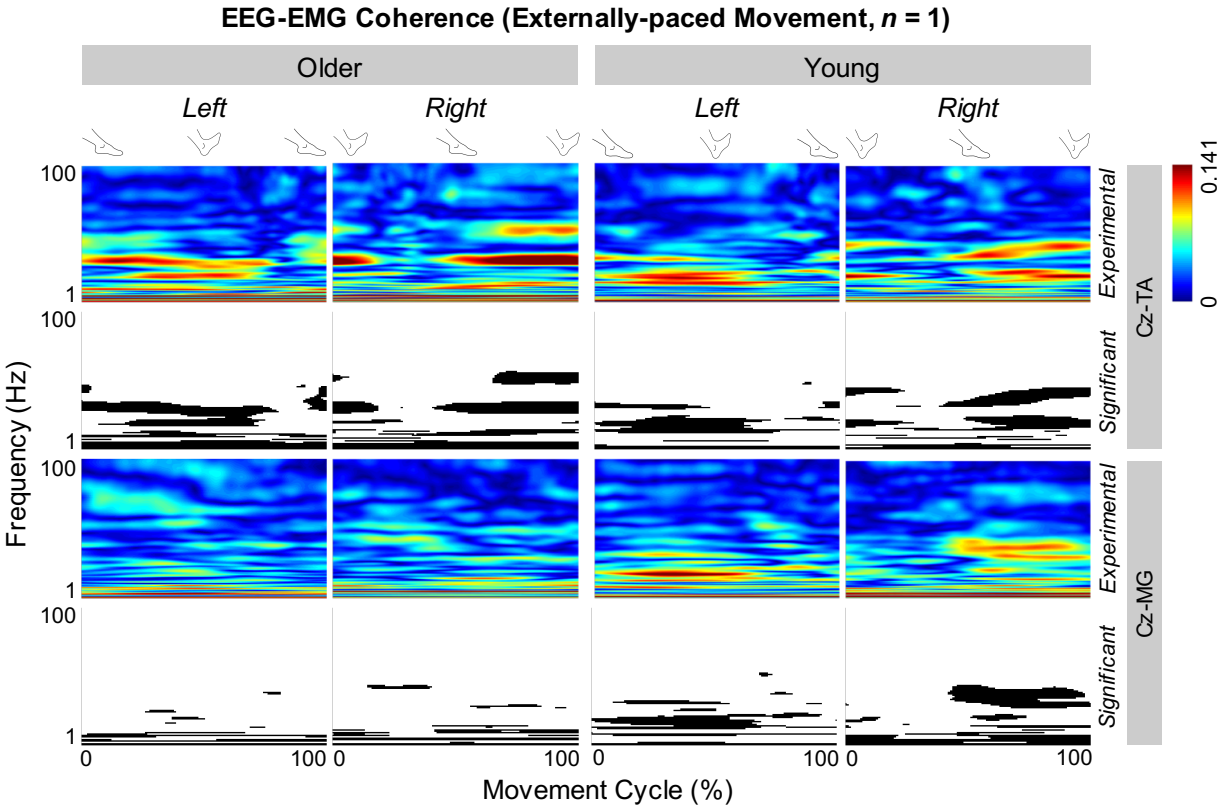

Figure 5.3. Cyclical corticomuscular coherence of representative older and young participants during externally-paced movements. Coherence is calculated between C_z and the tibialis anterior (TA) and medial gastrocnemius (MG) muscles. For each muscle, the black and white patterns in the bottom row indicate the significant portions of the patterns in the top row.

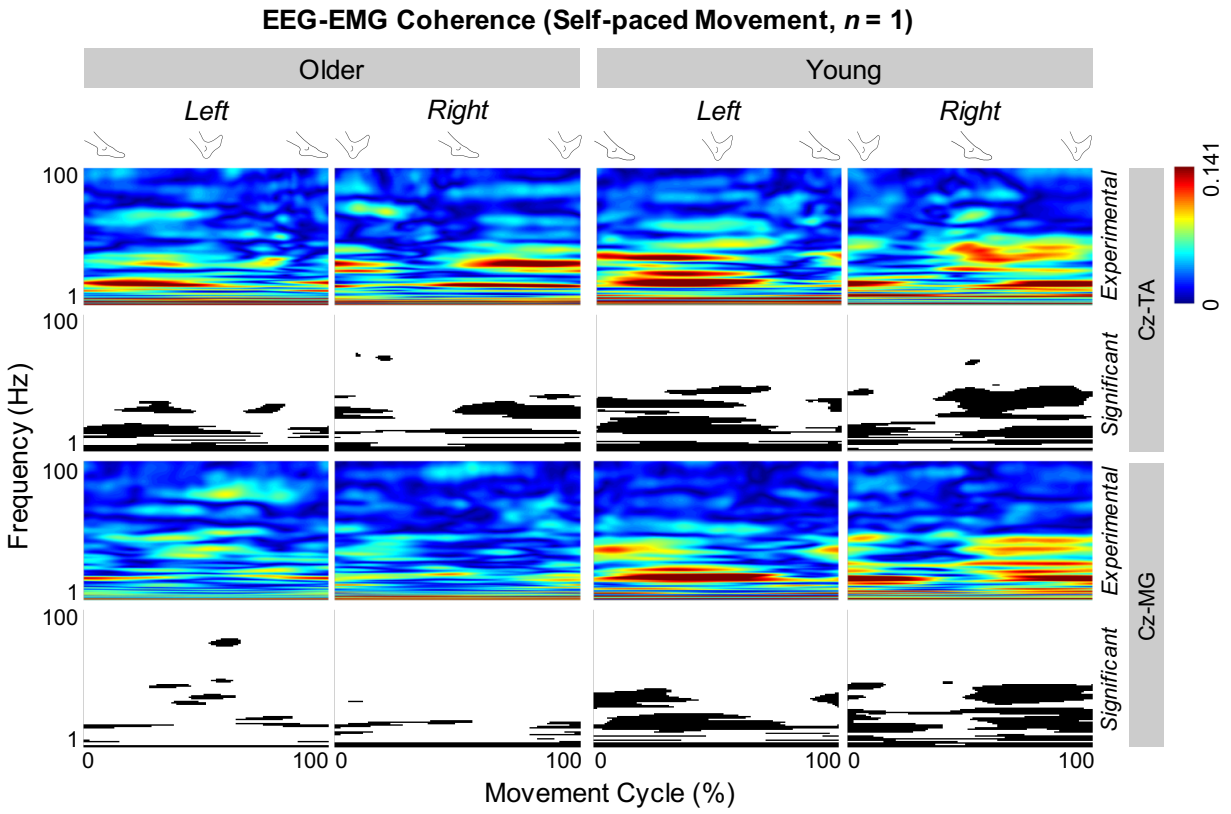

Figure 5.4. Cyclical corticomuscular coherence of representative older and young participants during self-paced movements. Coherence is calculated between C_z and the tibialis anterior (TA) and medial gastrocnemius (MG) muscles. For each muscle, the black and white patterns in the bottom row indicate the significant portions of the patterns in the top row.

5.4.3 Validating corticomuscular coherence

Figure 5.5 shows the significant portions of experimental and surrogate corticomuscular coherence for a representative older participant during externally-paced movements. Unlike experimental coherence, surrogate coherence did not show a cyclical increase at higher frequencies. Thus, shuffling the pairing between EEG and EMG signals abolished the cyclical increase in their coherence. However, shuffled pairing did not abolish their coherence at lower frequencies, typically below 6 Hz (Figure 5.5). According to 2-way analysis of variance (ANOVA), the volume of significant coherence was significantly affected by the shuffled pairing

above ($F_{1,372}$ = 70.2, p = .112×10^{-14}) and below 6 Hz ($F_{1,372}$ = 40.2, p = .674×10^{-9}). *Post hoc* analysis revealed that, after shuffling, the volume of significant coherence was *i*) significantly smaller (and almost negligible) above 6 Hz and *ii*) significantly larger below 6 Hz. Above 6 Hz, the volume of significant coherence was also significantly affected by aging ($F_{1,372}$ = 4.86, p = .281×10^{-1}), and *post-hoc* analysis revealed that the volume was significantly larger for young participants. Furthermore, above 6 Hz, aging and the type of coherence (i.e., surrogate or experimental) interacted significantly ($F_{1,372}$ = 4.58, p = .329×10^{-1}), probably indicating that young participants experienced greater reductions in the volume of significant coherence due to the shuffled pairing. Below 6 Hz, the volume of significant coherence was not significantly affected by aging ($F_{1,372}$ = 0.0922, p = .762), and aging and the type of pacing did not interact significantly ($F_{1,372}$ = 1.26, p = .262).

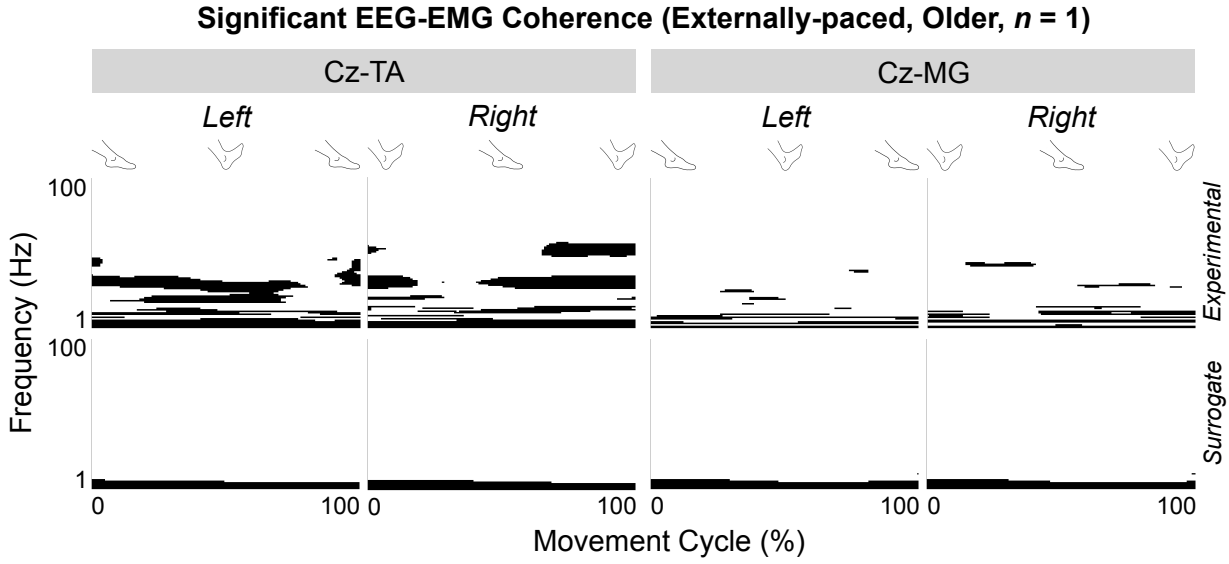

Figure 5.5. Significant portions of experimental and surrogate corticomuscular coherence for a representative older participant during externally-paced movements. Coherence is shown between C_z and the tibialis anterior (TA) and medial gastrocnemius (MG) muscles.

5.4.4 Magnitude and frequency of corticomuscular coherence

For all participants, the threshold of significance was 0.0847. The magnitude of significant coherence was significantly affected by aging ($F_{1,177} = 4.72$, $p = .311\times10^{-1}$), and *post hoc* analysis revealed that the magnitude was smaller for older participants (Figure 5.6). The magnitude was not significantly affected by the type of pacing ($F_{1,177} = 0.113$, $p = .737$), muscle ($F_{1,177} = 0.0815$, $p = .776$), or side of the body ($F_{1,177} = 0.286$, $p = .593$).

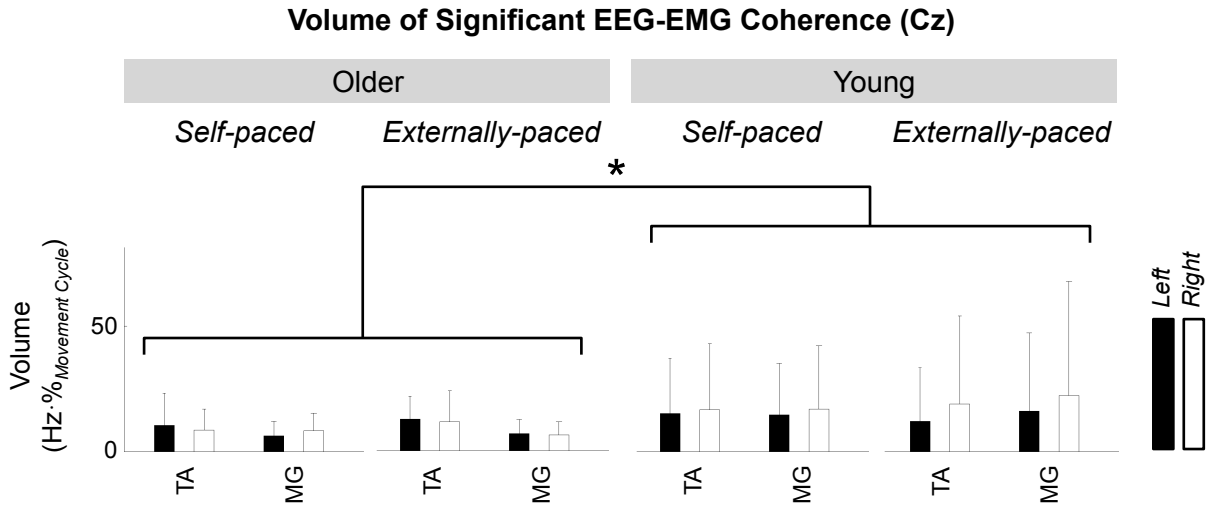

Figure 5.6. Volume of significant corticomuscular coherence between C_z and the tibialis anterior (TA) and medial gastrocnemius (MG) muscles. The error bars indicate inter-individual standard deviations.

For young participants, the center frequency of significant coherence during externally-paced movements were 20.3±4.2 and 20.5±5.5 Hz for the left and right tibialis anterior muscles, respectively, and 20.7±7.3 and 20.1±4.0 Hz for the left and right medial gastrocnemius muscles, respectively. The equivalent values during self-paced movements were 18.1±3.7 and 17.0±5.1 Hz for the left and right tibialis anterior muscles, respectively, and 18.3±4.1 and 18.7±5.2 Hz for the left and right medial gastrocnemius muscles, respectively. For older participants, the center frequency of significant coherence during externally-paced movements were 19.9±3.2 and

20.3±4.1 Hz for the left and right tibialis anterior muscles, respectively, and 18.2±5.5 and 20.3±4.1 Hz for the left and right medial gastrocnemius muscles, respectively. The equivalent values during self-paced movements were 17.3±3.5 and 19.0±3.9 Hz for the left and right tibialis anterior muscles, respectively, and 19.6±6.8 and 18.8±4.0 Hz for the left and right medial gastrocnemius muscles, respectively. The frequency was not significantly affected by aging ($F_{1,177} = 0.800$, $p = .372$), type of pacing ($F_{1,177} = 2.97$, $p = .866\times10^{-1}$), muscle ($F_{1,177} = 0.175$, $p = .676$), or side of the body ($F_{1,177} = 0.00747$, $p = .931$). For neither the magnitude nor the frequency, did the factors of 4-way ANOVA interact significantly (Table 5.3).

Table 5.3. Interactions between the factors of 4-way ANOVA on the magnitude and frequency of significant corticomuscular coherence.

Interactions	Magnitude	Center Frequency
Aging×Type of Pacing	$F_{1,177} = 0.00627$, $p = .937$	$F_{1,177} = 0.0161$, $p = .899$
Aging×Muscle	$F_{1,177} = 0.625$, $p = .430$	$F_{1,177} = 0.444$, $p = .506$
Aging×Side of Body	$F_{1,177} = 0.421$, $p = .517$	$F_{1,177} = 0.00260$, $p = .959$
Type of Pacing×Muscle	$F_{1,177} = 0.0245$, $p = .876$	$F_{1,177} = 0.673$, $p = .413$
Type of Pacing×Side of Body	$F_{1,177} = 0.137$, $p = .712$	$F_{1,177} = 0.0245$, $p = .876$
Muscle×Side of Body	$F_{1,177} = 0.0162$, $p = .899$	$F_{1,177} = 0.0705$, $p = .791$

5.4.5 Cortical distribution of corticomuscular coherence

Figure 5.7 shows the cortical distributions of significant coherence for representative young and older participants during externally-paced movements. The representative young participant generally showed cortical distributions that centered around C_z for both muscles. The representative older participant also showed such distributions for the tibialis anterior muscles, but not for the medial gastrocnemius muscles (Figure 5.7). These observations were also true for self-paced movements (Figure 5.8).

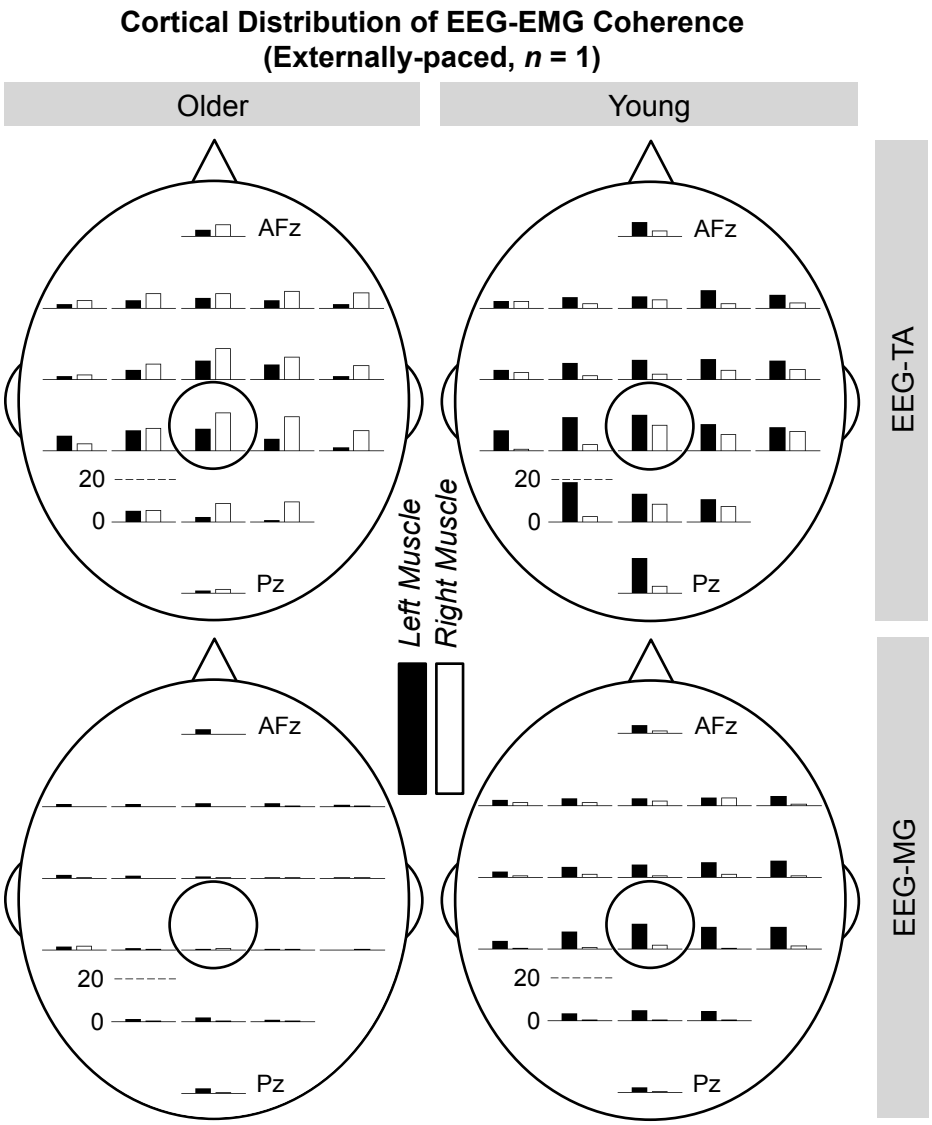

Figure 5.7. Cortical distributions of significant coherence between EEG signals and EMG signals from the tibialis anterior (TA) and medial gastrocnemius (MG) muscles of representative older and young participants during externally-paced movements. C_z is circled. At each electrode location, the bar indicates the volume of significant coherence, measured in Hz multiplied by the percentage of movement cycle ($Hz \cdot \%_{Movement\ Cycle}$). The scale of the vertical axis is the same for all distributions.

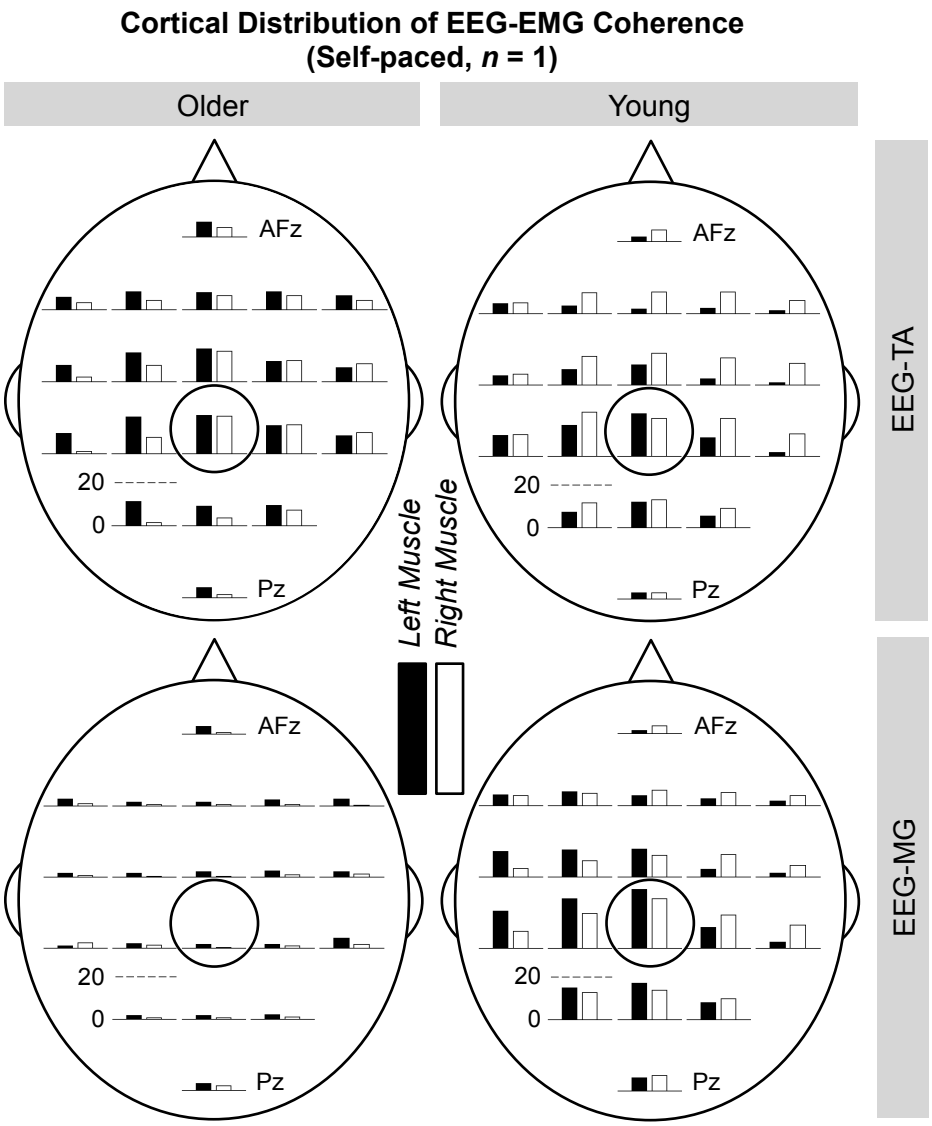

Figure 5.8. Cortical distributions of significant coherence between EEG signals and EMG signals from the tibialis anterior (TA) and medial gastrocnemius (MG) muscles of representative older and young participants during self-paced movements. C_z is circled. At each electrode location, the bar indicates the volume of significant coherence, measured in Hz multiplied by the percentage of movement cycle (Hz·%$_{Movement\ Cycle}$). The scale of the vertical axis is the same for all distributions.

Table 5.4 and Table 5.5 summarize the results of fitting a bivariate normal distribution to the cortical distributions of significant coherence for older and young participants, respectively.

Table 5.6 and Table 5.7 summarize the results of applying 4-way ANOVA on the parameters in Table 5.4 and Table 5.5. For optimally fitted normal distributions, the root-mean square deviation (RMSD), coefficient of determination (COD), and peak value (A) were not significantly affected by any of the factors: aging, type of pacing, muscle, or side of the body (Table 5.6).

Table 5.4. Parameters (Par.) of fitted bivariate normal distributions for older participants.

Par.	Self-paced Movement				Externally-paced Movement			
	TA		MG		TA		MG	
	Left	Right	Left	Right	Left	Right	Left	Right
n	6	5	5	6	9	5	5	2
RMSD	0.965±0.794	1.29±0.55	0.843±0.636	1.18±0.46	1.60±1.47	1.37±0.81	1.36±1.24	0.757±0.763
COD	0.758±0.151	0.732±0.117	0.703±0.158	0.741±0.142	0.666±0.139	0.719±0.117	0.751±0.074	0.858±0.044
A	8.53±8.92	8.77±6.42	5.95±5.79	7.88±4.78	8.65±7.23	8.07±6.53	7.41±5.89	5.72±5.27
σ_{RC}	1.07±0.33	1.33±0.22	1.31±0.23	1.38±0.25	1.32±0.36	1.25±0.27	1.19±0.17	1.15±0.21
σ_{ML}	1.44±0.49	1.52±0.29	1.83±0.54	1.55±0.46	1.51±0.63	1.77±0.62	2.18±0.74	1.56±0.20
μ_{RC}	0.498±0.791	0.587±0.363	0.622±0.541	0.506±0.284	0.183±0.671	0.468±0.190	0.685±0.357	0.736±0.071
μ_{ML}	0.151±0.603	0.122±0.355	0.0489±0.6677	0.0531±0.3943	-0.0552±0.4156	0.743±0.529	0.0115±0.8911	0.0283±0.590

Each entry is the mean±standard deviation for n cortical distributions of coherence between EEG signals and EMG signals from tibialis anterior (TA) and medial gastrocnemius (MG) muscles. RMSD stands for root-mean-square deviation, and COD stands for coefficient of determination. A, σ, and μ are respectively the peak value, standard deviation, and mean of the fitted bivariate normal distributions. A is measured in Hz multiplied by the percentage of movement cycle. The mean is located on the rostrocaudal-mediolateral (μ_{RC}, μ_{ML}) coordinate system, where (0,0) indicates C_z. A displacement by one on the coordinate system corresponds to a displacement by one electrode location in the rostrocaudal or mediolateral direction. Positive rostrocaudal and mediolateral coordinates respectively indicate anterior and left.

Table 5.5. Parameters (Par.) of fitted bivariate normal distributions for young participants.

Par.	Self-paced Movement				Externally-paced Movement			
	TA		MG		TA		MG	
	Left	Right	Left	Right	Left	Right	Left	Right
n	9	10	13	7	9	10	9	10
RMSD	1.46±1.17	1.69±2.01	1.27±0.85	2.01±1.35	2.37±3.17	2.44±4.61	1.96±3.50	3.10±6.40
COD	0.777±0.122	0.808±0.101	0.706±0.146	0.742±0.172	0.674±0.125	0.770±0.101	0.776±0.140	0.671±0.120
A	14.9±21.2	16.2±26.6	12.3±19.2	23.3±32.0	13.7±22.8	18.3±33.1	15.4±29.0	21.3±45.9
σ_{RC}	1.10±0.19	1.03±0.29	1.21±0.43	1.22±0.33	1.33±0.17	1.12±0.30	1.01±0.23	1.20±0.234
σ_{ML}	1.35±0.38	1.34±0.80	1.33±0.43	1.60±0.76	1.79±0.51	1.18±0.39	1.55±0.55	1.55±0.399
μ_{RC}	0.0580±0.3932	0.0136±0.4688	0.265±0.616	0.277±0.516	0.400±0.438	0.201±0.658	0.516±0.525	0.623±0.738
μ_{ML}	-2.86×10^{-3}±0.44	0.0194±0.5592	0.0908±0.7381	0.126±0.577	-0.125±0.383	0.0240±0.5900	0.0790±0.6149	0.340±0.412

Each entry is the mean±standard deviation for n cortical distributions of coherence between EEG signals and EMG signals from tibialis anterior (TA) and medial gastrocnemius (MG) muscles. RMSD stands for root-mean-square deviation, and COD stands for coefficient of determination. A, σ, and μ are respectively the peak value, standard deviation, and mean of the fitted bivariate normal distributions. A is measured in Hz multiplied by the percentage of movement cycle. The mean is located on the rostrocaudal-mediolateral (μ_{RC}, μ_{ML}) coordinate system, where (0,0) indicates C_z. A displacement by one on the coordinate system corresponds to a displacement by one electrode location in the rostrocaudal or mediolateral direction. Positive rostrocaudal and mediolateral coordinates respectively indicate anterior and left.

Table 5.6. Main effects of the factors of 4-way ANOVA on the parameters (Par.) of fitted bivariate normal distributions.

Par.	Independent Variables			
	Aging	Type of Pacing	Muscle	Side of Body
RMSD	$F_{1,113} = 2.19$, $p = .142$	$F_{1,113} = 1.10$, $p = .296$	$F_{1,113} = 0.00176$, $p = .967$	$F_{1,113} = 0.319$, $p = .573$
COD	$F_{1,113} = 0.0155$, $p = .901$	$F_{1,113} = 0.450$, $p = .504$	$F_{1,113} = 0.0281$, $p = .867$	$F_{1,113} = 0.673$, $p = .414$
A	$F_{1,113} = 3.67$, $p = .0580$	$F_{1,113} = 0.00585$, $p = .939$	$F_{1,113} = 0.00694$, $p = .934$	$F_{1,113} = 0.427$, $p = .515$
σ_{RC}	$F_{1,113} = 3.19$, $p = .0768$	$F_{1,113} = 8.62\times10^{-4}$, $p = .977$	$F_{1,113} = 0.254$, $p = .615$	$F_{1,113} = 0.186$, $p = .667$
σ_{ML}	**$F_{1,113} = 4.03$, $p = .0471$**	$F_{1,113} = 2.04$, $p = .156$	$F_{1,113} = 3.13$, $p = .0795$	$F_{1,113} = 0.596$, $p = .442$
μ_{RC}	**$F_{1,113} = 4.63$, $p = .0335$**	$F_{1,113} = 1.17$, $p = .282$	**$F_{1,113} = 4.75$, $p = .0314$**	$F_{1,113} = 0.0483$, $p = .826$
μ_{ML}	$F_{1,113} = 0.692$, $p = .407$	$F_{1,113} = 0.446$, $p = .506$	$F_{1,113} = 0.0313$, $p = .860$	$F_{1,113} = 3.17$, $p = .0779$

Significant effects are indicated by the bold typeface. RMSD stands for root-mean-square deviation, and COD stands for coefficient of determination. A, σ, and μ are respectively the peak value, standard deviation, and mean of the fitted bivariate normal distributions. The subscripts, RC and ML, respectively indicate rostrocaudal and mediolateral directions.

Table 5.7. Interactions between the factors of 4-way ANOVA on the parameters (Par.) of fitted bivariate normal distributions.

Par.	Interactions					
	Aging ×Type of Pacing	**Aging ×Muscle**	**Aging ×Side of Body**	**Type of Pacing ×Muscle**	**Type of Pacing ×Side of Body**	**Muscle ×Side of Body**
RMSD	$F_{1,113} = 0.229$, $p = .633$	$F_{1,113} = 0.0618$, $p = .804$	$F_{1,113} = 0.193$, $p = .661$	$F_{1,113} = 2.13\times10^{-4}$, $p = .988$	$F_{1,113} = 0.0126$, $p = .911$	$F_{1,113} = 0.261$, $p = .610$
COD	$F_{1,113} = 0.358$, $p = .551$	$F_{1,113} = 1.91$, $p = .170$	$F_{1,113} = 0.101$, $p = .751$	$F_{1,113} = 3.35$, $p = .0698$	$F_{1,113} = 0.0200$, $p = .888$	$F_{1,113} = 1.47$, $p = .228$
A	$F_{1,113} = 0.00658$, $p = .936$	$F_{1,113} = 0.130$, $p = .719$	$F_{1,113} = 0.311$, $p = .578$	$F_{1,113} = 0.00398$, $p = .950$	$F_{1,113} = 0.0122$, $p = .912$	$F_{1,113} = 0.171$, $p = .680$
σ_{RC}	$F_{1,113} = 0.141$, $p = .708$	$F_{1,113} = 0.00691$, $p = .934$	$F_{1,113} = 0.625$, $p = .431$	**$F_{1,113} = 6.27$, $p = .0137$**	$F_{1,113} = 0.293$, $p = .589$	$F_{1,113} = 1.92$, $p = .169$
σ_{ML}	$F_{1,113} = 0.0697$, $p = .792$	$F_{1,113} = 0.960$, $p = .329$	$F_{1,113} = 0.0277$, $p = .868$	$F_{1,113} = 0.0976$, $p = .755$	$F_{1,113} = 1.45$, $p = .231$	$F_{1,113} = 0.168$, $p = .683$
μ_{RC}	$F_{1,113} = 2.58$, $p = .111$	$F_{1,113} = 0.0275$, $p = .869$	$F_{1,113} = 0.350$, $p = .556$	$F_{1,113} = 0.749$, $p = .389$	$F_{1,113} = 0.110$, $p = .741$	$F_{1,113} = 0.0136$, $p = .907$
μ_{ML}	$F_{1,113} = 0.172$, $p = .679$	$F_{1,113} = 2.14$, $p = .146$	$F_{1,113} = 0.469$, $p = .495$	$F_{1,113} = 0.186$, $p = .667$	$F_{1,113} = 2.18$, $p = .143$	$F_{1,113} = 0.0759$, $p = .784$

Significant effects are indicated by the bold typeface. RMSD stands for root-mean-square deviation, and COD stands for coefficient of determination. A, σ, and μ are respectively the peak value, standard deviation, and mean of the fitted bivariate normal distributions. The subscripts, RC and ML, respectively indicate rostrocaudal and mediolateral directions.

The standard deviation in the rostrocaudal direction (σ_{RC}) was also not significantly affected by any of the factors, but the standard deviation in the mediolateral direction (σ_{ML}) was significantly affected by aging ($F_{1,113} = 4.03$, $p = .0471$). *Post hoc* analysis showed that σ_{ML} was slightly but significantly smaller for younger participants. The mean of the optimally fitted normal distributions in the rostrocaudal direction (μ_{RC}) was significantly affected by aging ($F_{1,113} = 4.63$, $p = .0335$) and muscle ($F_{1,113} = 4.75$, $p = .0314$). *Post hoc* analysis showed that the fitted normal distributions were located more rostrally for older participant and the medial gastrocnemius muscles. The mean of the optimally fitted normal distributions in the mediolateral direction (μ_{MC}) was not significantly affected by any of the factors. For σ_{RC}, the type of pacing and muscle interacted significantly ($F_{1,113} = 6.27$, $p = .0137$). This interaction probably indicated that, with external pacing, σ_{RC} tended to increase for the tibialis anterior muscles and decrease for the medial gastrocnemius muscles. For other parameters in Table 5.4 and Table 5.5, the factors of the 4-way ANOVA did not interact significantly (Table 5.7).

5.5 Discussion

Between young and older participants, we observed discrepancies in several aspects of corticomuscular coherence during bilateral cyclical ankle movements. As we hypothesized, the magnitude of cyclical corticomuscular coherence was lower for older participants than for younger participants (Figure 5.6). The lower magnitude of coherence suggests that the primary motor cortex participates differently in older individuals during simple cyclical movements: the participation is either *i*) less overall or *ii*) less linear, as coherence only quantifies the liner aspect of corticomuscular communication.

Our result agreed with previous studies that observed decreased magnitude of corticomuscular coherence in older individuals during sustained contractions of upper limb muscles [25], [26]. However, during sustained contractions of upper limb muscles, some studies reported age-related increase in the magnitude of coherence [27], [28]. Kamp et al. [28] had attributed the age-related increase to greater cortical involvement that occurred as compensation against the effects of aging. Although such phenomenon complies with the compensation hypothesis [42], it may be task-specific to sustained isometric contraction with continuous visual monitoring of the level of muscle activation [27], [28]. With greater conscious control of muscle activation than what the ankle movements required in this study, sustained contractions are more likely to depend on the primary motor cortex to directly activate the muscles. In this case, compensation by increasing the cortical involvement is plausible. Furthermore, the ankle movements in this study may have also depended on subcortical and spinal neuronal networks to generate the cyclical movements. If so, age-related increase in activity could have occurred outside the corticomuscular communication.

Unlike the magnitude of corticomuscular coherence, the parameters of motor performance did not indicate known age-related deteriorations (i.e., increased movement variability and impaired bilateral coordination). Thus, despite slower movements with self-pacing, the ability to perform the ankle movements was generally preserved among older participants (Table 5.1).

Despite the lack of age-related discrepancy in motor performance, aging affected the magnitude of corticomuscular coherence. This finding suggests several possibilities: *i*) the cyclical increase in corticomuscular coherence was irrelevant to the functional requirements of the ankle movements; *ii*) the observed age-related discrepancy indicated pre-symptomatic changes in motor control, in a similar fashion to the pre-symptomatic pathology of neurodegenerative diseases such as Parkinson's disease [43]; and *iii*) there was a floor effect (i.e., magnitude of coherence would have shown greater age-related discrepancy had the task been more demanding). To confirm the functional relevance of corticomuscular coherence, future research should consider tasks that are either *i*) challenging enough to induce a difference in performance between young and older individuals or *ii*) varied in difficulty to examine how the coherence relates to difficulty (e.g., inclusion of in-phasic movements or multiple movement frequencies). Alternatively, future studies could target older individuals, whose performance of a particular movement is known to be impaired.

The cortical distribution of corticomuscular coherence was slightly but significantly broader in the mediolateral direction for older participants (indicated by σ_{ML} in Table 5.4 and Table 5.5). Functional neuroimaging studies have shown that older individuals recruit additional cortical, subcortical, or cerebellar areas to perform various isolated movements of the fingers, wrists, and ankles [29]-[32], [44]-[47]. If older participants engaged a broader area of the primary motor cortex, its activity could have propagated to EEG electrodes that abut C_z in the mediolateral directions, thereby broadening the cortical distribution of coherence. Aging was also associated with a more rostrally centered cortical distribution of corticomuscular coherence (illustrated in Figure 5.7 and Figure 5.8). The sub-division of the primary motor cortex into rostral and caudal regions has been suggested by several studies [48]-[50]. For example, using retrograde transneuronal transmission of the rabies virus in rhesus monkeys, Rathelot and Strick [48] have shown that approximately 70 to 90% of corticospinal neurons, which project monosynaptically to the motoneurons of proximal and distal forelimb muscles, were located in the caudal region of the primary motor cortex. The rostral region contained approximately 5 to 10% of such corticospinal neurons, with the remainder located in rostral region of the post-central gyrus [48]. It is possible that the caudal region of the primary motor cortex is more vulnerable to age-related deterioration, thereby causing older individuals to engage the rostral region. Similarly, Plow et

al. [51] have reported that the cortical distribution of motor evoked potentials is more rostrally centered for older individuals (i.e., the center of corticospinal excitability is shifted rostrally).

There were several limitations in this study. First, our older participants included two individuals aged 51 and 61 years, who are younger than individuals normally considered old (e.g., 65 years old). Also, without imaging, we could not determine whether the older participants had experienced neural changes that would affect corticomuscular communication. However, out of such neural changes, *i*) the gray matter volume declines more or less steadily from the age of 20 years [9]-[13], *ii*) the white matter volume either starts to decline around the age of 40 years [13] or declines steadily from the age of 20 years [14], *iii*) the number of motor neurons decreases steadily from the age of 20 years old [17], [18] though the decrease may accelerate around the age of 60 years [19], and *iv*) the apparent re-organization of the motor units occurs more or less steadily from the age of 20 years [21], [22]. Furthermore, the reduction in corticospinal excitability [24] and corticomuscular coherence [26] has been observed in individuals older than 55 years of age. Therefore, despite the inclusion of two younger individuals, we assumed that our older participants had undergone at least some change in their corticomuscular communication. The second limitation is the uncertainty regarding the levels of muscle and central fatigue due to the ankle movements. Particularly, young participants may have experienced some muscle fatigue during the second run of externally-paced movements (i.e., the mean power frequency of the EMG signal from the right tibialis anterior muscle significantly decreased by 8.35±7.81 Hz during the last three cycles, compared to the first three cycles), and the fatigue could have enhanced corticomuscular coherence [52] though we suspect the effects to be modest [53]. Third, we did not consider a sedentary lifestyle as a significant confounder. Although the task that we chose for this study was not demanding in terms of power output, cardiopulmonary stress, precision, or complexity (i.e., the movements were unfamiliar to the participants yet simple enough to learn in a short amount of time and sustain for prolonged periods), a sedentary lifestyle could have affected corticomuscular communication independently from age-related changes. Fourth, the power of our statistical analysis may be limited due to the multi-factorial design and the small sample size. Lastly, coherence between surface EEG and EMG signals is only a gross measure of corticomuscular communication as a scalp EEG signal is the sum of all

electrical field potentials in the vicinity of the measuring electrode, and a surface EMG signal is the sum of all motor unit action potentials in the vicinity of the measuring electrode.

In this study, young and older participants performed cyclical, anti-phasic ankle movements. During this movement, we observed discrepancies in the magnitude and cortical distributions of corticomuscular coherence between young and older participants. The coherence of older participants was characterized by *i*) lower magnitude and *ii*) mediolaterally broader and more rostrally centered cortical distributions. The lower magnitude suggests that the primary motor cortex either participates less in the control of the movement or in a less linear fashion (e.g., polysynaptically via spinal circuits). The broader and rostrally shifted cortical contributions may indicate compensation against age-related neuromuscular changes. Thus, we have shown that corticomuscular communication is affected in older individuals during bilateral cyclical movements, which share specific functional requirements with walking. Aging may similarly affect corticomuscular communication during walking.

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5.7 Author Contributions Statement

T.Y, K.M, and K.Z designed the experiment. K.Z also provided technical consulting. T.Y performed the experiments and analyzed the data. T.Y, K.M, R.C, and M.R.P interpreted the data. T.Y drafted the manuscript. K.Z, R.C, and M.R.P edited the manuscript. T.Y and K.M revised the manuscript.

5.8 Additional Information

5.8.1 Competing Financial Interests

Authors declare that they have no competing financial interests.

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Chapter 6

6 Dynamic cortical participation during bilateral, cyclical ankle movements: effects of Parkinson's disease

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6.1 Abstract

Parkinson's disease (PD) is known to increase asymmetry and variability of bilateral movements. However, the mechanisms of such abnormalities are not fully understood. Here, we aimed to investigate whether kinematic abnormalities are related to cortical participation during bilateral, cyclical ankle movements, which required *i*) maintenance of a specific frequency and *ii*) bilateral coordination of the lower limbs in an anti-phasic manner. We analyzed electroencephalographic and electromyographic signals from nine men with PD and nine aged-matched healthy men while they sat and cyclically dorsi- and plantarflexed their feet. This movement was performed at a similar cadence to normal walking under two conditions: *i*) self-paced and *ii*) externally paced by a metronome. Participants with PD exhibited reduced range of motion and more variable bilateral coordination. However, participants with and without PD did not differ in the magnitude of corticomuscular coherence between the midline cortical areas and tibialis anterior and medial gastrocnemius muscles. This finding suggests that either the kinematic abnormalities were related to processes outside linear corticomuscular communication or PD-related changes in neural correlates maintained corticomuscular communication but not motor performance.

6.2 Introduction

Parkinson's disease (PD) is known to increase the variability and asymmetry of bilateral rhythmical movements, such as walking [1]-[8]. Although the hallmark of PD is well established as progressive neuronal degeneration, mechanisms of many specific kinematic abnormalities in PD are not clearly understood.

Corticomuscular coherence in the beta band had been used to suggest that synchronous cortical oscillations were functionally related to muscle activities during sustained contractions about single joints [9], [10]. In our previous studies, we demonstrated that the coherence between the primary sensorimotor cortex and the active leg muscles increased cyclically in the beta band (13 to 30 Hz) during bilateral, cyclical ankle movements [11], [12]. Because the ankle movements that we adopted had only a few intended functional requirements such as maintaining a specific movement frequency and coordinating the feet in an anti-phasic manner, our findings suggest that the primary sensorimotor cortex may contribute to these requirements via corticomuscular communication [11], [12].

In addition to the aforementioned effects on the consistency and symmetry of bilateral movements [1]-[8], PD can impair the performance of anti-phasic movements [13]-[19]. Because these kinematic features are fundamental to the aforementioned ankle movements, it is likely that individuals with PD will perform these movements abnormally. Furthermore, if the cyclical corticomuscular coherence during the ankle movements is relevant to specific functional requirements, kinematic abnormalities in PD would be accompanied by corresponding changes in corticomuscular coherence.

Only a few studies have examined how PD affects corticomuscular coherence, and the experimental evidence is limited to sustained contractions of upper limb muscles [20], [21].

During sustained isometric extension of the wrist, healthy individuals and individuals with PD on levodopa show similar magnitudes of coherence within the beta band [20]. In the off-medication condition, individuals with PD showed decreased beta coherence [20], suggesting that dopamine deficiency within the basal ganglia impairs corticomuscular synchronization. To our knowledge, no study has examined corticomuscular coherence during bilateral cyclical movements of the lower limbs at a cadence similar to normal walking in PD.

Although the corticospinal connection may be normal in PD, indicated by the preservation of central motor conduction time [22], [23], PD may still affect corticomuscular communication. This is suggested by the anatomical and physiological relationship between the basal ganglia and motor cortex. The basal ganglia, which is affected by degeneration of dopaminergic neurons in PD [24]-[26], is reciprocally connected with the motor cortices [27]-[30]. In rat models of PD, the motor cortex is coherent with the substantia nigra pars reticulata during treadmill walking [31] and the subthalamic nucleus during sustained exploratory movement [32]. Furthermore, such cortico-basal ganglia coherence is abolished by L-dopa or dopamine receptor agonist [31], [32] and restored by dopamine D_2 receptor antagonist [31], suggesting that the coherence is pathological. Similar cortico-basal ganglia coherence and its dopamine dependence have been observed in individuals with PD during rest or tonic wrist extension [33], [34]. If the basal ganglia and motor cortex interact abnormally during the ankle movements, then it is possible that changes in cortical activities may alter corticomuscular communication though the exact effects are uncertain.

Here, we aimed to investigate the mechanism of kinematic abnormalities in PD by examining the corticomuscular communication between the midline cortical areas and the active muscles during bilateral, cyclical ankle movements at a cadence similar to normal walking. To quantify the corticomuscular communication, we calculated the coherence between electroencephalographic (EEG) and electromyographic (EMG) signals. The experimental tasks were performed under two conditions (self-paced and externally-paced by a metronome) as rhythmic aural pacing, at or slightly faster than the preferred cadence, can acutely reduce movement variability in individuals

with PD [4], and such change in motor performance may be accompanied by changes in corticomuscular coherence.

Based on the existing evidence, we hypothesized that, compared to healthy individuals, the magnitude of coherence between contracting muscles and the midline primary sensorimotor cortex within the beta band would be lower in individuals with PD. Participants were assessed in the off-medication condition because dopamine has been shown to restore corticomuscular coherence [20] and normalize the interaction between the basal ganglia and motor cortex [31], [32].

6.3 Methods

6.3.1 Participants

We recruited ten men with PD and eleven aged-matched healthy men. The same sample of healthy men was reported in our previous study [12]. One participant with PD and two healthy participants were excluded from data analysis because of excessive EEG artifacts. The remaining nine participants with PD were 62±7 years old and healthy participants were 66±7 years old (mean±standard deviation). The two groups of participants did not differ significantly in age (p = .227, unpaired t-test). The clinical details of the participants with PD are summarized in Table 6.1.

Table 6.1. Clinical details of participants with PD.

Age (years)	Disease Duration (years)	Medication (mg/day)	Predominant Motor Symptom	UPDRS III Score (out of 108)	MoCA Score (out of 30)	GFQ Score (out of 64)
63	15	Levodopa (400 mg) Carbidopa (100 mg) Rasagiline (1 mg) Pramipexole (4.5 mg)	Bradykinesia and tremor in right arm; reduced swing of right arm during walking; postural lean to left side	23	29	16
51	9	Levodopa (450 mg) Carbidopa (112.5 mg)	Resting tremor in left hand	19	28	N/A

64	9	Levodopa (800 mg) Carbidopa (200 mg) Amantadine (200 mg)	Resting tremor in left hand; wearing off; difficulty raising left leg during walking	11	28	N/A
67	9	Levodopa (600 mg) Carbidopa (150 mg)	Tremor in left hand; dystonia of upper and lower extremities; micrographia; occasional extension of first left toe; bradykinesia	18	29	N/A
62	5	Levodopa (300 mg) Carbidopa (75 mg) Rasagiline (1 mg) Pramipexole (2.25 mg)	Reduced swing of right arm during walking; bradykinesia and reduced dexterity of right hand; micrographia; dystonia of second right toe	6	27	N/A
62	15	Levodopa (400 mg) Carbidopa (100 mg) Ropinirole (6 mg)	left-sided tremor; generalized dyskinesia; impaired speech; wearing off	28	25	10
52	3	Levodopa (300 mg) Carbidopa (75 mg) Domperidone (30 mg)	Right-sided rigidity; right-sided resting and action tremor; reduced swing of right arm during walking	20	24	N/A
66	6	Levodopa (700 mg) Carbidopa (175 mg)	Right-sided bradykinesia and rigidity	20	27	12
71	20	Levodopa (1000 mg) Carbidopa (100 mg)	Rigidity; generalized bradykinesia	13	25	10

GFQ stands for Gait and Falls Questionnaire.

All participants were able to walk unassisted and had no history of dementia. Participants with PD had been diagnosed with idiopathic PD, and their disease duration was 10.1±5.5 years (ranging from 3 to 20 years). All participants provided their written informed consent. The experimental protocol (12-5462) was approved by the University Health Network Research Ethics Board (Toronto, Ontario, Canada) and carried out in accordance with the relevant guidelines and regulations.

6.3.2 Motor and Cognitive Examination of Participants with Parkinson's Disease

All participants with PD were being treated with levodopa and were studied in the off-medication condition following overnight withdrawal from dopaminergic medications. We administered the motor section (Part III) of the UPDRS before the experimental task. After the experimental task, we administered the MoCA (Version 7.1).

On a separate day before the experiment, we administered the Gait and Falls Questionnaire [35] to four of the nine participants with PD that reported freezing of gait. The questionnaire quantified the severity of freezing and identified possible triggers of episodes.

6.3.3 Experimental Task

Each participant sat in a chair with a backrest and performed six runs of bilateral, cyclical ankle movements. The six runs alternated between being self-paced and externally paced by the sound of a metronome, with the first run always being externally paced (i.e., for each type of pacing, there were three runs). Each run lasted approximately one minute and was followed by a rest of approximately one minute.

Participants were instructed to maximally dorsiflex one foot and maximally plantarflex the other foot at each beat of the metronome (in an anti-phasic manner) without flexing or extending their toes. The metronome was set to 108 beats per minute (1.8 Hz), comparable to the cadence of normal overground walking [36]. For self-paced movements, the participants were instructed to replicate the rhythm of the metronome. The passive movements that resulted from the ankle movements (e.g., an upward movement of the knee as the foot dorsiflexed) were not constrained. Because the participants sat with their heels on an elevated footrest, the soles of their feet largely did not come into contact with any surface during the movement. Because the experimental task was performed with no resistance and supported heels, we assumed that the strength of contraction was relatively low with minimal effects of amplitude cancellation [37]. They were also instructed to focus their gaze on a bullseye, which was placed approximately 2 m in front of

them in their line of sight as they sat upright and gazed forward. To minimize EEG artifacts, the participants were instructed to relax their upper body and to refrain from talking, swallowing, coughing, clenching their jaw, or blinking excessively. While the participants performed the movement, their EEG signals, EMG signals, and body kinematics were recorded.

6.3.4 Data Collection

All signals were recorded in epochs of approximately one minute, which began several cycles after the movement had been initiated and preceded the termination of the movement. The sampling of all signals was synchronized by an analogic switch, which sent a transistor-transistor logic signal that initiated the recording of kinematic data and EMG signals and timestamped the EEG signals.

To track the ankle movements, we used an optical motion capture system: a data acquisition device (MX Giganet, Vicon Motion Systems Ltd., United Kingdom), nine optical cameras (Bonita, Vicon Motion Systems Ltd., United Kingdom), and data acquisition software (Nexus 1.8.5, Vicon Motion Systems Ltd., United Kingdom). We placed 14-mm retroreflective markers over the EEG electrode locations, AF_7 and AF_8, and over the following bony landmarks: greater trochanter, lateral epicondyle of the femur, lateral malleolus and second metatarsal head on both sides. The instantaneous positions of the markers were recorded at 100 Hz.

EMG signals were recorded using a wireless EMG system (Trigno™ Wireless EMG System, Delsys Inc., United States). Each EMG sensor used 99.9%-silver electrodes, which were 1 mm in diameter and 5 mm in length. The electrodes were in bipolar configuration with inter-electrode spacing of 10 mm. The EMG sensors were placed bilaterally over the belly of the tibialis anterior muscle and the medial head of the gastrocnemius muscle. EMG signals were sampled at 2 kHz with a bandwidth of 20 Hz to 450 Hz and the common mode rejection ratio of over 80 dB.

EEG signals were recorded using an active electrode system (g.GAMMAsys, g.tec medical engineering GmbH, Austria) with compatible signal amplifiers (g.USBamp, g.tec medical engineering GmbH, Austria) and recording software (g.Recorder, g.tec medical engineering GmbH, Austria). According to the 10-10 system [38], we recorded from AF_z, F_z, F_1, F_2, F_3, F_4, FC_z, FC_1, FC_2, FC_3, FC_4, C_z, C_1, C_2, C_3, C_4, CP_z, CP_1, CP_2, and Pz, which covered the midline primary sensorimotor cortex and its surrounding. EEG signals were sampled at 1.2 kHz using a monopolar montage with the reference electrode on the left ear lobe and the ground electrode over the right zygomatic process.

6.3.5 Data Analysis

Data analysis was performed offline using MATLAB R2016b (The MathWorks, Inc., United States). We quantified motor performance as the intra-individual mean and coefficient of variation of the following parameters: movement cycle duration, range of motion at the ankle, and the phase offset between the two feet. These parameters were selected to quantify the consistency and symmetry of the ankle movements. A movement cycle was defined such that dorsiflexion of the right foot was maximal at 0 and 100% of the cycle. The ankle angle was calculated between two lines: one line joining the markers over the lateral epicondyle of the femur and the lateral malleolus and another line joining the markers over the lateral malleolus and the second metatarsal head. The phase offset was calculated for angular velocities of the two ankles [16], such that the offset would be 180° for a symmetrically coordinated movement. For each participant, intra-individual mean and coefficient of variation of the above parameters were calculated across the minimum number of movement cycles that were completed among all participants after three epochs.

To assess the effects of head movements on EEG signals, we calculated the continuous wavelet transforms of the cyclical EEG signals at C_z using the complex Morlet wavelet. We also calculated the cyclical linear movements of the markers at the EEG electrode locations, AF_7 and AF_8 to assess the magnitude of head movements during the ankle movements.

For each epoch, EMG signals were centered by subtracting its mean and full-wave rectified to enhance the spectral power at the frequency of common input to the activated muscles [39], [40]. To assess the effects of rectification, we estimated the power spectral densities of the cyclical EMG signals using Welch's method. Cyclical EMG signals were down-sampled at 400 Hz and divided into eight sections of equal length with Hamming windows and 50% overlap. For each epoch, EEG signals were filtered by *i*) a second-order infinite impulse response notch filter, with a center frequency of 60 Hz and bandwidth of 1 Hz, and *ii*) a fourth-order Butterworth infinite impulse response filter, between 0.5 Hz and 100 Hz. For both processes, zero-phase digital filtering was used. The filtered EEG signals were decomposed by independent component analysis [41], [42]. The resultant components and filtered EEG signals were examined for artifacts visually [43]. The contributions of components that contained artifactual waveforms were subtracted from the filtered EEG signals to generate noise-reduced EEG signals. The subtraction was restricted to the observed duration of artifactual waveforms to minimize the loss of information.

The noise-reduced EEG signals and rectified EMG signals were down-sampled at 400 Hz, and their coherence was calculated for each epoch using the complex Morlet wavelet:

$$\psi(t) = F_b \pi^{-0.5} e^{j2\pi F_c t} e^{-\frac{t^2}{F_b}},$$

where j is the imaginary unit, F_b is a bandwidth parameter, and F_c is the center frequency of the wavelet in Hz. The bandwidth parameter was set to 10, and the center frequency was set to 1.

Corticomuscular coherence was calculated as three-dimensional data across frequency and time. For each participant, the corticomuscular coherence (approximately one-minute long) was segmented into individual movement cycles, and the segments were used to calculate an

ensemble average. Each ensemble average was calculated with the minimum number of cycles that were completed among all participants after three epochs.

The significance of each ensemble average was determined by a threshold value [10]:

$$SL = 1 - \left[\frac{1}{N}\left(1 - \frac{\alpha}{100}\right)\right]^{\frac{1}{L-1}},$$

where α is the confidence level in percent, L is the number of segments that are used to calculate the ensemble average, and N is the number of data points (across frequency and time) in the ensemble average. The confidence level was set to 95%. Before applying the threshold, the ensemble average was binned across frequency and time, resulting in one pixel per Hz (between 1 and 100 Hz) and per percent of the movement cycle. The magnitude of corticomuscular coherence was calculated as the volume of significant coherence: the magnitude of coherence above the threshold at each pixel, integrated over the frequency-time plane of the ensemble average. A similar method has been used by Kilner et al. to quantify corticomuscular coherence [44]. For the volume of significant coherence, we also calculated its center frequency as the geometric centroid along frequency.

The cyclical patterns of corticomuscular coherence at C_z were validated using surrogate coherence. For each participant, an ensemble average of coherence was calculated by pairing the i^{th}-cycle segment of the EEG signal with the j^{th}-cycle segment of an EMG signal, such that $i \neq j$. For each participant, such ensemble averages were calculated 100 times with differently permutated pairing of EEG and EMG signals, and the average magnitude of the 100 ensemble averages was used as surrogate coherence. Patterns of coherence, which were present in experimental coherence but abolished in surrogate coherence, were considered valid as these patterns indicate the synchronization between EEG and EMG signals that does not relate to the

mere power of the signals. We chose this approach to eliminate only the cyclical pairing between the EEG and EMG signals. The validation was only performed at C_z because it was the most relevant electrode location (i.e., over the midline primary sensorimotor cortex).

For the intra-individual mean and coefficient of variation of cycle duration and range of motion, we performed 3-way ANOVA with the *i*) presence of PD (present or absent), *ii*) type of pacing (self- or external pacing), and *iii*) side of body (left or right) as factors. For the intra-individual mean and coefficient of variation of the phase offset, we performed 2-way mixed-design ANOVA with the *i*) presence of PD as a between-subject factor and *ii*) type of pacing as a within-subject factor. To eliminate redundancy, we only analyzed the phase offset that was calculated with the right ankle as the leading side.

On the volume and center frequency of significant coherence at C_z, we performed 4-way ANOVA with the *i*) presence of PD, *ii*) type of pacing, *iii*) side of body, and *iv*) muscle (tibialis anterior or medial gastrocnemius muscles) as factors. To examine the cortical distribution of coherence, we performed 5-way ANOVA on the volume of significant coherence with the *i*) presence of PD, *ii*) type of pacing, *iii*) side of body, *iv*) muscle, and *v*) EEG electrode location as factors.

We examined how surrogate and experimental coherence at C_z differed in magnitude by performing 2-way ANOVA with *i*) the presence of PD and *ii*) type of coherence (experimental or surrogate) as factors. Preliminarily, we had observed that surrogate coherence showed relatively high magnitudes of coherence below 6 Hz. Thus, the 2-way ANOVA was performed separately above and below 6 Hz.

For significant main effects, we performed *post hoc* multiple comparison tests with Tukey's honestly significant difference criterion. The significance level was set to 5% for all tests. We

also performed multiple-sample tests for equal variances (Bartlett's test) and Royston's multivariate normality tests [45] on the data for ANOVA.

6.4 Results

6.4.1 Motor and Cognitive Examination of Participants with Parkinson's Disease

For participants with PD, 11.9±1.7 hours had elapsed since their last dose. The motor scores of the Unified Parkinson's Disease Rating Scale (UPDRS) were 17.6±6.6 (out of 108), with a higher value indicating greater motor impairment. The leg agility subscores were 1.2±0.9 (out of 4) for the right and 1.3±0.9 for the left.

The Montreal Cognitive Assessment (MoCA) scores were 26.9±1.83 (out of 30), with a lower value indicating greater cognitive impairment. The scores for the Freezing of Gait Questionnaire, which is a subset of the Gait and Falls Questionnaire [35], were 9.0±1.6 (out of 24), with a higher score indicating greater severity of freezing. Of the four participants with PD that reported freezing of gait, three reported start hesitation and one reported freezing while walking straight.

6.4.2 Motor Performance of Ankle Movements

For each type of pacing, healthy participants completed 167±8 cycles and participants with PD completed 166±21 cycles after three one-minute runs. Among all participants, the minimum number of completed cycles was 111. The inter-run rest was 80.6±30.7 seconds for healthy participants and 116±23 seconds for participants with PD.

Figure 6.1 compares the motor performance of the two groups during the ankle movements. The intra-individual mean of cycle duration was significantly shorter for participants with PD ($F_{1,65}$ = 4.89, p = .0305) but was not significantly affected by the type of pacing ($F_{1,65}$ = 1.35, p = .250)

or side of body ($F_{1,65} < 0.001$, $p = .994$). The coefficient of variation of cycle duration was not significantly affected by the presence of PD ($F_{1,65} = 2.73$, $p = .103$), type of pacing ($F_{1,65} = 2.78$, $p = .100$), or side of body ($F_{1,65} = 1.42$, $p = .237$). The intra-individual mean of the range of motion was significantly smaller for participants with PD ($F_{1,65} = 31.4$, $p < .001$) but was not significantly affected by the type of pacing ($F_{1,65} = 0.270$, $p = .605$) or side of body ($F_{1,65} = 0.295$, $p = .589$). The coefficient of variation of the range of motion was significantly more variable for participants with PD ($F_{1,65} = 41.4$, $p < .001$) but was not significantly affected by the type of pacing ($F_{1,65} = 1.68$, $p = .199$) or side of body ($F_{1,65} = 2.03$, $p = .159$). The intra-individual mean of the phase offset was not significantly affected by the presence of PD ($F_{1,32} = 0.295$, $p = .591$) or type of pacing ($F_{1,32} = 0.784$, $p = .383$). The coefficient of variation of the phase offset was significantly more variable for participants with PD ($F_{1,32} = 7.67$, $p = .00928$) but not significantly affected by the type of pacing ($F_{1,32} = 0.340$, $p = .564$). According to multiple-sample tests for equal variances and Royston's multivariate normality tests, the mean cycle duration was neither homogeneous ($T = 149.37$, $p < .001$) nor normal ($H = 34.53$, $p < .001$), the coefficient of variation of cycle duration was homogeneous ($T = 5.28$, $p = .626$) and normal ($H = 5.15$, $p = .639$), the mean range of motion was homogeneous ($T = 2.36$, $p = .937$) and normal ($H = 3.83$, $p = .320$), the coefficient of variation of the range of motion was not homogeneous ($T = 14.20$, $p = .048$) but normal ($H = 3.78$, $p = .786$), the mean phase offset was homogeneous ($T = 6.03$, $p = .110$) and normal ($H = 2.85$, $p = .524$), and the coefficient of variation of the phase offset was homogeneous ($T = 1.59$, $p = .663$) and normal ($H = 2.14$, $p = .694$).

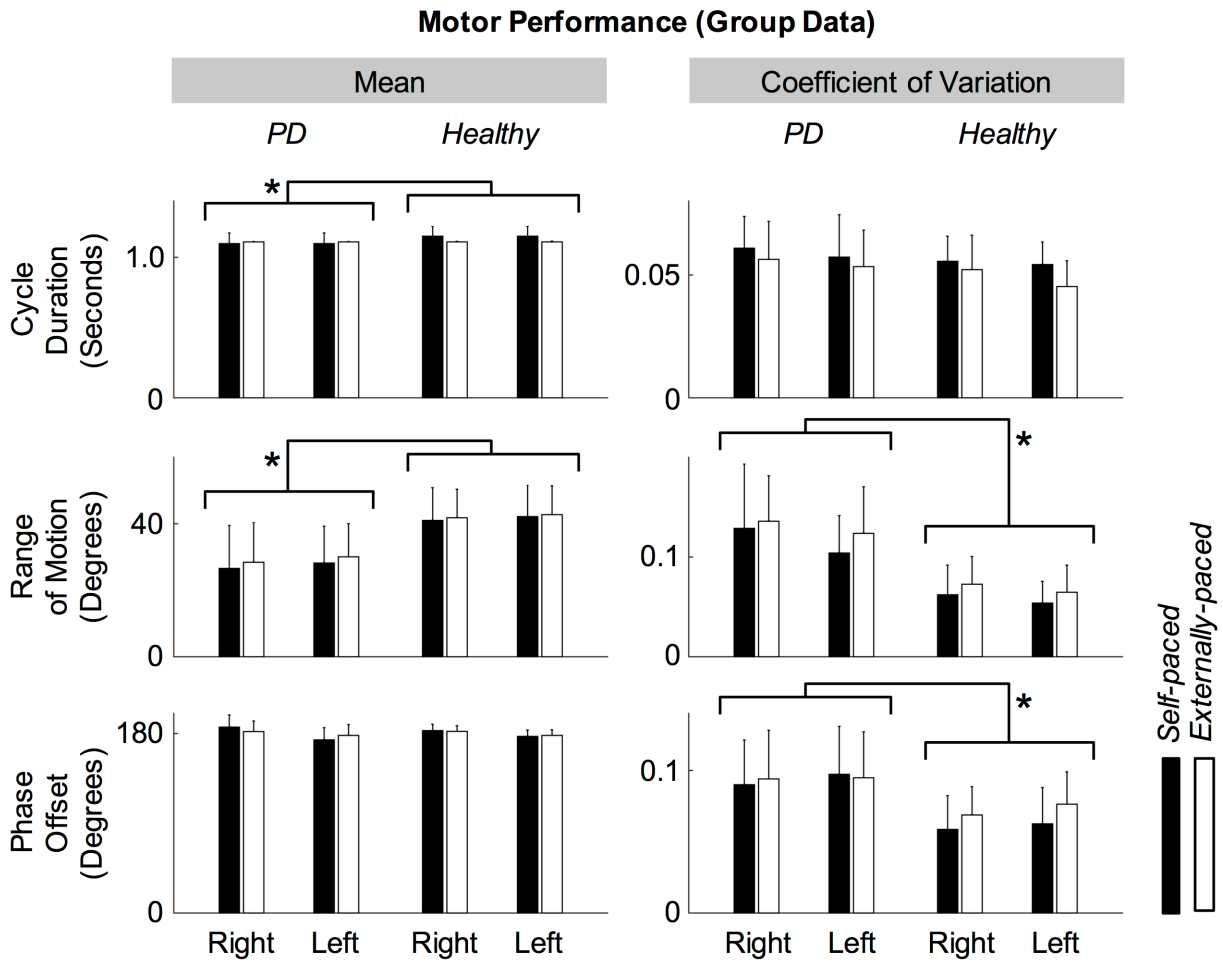

Figure 6.1. Intra-individual mean and coefficient of variation of parameters of motor performance during self-paced and externally-paced ankle movements. Error bars indicate inter-individual standard deviations.

Among the factors of analysis of variance (ANOVA) on the parameters of motor performance, the only significant interaction was between the presence of PD and type of pacing on the intra-individual mean of cycle duration ($F_{1,65} = 4.59$, $p = .0360$), indicating that cycle durations of healthy participants were more affected by the type of pacing.

For both participant groups, regardless of the type of pacing, markers at AF_7 and AF_8 were within a volume of approximately 1 cm^3 during each movement cycle. For healthy participants,

the average linear head movement was less than 8 mm, 7 mm, and 4 mm, in the anteroposterior, mediolateral, and longitudinal directions, respectively. The equivalent measures for participants with PD were less than 5 mm, 4 mm, and 2 mm.

6.4.3 Cyclical Corticomuscular Coherence during Ankle Movements

Figure 6.2 shows the full-wave rectified EMG signals from representative participants during self-paced movements. Both participants showed cyclical increase in the activation of the tibialis anterior muscles during dorsiflexion and relatively weak activation of the medial gastrocnemius muscles. These observations were also true for externally-paced movements (Figure 6.3). The continuous wavelet transforms of EEG signals at C_z did not show observable peaks at harmonics of the movement frequency (1.8 Hz) above 5 Hz (Figure 6.4). Figure 6.5 shows how the full-wave rectification modulated the estimated power spectral densities of EMG signals, and Figure 6.6 shows the corresponding change in the pattern of corticomuscular coherence around 20 Hz.

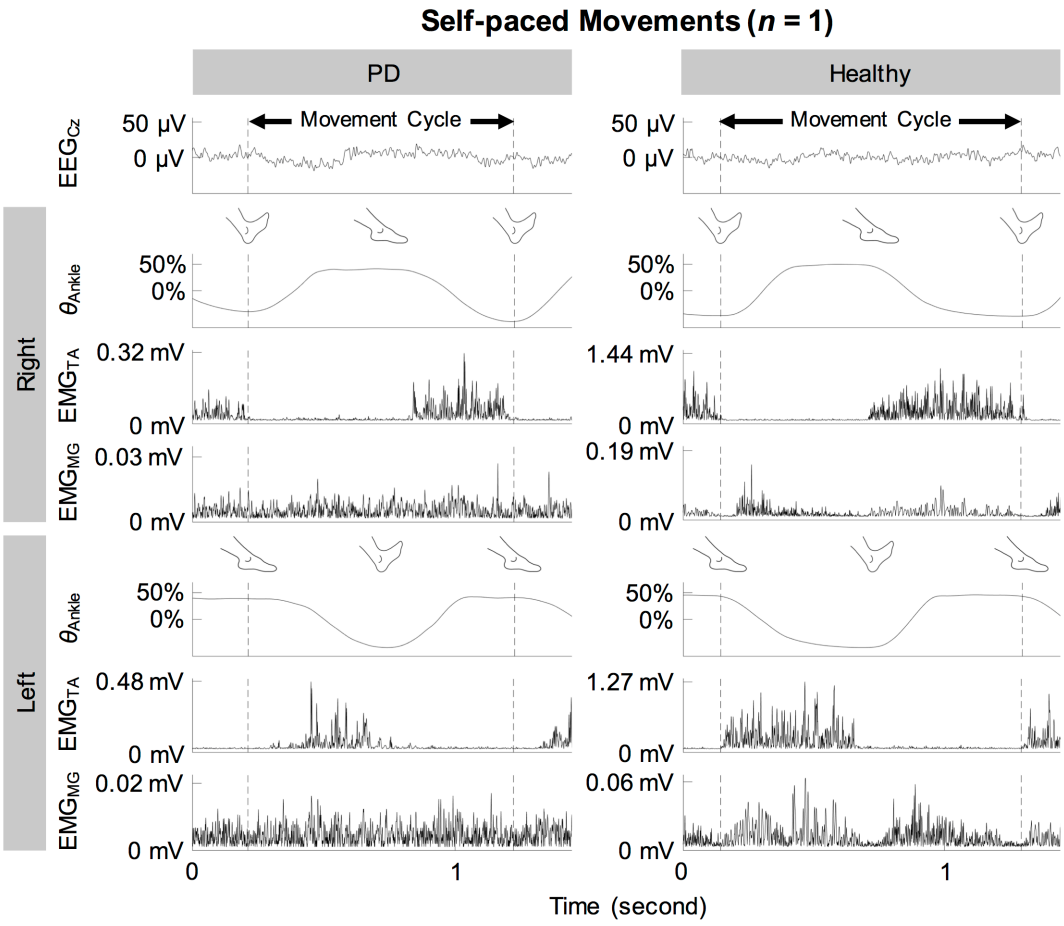

Figure 6.2. EEG, kinematic, and EMG signals of representative participants during self-paced ankle movements. Noise-reduced EEG signal from C_z (EEG_{Cz}), ankle angle (θ_{Ankle}), and full-wave rectified EMG signals from the tibialis anterior (EMG_{TA}) and medial gastrocnemius (EMG_{MG}) muscles are shown. Ankle angles have been centered and normalized to its range.

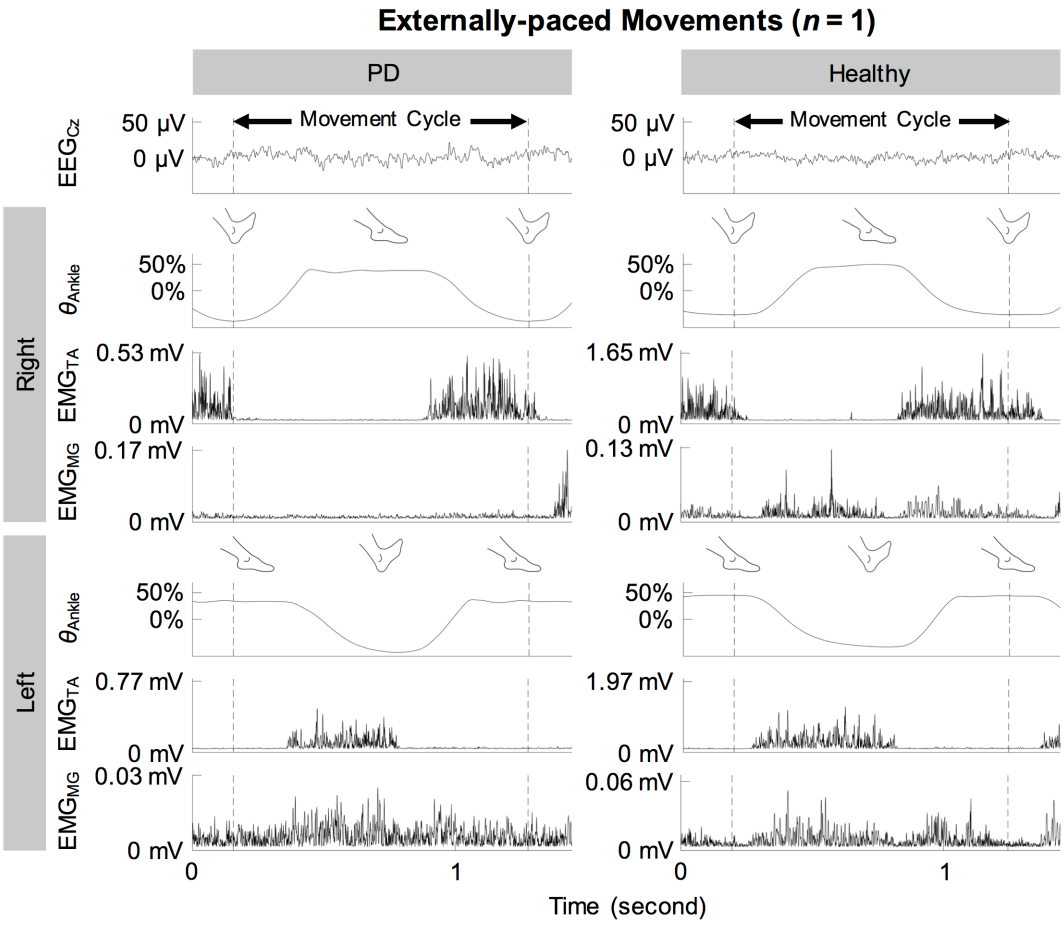

Figure 6.3. EEG, kinematic, and EMG signals of representative participants during externally-paced ankle movements. Noise-reduced EEG signal from C_z (EEG_{Cz}), ankle angle (θ_{Ankle}), and full-wave rectified EMG signals from the tibialis anterior (EMG_{TA}) and medial gastrocnemius (EMG_{MG}) muscles are shown. Ankle angles have been centered and normalized to its range.

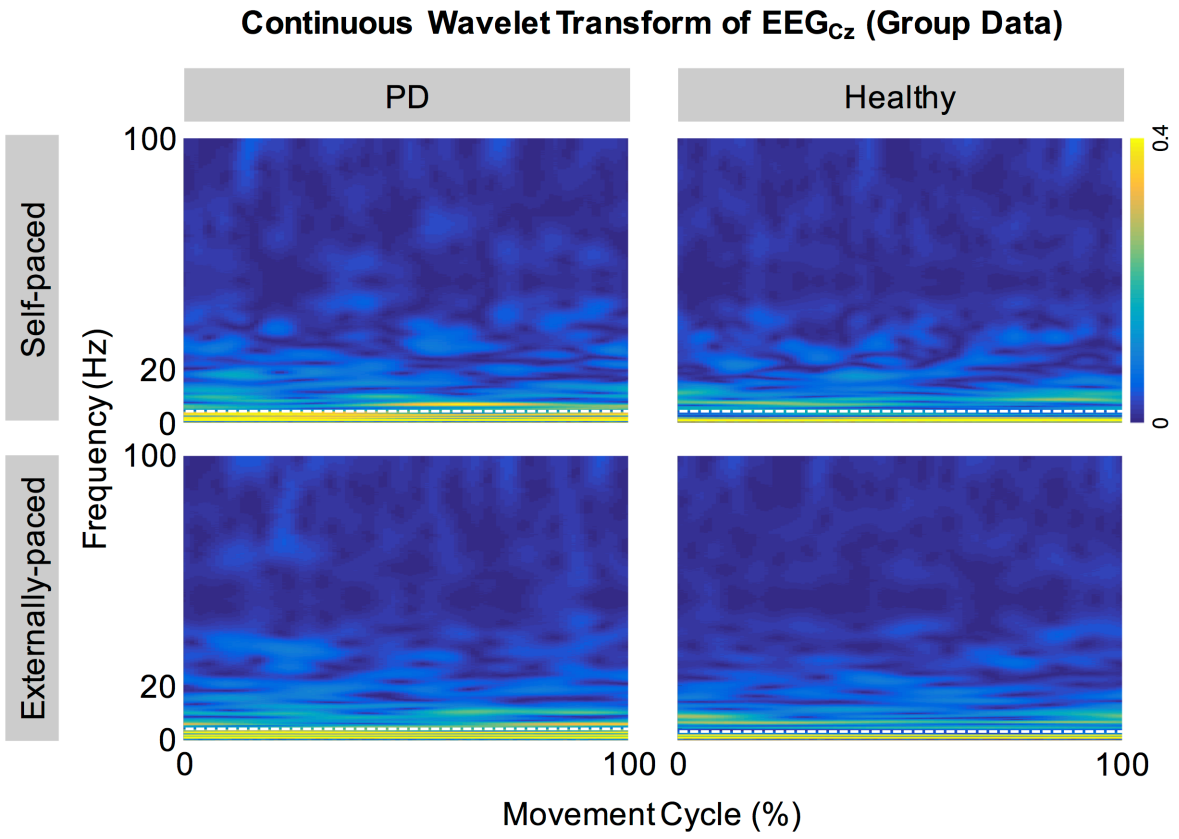

Figure 6.4. Continuous wavelet transforms of cyclical EEG signals at C_z. Group averages are shown. The white dotted lines indicate 5 Hz.

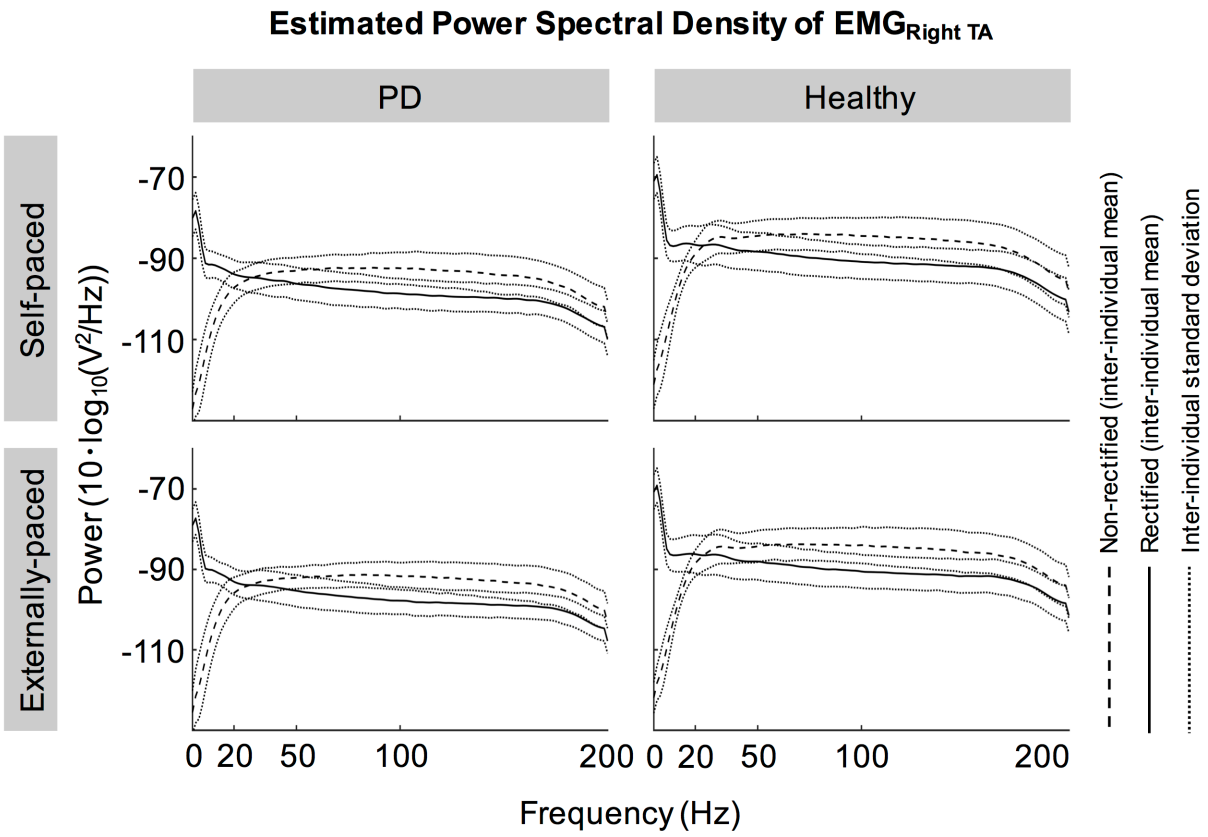

Figure 6.5. Estimated power spectral densities of EMG signals from the right tibialis anterior (TA) muscle.

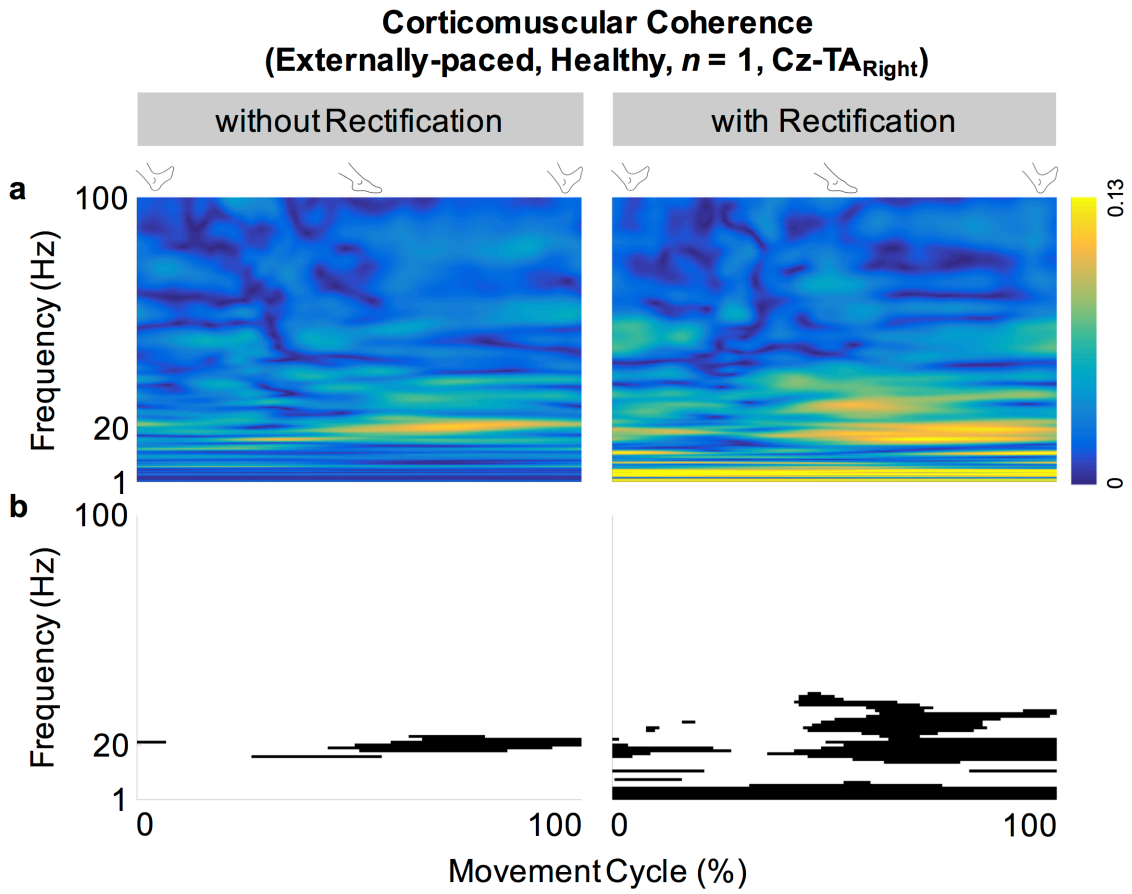

Figure 6.6. Effects of rectifying EMG signals on cyclical corticomuscular coherence. (a) Cyclical coherence between C_z and the right tibialis anterior (TA) muscle of a healthy participant during externally-paced movements. (b) Significant portions of the cyclical coherence in (a).

Figure 6.7a shows the cyclical coherence between C_z and the tibialis anterior muscles of a participant with PD during externally-paced movements. Within the movement cycle, corticomuscular coherence increased dynamically in the beta band, coinciding with ankle dorsiflexion (*cf*. Figure 6.2). Figure 6.7b shows the group average of cyclical corticomuscular coherence in the beta band. Generally, between C_z and the tibialis anterior muscles, corticomuscular coherence in the beta band increased cyclically during dorsiflexion (*cf*. Figure 6.2). Volumes of significant corticomuscular coherence were centered about the beta band (Table

6.2). The cyclical patterns of coherence were less consistent between C_z and the medial gastrocnemius muscles (Figure 6.7b).

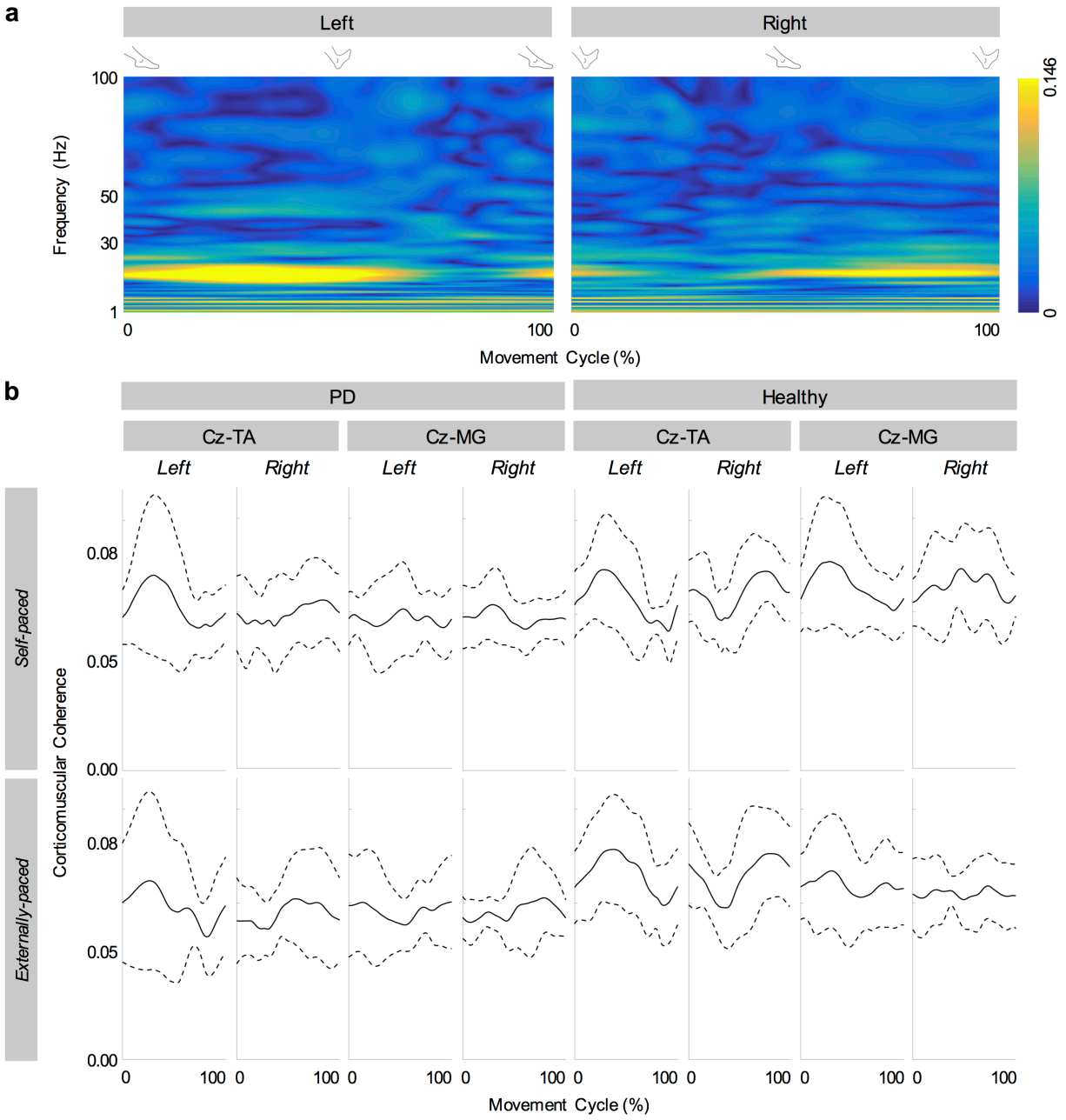

Figure 6.7. Cyclical corticomuscular coherence. (a) Cyclical coherence between C_z and tibialis anterior muscles of a participant with PD during externally-paced movements. (b) Group averages of cyclical corticomuscular coherence in the beta band (13 to 30 Hz).

Coherence is calculated between C_z and the tibialis anterior (TA) and medial gastrocnemius (MG) muscles. Solid lines indicate inter-individual mean and dotted lines indicate inter-individual standard deviations.

Table 6.2. Volume and center frequency of significant coherence between EEG signal from C_z and EMG signals from the tibialis anterior (TA) and medial gastrocnemius (MG) muscles.

Group	Measurement	Muscle	Self-pacing		External Pacing	
			Left	Right	Left	Right
Healthy	Volume ($Hz \cdot \%_{Movement\ Cycle}$)	TA	6.44±7.60	4.53±5.91	6.93±5.17	8.37±9.87
		MG	5.11±4.23	5.23±3.77	3.91±3.58	3.44±2.46
	Center Frequency (Hz)	TA	15.4±4.7	17.2±4.7	16.7±4.9	17.2±6.9
		MG	14.8±3.5	14.9±4.5	14.2±4.6	14.8±6.1
PD	Volume ($Hz \cdot \%_{Movement\ Cycle}$)	TA	6.78±7.47	4.61±4.03	6.19±9.69	4.20±3.30
		MG	4.20±3.65	2.41±1.70	3.79±5.07	3.39±2.65
	Center Frequency (Hz)	TA	15.0±5.8	14.7±6.0	14.6±6.4	18.4±9.6
		MG	12.4±4.0	16.7±4.3	16.2±4.8	16.4±5.7

Each entry shows the inter-individual mean±standard deviation. The values did not significantly differ between groups.

Table 6.2 summarizes the volume and center frequency of significant corticomuscular coherence for the two groups. At C_z, the volume of significant coherence was significantly affected by the muscle ($F_{1,133} = 5.12$, $p = .0253$) but not by the presence of PD ($F_{1,133} = 1.31$, $p = .254$), type of pacing ($F_{1,133} = 0.0160$, p = .900), or side of body ($F_{1,133} = 0.954$, $p = .330$). *Post hoc* analysis revealed that the volume of significant coherence between C_z and the tibialis anterior muscles was larger than that between C_z and the medial gastrocnemius muscles. The center frequency was not significantly affected by the presence of PD ($F_{1,133} = 0.0163$, $p = .899$), type of pacing ($F_{1,133} = 0.978$, $p = .325$), muscle ($F_{1,133} = 1.37$, $p = .244$), or side of body ($F_{1,133} = 2.17$, $p = .143$). Neither for the volume nor the center frequency of significant coherence did the factors of ANOVA interact significantly. According to multiple-sample tests for equal variances and Royston's multivariate normality tests, the magnitude of coherence was neither homogeneous ($T = 53.04$, $p < .001$) nor normal ($H = 61.68$, $p < .001$). The same tests indicated that the frequency of coherence was homogeneous ($T = 14.35$, $p = .499$) but not normal ($H = 21.53$, $p = .029$).

Figure 6.8 shows the cortical distributions of the volume of significant coherence in the beta band between EEG signals and EMG signals from the tibialis anterior muscles. Figure 6.9 shows the same distributions for the medial gastrocnemius muscles. Generally, the cortical distribution peaked at C_z although this pattern appeared to be more distinct for the tibialis anterior muscles. ANOVA shows that the magnitude of coherence at C_z was significantly larger than the magnitude at all other locations in 89% of the conditions (i.e., combinations between the factors of ANOVA). This was followed by the magnitude at FC_z, which was larger than the magnitude at all other locations in 54% of the conditions, and the magnitude at C_1, which was larger than the magnitude at locations other than C_z and C_2 in 44% of the conditions. The analysis did not show PD-related differences in the cortical distribution of coherence.

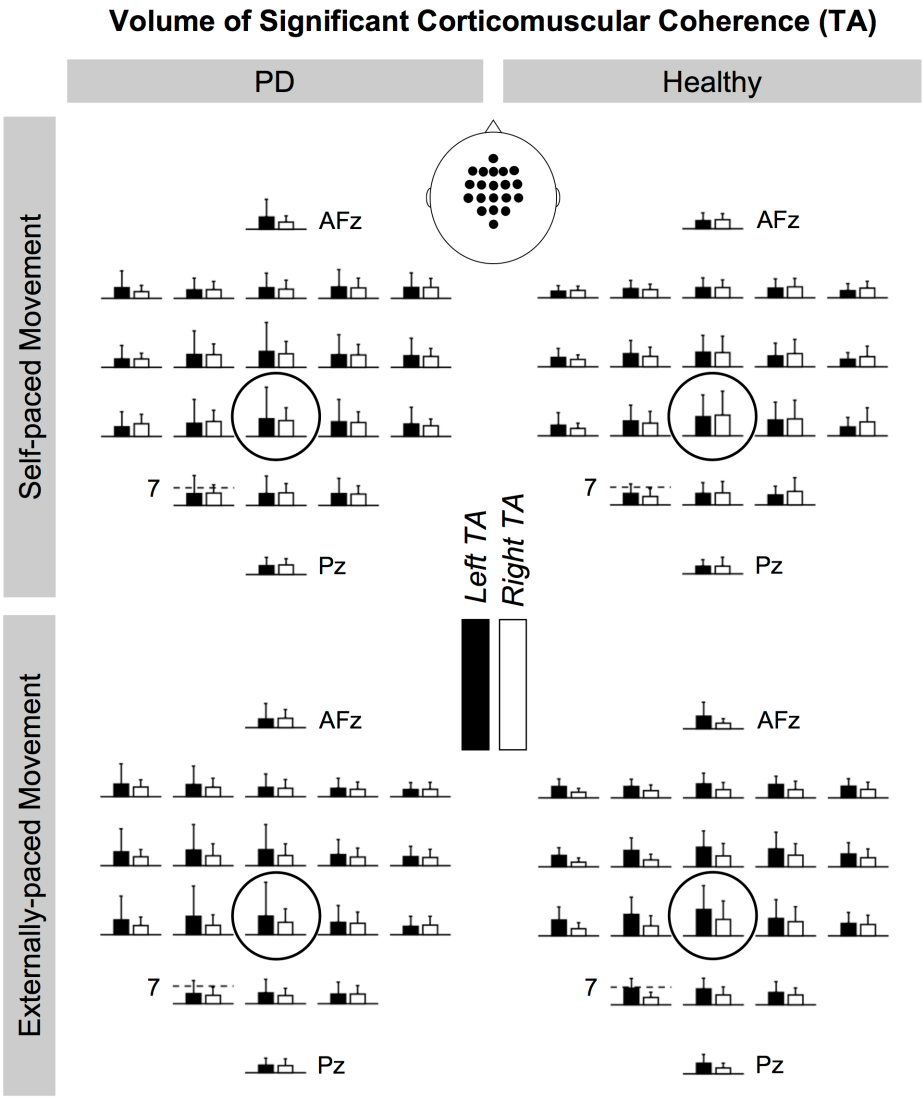

Figure 6.8. Cortical distributions of significant beta-band corticomuscular coherence for the tibialis anterior (TA) muscles. All bars show the volume of corticomuscular coherence in the units of Hz·%$_{Movement\ Cycle}$. C_z is circled. The scale of the vertical axis is the same across electrode locations, and the magnitude of the bar graphs is indicated at CP_1. The rostral direction is towards the top of the page.

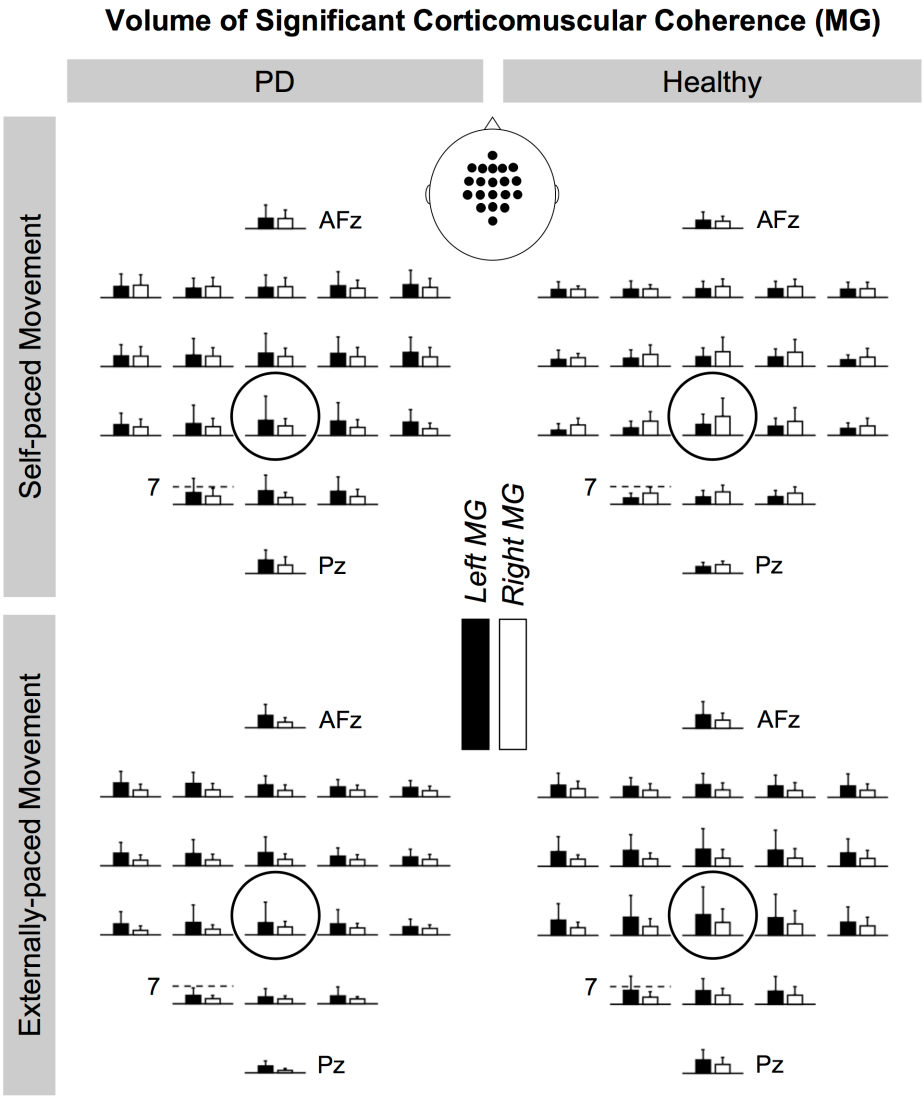

Figure 6.9. Cortical distributions of significant beta-band corticomuscular coherence for the medial gastrocnemius (MG) muscles. All bars show the volume of corticomuscular coherence in the units of Hz·%$_{Movement\ Cycle}$. C_z is circled. The scale of the vertical axis is the same across electrode locations, and the magnitude of the bar graphs is indicated at CP_1. The rostral direction is towards the top of the page.

6.4.4 Validation of Experimental Corticomuscular Coherence

Figure 6.10 illustrates the validation of experimental coherence using surrogate coherence. Patterns of significant experimental coherence were preserved in surrogate coherence below 6 Hz but were abolished above 6 Hz. Below 6 Hz, the volume of significant coherence was

significantly affected by the presence of PD ($F_{1,284} = 31.2$, $p < .001$) and surrogation of coherence ($F_{1,284} = 45.5$, $p < .001$). *Post hoc* analysis revealed that the volume of significant coherence was larger for healthy participants and for surrogate coherence. Above 6 Hz, the volume of significant coherence was significantly affected by the surrogation of coherence ($F_{1,284} = 171$, $p < .001$) but not by the presence of PD ($F_{1,284} = 1.445$, $p = .230$). *Post hoc* analysis revealed that the volume of significant coherence was smaller for surrogate coherence.

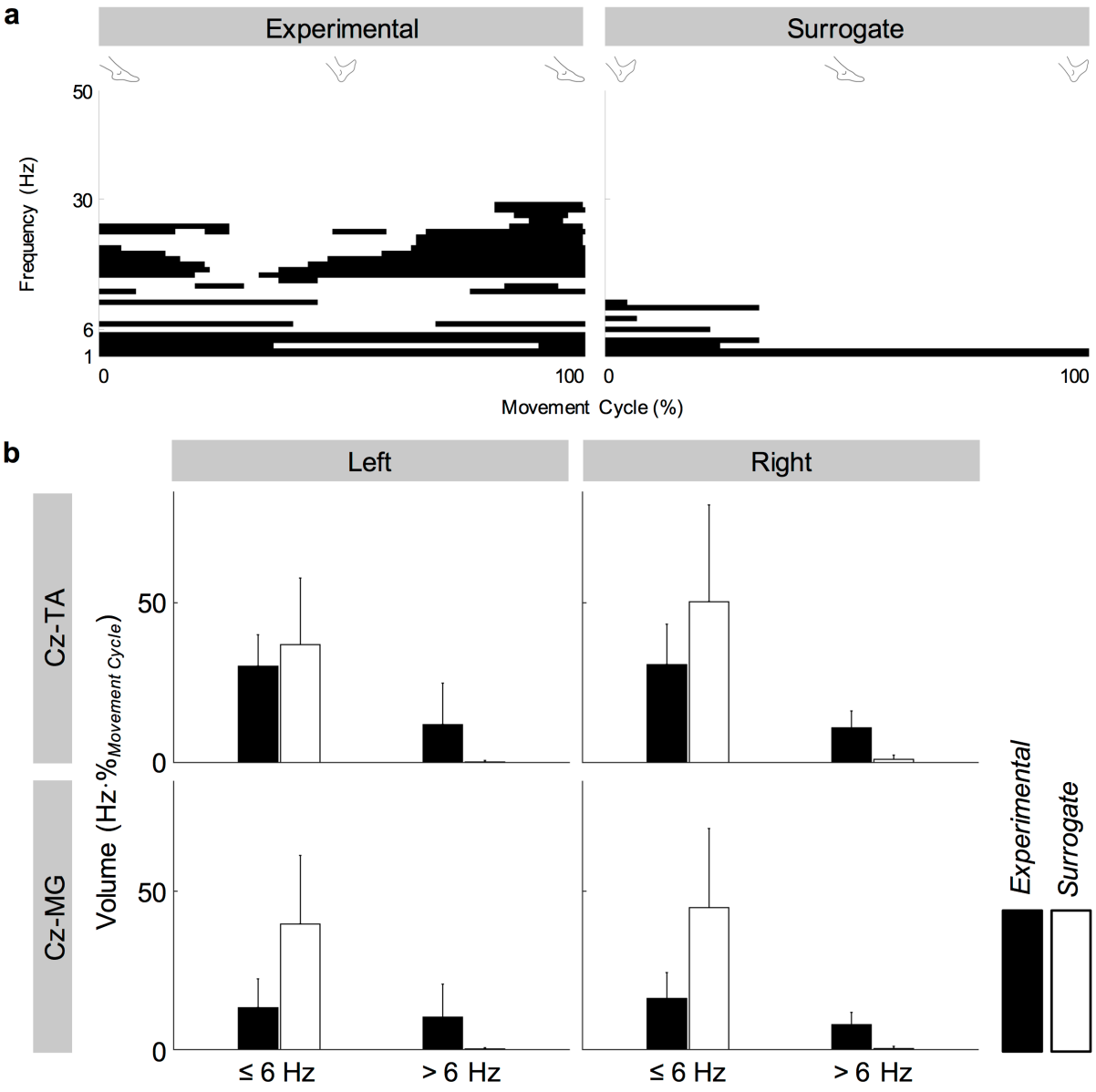

Figure 6.10. Validation of experimental corticomuscular coherence. (a) Significant experimental and surrogate coherence between C_z and the right tibialis anterior muscle of a participant with PD during externally-paced movements. Pixels with significant coherence are shown in black. (b) Volumes of significant coherence between C_z and the tibialis anterior (TA) and medial gastrocnemius (MG) muscles of participants with PD during self-paced movements. Error bars indicate inter-individual standard deviations.

Below 6 Hz, the presence of PD and type of coherence interacted significantly ($F_{1,284} = 4.61$, $p = .0326$), indicating that the difference in the volume of significant coherence between experimental and surrogate coherence was larger for participants with PD. Above 6 Hz, the interaction between the two factors was not significant ($F_{1,284} = 1.69$, $p = .194$).

6.5 Discussion

Participants with PD exhibited several kinematic abnormalities during the ankle movements: faster movement frequencies (especially with self-pacing), reduced and more variable range of motion, and more variable bilateral coordination compared to healthy participants (Figure 6.1). Similar increase in movement frequency has been reported for self-paced finger tapping at a specified frequency [46]-[50], reduced range of motion has been reported for walking [36] and self-paced finger tapping [51], [52], and increased variability has been reported for various parameters of gait in PD [1]-[4]. Tests for homogeneity and normality indicated that the observed abnormalities in participants with PD were valid for the reduced range of motion and more variable bilateral coordination. Thus, the consistency and symmetry of the ankle movements differed significantly between participants with and without PD.

The observed kinematic abnormalities may have been caused partially by the requirement for anti-phasic coordination. Compared to healthy individuals, anti-phasic movements in PD can transition spontaneously into in-phasic movements at lower frequencies [15], exhibit greater asymmetry [14], [16], [17], [53], induce freezing [53], or simply fail [18], [19]. Although our

participants with PD did not exhibit these abnormalities, the existing evidence suggests that individuals with PD experience difficulty with performing anti-phasic movements.

In addition to anti-phasic coordination, participants with PD may have had deficits in learning and automatizing the ankle movements. In monkeys and humans, the basal ganglia appears to participate in learning an unfamiliar motor task [54]-[57] and automatizing its execution [55], [58]-[61]. Although the ankle movements were relatively simple, impaired motor learning and task automatization could have contributed to the observed kinematic abnormalities.

In participants with and without PD, coherence between C_z and the tibialis anterior muscles increased cyclically in the beta band during dorsiflexion of the feet (Figure 6.7b). This increase occurred bilaterally and regardless of the type of pacing (Figure 6.7b). Furthermore, these patterns of coherence were validated using surrogate coherence. With the shuffled pairing between cycles of EEG and EMG signals, the volume of significant coherence above 6 Hz significantly decreased and became almost negligible (Figure 6.10). Thus, the patterns of coherence above 6 Hz could be attributed to the cyclical ankle movements. Conversely, the volume of significant coherence below 6 Hz significantly increased with the shuffled pairing (Figure 6.10). Thus, coherence below 6 Hz was not validated. The patterns of coherence were less distinct between C_z and the gastrocnemius muscles (Figure 6.7b), possibly due to the relative absence of phasic activation of the gastrocnemius muscles (Figure 6.2). We observed that full-wave rectification of EMG signals enhanced their power (Figure 6.5) and the pattern of corticomuscular coherence (Figure 6.6) around 20 Hz. Similar modulation of the power spectrum by full-wave rectification has been reported previously [62]. Although this frequency was at the lower threshold of the bandwidth of the EMG system, rectification appears to amplify the power at the common motor unit recruitment frequency based on a broad spectrum of the original, unrectified signal. Such behavior has been supported by experimental evidence [40] and computational modeling [37], [39].

For the tibialis anterior muscles, the cortical distributions of significant beta corticomuscular coherence generally peaked at C_z (Figure 6.8). Such somatotopy has been observed for the tibialis anterior muscle during isometric contractions [63]. The cortical distributions were less distinct for the medial gastrocnemius muscles (Figure 6.9). Again, this may have been due to the muscle being less active than the tibialis anterior muscle.

The minimal influence from movement artifacts was suggested by the absence of peaks in the estimated power spectral densities of cyclical EEG signals at C_z (Figure 6.4): during tasks that induce substantial electrode movements, artifacts can be present in EEG signals at the movement frequency and its harmonics [64]. The absence of significant artifacts was also indirectly supported by the kinematic data, as the head markers stayed within a space of approximately 1 cm^3 during each movement cycle.

Contrary to our hypothesis, the magnitude of corticomuscular coherence did not significantly differ between the two groups (Table 6.2). As participants with PD exhibited several kinematic abnormalities (Figure 6.1), the lack of group discrepancy in the magnitude of coherence suggests that the pathological processes, which impaired motor performance, occurred outside linear corticomuscular communication or that changes in neural correlates maintained corticomuscular communication but not motor performance.

Whichever the case, it is likely that pathological processes that affected motor performance involved the basal ganglia, which is implicated in many aspects of motor control [27] and is affected by neuronal degeneration in PD [24]-[26]. Pathological activities within the ganglia may affect motor control via the recipients of the basal ganglia output: the ventral anterior and ventrolateral nuclei of the thalamus, which project back to the motor cortex [27], [65], [66], or the pedunculopontine nucleus (PPN). Abnormal cortico-basal ganglia interaction has been observed in rat models of PD [31], [32] and individuals with PD [33], [34] although its exact implications for the ankle movements are unknown. As for the basal ganglia output to the PPN,

this may particularly affect the performance of anti-phasic ankle movements. The PPN comprises the mesencephalic locomotor region [67]-[69], which is implicated in initiating and sustaining locomotive actions [70]-[72]. The notion that PD involves pathological oscillations within the PPN, which contribute to the impairment of locomotive actions, is supported by the finding that deep brain stimulation of the PPN improves gait in individuals with PD in the off-medication condition [73], [74]. Also, in individuals with PD, brisk ankle movements modulate oscillations in the PPN and cortical-PPN coherence in the beta band [75]. Although the ankle movements in this study were substantially different from locomotion, they share some key functional requirements with locomotion such as the maintenance of rhythm and anti-phasic coordination of the lower limbs. Thus, pathological output from the basal ganglia may have affected the performance of the ankle movements via the PPN and a subsequent pattern generating neuronal circuit at the spinal level [76], [77].

Several studies indicated that the neural correlates of cyclical hand movements are affected by PD [13], [47], [78]. Particularly, during an anti-phasic bimanual task, individuals with PD show greater activation of the primary motor cortex and less activation within the basal ganglia than healthy individuals [13]. Although our experimental task involved lower limbs, the functional requirement (of performing a bilateral, anti-phasic movement) was similar to that of the aforementioned study, as was the disease severity of the participants [13]. Thus, it is possible that our participants with PD also recruited neural correlates that differed from those of healthy participants. However, the exact changes in neural correlates could not be determined without additional studies. Identifying the neural correlates in individuals with and without PD may help delineate how linear corticomuscular communication is maintained during the ankle movements.

Our observations differed from the results of a previous study, which found decreased beta coherence in PD during sustained isometric wrist extension [20]. Such discrepancy may have been due to the difference in the tasks: sustained isometric contraction compared to cyclical movements. Compared to cyclical movements, sustained contractions may require greater conscious control of the level of muscle activation, thus inducing greater participation by the primary sensorimotor cortex. It has also been shown that, between isometric and dynamic

concentric plantarflexion with comparable ankle angles and forces, the motor unit discharge rate is significantly higher during dynamic plantarflexion [79], suggesting that the nature of contraction affects how motor units are recruited. If isometric and dynamic contractions differ substantially in how they are controlled, then it is possible that corresponding corticomuscular communication is differentially vulnerable to PD-related changes during isometric and dynamic contractions. The discrepancy between our findings and the previous study [20] may have also been related to the difference between upper and lower limb muscles, with upper limb muscle receiving stronger corticospinal projections [80]. Because of the stronger projections, upper limb muscles may rely more on corticospinal communication during contractions. Assuming that such communication is reflected in corticomuscular coherence, tasks with greater corticospinal communication may be more affected by PD.

Corticomuscular coherence can be affected in diseases other than PD. It has been reported that stroke can significantly decreases the magnitude of beta corticomuscular coherence on the affected side [81] and shift the location of maximum beta corticomuscular coherence away from the expected location: contralateral sensorimotor cortex [82]. Cerebral palsy has been associated with increased magnitude of beta corticomuscular coherence [83]. We did not observe such phenomena in PD. Although our findings differed from those of previous studies, several discrepancies make the comparison difficult. The main discrepancies are in the experimental task and pathophysiology. The studies on stroke used sustained wrist extension or a gripping task with visual feedback of force production [81], [82], and the study on cerebral palsy used externally-cued ballistic hand movements [83]. In the stroke studies, only a small percentage of participants (2 of 6 participants or 3 of 25 participants) showed lesions in the basal ganglia [81], [82]. In the cerebral palsy study, it is uncertain how much the interaction between the basal ganglia and the sensorimotor cortex is affected.

Despite reported evidence that aural pacing evokes synchronized periodic fields in the primary auditory cortex [84] and that increased attention or effort increases corticomuscular coherence [44], [85]-[92], we did not observe any significant effects of aural pacing on the magnitude of coherence.

This study had several limitations. As we used coherence, our analysis focused on the linear aspect of corticomuscular communication. Because of the complex interconnections that the primary motor cortex forms with adjacent cortical areas and subcortical structures [93], the linear aspect alone probably cannot comprehensively capture how PD affects corticomuscular communication. Indeed, non-linear communication is likely if pathological signals are transmitted from the basal ganglia to the spinal cord as speculated above. Recently, Yang et al. have propose a new method to calculate non-linear corticomuscular coherence [94], with which they have found non-linear corticomuscular coherence during isometric wrist extension and attributed it to somatosensory feedback [95]. Such method may be extended to dynamic movements in the future.

With coherence, we also could not infer the directionality of corticomuscular communication. Although the EEG signal from C_z is likely to consist primarily of electrical cortical activities in the midline cortical structures such as the primary motor and sensory cortices and the supplementary motor area, the signal can also contain activities from the adjacent cortical areas through volume conduction. To determine the sources of the signal from C_z, detailed source localization is required. However, as coherence is a linear measure, it seems more likely that coherence exists via the monosynaptic corticospinal connection rather than the polysynaptic connections for somatosensory feedback.

This study was also limited by the absence of freezing episodes among participants with PD. Such episodes could have been accompanied by observable discrepancies in corticomuscular coherence between healthy participants and participants with PD.

All our participants with PD were responsive to dopaminergic medications and were tested after overnight medication withdrawal in the practically defined off state. However, there could have been some residual effects of dopaminergic medications at the time of testing.

6.6 Conclusions

In this study, participants with and without PD performed bilateral, anti-phasic ankle movements. Despite abnormal consistency and symmetry of movement, participants with PD did not significantly differ in the magnitude of corticomuscular coherence from participants without PD. This finding suggests that, for participants with PD, either *i*) pathological processes outside linear corticomuscular communication contributed to the kinematic abnormalities or *ii*) PD-related changes in the neural correlates of movement maintained corticomuscular communication but motor performance was still impaired. To delineate whether corticomuscular communication is involved in kinematic abnormalities in PD, future studies should also compare the neural correlates of movement between individuals with and without PD.

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6.8 References

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Chapter 7

7 Discussion

The overall objective of my thesis was to examine how Parkinson's disease (PD) affected the cortical participation in the motor control of bilateral cyclical ankle movements. This objective was pursued in three experimental studies, presented in Chapters 4 through 6. Although the hallmark neuronal degeneration in PD has been well established [1]-[3], and some cardinal signs such as akinesia and bradykinesia may be explained by the increased inhibitory output from the basal ganglia in classical models of PD [4]-[7], the mechanisms of many kinematic abnormalities in PD are not well understood. Such abnormalities include gait disturbances, which can significantly impact an individual's quality of life through falls [8]-[12], subsequent injuries [10], [12], [13] and secondary complications from reduced mobility [10], [14]. Because the mechanisms of gait disturbances in PD are not well understood, the current treatments are not universally or comprehensively effective (see *Effects of current treatments* in Chapter 1). Thus, the initial aim of this study was to understand how PD affected locomotor control. However, because of the complexity of bipedal locomotion and its inherent risk of movement artifacts, the scope of the thesis was modified to study the effects of PD on a simpler movement (cyclical, bilateral dorsi- and plantarflexion of the feet), which substantially reduced the risk of movement artifacts while retaining some key functional requirements that are also present in locomotion: maintaining rhythm and coordinating the feet in an anti-phasic manner. To quantify the effects of PD, corticomuscular coherence was selected as the primary outcome, with which I attempted to quantify corticomuscular communication. Corticomuscular communication was of particular interest because of the reciprocal connection between the basal ganglia and motor cortices [4]-[7] as well as the apparent functional relevance of the primary sensorimotor cortex in normal steady-state walking [15]-[20].

7.1 Study 1: young healthy individuals

First, the presence of corticomuscular coherence was observed and validated during the abovementioned ankle movements (Chapter 4). To my knowledge, among many previous studies on corticomuscular coherence (e.g., [20]-[23]), only Petersen et al. [20] have reported

corticomuscular coherence during bilateral cyclical movements of the lower limbs. In Chapter 4, I showed that the bilateral cyclical ankle movements were accompanied by a cyclical increase in the beta corticomuscular coherence in young healthy participants [24]. Such cyclical modulation of coherence was observed most prominently between the EEG signal from C_z and the EMG signals from the co-contracting dorsi- and plantarflexors on both sides during dorsiflexion [24]. These findings corroborated the previously reported characteristics of corticomuscular coherence [20], [22], [23], [25]-[41] and suggested that the midline cortical areas were functionally engaged in the movement. To my knowledge, this is the first time that the dynamic modulation of corticomuscular coherence has been observed and validated for simple cyclical movements of the lower limbs.

7.2 Study 2: young vs. older individuals

Because PD disproportionately affects older individuals [42], the effects of aging on corticomuscular coherence were examined (Chapter 5). Only a few studies have compared the corticomuscular coherence of young and older individuals, and all of them have examined sustained contractions of the upper limb muscles with contradicting results [43]-[46]. In Chapter 5, I showed that the magnitude and cortical distribution of corticomuscular coherence were affected by aging without significant discrepancies in the parameter of motor performance between young and older participants [47]. For older participants, the magnitude of corticomuscular coherence was lower and the cortical distribution was more rostrally centered and mediolaterally broader [47]. The lower magnitude suggested that the corticomuscular communication was either impaired or became less linear after aging. Such notion is supported by the existing evidence of neuromuscular changes in aging [48]-[61] and age-related changes in the neural correlates of movement [62]-[68]. The rostral shift and mediolateral broadening of the cortical distribution of coherence support the notion that the neural correlates differed between young and older participants. Age-related discrepancies in the neural correlates of movement may indicate compensation against aging. Previous studies have reported greater activation of neural correlates in elderly individuals with improved task performance [64], [69] or comparable performance to young individuals [67], [68]. During the ankle movements, similar compensation

may have contributed to the observed group discrepancies in coherence without significant group discrepancies in motor performance [47].

Previous studies have reported contradicting effects of aging on the magnitude of coherence. During sustained contractions of upper limb muscles, some studies have observed decrease in the magnitude of coherence [43], [44] while others have reported the opposite [45], [46]. This discrepancy may be explained by several differences in the nature of the experimental tasks. The studies that reported age-related increase in the magnitude had required their participants to visually monitor the level of muscle activation during sustained isometric contraction [45], [46]. The isometric contractions and dynamic ankle movements may have recruited different neural correlates, on which the effects of aging also differed. The outcomes could have also been influenced by the strength of corticospinal projections, which was probably stronger for upper limb muscles compared to lower limb muscles [70]. Finally, due to the continuous visual monitoring, the isometric contractions may have required greater conscious control of muscle activation and, consequently, greater participation of the primary motor cortex compared to the ankle movements. For tasks that require substantial conscious control of muscle activation, older individuals may exhibit greater cortical involvement than young individuals as compensation against age-related neuromuscular changes [45]. To my knowledge, this is the first time that the effects of aging on corticomuscular coherence were reported for bilateral cyclical movements of the lower limbs. Furthermore, the above findings provided a benchmark for examining how PD affected corticomuscular coherence during the ankle movements.

7.3 Study 3: older healthy individuals vs. individuals with Parkinson's disease

In Chapter 6, the effects of PD on corticomuscular coherence were examined. Very few studies have compared corticomuscular coherence between healthy individuals and individuals with PD, and these studies have only examined sustained contractions of the upper limb muscles [71], [72]. In Chapter 6, I showed that, despite the absence of significant difference in the magnitude of coherence between participants with and without PD, participants with PD showed significant

abnormalities in several kinematic parameters that indicated consistency and symmetry of movement. This finding suggested that either *i*) the linear corticomuscular communication was preserved in PD and the motor performance was affected by pathological processes outside the corticomuscular communication or *ii*) the corticomuscular communication was maintained through compensation, but the motor performance was still affected. Whichever the case, it is likely that the pathological processes in PD involved the basal ganglia, which can interact abnormally with the motor cortex [73]-[76] or affect the motor performance through its projection to the PPN [77]. The projection to the PPN seems particularly relevant to the control of anti-phasic movements of the feet as the PPN has been implicated in initiating and sustaining locomotive actions [78]-[80]. If the cyclical ankle movements activated a similar neuronal circuit to locomotion, pathological output to the PPN could have contributed to kinematic abnormalities.

In Chapter 6, the requirement for anti-phasic coordination may have been a significant cause of the observed kinematic abnormalities. In PD, the ability to perform unilateral cyclical movements seems to be relatively preserved [81]-[84]. However, impaired motor performance has been observed by numerous studies during bilateral anti-phasic movements by individuals with PD [85]-[92]. Apart from anti-phasic coordination of the feet, participants with PD may have reacted differently to learning and automatizing the experimental task. In monkeys and humans, the basal ganglia appears to be involved in learning an unfamiliar motor task [93]-[96] as well as automatizing the task execution [67], [94], [97]-[99]. Although the task in Chapter 6 was relatively simple, impaired motor learning and task automatization may have nonetheless contributed to the abnormal motor performance.

My findings differed from a previous study that observed a decrease in the magnitude of coherence in individuals with PD in the off-medication condition [71]. Again, this discrepancy may have been due to the difference in the tasks: isometric, voluntary contraction of an upper limb muscle [71] compared to cyclical movements of the lower limbs [47]. To my knowledge, this is the first time that the effects of PD on corticomuscular coherence were reported for simple cyclical movements of the lower limbs.

7.4 Summary of experimental studies

The current literature lacks experimental evidence on *i*) corticomuscular communication during dynamic bilateral movements of the lower limbs and *ii*) how such communication is affected by aging or PD. Together, the experimental studies in Chapters 4 through 6 supplement these gaps in knowledge. The results from Chapter 4 suggest that the midline cortical areas are functionally involved in the bilateral cyclical ankle movements. The results from Chapter 5 suggest that the cortical involvement may be affected by aging through changes in the corticomotoneuronal connection and the neural correlates of movement as compensation to maintain motor performance. The results from Chapter 6 suggest that the cortical involvement is either not affected by PD or maintained by changes in the neural correlates of movement although PD-related changes in the central nervous system probably contributed to abnormal motor performance. Furthermore, the abnormal motor performance (impaired consistency and symmetry of movement) reflected the known gait disturbances in PD [100]-[107].

7.5 Functional role of corticomuscular coherence

Even after the three experimental studies discussed above, the exact functional role of corticomuscular coherence is unclear. It is possible that corticomuscular coherence is an epiphenomenon of muscle activation. However, existing evidence suggests that corticomuscular coherence indicates some aspect of motor control. Previous studies have reported modulation of corticomuscular coherence due to varied task parameters [30], [35], [36], [38], level of muscle contraction [22], [23], [25], sensory stimuli [33], training [108], muscle fatigue [39], and pathologies of the central nervous system such as stroke [109], [110] and cerebral palsy [111].

In Chapter 2, I stated that corticomuscular coherence may indicate monosynaptic motor unit recruitment via the corticospinal tract. During such recruitment, it is likely that the motor units, which receive common supraspinal input, would be synchronized. The synchronized activation of motor units may be advantageous for rapid force production as well as co-activation of distinct muscles (e.g., an agonist-antagonist pair) [112]. Both of these requirements are applicable to the cyclical ankle movements performed by young healthy participants in Chapter 4 [24]. In Chapter 5, older healthy participants showed decreased magnitude of coherence, and this

was accompanied by slower movement with self-pacing as well as the absence of co-contraction between the tibialis anterior and medial gastrocnemius muscles [47]. These findings suggest that corticomuscular coherence may represent a specific control strategy for the cyclical ankle movements.

The study in Chapters 4 also showed that the center frequency of corticomuscular coherence was higher with aural pacing [24], with such shift in frequency possibly indicating multisensory integration [34]. Other than this observation, however, a relationship could not be established between the selected parameters of motor performance and corticomuscular coherence in the three experimental studies. To delineate the functional role of corticomuscular coherence during bilateral cyclical ankle movements, additional experiments are required in which specific aspects of movement are varied. For example, coherence can be compared between in-phasic and anti-phasic movements or between bilateral and unilateral movements to examine the relationship between corticomuscular coherence and bilateral coordination. Also, coherence can be examined during externally-paced cyclical movements with small, random changes in the imposed cycle duration to examine the relevance of corticomuscular coherence to the rhythmicity of movement.

7.6 Limitations of corticomuscular coherence

By using coherence, my analysis was limited to the linear aspect of corticomuscular communication. This approach is probably too simplistic given the complexity of the neuromuscular system. Recently, Yang et al. have proposed a new method to calculate non-linear corticomuscular coherence at harmonics, subharmonics, and intermodulation frequencies [113]. Subsequently, they have found statistically significant non-linear corticomuscular coherence during isometric wrist extension and attributed it to somatosensory feedback [114]. Whether this method can be extended to dynamic movements remains to be seen. Other common non-linear measures (e.g., detrended fluctuation [115] or entropy [116]) typically focus on neural activities alone rather than a functional relationship between neural and muscle activities. These measures were excluded from analysis because of the decision to examine cortical and muscle activities as the input and output of the relevant neuromuscular correlates.

Another limitation of coherence was that the directionality of corticomuscular communication could not be inferred although it is conceptually more likely for a linear relationship to exist between the motor cortex and muscles via the monosynaptic corticospinal connection as opposed to the polysynaptic connections for afferent somatosensory feedback or other efferent processes that are mediated by interneurons. The phase of coherence can suggest directionality if the phase offset and frequency are linearly related with a zero *y*-intercept. But, such relationship could not be established for the experimental data in the present studies. Also, the actual phase offset may not be the principal value that coherence indicates. The experimental data was analyzed using commonly used measures that specify the direction of neuromuscular communication (see *Application of DTF and PDC to cyclical ankle movements* in Appendices). Although these measures supported the efferent direction of communication, the results could not be validated.

7.7 Future directions

Although the observed group differences could be supported by existing evidence on the effects of aging or PD, the sample size in the presented experimental studies was relatively small. As smaller samples lower the positive predictive value [117], follow-up studies should increase the sample size to reinforce the statistical validity of the current findings. Follow-up studies should also examine the entire neural correlates of movement to better understand how corticomuscular communication is impaired by aging and how corticomuscular communication is maintained in PD with abnormal motor performance.

In follow-up studies, the experimental task should be modified for two reasons. First, to induce greater group discrepancies in motor performance or corticomuscular coherence, the task should be more challenging to older individuals or individuals with PD. For example, a more complicated sequence of ankle actuation that challenges motor learning and automatization may induce greater discrepancies between groups with and without PD. Second, to examine whether the observations with simpler movements can be extended to walking, the task should include

additional functional requirements of bipedal walking. A major limitation of the presented experimental studies was that the ankle movements were substantially different from bipedal walking despite the inclusion of some key functional requirements for locomotion. Kinematically, the ankle movements may correspond to the dorsiflexion on the side of a swinging leg for foot clearance during steady-state level walking. Such interpretation is based on the assumption that a complex movement can be viewed as a combination of simpler components (e.g., motor primitives [118]), each of which represents different aspects of the movement's kinematic or kinetic characteristics as well as neuromuscular activations. One possible task modification that should be investigated is the inclusion of resistance to plantarflexion, which would resemble the push-off that is required for the forward propulsion of the body during walking.

7.8 Reference

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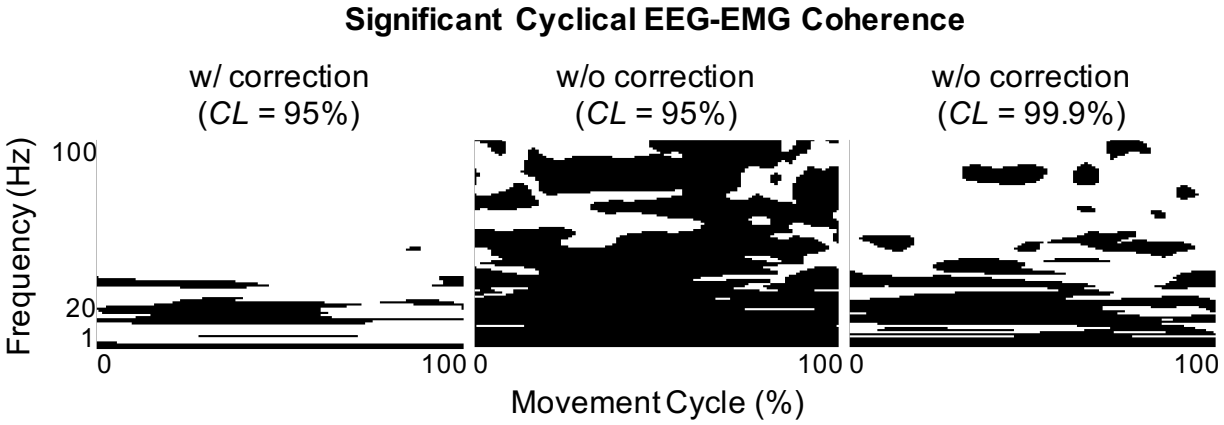
Appendices

8 Effects of Bonferroni correction on significant coherence

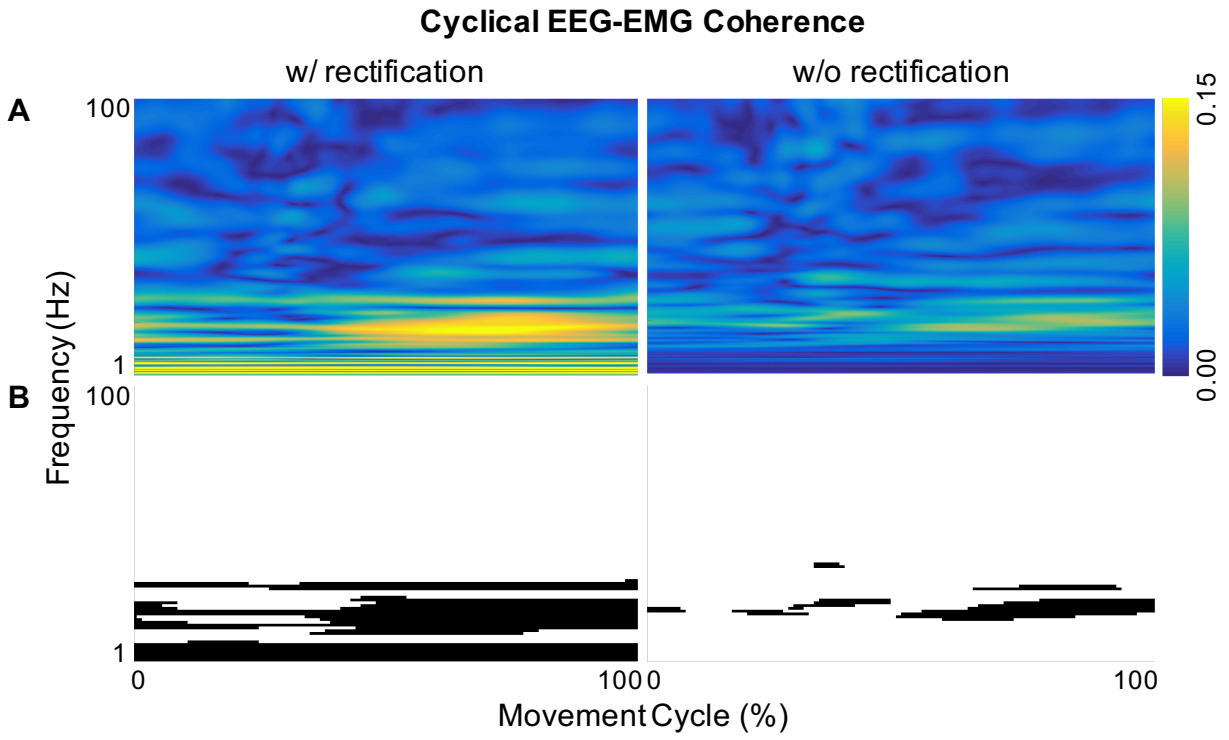
In previous studies on corticomuscular coherence, the most common definition of significant coherence (*SC*) is given by Rosenberg et al. [1]: $SC = 1-(1-\alpha)^{1/(L-1)}$, where α is the confidence level and L is the number of data segments that are used to calculate the coherence. However, the above definition applies to one particular frequency [1]. In previous studies that used the above definition, only a few groups have accounted for multiple observations (i.e., across frequency or time) by using the Bonferroni correction [2]-[6]. Appendix Figure 1 shows how the extent of significance is exaggerated without the Bonferroni correction. Compared to the significant coherence with the correction (Appendix Figure 1, left), coherence without the correction (Appendix Figure 1, center) does not show a meaningful pattern in the beta frequencies. Moreover, merely increasing the confidence level does not completely compensate for the lack of correction (Appendix Figure 1, right). Thus, for examining dynamic changes in corticomuscular coherence across a wide frequency band, the Bonferroni correction should be applied to the definition of significant coherence.



Appendix Figure 1. Patterns of significant cyclical EEG-EMG coherence (in black) with Bonferroni correction at confidence level (*CL*) of 95% (left), without correction at *CL* of 95% (center), and without correction at *CL* of 99.9% (right).

9 Effects of rectifying EMG signals on corticomuscular coherence

In Chapters 4, 5, and 6, corticomuscular coherence was calculated between EEG signals and full-wave rectified EMG signals. For the use of full-wave rectification, I assumed that *i*) the motor units, which comprised the measured surface EMG signals, were recruited by a common presynaptic input and that *ii*) rectification enhanced the power spectral density of the EMG signal at the frequency of the common input. The latter assumption is supported by experimental evidence [7], computational modeling [8], as well as the experimental corticomuscular coherence from Chapter 4. Appendix Figure 2 shows cyclical patterns of EEG-EMG coherence of a young participant with and without the rectification of the EMG signal. Appendix Table 1 summarizes the magnitude and center frequency of significant EEG-EMG coherence of young participants from Chapter 4, with and without the rectification of EMG signals. Four-way analysis of variance (ANOVA) showed that the magnitude was significantly lower without rectification ($F_{1,221} = 12.3$, $p < .001$). The magnitude was not significantly affected by the type of pacing ($F_{1,221} = 0.102$, $p = .750$), muscle ($F_{1,221} = 0.880$, $p = .349$), or side of the body ($F_{1,221} = 0.0117$, $p = .914$). The center frequency was significantly lower with rectification ($F_{1,221} = 61.0$, $p < .001$) but was not significantly affected by the type of pacing ($F_{1,221} = 1.61$, $p = .207$), muscle ($F_{1,221} = 1.23$, $p = .268$), or side of the body ($F_{1,221} = 1.34$, $p = .249$). For neither the magnitude nor the center frequency, did the factors of ANOVA interact significantly (Appendix Table 2).



Appendix Figure 2. Cyclical EEG-EMG coherence between C_z and the right tibialis anterior muscle of a young participant, with (w/) and without (w/o) full-wave rectification of the EMG signal. The patterns in the bottom row (Panel B) are significant portions of the patterns in the top row (Panel A).

Appendix Table 1. Volumes and center frequencies of significant EEG-EMG coherence between C_z and bilateral tibialis anterior (TA) and medial gastrocnemius (MG) muscles of young participants, with and without the rectification of EMG signals.

EMG Rectification	Measurement	Muscle	Self-pacing		External Pacing	
			Left	Right	Left	Right
With	Volume ($Hz \cdot \%_{Movement\ Cycle}$)	TA	18.7±22.3	20.2±28.6	15.2±24.3	22.6±37.9
		MG	18.3±22.5	19.7±25.7	18.9±32.0	25.9±48.2
	Center Frequency (Hz)	TA	17.7±3.4	17.4±5.1	19.3±3.8	19.5±6.1
		MG	17.4±3.8	19.1±5.4	19.7±7.5	19.7±4.7
Without	Volume ($Hz \cdot \%_{Movement\ Cycle}$)	TA	5.27±8.50	6.14±9.98	5.95±5.72	9.23±19.97
		MG	11.1±13.0	11.7±14.6	10.1±15.3	11.2±15.4
	Center Frequency (Hz)	TA	26.0±7.8	24.4±5.3	25.1±4.7	28.7±11.5
		MG	23.6±7.1	24.8±5.6	22.1±5.5	24.6±4.3

Each entry shows inter-individual mean±standard deviation.

Appendix Table 2. Interaction between factors of 4-way ANOVA on the magnitude and center frequency of EEG-EMG coherence of young participants.

Interactions	Magnitude	Center Frequency
Type of Pacing×Muscle	$F_{1,221} = 0.0117$, $p = .914$	$F_{1,221} = 0.865$, $p = .353$
Type of Pacing×Side of Body	$F_{1,221} = 0.326$, $p = .569$	$F_{1,221} = 0.708$, $p = .401$
Type of Pacing×Rectification	$F_{1,221} = 0.0178$, $p = .894$	$F_{1,221} = 0.576$, $p = .449$
Muscle×Side of Body	$F_{1,221} = 0.0142$, $p = .905$	$F_{1,221} = 0.240$, $p = .625$
Muscle×Rectification	$F_{1,221} = 0.189$, $p = .665$	$F_{1,221} = 3.23$, $p = .0738$
Side of Body×Rectification	$F_{1,221} = 0.216$, $p = .643$	$F_{1,221} = 0.501$, $p = .480$

10 Computational modeling

In computational modeling, a surface EMG signal is often simulated as a sum of multiple trains of motor unit action potentials [9], with each train calculated by convolving a train of unit impulses with the impulse response of a linear time-invariant system [8], [10]:

$$s(t) = \sum_{i=1}^{M} \sum_{j=-\infty}^{+\infty} \varphi_i(t)\delta(t - t_{ij}),$$

where M is the total number of motor units that contribute to the simulated EMG signal, $s(t)$; $\varphi_i(t)$ is the impulse response, which represents the waveform of the action potential for the i^{th} motor unit; and $\delta(t-t_{ij})$ is the unit impulse at t_{ij}, which represents the i^{th} motor unit firing at the j^{th} instance. Using the above equation, a rectified EMG signal can be expressed as follows [10], [11]:

$$\left|s(t)\right| = \sum_{i=1}^{M} \sum_{j=-\infty}^{+\infty} \left|\varphi_i(t)\right| \delta(t - t_{ij}) + c(t).$$

The frequency of common input is contained in the rectified action potentials, $|\varphi_i(t)|$ [10]. However, the rectified signal also contains noise, $c(t)$, whose power increases with greater amplitude cancellation [10]. Amplitude cancellation occurs when multiple motor unit action potentials are summed in the time domain and amplitudes with opposite polarities cancel each other out [9], [12]. Greater amplitude cancellation occurs as more motor units are recruited for a stronger contraction [10], [13], [14], thus disabling rectification from detecting the frequency of common input. According to the above model, rectification is useful for movements with low contraction forces. In Chapters 4, 5, and 6, participants cyclically moved their feet without resistance. Thus, it is reasonable to assume that amplitude cancellation did not significantly impair the benefit of rectification.

There is some debate about whether full-wave rectification of the EMG signal is appropriate for calculating corticomuscular coherence as rectification is a non-linear process [15], [16]. Particularly, rectification has been criticized for its inability to detect a change in a narrow frequency band: the power spectral density of a rectified signal does not reflect the amplification or attenuation of the original, non-rectified signal within a narrow frequency band [15], [16].

Such criticism is invalid, as the frequency of common supraspinal input is contained in a broadband signal.

11 Alternatives to corticomuscular coherence

11.1 Theoretical background

Apart from coherence, directed transfer function (DTF) and partial directed coherence (PDC) have been used to quantify the functional relationship between electrocortical and muscle activities [17]-[20]. DTF and PDC measure causality between measured signals by quantifying the amount and direction of information flow between them. For corticomuscular communication, the information flow can be evaluated between electrocortical and muscle activities. To calculate DTF and PDC, it is necessary to define a multivariate autoregressive model with the measured signals. For N measured signals, the model is defined as the following [21], [22]:

$$\sum_{k=0}^{p} \Lambda(k)\mathrm{X}(t-k) = \mathrm{E}(t),$$

where p is the model order, which is determined by the Akaike Information Criteria; $\Lambda(k)$ is an $N \times N$ matrix of model coefficients (an identity matrix for $k = 0$); $\mathrm{X}(t)$ is a vector of measured signals; and $\mathrm{E}(t)$ is a vector of zero-mean uncorrelated white noise. The frequency-domain equivalent of the above model is defined as the following [21], [22]:

$$\begin{aligned} &\Lambda(f)\mathrm{X}(f) = \mathrm{E}(f) \\ &\mathrm{X}(f) = \Lambda^{-1}\mathrm{E}(f) = \mathrm{H}(f)\mathrm{E}(f) \\ &\Lambda(f) = \sum_{k=0}^{p} \Lambda(k) e^{-j2\pi f \Delta t k} \end{aligned},$$

where Δt is the time interval between samples and $H(f)$ is the transfer matrix, in which the element, H_{ij}, characterizes the information flow from the j^{th} source to the i^{th} signal. Normalized DTF at a particular frequency, $\gamma_{ij}^2(f)$, can be calculated using the following equation [21], [23]:

$$\gamma_{ij}^{\ 2}\left(f\right)=\frac{\left|\mathrm{H}_{ij}\left(f\right)\right|^2}{\sum_{m=1}^{N}\left|\mathrm{H}_{im}\left(f\right)\right|^2},$$

where the numerator represents the output of the j^{th} source to the i^{th} signal and the denominator represents the output from N sources to the i^{th} signal. Thus, normalized DTF quantifies the fraction of information flow to the i^{th} signal that originates exclusively from the j^{th} source. Normalized DTF has a value between [0,1], and the sum of all normalized DTFs to the i^{th} signal equals one. Similarly, PDC at a particular frequency, $\Pi_{ij}(f)$, can be calculated using the following equation [23]:

$$\Pi_{ij}\left(f\right)=\frac{\left|\Lambda_{ij}\left(f\right)\right|}{\sqrt{\sum_{m=1}^{N}\left|\Lambda_{mj}\left(f\right)\right|^2}},$$

where the numerator represents the output of the j^{th} source to the i^{th} signal and the denominator represents the output of the j^{th} source to N signals. Thus, PDC quantifies the fraction of information flow from the j^{th} source that is exclusive to the i^{th} signal. The value PDC also ranges between [0,1], and the sum of all PDCs from the j^{th} source equals one.

11.2 Application of DTF and PDC to cyclical ankle movements

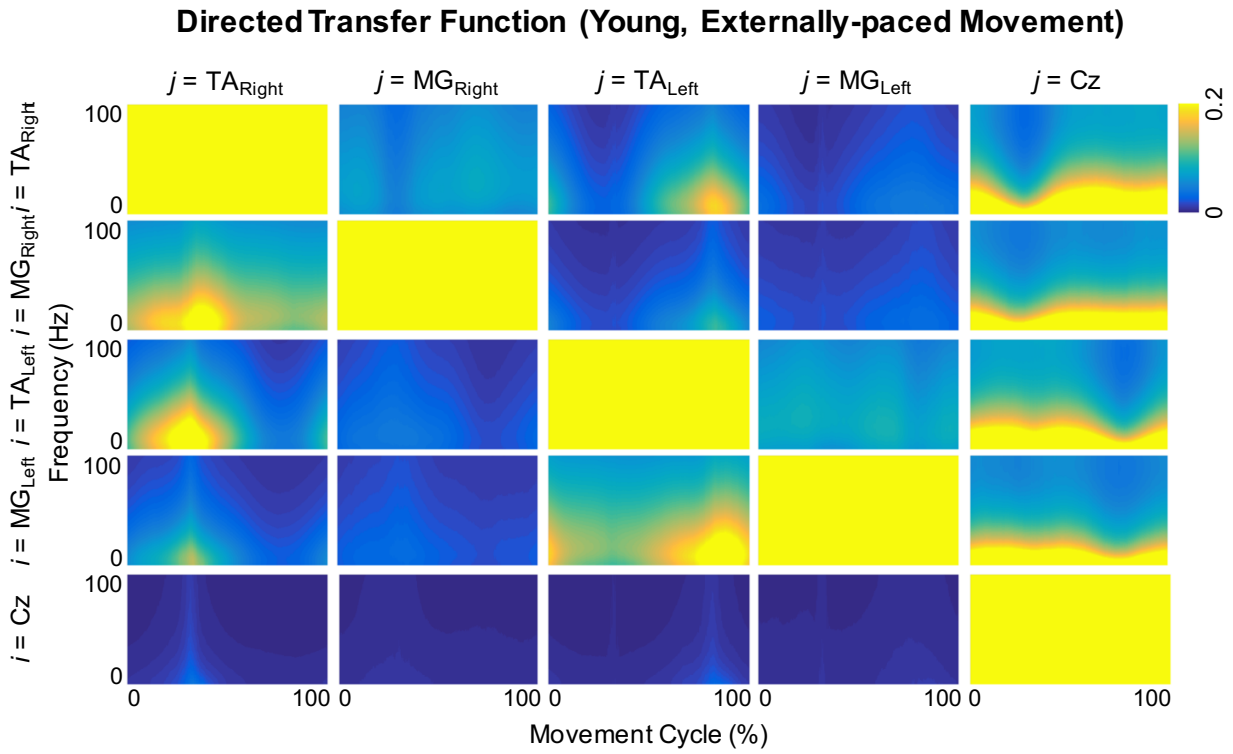
Here, I calculate the normalized DTF and PDC for the cyclical ankle movements in Chapter 4. Appendix Figure 3 and Appendix Figure 4 show the normalized cyclical DTF and PDC between the EEG signals from C_z and EMG signals from the bilateral tibialis anterior and medial gastrocnemius muscles of young participants during externally-paced movements. Before estimating the model coefficients, all signals were centered by subtracting the mean and divided by the standard deviation [20]. The model coefficients were estimated for each sliding time window of 400 data points, using the algorithm from Schneider and Neumaier [24]. The algorithm was implemented in MATLAB (version R2016b, The MathWorks, Inc., United States) and validated using previously reported models [23], [25]. Furthermore, to account for the non-zero off-diagonal elements of E(*f*), the estimated model coefficients were adjusted in the following manner [22]:

$$\Lambda_{new}\left(k\right) = L^{-1}\Lambda\left(k\right)$$
$$\mathrm{E}\left(f\right) = LDL^{*}$$
,

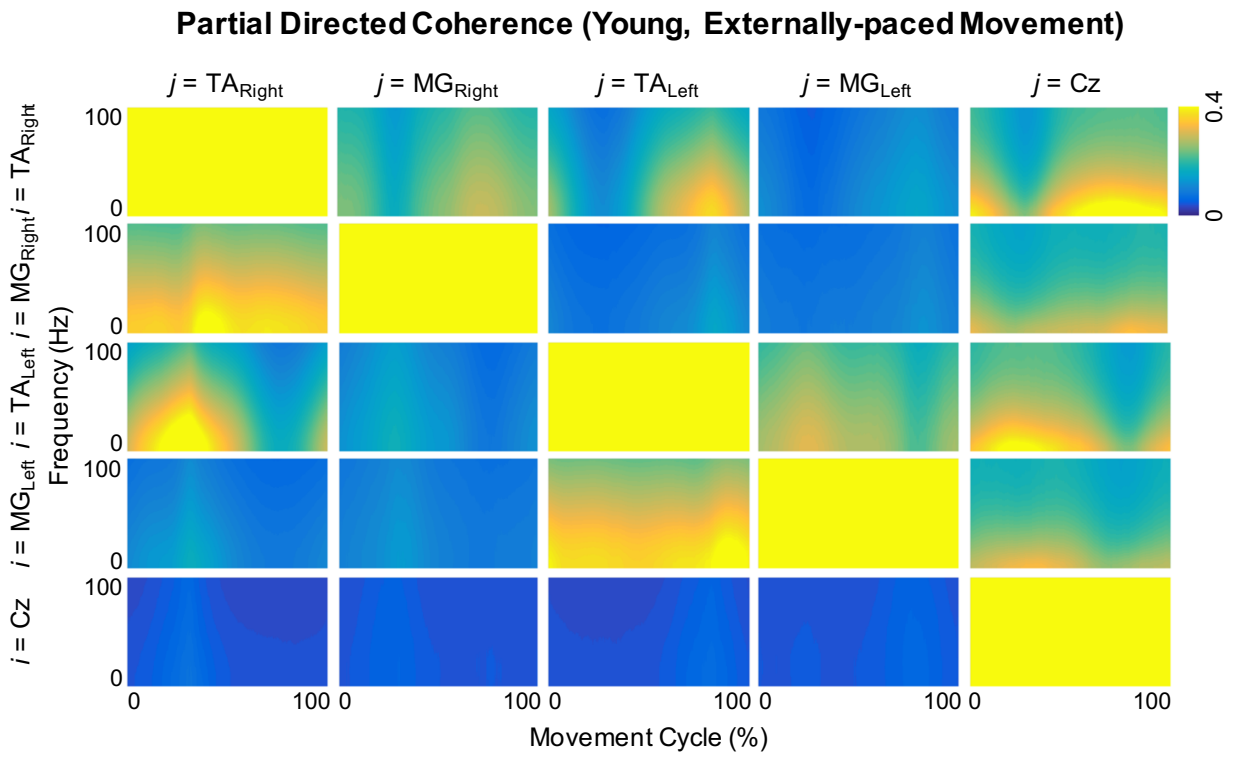
where $\Lambda_{new}(k)$ is the matrix of adjusted coefficients; L and D are square matrices with lower triangular and diagonal components of E(*f*), respectively; and the asterisk denotes the complex conjugate. Based on the adjusted coefficients, normalized DTF and PDC were calculated for each participant. The resultant model order was 2.28±0.27 (inter-individual mean±standard deviation).

Appendix Figure 3 and Appendix Figure 4 show the normalized cyclical DTF and PDC between the EEG signals from C_z and EMG signals from the bilateral tibialis anterior and medial gastrocnemius muscles of young participants during externally-paced movements. The corticomuscular communication from C_z to muscles increased in similar temporal patterns to muscle activation (right most column, Appendix Figure 3 and Appendix Figure 4) whereas the

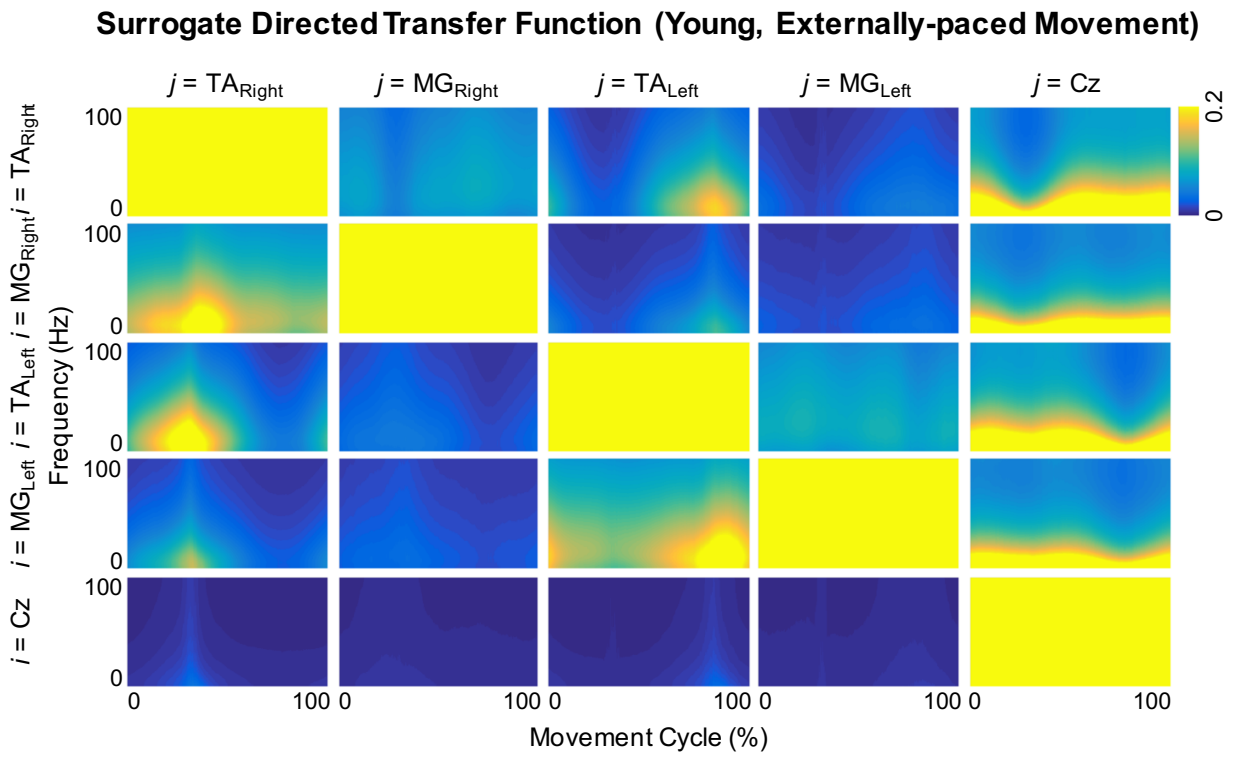
communication in the opposite direction was substantially lower in magnitude (bottom row, Appendix Figure 3 and Appendix Figure 4). The calculated patterns also showed ipsilateral intermuscular communication from dorsiflexor to plantarflexor and between bilateral dorsiflexors (Appendix Figure 3 and Appendix Figure 4). However, neither the normalized DTF nor PDC showed a distinct pattern of corticomuscular communication within the beta band. Furthermore, surrogate DTF and PDC, which were calculated with augmented EEG signals, did not show obvious deviation from the experimental DTF and PDC (Appendix Figure 5 and Appendix Figure 6). For calculating the surrogate DTF and PDC, each EEG signal was augmented by randomly assigning a unique phase between $[0,2\pi]$ to each component of its Fourier transform without changing the magnitude. Thus, the experimental patterns of corticomuscular communication could not be validated.



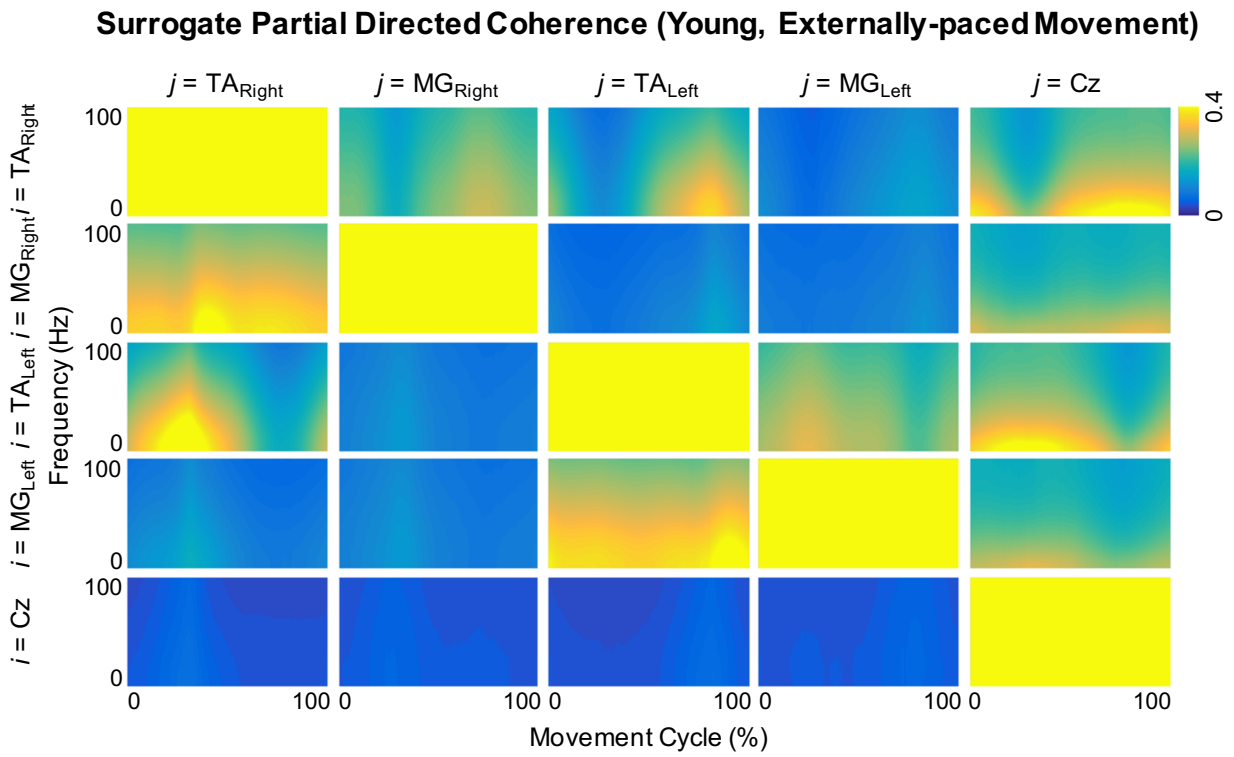
Appendix Figure 3. Normalized DTF between C_z and bilateral tibialis anterior (TA) and medial gastrocnemius (MG) muscles of young participants during externally-paced movements (group average).



Appendix Figure 4. Partial directed coherence between C_z and bilateral tibialis anterior (TA) and medial gastrocnemius (MG) muscles of young participants during externally-paced movements (group average).



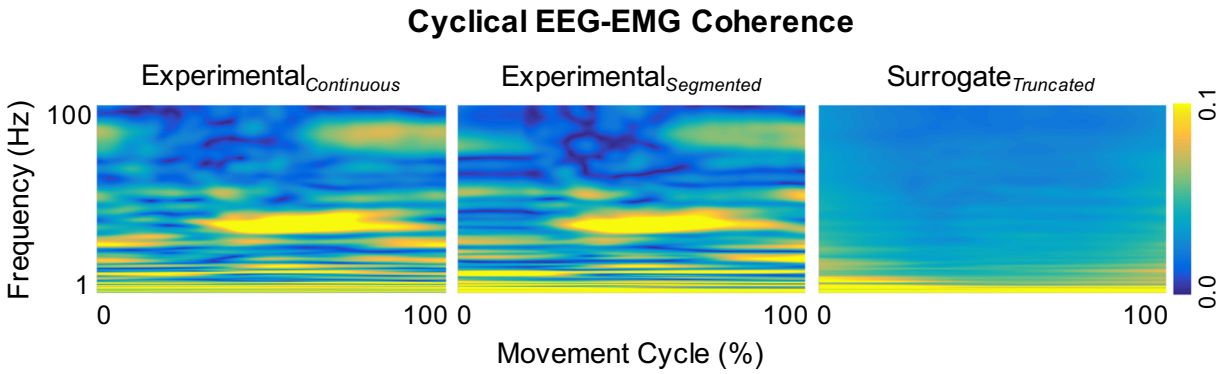
Appendix Figure 5. Normalized directed transfer function between augmented C_z and bilateral tibialis anterior (TA) and medial gastrocnemius (MG) muscles of young participants during externally-paced movements (group average).



Appendix Figure 6. Partial directed coherence between augmented C_z and bilateral tibialis anterior (TA) and medial gastrocnemius (MG) muscles of young participants during externally-paced movements (group average).

12 Validation of corticomuscular coherence

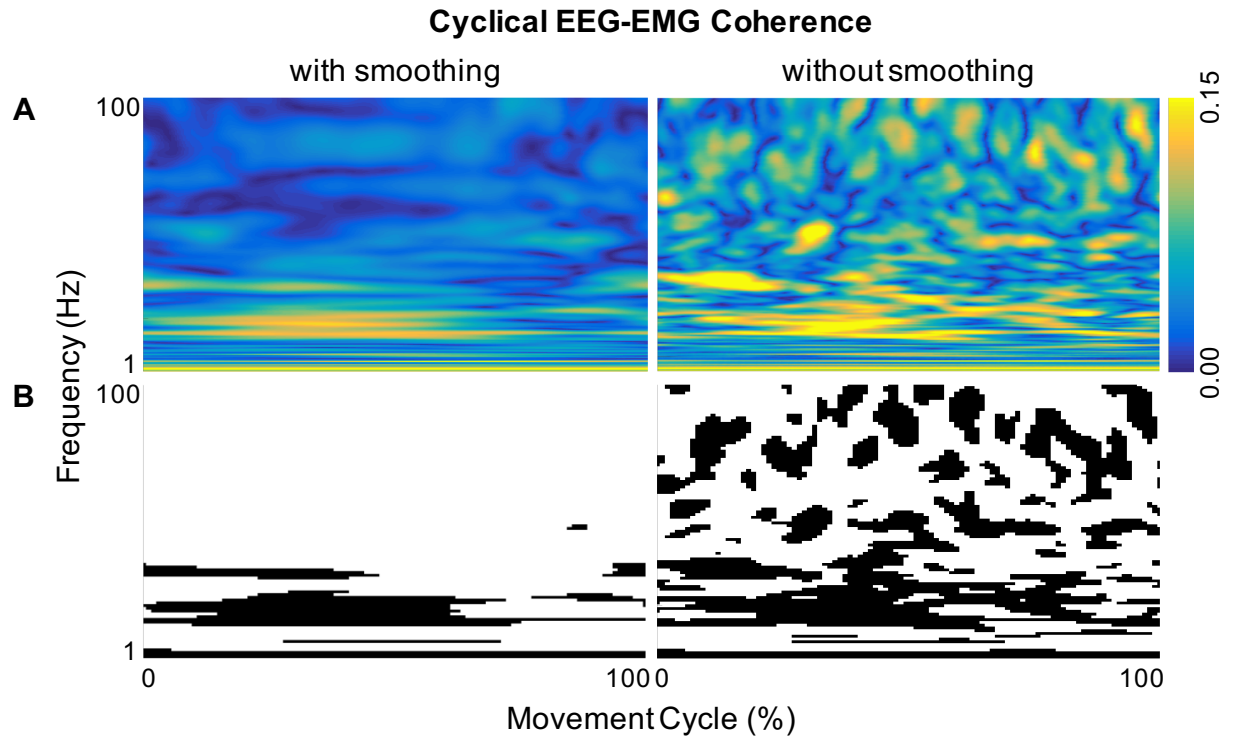
In Chapters 4, 5, and 6, experimental coherence was validated using surrogate coherence. However, the relative absence of significant patterns in surrogate coherence could have been caused by how it was calculated. Specifically, the patterns in surrogate coherence could have been abolished by *i*) the segmentation of EEG and EMG signals before calculating their coherence or *ii*) re-sampling of the segmented signals to match their durations. Appendix Figure 7 supports that neither of the above processes caused the absence of coherence. First, the cyclical increase in coherence remains if EEG and EMG signals are segmented before their coherence is calculated without shuffling their pairing (Appendix Figure 7, left and center). Second, the cyclical increase in coherence is abolished if the randomly paired segments of EEG and EMG signals are truncated to the shorter segment without re-sampling (Appendix Figure 7, right).



Appendix Figure 7. Experimental EEG-EMG coherence with segmentation (center) and without segmentation (left) of signals. Surrogate EEG-EMG coherence, calculated with randomly paired segments of EEG and EMG signals, whose durations were truncated to that of the shorter segment (right).

13 Effects of temporal smoothing on corticomuscular coherence

In Chapters 4, 5, and 6, wavelet coherence between EEG and EMG signals was calculated with temporal smoothing, using a moving average filter with a window length of 200 data points. Appendix Figure 8 illustrates the effects of such smoothing. Without smoothing, significant sporadic coherence remains even after ensemble averaging (Appendix Figure 8, right). Thus, temporal smoothing is necessary to delineate the relevant patterns of coherence during dynamic movements (Appendix Figure 8, left).



Appendix Figure 8. Cyclical EEG-EMG coherence with and without temporal smoothing. The cyclical pattern with smoothing was calculated using a moving average filter with a window size of 200 data point whereas the pattern without smoothing was calculated using a window size of 20 data points. The patterns in the bottom row (Panel B) are significant portions of the patterns in the top row (Panel A).

14 Independent Component Analysis

14.1 Theoretical Background

In Chapters 4, 5, and 6, independent component analysis was used to reduce noise from EEG signals. Independent component analysis assumes that each of n measured signals is a linear sum of independent components, each of which is assumed to be emitted from its own spatially fixed source and propagate to the measuring electrodes with negligible delays [26], [27]. The linear combinations of independent components can be expressed as a system of equations [26]-[28]: $x = As$, where x and s are matrices, whose rows are the measured signals and independent components, respectively. Independence of the components can be defined in different ways,

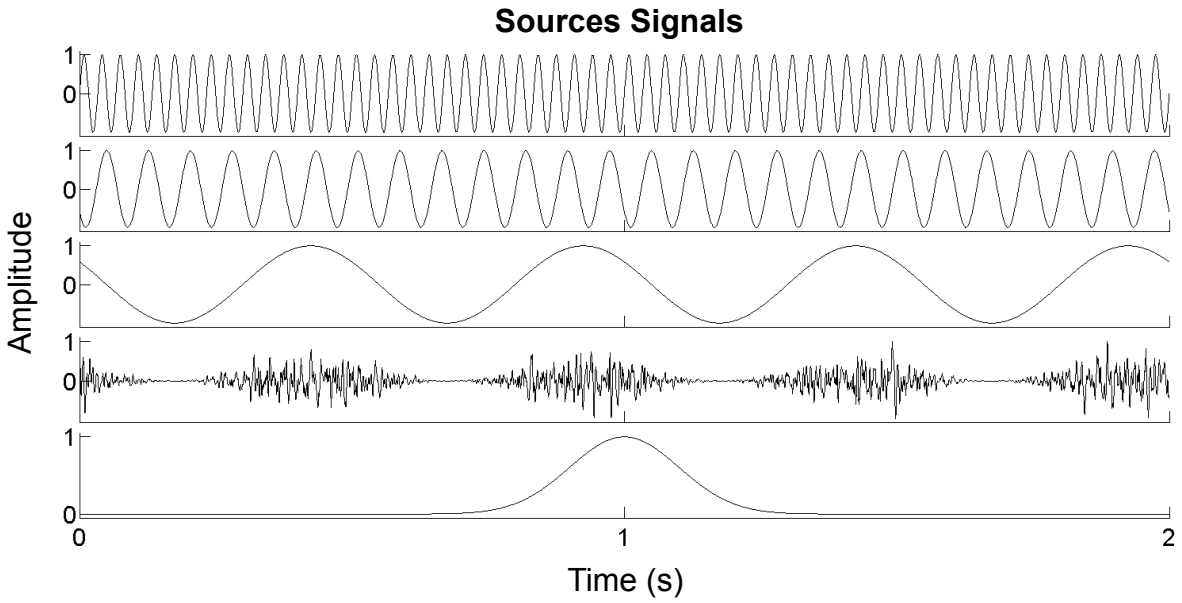
including maximal non-gaussianity and minimal mutual information [28]. A is often called the mixing matrix because its multiplication with the independent components (s) yields weighted linear sums of the components (i.e., x). A is a square matrix, and its columns represent the contribution of each independent component to the measured signals. To remove the contribution of the i^{th} independent component, the product of the i^{th} column of A and the i^{th} row of s is subtracted from x.

14.2 Example

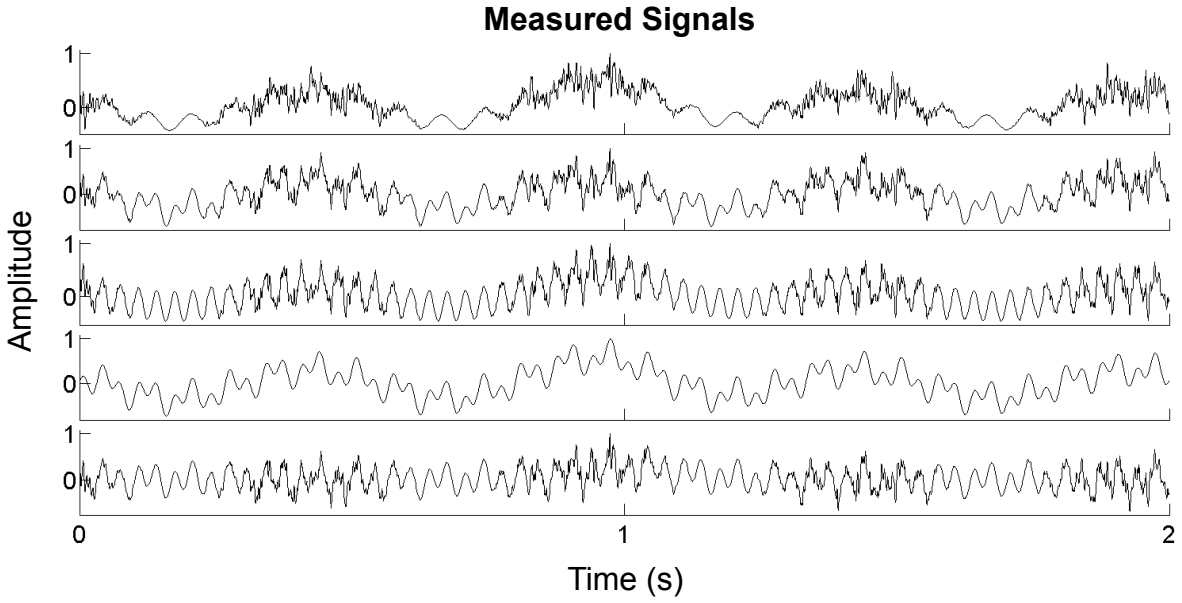
Here, I illustrate how independent component analysis can be used to reduce artifactual waveforms from measured signals. Five sources signals (x_i) were linearly added to simulate five measured signals (y_i):

$$
\begin{aligned}
y_1 &= 0.1x_2 + 0.2x_3 + 0.3x_4 + 0.2x_5 \\
y_2 &= 0.2x_1 + 0.2x_2 + 0.3x_3 + 0.4x_4 \\
y_3 &= 0.3x_1 + 0.2x_3 + 0.4x_4 + 0.3x_5 \\
y_4 &= 0.2x_1 + 0.2x_2 + 0.3x_3 + 0.3x_5 \\
y_5 &= 0.2x_1 + 0.1x_2 + 0.3x_4 + 0.2x_5,
\end{aligned}
$$

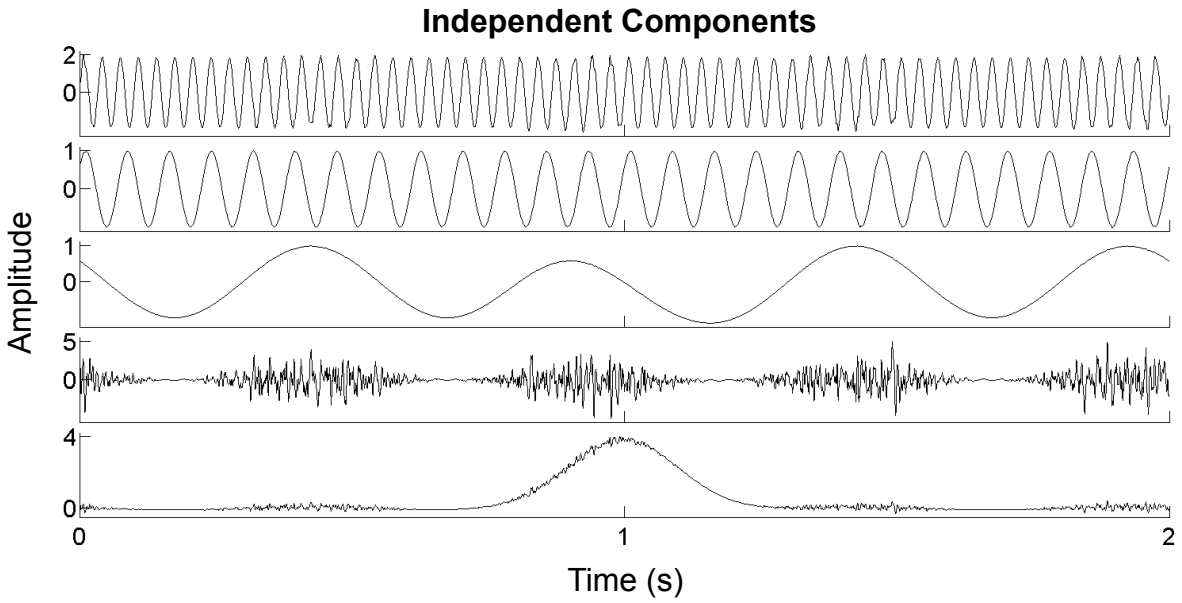
where x_1 is a sinusoid at 30 Hz, x_2 is a sinusoid at 13 Hz, x_3 is a sinusoid at 2 Hz, x_4 is a broadband signal with a bandwith of 20 to 200 Hz, and x_5 is a Gaussian function (Appendix Figure 9). The sinusoids at 13 and 30 Hz are the signals of interest while other source signals are noise. The simulated measured signals (Appendix Figure 10) were decomposed by independent component analysis (Appendix Figure 11). Then, the contributions of independent components that contained artifactual waveforms (Appendix Figure 11, bottom three signals) were subtracted from the simulated measured signals.



Appendix Figure 9. Source signals for simulating measured signals. From top to bottom, the source signals are *i*) sinusoid at 30 Hz, *ii*) sinusoid at 13 Hz, *iii*) sinusoid at 2 Hz, *iv*) broadband signal with bandwidth of 20 to 200 Hz, and *v*) Gaussian function.

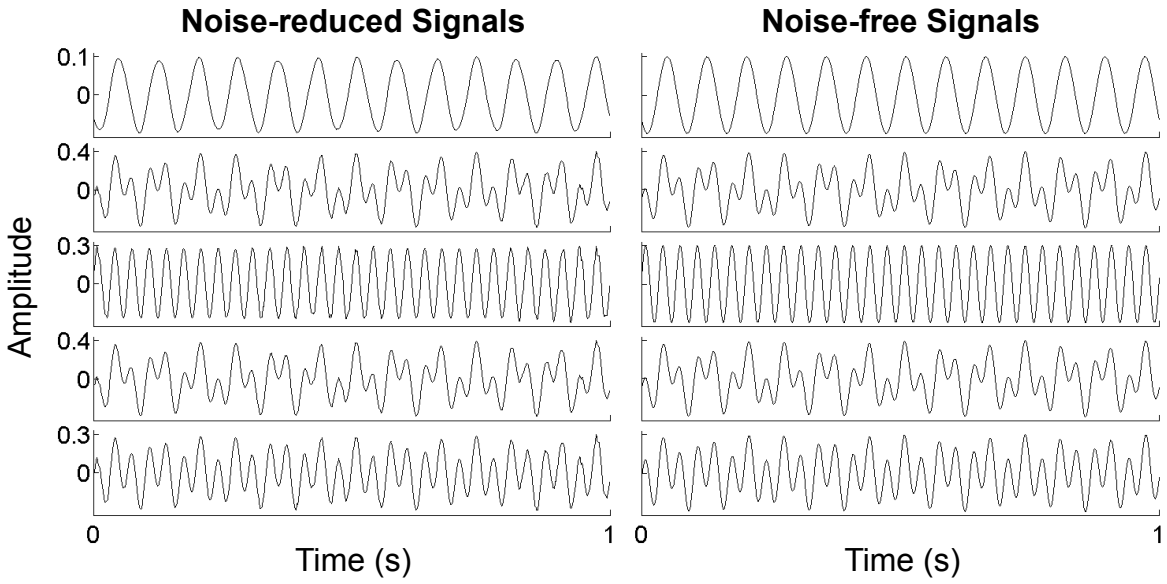


Appendix Figure 10. Simulated measured signals. Each measured signal is a linear combination of the source signals. From top to bottom, the signals are y_1, y_2, y_3, y_4, and y_5.



Appendix Figure 11. Independent components of the simulated measured signals.

Appendix Figure 12 shows the result of subtracting the contributions of artifactual components. The waveforms of the resultant noise-reduced signals (Appendix Figure 12, left) closely resemble those of the theoretically noise-free signals (Appendix Figure 12, right), which are linear sums of sinusoids at 13 and 30 Hz alone.



Appendix Figure 12. Comparison between noise-reduced (left) and noise-free (right) signals. The noise-reduced signals are calculated by subtracting the contributions of artifactual waveforms. The noise-free signals are calculated by excluding x_3, x_4, and x_5 from the original system of equations.

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