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Arm swing in healthy and Parkinsonian gait

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General introduction

Locomotion is a fundamental skill for all living organisms, excluding plants, to move from one place to another. In vertebrates, this is achieved by organized contractions of muscles that are attached to the bones, resulting in movement of the joints that is eventually expressed in various forms of locomotion, such as walking, swimming, running and hopping. Locomotion of quadrupeds obviously requires coordination between movements of the four limbs: while opposite limbs move in antiphase, the front limbs also move in anti-phase with ipsilateral hind limbs. Interestingly, human bipedal gait similarly exhibits a comparable four-limb pattern, with anti-phase arm swing in the same frequency as the lower limb oscillations (illustrated in Fig. 1.1). Although the role of these arm movements in human bipedal gait is not as obvious as in quadrupedal gait, they are proposed to bring certain advantages. Gait related arm swing has been suggested to contribute to stabilization[1,2], energetic efficiency[2–4], and recruitment of neuronal support for maintaining the cyclic motor pattern[5]. The latter has been inferred from previous studies reporting that adding upper limb movements during rhythmic lower limb tasks improved lower limb muscle recruitment[6–13], suggesting a neural coupling between upper and lower limb muscles. The main aim of this thesis is to explore this supporting role of arm swing in gait control in healthy participants and patients with Parkinson's Disease (PD), a neurodegenerative disease that affects both lower-limb gait and gait related arm swing. We will use a multi-level approach including electroencephalography (EEG), electromyography (EMG) and gait analyses to explore how this is organized within and between brain, muscle and movement level, respectively.

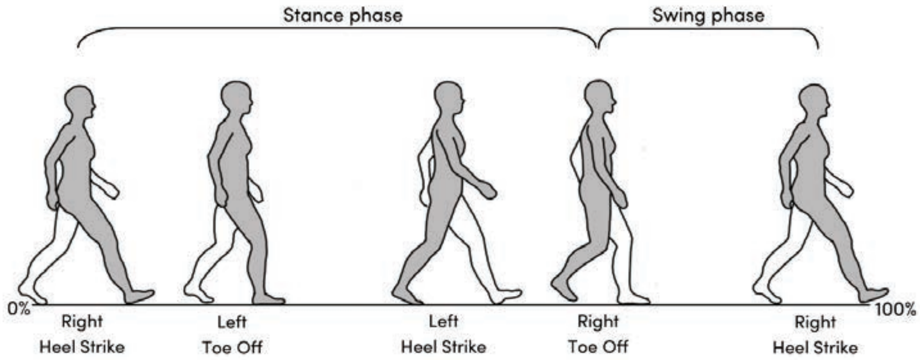


Figure 1.1: Phases of the human gait cycle

Multi-level approach for exploring gait control

Although one perceives walking as a simple self-evident task, it is a complex task for the central nervous system as it must somehow perform numerous complicated tasks simultaneously. During gait several muscles from the legs, arms and trunk need to collaborate and contract at exact predetermined periods of the gait cycle, which requires tight synchronization between these muscles. In addition, to continuously adapt the gait movements when e.g. obstacles are encountered, the system should also be able to select the most optimal context-specific sensory information and incorporate this information into the executed movements. All this must be performed within milliseconds and in conjunction with coordinating multiple other bodily functions and movements. To accomplish all these challenging tasks simultaneously, gait control depends on a tight communication within and between brain, muscle and movement level. In this thesis, we will use a multi-level approach to explore the role of arm swing in gait control on these three levels with all measurements performed in an ambulant manner that allows participants to walk freely in space. Cortical and muscle activity will be examined using ambulant EEG and EMG measurements that are synchronized. In addition, tri-axial accelerometers on both legs and trunk together with synchronized video recordings enable gait analysis and subsequent demarcation of gait events in this EEG and EMG data. This experimental set-up allows to answer specific gait-related and in our case also arm swing-related questions that were previously difficult to answer in humans with other (static) neuroimaging techniques, such as functional magnetic resonance imaging.

Brain level: neural control of gait

Nonetheless, these previous static or animal related research techniques have provided fundamental insight in how the different levels of the central nervous system contribute to gait control. At spinal level, central pattern generators generate tightly-coupled patterns of neural activity that drive stereotyped motor behaviours including gait[14]. Propriospinal pathways interconnect these central pattern generators from cervical and lumbar levels that control the individual limbs, providing an important contribution in generating these synchronized interlimb movements[15–18]. These spinal pathways modify their activity in cooperation with descending signals from higher order regulation at subcortical and cortical level[19–23]. Important players at a subcortical level include (i) the reticulospinal pathway, which produces repetitive locomotor commands[24,25], and (ii) the basal ganglia and cerebellum, which affect both automatic and cognitive processes involved in posture-gait control[26]. These subcortical pathways are in turn controlled or influenced by cortical sources, which enables higher order gait control with dynamic involvement of multiple sensory domains. The primary motor cortex is one of the most important cortical areas involved in general motor control and has also been found to directly drive muscles used in steady-state walking[27–29].

However, the supplementary motor area (SMA) that lies directly in front of the primary motor cortex has also been proposed to play a pivotal role in gait control, which can be inferred from SMA lesions resulting in gait abnormalities and disequilibrium[30–33]. The SMA has strong and widespread connections with the motor field of its contralateral cortex, explaining its contribution in opposite-limb coordination including the four limb gait pattern[34,35]. Aside from its role in multi-limb co-ordination, the SMA plays a crucial role in voluntary movement initiation including gait initiation[36–38]. This involvement of the SMA in both multi-limb movement coordination and movement initiation suggests that this area has a central role in pacing the cyclic gait pattern. To further enable higher order organization and somatosensory guidance during gait, premotor and parietal regions have also been proposed to be involved in this distributed network upstream of the primary motor cortex[39–41].

Although these previous studies using (static) neuroimaging techniques have enlarged our knowledge about the involvement of certain brain areas in these different aspects of gait control, these techniques require the participants to lay still during the experiment and are therefore not able to measure brain activity during actual gait. The emergence of ambulant EEG devices makes is possible to examine cortical activity while the participant walks freely in space. EEG measures oscillatory activity that represent synchronous activity of many thousands of anatomically aligned neurons. These oscillations in the EEG can be analysed using event related spectral perturbations (ERSP), which enables the assessment of average dynamic changes in power across the broad band frequency spectrum as a function of time relative to (gait-related) events[42]. Such power modulations of frequency specific EEG oscillations are proposed to represent the transmission of neural information between brain areas and each frequency band supposedly serves a different purpose. Alpha (8-12Hz) and beta-oscillatory (12-30 Hz) activity have been found to play a predominant role in the initiation and modulation of motor activity, with a power decrease (event related desynchronization (ERD)) prior to and during movement followed by post-movement rebound (i.e. event related synchronization (ERS))[43–45]. During gait, previous studies found a within-step ERD-ERS alternation in these alpha and beta frequency bands over the sensorimotor cortex[46–49], which has been proposed to be crucial for efficient gait control. Such cyclic pattern of ERD-ERS alternation was also observed in the low-gamma frequency band (30-60 Hz) and has been related to especially the organization of active walking[48,50]. These frequency specific power modulations are thought to reflect communication within the central nervous system, which is required for coordinating and producing gait. The assessment of these power modulations in EEG during various arm swing conditions in both healthy and PD gait provides new insights in the role of arm swing in gait control on a brain level and allows to explore which cortical areas are involved in this.

Muscle level

Closely related to communication within the central nervous system, the brain communicates with the muscles in order to command the orchestration of muscle contractions that will eventually lead to effective limb movements. This is achieved by sending electrical potentials along the chain of cerebral and spinal motor neurons that subsequently activate the muscle cells. Such muscle activity is typically studied using EMG recordings that detect these electrical potentials produced by muscle cells when these are neurologically activated by a spinal motor neuron, together constituting a motor-unit. These motor-units need to synchronize their firing pattern to smoothly contract the entire muscle, which requires a common drive to these motoneurons. The shape, size and frequency of the resulting electrical muscle signals can be assessed. The increased strength of a muscle contraction results from an increased number of active motor units, producing electrical potentials that result in an increase of EMG activity. Measuring such EMG activity simultaneously with EEG allows us to explore whether altered EEG activity is accompanied by increased or reduced EMG activity. Besides examining such 'basic' activity patterns in the EMG one can also detect frequency specific oscillatory EMG activity, which is proposed to be a reflective of oscillations from the central nervous system that are send via the corticospinal pathways to the muscles[28,51,52]. By means of the neuronal activation patterns that give rise to these oscillations, the central nervous system is able to communicate specific motor commands to the muscles to orchestrate and synchronize muscle contractions, which is necessary to achieve multiple muscles to collaborate and contract at exact predetermined periods of the gait cycle to produce an efficient gait pattern. Such synchronization or coupling between two muscles can be examined using intermuscular coherence analysis, which provides a measure of the linear correlation between two EMG signals in the frequency domain and provides information about the organization of this neural connectivity between muscles[53–55]. Intermuscular coherence in the alpha band was found to be primarily a reflective of coupling via subcortical pathways[56–58], whereas coherence in the beta/gamma frequency bands is proposedly a result of cortical coupling[56,59,60]. During gait, such intermuscular coherence has indeed been found between leg muscles in alpha and beta/gamma frequencies, supporting the presence of a common subcortical and cortical driver that coordinates and synchronizes these leg muscles[61,62]. As the gait pattern consists of a precise coordination between upper and lower limbs, it is hypothesized that a similar synchronization also occurs between upper and lower limb muscles but this has not yet been reported. Unfortunately, regular coherence analysis cannot distinguish directed connections between two muscles. E.g., one cannot distinguish whether one muscle drives the other or whether two muscles receive input from a third area in the central nervous system. It can therefore not be used to test the hypothesis that arm muscles can drive leg muscles, as was suggested by previous studies reporting that adding upper limb movements improved lower limb muscle recruitment[6–10].

Directed connectivity analysis, however, enables making this distinction as it can establish directionality or causal effects between two signals[63]. This type of analysis will be used in this thesis to explore whether upper limb muscles can indeed drive lower limb muscles during gait and vice versa.

Movement level

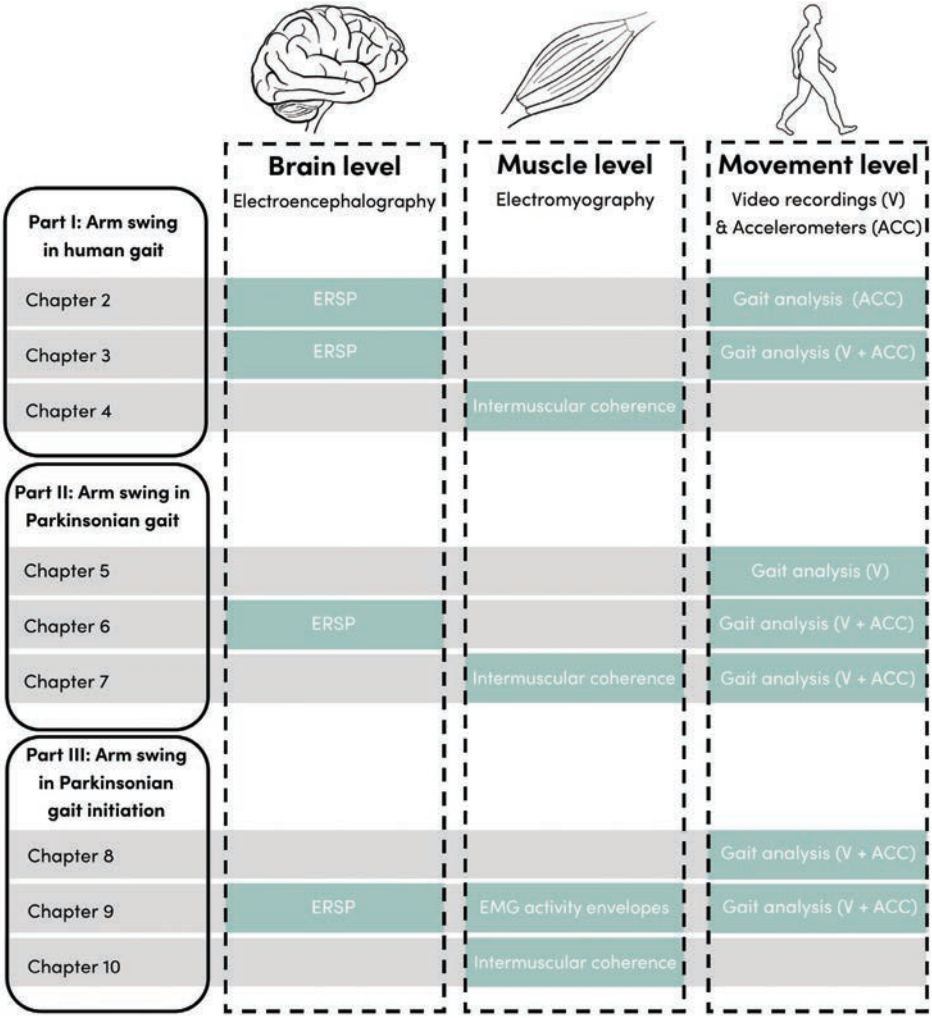
In addition to examining what happens on the inside (i.e. brain and muscle level), we also examine what happens on the outside of the individual (i.e. the movement level). Human movement implies that neuronal information codes are transformed in kinetic patterns, for which the previously described interaction between the brain and muscles is crucial. In this thesis, these movements are quantitatively examined using accelerometers and video recordings that are synchronized with EEG and EMG data, which allows us to relate brain and muscle outcomes with behavioural consequences. We are primarily interested in robust movement outcomes of gait that are also clinically relevant: How fast do participants walk? How large are their steps? How stable or variable is their gait pattern? How long does it take to make the first step after the starting cue? Besides extracting these spatial and temporal features, this synchronized accelerometer and video data also allows demarcation of gait events in the EEG and EMG data.

Outline of the thesis

This multi-level experimental set-up allows to explore the supporting role of arm swing in human gait control on brain, muscle and movement level, simultaneously, and thus provides a condition to answer questions about the relationship between these functional levels. The following section describes which questions will be answered in each chapter of this thesis while Fig. 1.2 provides an overview of which techniques and analyses are used in each chapter.

Part I: Arm swing in human gait

In the first part of this thesis we focus on the role of arm swing in healthy human gait and explore the neural circuitries involved in the production of this typical four-limb gait pattern. As previously described, gait-related arm swing is proposed to recruit neuronal support for maintaining the cyclic gait pattern. In **Chapter 2** we explore cortical mechanisms involved in this apparent supporting role of gait-related arm swing by examining EEG activity in healthy participants during walking with and without arm swing, with a special focus on activity recorded from the putative SMA (mediofrontal EEG electrode Fz). This supporting role of gait-related arm swing is inferred from previous studies reporting that adding upper limb movements during rhythmic lower limb tasks improved lower limb muscle recruitment[6–12], which indeed suggest a neural link between upper and lower limb movements. However, these experiments remain circumstantial and no direct coupling between upper and lower limb muscles has been reported yet.



	Brain level Electroencephalography	Muscle level Electromyography	Movement level Video recordings (V) & Accelerometers (ACC)
Part I: Arm swing in human gait			
Chapter 2	ERSP		Gait analysis (ACC)
Chapter 3	ERSP		Gait analysis (V + ACC)
Chapter 4		Intermuscular coherence	
Part II: Arm swing in Parkinsonian gait			
Chapter 5			Gait analysis (V)
Chapter 6	ERSP		Gait analysis (V + ACC)
Chapter 7		Intermuscular coherence	Gait analysis (V + ACC)
Part III: Arm swing in Parkinsonian gait initiation			
Chapter 8			Gait analysis (V + ACC)
Chapter 9	ERSP	EMG activity envelopes	Gait analysis (V + ACC)
Chapter 10		Intermuscular coherence	

Figure 1.2: A general overview of the methods used in the separate chapters to explore the role of arm swing in healthy and Parkinsonian gait on brain, muscle and behavioural level.

In **Chapter 3** we aim to demonstrate such direct evidence of a coupling between upper and lower limb muscles during gait and explore whether upper limb muscles can indeed drive lower limb muscles or vice versa using directional intermuscular coherence analysis. Finally, to gain more insight in the dynamic qualities of cerebral activity associated with multi-limb coordination in human gait, in **Chapter 4** the cortical circuitry is challenged by introducing the experimental condition of amble gait while measuring EEG activity. In this condition, antiphase movements were re-ordered in such a way that the antiphase mode of opposite limb movements remained the same while ipsilateral limb movements were performed in an in-phase pattern. This gait pattern is less overlearned and therefore considered more challenging, demanding recruitment of wider distributed networks. Such additional circuitry might potentially serve compensation in conditions of impaired gait control.

Part II: Arm swing in Parkinsonian gait

A disease which affects both upper and lower limb movements during gait is PD. PD is a chronic, progressive neurodegenerative condition characterized by a wide spectrum of motor and non-motor features. With a prevalence of 1% in people over the age of 60, PD is the most common motor neurodegenerative disease in the world[64]. Typical disease manifestation resulting from disruption of neuronal motor circuitry is marked by four cardinal physical symptoms: resting tremor, bradykinesia, rigidity and postural instability. One of the most invalidating symptoms for PD patients is their impaired walking ability, which is associated with a reduced quality of life and frequent falls. These walking impairments typically manifest as reduced walking speed and step length, increased asymmetry and reduced automaticity[65,66]. Besides alterations in lower limb functioning, upper limb movements are also affected, resulting in a reduction of amplitude as well as symmetry in the early or even prodromal stages of PD[67–69].

In the second part of this thesis, we try to gain more insight in the causes and consequences of this altered arm swing in PD gait and explore whether arm swing instructions can improve PD gait and could thus be potentially useful for PD gait rehabilitation. Moreover, disease-related changes may also add to insight in cerebral activity involved in normal gait control. To examine whether these upper and lower limb alterations in PD patients co-occur or may occur independent from each other, **Chapter 5** examines whether this reduced arm swing amplitude and symmetry is correlated with walking speed and step length in PD patients using video-based gait analysis. While significant asymmetries in limb control typically arise from a unilateral neurologic insult such as occurring in stroke, spinal cord injury or traumatic brain injury, the neural mechanisms underlying the asymmetries in upper and lower limb functioning in people with PD remain poorly understood, but likely imply functional changes at the level of distinct functional systems. In this respect, PD especially affects the dopaminergic neurons in substantia nigra pars compacta leading to dopaminergic denervation of the striatum, which subsequently influences the cortical-subcortical loops. On a cortical level, especially the reduction in SMA activity observed in PD patients has been found to be associated with their gait deficits of both upper (reduced arm swing) and lower limbs (reduced step length and walking speed)[70–72]. Interestingly, instructing PD patients to enhance their arm swing has been found to improve their gait on a behavioural level[73], which is in line with the previously described studies in healthy participants and other neurologically impaired patients that also found a facilitating effect of arm movements on leg muscle activity and movements[6–11,13]. In **Chapter 6,** we aim to reveal a facilitating effect of arm swing in PD gait with specific changes in regional EEG activity, thus exploring cortical pathways involved. To that end, four conditions were compared: (i) baseline walking of PD patients, with reduced arm swing, (ii) PD walking with enhanced arm swing, (iii) normal gait of healthy participants (i.e. with arm swing) and (iv) healthy participants walking without arm swing. A facilitating effect of arm swing on PD gait and the co-occurrence of upper and lower limb alterations in PD would suggest that the neural interlimb coupling during gait remains, to a certain level, preserved in PD. Previous studies did report reduced interlimb coordination in PD gait [65,74], but the magnitude of disturbed coupling between upper and lower limb muscles remains uncertain. In **Chapter 7** we explore to what extent and in which directions this neuronal interlimb coupling is either preserved or affected in PD patients using directional intermuscular coherence analysis. Improved understanding of this interlimb coupling during gait in PD patients may provide input for novel rehabilitation strategies concerning their impaired walking ability.

Part III: Support of arm swing in Parkinsonian gait initiation

Besides impaired steady state gait, difficulty of initiating gait is also often observed in PD patients, with freezing of gait being the most extreme form. Such freezing implies that PD patients are suddenly unable to initiate or continue gait. When a patient attempts to lift a foot to step forward, the foot is ‘stuck’ to the ground. Several compensation strategies have been described in the literature to overcome such freezing (for a review see Nonnekes et al., (2019)[75]). These compensation strategies include cueing that invigorates and facilitates motor sequences, which can be either external (i.e. meaningful auditory, proprioceptive or visual stimuli) or internal (i.e. orientation or focusing of attention toward gait by using specific self-prompting instructions). These compensation strategies have been proposed to employ instructions that focus their deliberate attention to specific elements of ‘normal’ walking that may bypass basal ganglia circuitry and activate prefrontal and premotor areas to prepare the motor cortex for locomotion[76,77]. We hypothesize that arm swing instructions by a short verbal command can also serve as such a compensation strategy, in such a way that cerebral circuitry underlying (enhanced) upper limb antiphase movements, co-activates the lower limb movement pattern. Based on this concept, the third part of this thesis tests whether arm swing instructions can indeed facilitate the initiation of gait.

In **Chapter 8**, we describe an experiment on a movement level, testing whether forward arm extension can indeed serve as such a cue to facilitate gait initiation in PD patients using video analysis. This experimental line is further elaborated in

Chapter 9 describing the performance of an experiment in which PD patients are instructed to start with an enhanced arm swing while EEG and EMG measures are employed, which allows us to explore the involved neural pathways. Interestingly, previous studies and chapters of this thesis all mainly focused on producing or enhancing forward arm swing (i.e. anteflexion of the shoulder), whereas the deltoideus posterior (i.e. responsible for retroflexion of the shoulder) also exhibits active muscle activity during gait and gait initiation[20,78,79]. This suggests that backward arm swing also serves a certain purpose in gait. Therefore, **Chapter 10** examines whether both forward and backward arm swing could drive lower limb muscles during gait initiation using time dependent directional intermuscular coherence analysis.

In the final **Chapter 11** the findings of this thesis will be integrated and treated in a wider perspective and future perspectives for this multi-level approach as well as the use of arm swing in gait rehabilitation will be covered.

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PART I

Arm swing in human gait