# Bilateral upper-limb coordination in aging and stroke

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## List of abbreviations

| | |
|---|---|
| AP | anti-phase |
| BOLD | blood oxygen level dependent |
| CC | corpus callosum |
| EEG | electroencephalography |
| FMA | Fugl-Meyer assessment |
| fMRI | functional magnetic resonance imaging |
| IP | in-phase |
| LHS | left hemispheric stroke |
| LMM | linear mixed model |
| M1 | primary motor cortex |
| PMd | dorsal premotor cortex |
| PSI | phase slope index |
| RHS | right hemispheric stroke |
| SMA | supplementary motor area |
| TACS | transcranial alternative current stimulation |
| TDCS | transcranial direct current stimulation |
| TMS | transcranial magnetic stimulation |
| TRPow | task-related power change |

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# Chapter 1. General introduction

## 1.1. Introduction

Our daily activities depend on effective coordination between bilateral upper limbs. Bilateral movements with upper-limbs can be classified into two movement modes: in-phase and anti-phase movements. During in-phase movements, bilateral homologous muscles contract simultaneously, e.g., when we are clapping or lifting a box. In contrast, during anti-phase movements, different muscle groups from bilateral arms activate simultaneously, e.g., driving or bathing.

In both normal aging and pathological conditions such as stroke, the decline in motor control has been a central topic of investigation. Motor decline, such as the loss of muscle power and decreased coordination ability, has been found to reduce the living independence of older adults and patients, as well as their quality of life. In particular, bilateral coordination is essential for maintaining day-to-day functioning, since most of our daily tasks require this ability. To further develop an efficient intervention, a deeper understanding of bilateral coordination control and its decline is needed. Therefore, this dissertation sought to investigate the behavioral and neural characteristics of bilateral coordination control in adults with normal aging and stroke.

In the remainder of this chapter, the literature on bilateral coordination and the known influence of aging and stroke on its decline are reviewed. Section 1.2 begins with the existing literature on movement characteristics during bilateral movement, followed by a review on the neural bases of bilateral coordination. Section 1.3 introduces the effect of aging on motor decline, from both the behavioral and neural perspectives. Section 1.4 presents the literature on stroke-induced motor impairments in general, and the potential influence of stroke lesions on bilateral coordination.

## 1.2. Bilateral coordination in human upper extremities

### 1.2.1. The two basic bilateral movement modes

Coordinating bilateral limbs in a meaningful way is essential for our daily living, since most of our daily activities require integrated actions between the two upper-limbs. There are two basic bilateral movement patterns defined in the literature: bilateral in-phase and anti-phase movements (Swinnen, 2002). A bilateral in-phase mode means that bilateral homologous muscles contract synchronously, such as clapping hands or holding a box with two hands equally. A bilateral anti-phase mode means that bilateral homologous muscles contract alternately, such as driving a car or operating a fork and a knife at the same time (Waller *et al.*, 2006). Both anti-phase and in-phase movements are crucial for our daily activities, and have been investigated under different experimental settings. Starting from the seminal work by Kelso and colleagues (Kelso *et al.*, 1979), a consistent finding is that in-phase movements tend to be performed more accurately and effortlessly with less attentional load (Wuyts *et al.*, 1996; Pollok *et al.*, 2007). Contrastingly, anti-phase movements require practice to maintain accurate performance (Lee *et al.*, 1995), and participants show decreased movement accuracy, particularly evident in the non-dominant hand, when the movement frequency during anti-phase movements increases (Byblow *et al.*, 2000). Furthermore, psychophysical studies have demonstrated that when the frequency of anti-phase movements is increased, the movement of the non-dominant hand would unintentionally change to the mirrored movement of the dominant hand (Assisi *et al.*, 2005). Based on this, it can be argued that there is a guiding influence of the dominant hand over the non-dominant hand in bilateral coordination.

Taken together, the evidence suggests that in-phase movements represent a more natural bilateral coordination mode of the human motor system compared to anti-phase movements. However, previous studies have mainly examined fine motor movements or movements involving a single joint (Spencer *et al.*, 2005; Pollok *et al.*, 2007; Fling *et al.*, 2011b). Whether these results transfer to our daily activities is unclear, since almost all functional tasks involve multiple joints at the same time. Unlike bilateral upper-limb movements involving only a single joint, those involving multiple joints rely on both inter- and intra-limb coordination (Shih *et al.*, 2019). Also, a previous study found that movements with single and multiple joints show different levels of decline in older adults (Seidler *et al.*, 2002). Therefore, an investigation on bilateral movements engaging multiple joints is essential to further our understanding of bilateral movement patterns in our daily activities and its impairments.

### 1.2.2. Neural basis of bilateral coordination

In both animal and human studies, specific brain regions were identified to be involved in bilateral movements. Early monkey studies found that bilateral coordination deficits are more strongly associated with neuronal activity in the supplementary motor area (SMA) and premotor cortex, compared to the primary motor cortex (M1) (Brinkman, 1984; Tanji *et al.*, 1988). On the other hand, later neuroimaging studies demonstrated that firing patterns of the neurons in M1 were more specific to bilateral movement compared to the SMA (Donchin *et al.*, 1998; Gribova *et al.*, 2002). Therefore, it could be that the engagement of brain areas depends on the characteristics of the performed bilateral movement. This view is supported by experiments that investigated phase transition between in-phase and anti-phase movements. For instance, when participants were asked to switch from an anti-phase to an in-phase movement, motor-related regions such as the SMA, dorsal premotor cortex (PMd) and prefrontal areas were activated (Meyer-Lindenberg *et al.*, 2002; Aramaki *et al.*, 2005). This result implies that different control processes underlie these two movement modes. Indeed, when comparing the task-related BOLD signal changes between the two movement modes directly, it has been observed that a widespread motor network is activated during anti-phase compared to in-phase movements (Ullén *et al.*, 2003; Walsh *et al.*, 2008). More specifically, during in-phase movements, the non-dominant motor cortex showed less BOLD signal change compared to the dominant motor cortex. In contrast, during anti-phase movements, the two motor cortices showed similar levels of BOLD signal changes, indicating a more bilateral activation pattern (Jäncke *et al.*, 1998; Viviani *et al.*, 1998; Aramaki *et al.*, 2006). Therefore, in-phase movements are considered to be a movement mode associated with a more left-dominant control, while anti-phase movements require equal contributions of bilateral cortices.

Since a successful bilateral movement requires cooperation of both hemispheres, interhemispheric interactions have also been a popular target for investigation (Geffen *et al.*, 1994; Liuzzi *et al.*, 2011). Results from a transcranial magnetic stimulation (TMS) study have further supported the idea of interhemispheric influences on bilateral coordination (Chen *et al.*, 2005). During bilateral in-phase movements, TMS pulses applied over one motor cortex interrupted the movements of both hands, whereas during anti-phase movements, only the contralateral hand was affected. The authors suggested that during anti-phase movements, both hemispheres are controlled with different rhythms, and therefore TMS produced an asynchronous effect on the movements of both sides (Chen *et al.*, 2005). In contrast, during in-phase movements, the two hemispheres are more synchronized with each other, and the connectivity between the motor cortices is stronger (Maki *et al.*, 2008). Together, these neuroimaging studies imply that the left hemisphere plays an important role in coordinating in-phase movements, while the right hemisphere and the connectivity between the two hemispheres are essential for executing anti-phase movements. These characteristics can thus be potential targets when examining the neural response of bilateral coordination decline in aging.

## 1.3. Age-related motor decline

### 1.3.1. Impact of aging on motor control

Normal aging is associated with motor decline due to dysfunction of the central and peripheral nervous systems (Seidler *et al.*, 2010). For example, older adults show a decrease in muscle power and movement speed compared to young adults (Granacher *et al.*, 2012). Besides the slowing of movement, older adults display larger spatial and temporal movement variability in both upper and lower limbs (Contreras-Vidal *et al.*, 1998; Christou and Enoka, 2011; Skiadopoulos *et al.*, 2020). Also, aging has been found to be associated with impaired ability in movement coordination and movement planning (Seidler *et al.*, 2002; Stöckel *et al.*, 2017). These motor deficits reduce the function of daily activities of older adults, and thus reduce their quality of life (Ferrucci *et al.*, 2016). Furthermore, decline in the ability to coordinate the two arms has been found to predict the development of mobility impairments (James et al. 2016). Therefore, understanding the decline of bilateral coordination in aging could help establish early awareness to more severe age-related motor deficits.

Previous behavioral studies have shown that aging affects bilateral anti-phase and in-phase movements differently. During in-phase movements, the performance between young and older adults were similar to each other (Greene and Williams 1996; Swinnen et al. 1998). In contrast, during anti-phase movements, older adults typically exhibit decreased inter-limb phase accuracy and increased variability compared to young individuals (Greene and Williams 1996; Lee et al. 2002; Sparrow et al. 2005). The decrease in performance of anti-phase movements in older adults is further enhanced when movement frequency increases (Wishart *et al.*, 2000). Also, compared to in-phase movements, anti-phase movements are considered a movement mode with higher task complexity that requires more attentional resources (Bangert *et al.*, 2010).

The differences in performance between in-phase and anti-phase movements could be due to age-related changes in the peripheral system such as impairments in sensory receptors (Shaffer and Harrison, 2007; Linford *et al.*, 2011). Sensory information, especially proprioceptive input, is important to inform about the status of our body within the environment (Shumway-Cook and Woollacott, 2001), as well as to maintain the stability of the movements and their coordination (Goble *et al.*, 2009). Since increasing task complexity requires integration of more sensory input (Teasdale *et al.*, 1993; Kristinsdottir *et al.*, 2001), decline in the peripheral system could influence differences in performance between bilateral in-phase and anti-phase movements. Besides the impact of the peripheral nervous system on movement decline, the central nervous system has also been extensively studied and has been shown to be associated with motor impairments in older adults (Seidler *et al.*, 2010). These are reviewed in the section below.

### 1.3.2. Neural factors influencing motor decline in aging

Aging is associated with structural changes in the central nervous system, even if there are no clinical symptoms. Neuroimaging studies have shown that aging is related to gray matter changes such as cortical thinning (Salat *et al.*, 2004), and white matter changes such as hyperintensities (Habes *et al.*, 2016). On the functional level, compared to young adults, older adults show decreased functional connectivity in several brain networks, such as the default-mode and motor network in resting-state fMRI (Ferreira and Busatto, 2013).

Furthermore, aging has been shown to alter cortical activity during task execution. Cabeza (Cabeza, 2002) proposed the Hemispheric Asymmetry Reduction in Older Adults (HAROLD) model, which states that older adults show decreased brain lateralization when performing memory and cognitive tasks. Simply put, this is because older adults tend to recruit more brain regions to compensate for the decline caused by aging. This compensatory response in older adults is typically found in the contralateral hemisphere (Steffener and Stern, 2012), but is also observed in other brain areas that are not activated by young adults (Davis *et al.*, 2008). Although the HAROLD model was based on the observation during cognitive tasks, similar results were found in motor studies. For example, during unilateral movement, older adults showed more widespread brain activities compared to young adults, and this compensatory brain activity in contralateral hemisphere is even correlated with better behavioral performance (Ward and Frackowiak, 2003; Heuninckx *et al.*, 2008). Regarding bilateral movements, in particular anti-phase movements, older adults showed higher cortical activation over the SMA and regions related to cognitive function, such as the inferior parietal cortex, compared to young adults (Coxon et al. 2010; Goble et al. 2010). However, with the additional recruitments of brain areas during bilateral anti-phase movements, older adults still worse behavioral performance compared to young adults (Coxon et al. 2010; Goble et al. 2010). This could be because regardless of age, anti-phase movements recruit more brain areas (Aramaki *et al.*, 2006), and the additional brain resources that can be further recruited in older adults for compensation is limited compared to the young adults. Thus, the effects of aging on motor decline seem to depend on the characteristics of the executed movements.

Inter-hemispheric connectivity is another important factor that can influence motor decline in aging. There is empirical evidence that reduced interhemispheric connectivity is associated with the loss of the ability to inhibit information flow from the ipsilateral hemisphere during unilateral motor performance in older adults (Fling *et al.*, 2011a). And since bilateral coordination is highly dependent on the relationship between bilateral hemispheres (Liuzzi *et al.*, 2011), changes in inter-hemispheric connectivity in aging can affect not only unilateral but also bilateral movements. Indeed, one previous study used dynamic causal modeling in electroencephalography (EEG) and found that compared to young adults, older adults showed larger bidirectional inhibitory connectivity between the two motor cortices during bilateral asymmetrical movements (Loehrer *et al.*, 2016). However, no correlation between connectivity and individual behavioral performance was found. This could be because a broader oscillatory frequency range (1-48Hz) was examined, which may potentially diminish the effects found in specific frequency bands.

### 1.3.3. Electroencephalography as a measure to assess neural changes underlying bilateral coordination decline in aging

Motor-related neural oscillations are useful for examining the neural mechanisms behind age-related bilateral coordination decline, as it is a non-invasive measurement of neural activity in the brain (Lord and Opacka-Juffry, 2016). Investigating neural oscillations at different frequency bands could help resolve the neural mechanisms underlying bilateral coordination decline, since different frequency bands have been suggested to represent different physiological processes. For example, alpha band oscillations are shown to be dominant at rest, and also thought to play an important role in attention by gating sensory processing (Klimesch *et al.*, 2007). Beta band oscillations have mostly been associated with the activity of the sensorimotor network (Roopun *et al.*, 2006). Power decreases in both alpha and beta frequency bands over bilateral parietal and sensorimotor regions during motor execution have been observed in a variety of motor tasks (Toro et al. 1994; Manganotti et al. 1998; McFarland et al. 2000; Cheyne 2013) but with distinct characteristics. Specifically, task-related power change (TRPow) in alpha rhythm usually represents a more non-somatotopical pattern (Crone et al. 1998; Nierula et al. 2013), i.e. a more diffusive topography, and has been associated with general task complexity and task demand (Manganotti et al. 1998; Fink et al. 2005). On the other hand, TRPow in the beta band was observed to be more discrete, i.e., the timing of oscillation changes were tightly associated with the movement itself (Crone et al. 1998; vanWijk et al. 2012), and were strongly coherent with electromyography (EMG) signals during force generation (Liu et al. 2019). Also, recent studies have shown that the amplitude of beta TRPow changes over the motor and parietal areas are related to online movement monitoring and correction (Boonstra et al. 2007; Tan et al. 2014; Xifra-Porxas et al. 2019). These results indicate that alpha and beta oscillations play different functional roles during movement execution. Furthermore, when examining the two frequency bands in older adults, alpha power changes have been found to predict age-related deficits in sensory prediction, while beta power changes predict motor timing (Johari and Behroozmand, 2020). Therefore, considering how alpha and beta frequency bands showed distinct characteristics during movement execution, examining both frequency bands separately would be useful to advance our understanding on the neural mechanism of bilateral control and its decline.

## 1.4. Stroke-induced motor impairments

### 1.4.1. Upper limb impairments after stroke

A motor deficit of the upper limb is the most common impairment after stroke (Pollock et al. 2014). Impaired motor function of contralesional limbs has been observed in more than 50% of stroke patients (Nakayama et al. 1994; Lawrence et al. 2001), and the symptoms include muscle weakness/paresis, abnormal muscle tone and decreased coordination ability. As a result of these impairments, patients experience decreased living independency and thus reduced quality of life (Broeks *et al.*, 1999; Franceschini *et al.*, 2010). Therefore, many research studies have been devoted to the investigation of proper assessment of upper-limb motor function to improve prognosis and treatment strategies for stroke patients (Coupar *et al.*, 2012).

Fortunately, motor impairments after stroke are not static. Rehabilitation at both the early and later stages after stroke have shown to improve upper-limb function in stroke patients (Ballester *et al.*, 2016). On the other hand, if a paretic arm stays without treatment, the limb function can worsen (Sterr *et al.*, 2002). Although stroke patients generally used their ipsilesional arm more than their contralesional arm, the degree of this usage preference is dependent on the side of the lesion (Rinehart *et al.*, 2009). Rinehart and colleagues found that patients with left hemispheric lesions used their ipsilesional arm twice as much as their contralesional arm, while patients with right hemispheric lesions used it four times more frequently. Also, stroke patients with left hemispheric lesions used more bilateral movements to complete a task, while patients with right lesions preferred to use only the contralesional arm alone (Haaland *et al.*, 2012). These results suggest that patients with left and right hemispheric lesions show different motor characteristics. That is, patients with left hemispheric lesions still preserve the usage of the contralesional arm (right hand), which is usually their previous dominant hand, while patients with right hemispheric lesions reduce their use of the contralesional arm (left hand) significantly.

These differences in hand usage between patients with left and right hemispheric stroke, respectively, might be due to a higher motivation in improving the previous dominant hand compared to non-dominant hand (Harris and Eng, 2006). However, increasing studies have shown that the differences in motor performance between patients with left right hemispheric lesions are a result of hemispheric specialization (Harris and Eng, 2006; Schaefer *et al.*, 2009; Tretriluxana *et al.*, 2009). For example, previous studies have shown that the side of the lesioned hemisphere can lead to distinct motor impairments in unilateral movements of both contra- and ipsilesional limbs after stroke (Sainburg and Duff, 2006; Schaefer *et al.*, 2009). During contralesional arm reaching, patients with lesions in the left hemisphere showed worse performance in predictive control (e.g., larger trajectory errors at the early phase of reaching), while those with right hemispheric lesions had more impairments in impedance control (e.g., final position errors) (Haaland *et al.*, 2004; Mani *et al.*, 2013). Such impairments were observed in the ipsilesional arm of the stroke patients as well (Schaefer *et al.*, 2007, 2009). Together, these findings used stroke patients as a lesion model and revealed that there is a hemispheric specialization in unilateral movements. However it remains thus unknown whether there is also a functional hemispheric specialization for bilateral coordination, a question that will be addressed in the current dissertation.

### 1.4.2. Impairments in bilateral movements after stroke

When examining bilateral movements after stroke, patients generally show greater movement variability in both limbs (Garry *et al.*, 2005) and unsteady force control between hands (Lai *et al.*, 2019) during bilateral movements, regardless whether they perform in-phase or anti-phase movement. In addition, consistent with findings in healthy adults, stroke patients experienced more difficulty performing bilateral anti-phase than in-phase movements (Lewis and Byblow, 2004; Kim and Kang, 2020). However, as reviewed in Chapter 1.2.2, the two hemispheres are differentially involved during in- and anti-phase movements in healthy adults. Considering the neural mechanisms behind these two movement modes, we would expect that bilateral coordination impairments after left and right hemispheric stroke show distinct characteristics. Indeed, one study examined the inter-limb synchronization during bilateral elbow pronation-supination movements, and showed that patients with left hemispheric lesion performed in-phase movements more synchronously compared to patients with right hemispheric stroke (Lewis and Perreault, 2007a). In line with this idea, one study found that patients with left hemispheric lesions benefitted more from a bilateral training regime than patients with right hemispheric lesions, indicating that the response to bilateral training is dependent on the lesioned side (McCombe Waller and Whitall, 2005). These studies underlined the differential impact of the lesion side on bilateral movements. However, since only inter-limb performance was examined, it is still unclear how individual limb performance (i.e. intra-limb performance) during bilateral movements is affected after left versus right hemispheric stroke, respectively. Therefore, examining both between-hand synchronization and within-limb trajectory control is equally essential for characterizing impairment. In the next chapter, I summarize limitations in the literature and accordingly, I propose three research questions.

# Chapter 2. Rationale of the Dissertation

The present dissertation aims to understand the decline of bilateral coordination in aging and stroke on the behavioral and neural level.

Regarding the design of the bilateral coordination paradigm, previous studies have mostly used single joint movements, for example index-finger tapping or forearm pronation-supination. However, most of our daily activities involve movements engaging multiple joints simultaneously (Keenan *et al.*, 2006; Murphy *et al.*, 2006). Contrary to single joint movements, bilateral movements engaging multiple joints require not only inter-limb coordination, but also additional intra-limb coordination (Tseng *et al.*, 2009) Therefore, it is unclear whether previous findings from single joint movements can be directly applied to multiple joint movements.

Regarding the decline in bilateral coordination in aging, previous studies have shown that anti-phase movements are more affected by aging than in-phase movements (Serrien *et al.*, 2003; Sparrow *et al.*, 2005). On the neural level, studies have shown an equal bilateral activation pattern during anti-phase movements, and a left-dominant activation pattern during in-phase movements (Maki *et al.*, 2008). However, no behavior-brain correlation has been found with respect to the behavioral decline in aging (Liuzzi *et al.*, 2011). Therefore, it remains unclear how the neural characteristics of the two bilateral coordination modes lead to differential behavioral decline in aging. Moreover, even if corresponding brain responses are identified using neuroimaging tools, direct causal evidence is lacking to support the specificity of bilateral hemispheres in bilateral coordination.

Investigating stroke patients with hemiparesis could help to demonstrate the causal influence of the lesioned hemisphere on impairments in bilateral coordination.

However, so far both clinical research and rehabilitation for stroke have predominantly focused on examining the contralesional arm (Sainburg *et al.*, 2013). Bilateral movements, which our daily activities are highly dependent on, have received far less attention (Kantak *et al.*, 2017). Therefore, a better understanding of the characteristics of bilateral coordination impairments after motor stroke is needed to establish awareness for clinicians and to develop effective rehabilitation strategies.

This dissertation thus aimed to address the following research questions:

1) How do the two basic bilateral movement modes (i.e. in-phase and anti-phase movements) differ from each other regarding movement kinematics when engaging multi-joint movements?

2) How does aging affect the two bilateral coordination patterns, and what are the underlying neural mechanisms?

3) How is bilateral coordination affected in stroke? How does the lesioned hemisphere influence bilateral coordination impairments?

Three studies have been conducted to answer these questions. In study 1, healthy right-handed young participants performed a bilateral circle drawing task involving shoulder and elbow joints. We examined intra-limb (trajectory variability of each hand) and inter-limb (phase synchronization between hands) coordination during bilateral anti-phase and in-phase circle drawing movements using the exoskeleton KINARM to approach our first research question.

In Study 2, healthy young and older adults performed the same bilateral coordination task while their neural activity was recorded simultaneously using EEG. We measured both the task-related power change and inter-hemispheric connectivity within the alpha (8-12 Hz) and beta (15-25 Hz) band separately. This was because these two frequency bands have previously been shown to be involved in motor execution with different physiological meaning. Regression analyses were conducted to examine the association between brain oscillatory responses and behavioral decline in aging.

Study 3 investigated the potentially differential impact of the lesioned hemisphere on bilateral coordination. Stroke patients with left and right hemispheric lesions, as well as matched healthy controls participated in this experiment. Besides examining the intra-limb and inter-limb coordination separately, we further studied how the performance of each limb contributed to bilateral coordination performance. This allowed to investigate how unilateral lesions lead to impairments in bilateral coordination, and whether this effect was dependent on the lesioned hemisphere.

# Chapter 3. Study I: Human motion characteristics during bilateral in-phase and anti-phase movements

## 3.1. Introduction

As introduced in Chapter 1.2, the two basic upper-limb coordination modes – bilateral in-phase and anti-phase movements –have been widely investigated in the past decades (Swinnen, 2002; Swinnen and Wenderoth, 2004). Previous studies have quantified inter-limb performance during bilateral coordination using indices such as the mean and standard deviation of the phase difference between hands (Semjen *et al.*, 1995; Debaere *et al.*, 2004). With these measures, it has been demonstrated that a larger average phase difference between hands (with the dominant hand leading), and higher variability in phase difference is present during anti-phase movements compared to in-phase (Maki *et al.*, 2008).

However, a limitation of the literature is the design of the existing paradigms. While most of our daily activities involve movements engaging multiple joints at the same time (Keenan *et al.*, 2006; Murphy *et al.*, 2006), previous studies mostly investigated single joint movements (e.g. index finger tapping, forearm pronation-supination). Contrary to single joint movements, bilateral movements engaging multiple joints require not only inter-limb coordination (i.e. coordination between the two hands), but also additional intra-limb coordination (i.e. coordination between joints within each hand) (Jaric *et al.*, 2006). Therefore, it is unclear whether the previous findings from single joint movements could be directly applied to multiple joint

Please note that this study has been published as Shih, P.-C., Steele, C.J., Nikulin, V. et al. Kinematic profiles suggest differential control processes involved in bilateral in-phase and anti-phase movements. Sci Rep 9, 3273 (2019). https://doi.org/10.1038/s41598-019-40295-1 movements. Furthermore, previous studies usually used a paradigm have low sample size (8 to 16 participants) which resulted in a low statistical power. Considering the current reproducibility crisis in science (Open Science, 2015; Baker, 2016), this experiment aimed at not only characterizing the bilateral movements engaging gross movements, but also using a larger sample size to provide a better statistical power on the results. Here, we adapted the classic circle-drawing task into KINARM (BKIN Technologies Ltd, Ontario, Canada), a device that has a temporal resolution of 1000Hz and spatial resolution in the millimeter range to assess upper-limb bilateral coordination. Taking advantage of the high temporal and spatial resolution of the device, we computed measurements that captured intra-limb coordination, inter-limb coordination, as well as a metric quantifying the inter-limb acceleration relationship during different bilateral coordination patterns. Based on the previous literature, we hypothesized that both intra-limb and inter-limb measures will be differentially affected by in-phase movements and anti-phase movements; more specifically, movement coordination during in-phase conditions would be better compared to anti-phase conditions.

## 3.2. Materials and methods

### 3.2.1. Participants

Thirty healthy young adults (age: 26.24 ± 3.13 years, 15 male) participated in this study. All participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971) (score: 88.52 ± 15.77). Participants did not have experience in the testing paradigm and were naive to the purpose of the study. The experiment was approved by the ethics committee of the University of Leipzig and performed in agreement with the Declaration of Helsinki; all participants gave written informed consent to join the experiment.

### 3.2.2. Experimental device

The experiments were performed using the KINARM upper limb robotic exoskeleton system. KINARM has been widely used as a motor assessment device (Coderre *et al.*, 2010; Dukelow *et al.*, 2010). It is capable of recording movements in the millimeter range at a sampling rate of 1000 Hz, which help to better quantify sensory and motor characteristics in healthy subjects as well as subjects with neurological disorders. The KINARM device includes a height-adjustable chair with bilateral arm-gravitational-support platform, two cylinder grips for the hands, a monitor linked to the operator's computer, and a screen under the monitor to present the task paradigm (Figure 3.1). This environment allows participants to perform two-dimensional planar shoulder and elbow movements under the presentation screen, which means both arm movements and the visual display of the motor task are within the same workspace. Participants' movements were continuously recorded by the Dexterit-E (3.5v, BKIN Technologies Ltd, Ontario, Canada) software during the task performance at a sampling rate of 1000 Hz. The recorded data were saved automatically to a c3d data file, containing the hand position coordinates (x,y) and the movement velocity along the transverse plane.

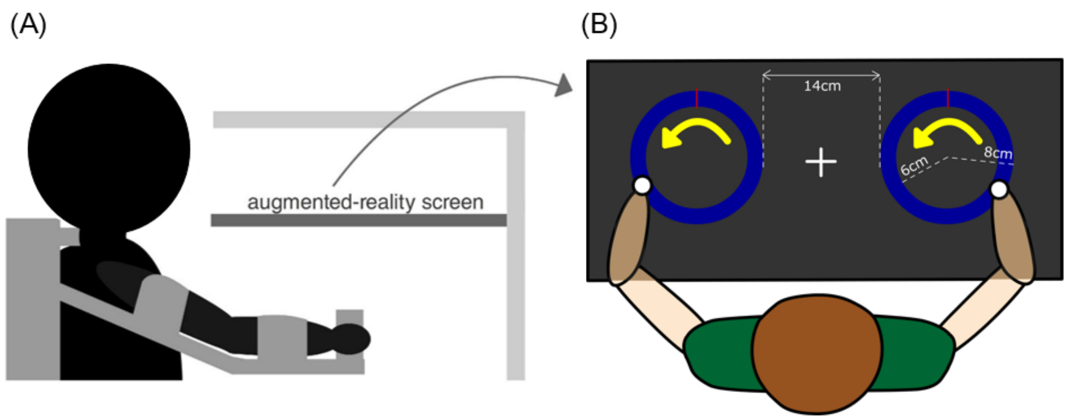


**Figure 3.1. Experimental device.**

(A) Participants put their arms on the gravity-support platforms, with the hands holding the handrails. The augmented-reality screen displayed the paradigm projected by the monitor. (b) The relative position of the participant and the circle position. The white fixation cross is presented at the midline of participants. The yellow arrows inside the circle path were used to indicate the required movement direction. The red bar indicates the starting hand position for the task.

### 3.2.3. Circle Drawing Task

We adapted the classic bilateral circle drawing task (Kelso *et al.*, 1979) and programed the task on Simulink (R2015, The MathWorks, USA) and Dexterit-E to probe upper-limb coordination. As shown in Figure 3.1B, two target circles were displayed side by side on the screen with the distance between their centers set at 22 cm. The inner/outer diameter of each circle is 6/8 cm, which creates a 2-cm-thick circle path (shown in blue). The distance and size of the circles were determined by pilot testing with young adults. A white fixation cross was positioned between the two circles. A red vertical line at the top of each circle indicated the starting point of the task, and a yellow arrow was projected inside the circle to point out the active hand(s) and the upcoming movement direction(s). An auditory metronome (0.85 Hz) started at the beginning of each trial in order to provide a cue for the required movement frequency. The frequency of the metronome was selected based on a pilot experiment and provided participants with a comfortable speed for rhythmic movements without potential phase transition.

As shown in Figure 3.2A, there were a total of eight testing conditions, which were classified into four main movement patterns: left unilateral movements, right unilateral movements, bilateral anti-phase and bilateral in-phase movements. Each movement condition was conducted in a 15s trial, preceded by a 5s preparation phase. Participants were instructed to (1) check the upcoming movement direction(s) on the screen and then put the active hand(s) on the starting point(s); (2) wait for the start of the trial as indicated by the auditory metronome (which sounded 5 seconds after the hand(s) was/were at the starting point); (3) draw continuous circles in synchrony with the metronome, in a way that the hands are at the starting point during the sound of the metronome; (4) try to keep the hands within the circle path. Participants were instructed to focus their eyes on the central fixation cross during drawing to minimize head movement and attentional bias, since focal attention has been shown to improve upper-limb movement accuracy (Swinnen *et al.*, 1996).

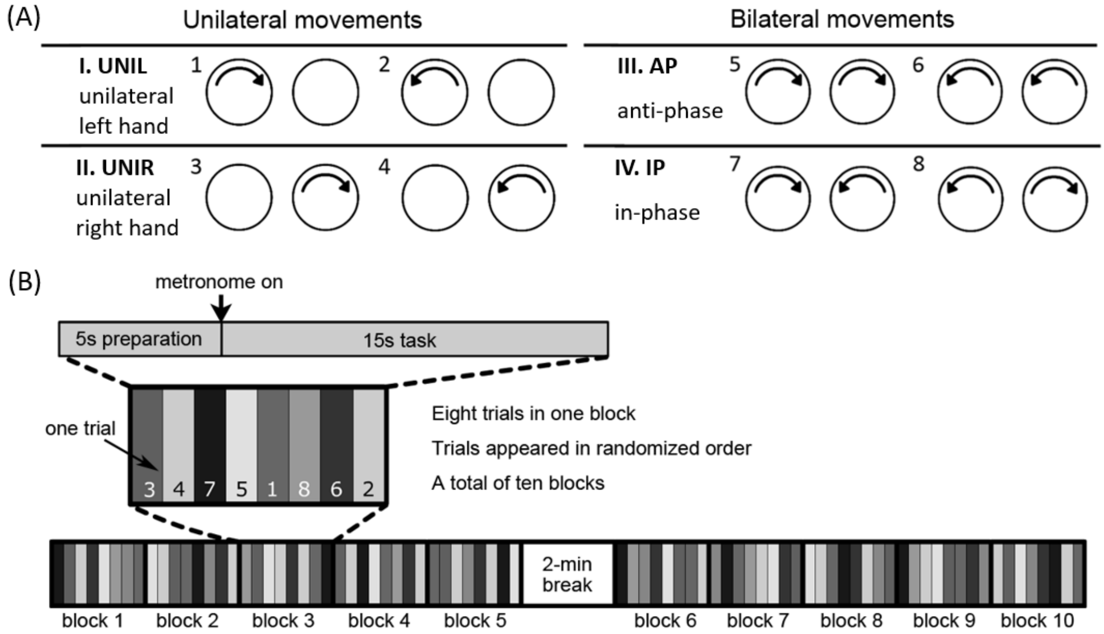


**Figure 3.2. Experimental design.**

(A) Testing conditions. I. Unilateral left hand (UNIL). II. Unilateral right hand (UNIR). III. Anti-phase condition (AP). IV. In-phase condition (IP). (B) Task design. Eight trials (eight movement patterns) were displayed as a 15s trial in randomized order within one block, and a total of 10 blocks were performed in the whole experiment. Before each of the 15s trial started, participants had to hold their hands on the starting point for 5 seconds.

As shown in Figure 3.2B, each condition was performed once in a randomized order in a block. There were a total of 10 blocks within the whole experiments, and a two minute break between blocks 5 and 6, resulting in the total time of approximately 30 minutes for the entire experiment. Before the experiment started, all participants had already practiced every movement condition once (in the order of condition 1-8, as shown in Figure 3.2A) to be familiarized with circle size and metronome frequency. Hence, we did not observe a learning effect across performance of the experiment (please see Appendix 1.1).

### 3.2.4. Data processing and outcome measurements

All raw data files, containing hand position and velocity information, were imported into Matlab (R2017a, The MathWorks, USA) for offline processing using BKIN TOOLS and custom processing scripts. To specifically focus on the steady performance within one trial, we discarded the first two metronome cycles after the metronome started; thus, only the 3rd to 11th (inclusive) metronome cycles were analyzed. The 8 movement conditions were pooled for analysis under the same category (i.e. unilateral left, unilateral right, in-phase and anti-phase; labelled as category I-IV in Figure 3.2A), since the effect of movement direction on the behavioral indices was not of primary interest in this study. In this study, kinematic indices in each condition were computed first on a single-trial basis and then averaged across the ten repeated trials of the same condition.

#### *3.2.4.1. Intra-limb performance*

We developed three measures to characterize spatiotemporal performance of each hand. In each trial, the center of mass of the circle trajectories was set at (0, 0) individually for each hand.

(1) Mean cycle period and cycle period variability: we examined mean cycle period and cycle period variability to investigate participants' ability to synchronize the movement with the metronome during the task. The cycle period was first estimated by computing the interval between the peak Y-coordinates in each trial (Figure 3.3). Mean cycle period was the averaged cycle value within each trial. The cycle of the metronome was set at 1177ms; therefore, a successfully synchronized performance should show a mean cycle period that is close to this value. Cycle period variability

was defined as the coefficient of variation of the cycle periods within each trial. Lower cycle period variability indicates a more consistent ability to synchronize with the metronome within a trial.

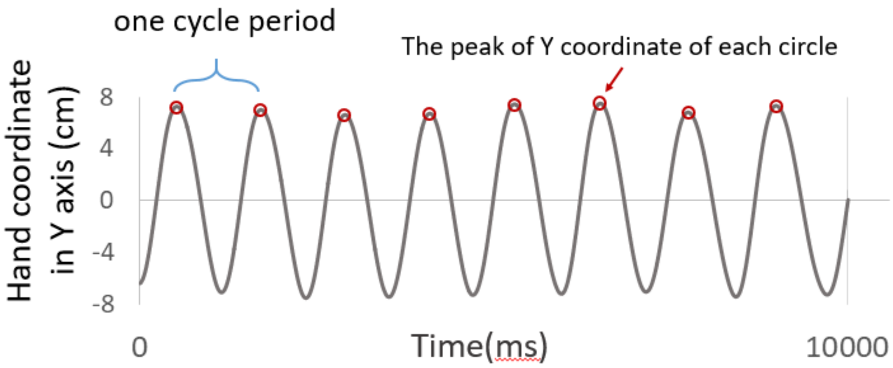


**Figure 3.3. Assessment of mean cycle period and cycle period variability.**
An illustration of one representative participant's trial. The red circles indicate the positions of the peak Y coordinate of each circle, and the peak-to-peak duration represents a cycle period (the blue window).

(2) Trajectory variability: this measurement is used to examine the spatial variability of movements within a trial (Tseng and Scholz, 2005). The data was converted from Cartesian (x, y) to polar (r,θ) coordinates and the radius extracted from each sampling point. Within each trial, the coefficient of variation of the radius values across all sampling points was calculated to represent trajectory variability. A lower value indicates a more consistent trajectory during the drawing movement.

(3) Peak speed variability: this measurement assesses the temporal variability of the repetitive circle drawing (Lee *et al.*, 1995), thus providing information on temporal consistency during the continuous movement. The peak velocity of each cycle was computed, and then the coefficient of variation across cycles was calculated to represent temporal variability. A lower value indicates that participants drew the 12 circles within a trial in a more consistent speed.

For all three indices, a lower value implies a more consistent spatial or temporal performance, while a higher value represents more variance in performance.

*3.2.4.2. Inter-limb performance*

We developed additional indices to examine the phase relationships between both limbs to assess how they interact with each other during the bilateral conditions. As a first step, we performed a curvature correction to reduce the effect of participants' unintentional center-shifting on phase calculations. This was performed to avoid inaccuracy of the phase value based on center shifts (see Figure 3.4A for a graphical explanation). We first estimated the centroid for each sampling point based on the circle cycle using least-squared fitting and then corrected its position (Gander et al., 1994). This method preserved the phase relationship between each sampling point, while excluding the potential influence of spatial shifting on the phase calculation (Figure 3.4B). As an additional information, the offset of the centroid is analyzed (please see Appendix 1.2). We found significant increases of centroid offset during the anti-phase condition in the left hand. Therefore, centroid correction is essential to reduce potential biases of the phase calculation from the spatial shift.

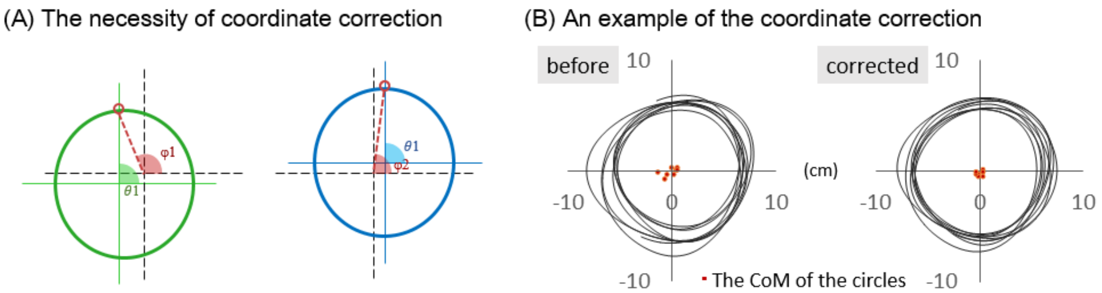


**Figure 3.4. Coordinate correction for phase synchronization analysis.**
(A) The necessity of coordinate correction before calculating the phase values. From the Center of Mass (CoM) of the left (green) and right (blue) circles, the two small red dots both lie on 90

degrees of the circles (θ1=θ2). However, when the two circles are lying on a common coordinate (black coordinate) with a spatial shift, the phase value of the two dots become different (φ1≠φ2). (B) An example of coordinate correction. The participant had slight movement of the CoM between each cycle. After correction, the CoM between cycles becomes more stable. The tiny red dots represent the CoM of each circle.

Following the curvature correction, three indices were then computed to measure inter-limb coordination ability in different bilateral conditions:

(1) Mean phase difference between hands: we calculated the averaged phase difference value $\varphi_{(R,L)} = \varphi_R(t) - \varphi_L(t)$ in each trial to examine whether there is an effect of a particular hand leading. A positive value suggests that the right hand is in leading position, while a negative value indicates that the left hand is in leading position.

(2) Phase synchronization index: we used phase synchronization index to quantify how well the two hands synchronized with each other. Since standard deviation is prone to errors in estimating circular variability as the data is periodic (Berens, 2009), we used the phase synchronization index, which is instead based on the circular variance of the angular distribution, to prevent this problem (Rosenblum *et al.*, 2001). It thus measures the angular deviation and quantifies how consistent the phase oscillation between the two hands are. The index is obtained by projecting the phase differences between two hands onto the unit circle and calculating the absolute value of the mean phase difference between hands:

$$synchronization\ index = \left| \frac{1}{T} \sum_{t=1}^{T} e^{i[\varphi_R(t) - \varphi_L(t)]} \right| \qquad \text{Eq. 3.1}$$

,where $\varphi_R(t)$ and $\varphi_L(t)$ represents the unwrapped phase of the left and right hand during the sampling point $t$, and $T$ represents the total amount of the sampling points in a trial. This index ranges from 0 to 1. A value close to zero indicates no phase synchronization, while 1 corresponds to perfect phase synchronization. Note that the mean phase difference itself does not affect the strength of the synchronization index.

(3) Inter-limb acceleration index: this measure was used to examine whether the two hands are accelerating synchronously with each other. First, the speed data were smoothed using a third-order one-dimensional median filter through the Matlab *medfilt1* function. Second, we took the differentiation of the angular speed to obtain the instantaneous rate of change of speed from the left hand ($aL$) and right hand ($aR$). Then, we calculated the Pearson correlation coefficient (Matlab *corr* function) from the respective acceleration values. This provides a bounded value that examines the tendency of bilateral hands' acceleration relationship. Value -1 denotes a complete anti-phase acceleration relationship between hands; value +1 indicates a complete in-phase acceleration relationship between hands; while a value close to 0 stands for no specific phase relationship.

### 3.2.5. Statistical analyses

All statistical analyses were performed using SPSS 20 (IBM, NY, USA), and results are presented as mean±SD. For intra-limb performance, paired-t tests were used to compare the performance in the unilateral conditions between left and right hand; two-way repeated-measures Analysis of Variance (ANOVA) were used in the bilateral conditions for comparing anti-phase movements and in-phase movements, which aimed at determining the effect of hand (left, right) and condition (anti-phase movements, in-phase movements). For inter-limb performance, we used paired-t tests to examine potential differences between anti-phase movements and in-phase conditions.

## 3.3. Results

### 3.3.1. Intra-limb performance

Result of intra-limb performance is summarized in Table 3.1

**Table 3.1. Intralimb parameters: mean cycle period, cycle period variability, trajectory variability and peak speed variability.**

| Left hand | Unilateral | Anti-phase | In-phase |
|---|---|---|---|
| Mean cycle period (ms) | 1123.35±32.14 | 1147.54±20.72 | 1153.14±20.80 |
| Cycle period variability | 0.0464±0.0108 | 0.04205±0.0015 | 0.0423±0.0019 |
| Trajectory variability | 0.156±0.0029 | 0.158±0.027 | 0.137±0.026 |
| Peak speed variability | 0.0374±0.0013 | 0.0365±0.0016 | 0.0376±0.0011 |
| Right hand | Unilateral | Anti-phase | In-phase |
| Mean cycle period (ms) | 1150.84±21.69 | 1147.54±20.72 | 1153.14±20.80 |
| Cycle period variability | 0.0457±0.0109 | 0.0415±0.0014 | 0.0042±0.0021 |
| Trajectory variability | 0.136±0.029 | 0.137±0.028 | 0.135±0.030 |
| Peak speed variability | 0.0033±0.0010 | 0.0034±0.0012 | 0.0033±0.0011 |

Results are shown as mean±SD.

#### *3.3.1.1. Mean cycle period and cycle period variability*

We used mean cycle period and cycle period variability to investigate whether participants consistently synchronized with the metronome in all conditions.

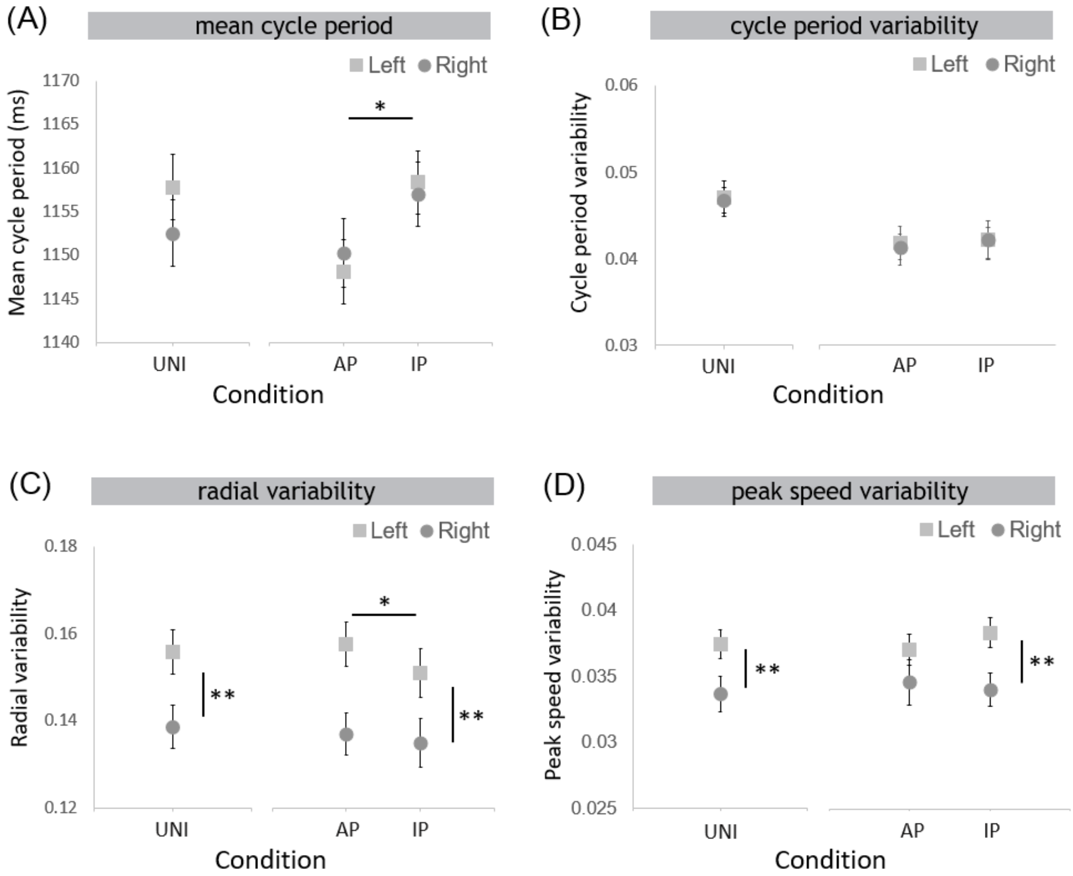


**Figure 3.5. Results for kinematic analyses during unilateral, bilateral anti-phase and in-phase conditions**

(A) Mean cycle period, (B) cycle period variability, (C) trajectory variability, and (D) peak speed variability of the unilateral and the bilateral conditions. *p<0.05, **p<.001. Values for left hand are shown as squares, right hand as circles. UNI = unilateral condition. AP = anti-phase condition. IP = in-phase condition.

In the unilateral conditions, no significant difference between hands was found in both mean cycle period ($t_{(29)} = 1.358$, $p = 0.185$) and cycle period variability ($t_{(29)} = 0.307$, $p = 0.761$). For mean cycle period during bilateral conditions (Figure 3.5A), there was no interaction between *Hand* and *Condition* ($F_{(1,29)} = 2.196$, $p = 0.149$, $\eta^2 = 0.070$), no significant main effect of *Hand* ($F_{(1,29)} = 0.208$, $p = 0.613$, $\eta^2 = 0.075$) but *Condition* ($F_{(1,29)} = 5.028$, $p = 0.027$, $\eta^2 = 0.410$), suggesting that participants' cycle period was closer to the optimal cycle (i.e. 1177ms) during the in-phase compared to the anti-phase movements. For cycle period variability during bilateral conditions

(Figure 3.5B), there was no *Hand*Condition* interaction ($F_{(1,29)}$ = 1.081, p = 0.205, $\eta^2$ = 0.036), no significant main effect of *Hand* ($F_{(1,29)}$ = 0.228, p = 0.636, η2 = 0.008) nor *Condition* ($F_{(1,29)}$ = 0.365, p = 0.551, $\eta^2$ = 0.012). Taken together, participants showed more accurate mean cycle period during the in-phase condition compared to the anti-phase condition, while no differences in cycle period variability were found.

#### *3.3.1.2. Trajectory variability*

In the unilateral conditions, left hand showed significantly higher ($t_{(29)}$ = 7.564, p < .001) circle trajectory variability when compared to right hand. In the bilateral conditions, anti-phase movements had greater trajectory variability compared to in-phase movements, and the left hand showed significant higher variability than the right hand (0.136±0.05). These effects were supported by a main effect of *Hand* ($F_{(1,29)}$ = 45.642, p < 0.001, $\eta^2$ = 0.611) as well as *Condition* ($F_{(1,29)}$ = 5.64, p = 0.022, $\eta^2$ = 0.168). In addition, there was an interaction between *Hand* and *Condition* ($F_{(1,29)}$ = 4.398, p = 0.045, $\eta^2$ = 0.132, Figure 3.5C) such that the non-dominant hand decreased in trajectory variability during in-phase movements, while performance of the dominant hand remained stable during anti-phase movements and in-phase movements.

#### *3.3.1.3. Peak speed variability*

In unilateral conditions, left hand showed significant higher ($t_{(29)}$=3.356, p=.002) peak speed variability than right hand. In bilateral conditions, the left hand showed higher peak speed variability compared to the right hand, a result supported by a significant main effect of *Hand* ($F_{(1,29)}$ = 20.410, p < 0.001, $\eta^2$ = 0.413). There were no differences between anti-phase movements and in-phase movements (*Condition*: $F_{(1,29)} = 0.132$, $p = 0.719$, $\eta^2 = 0.005$), nor was there an interaction *Hand**Condition* ($F_{(1,29)} = 1.835$, $p = 0.187$, $\eta^2 = 0.064$, Figure 3.5D).

Together, the results from the spatiotemporal analyses (i) confirmed that the non-dominant hand shows more variance than the dominant hand, and (ii) demonstrated that performance of the non-dominant hand is easier to be affected by movement modes; i.e., that trajectory variability is higher during the anti-phase movement mode.

### 3.3.2. Inter-limb performance

#### *3.3.2.1. Phase difference and phase synchronization index*

For the mean phase difference, the averaged values during anti-phase movements (6.33±1.204º) and in-phase movements (4.22±0.628º) were both positive (indicating right-hand leading), and the paired-t test revealed that the phase difference between hands was significantly more pronounced ($t_{(29)} = 2.777$, $p = .030$) during anti-phase movements compared to in-phase movements (Figure 3.6B). Although bilateral phase synchronization was consistently high in all conditions, we observed that participants performed the in-phase movements (0.98±.001) condition with greater ($t_{(29)} = 8.276$, $p < .001$) synchronization compared to anti-phase movements (0.96±.001) (see Figure 3.6A for a single trial of an individual subject; Figure 3.6C for group average).

#### *3.3.2.2. Inter-limb acceleration index*

During in-phase movements, bilateral hands have a strong tendency to accelerate with the in-phase relationship, while in anti-phase movements, two hands accelerate and decelerate without a specific relationship (IP: 0.25±0.052, AP: 0.06±0.050; $t_{(29)}$ = -12.557, p < .001) (see Figure 3.7A for the speed/acceleration profile of an individual subject; Figure 3.7B for the group result). This result indicated that in in-phase condition, participants performed the task with a convergent inter-limb hand acceleration relationship; i.e., during in-phase movements, both hands predominantly accelerated and decelerated at the same time, while in anti-phase condition, the inter-limb acceleration profile was random.

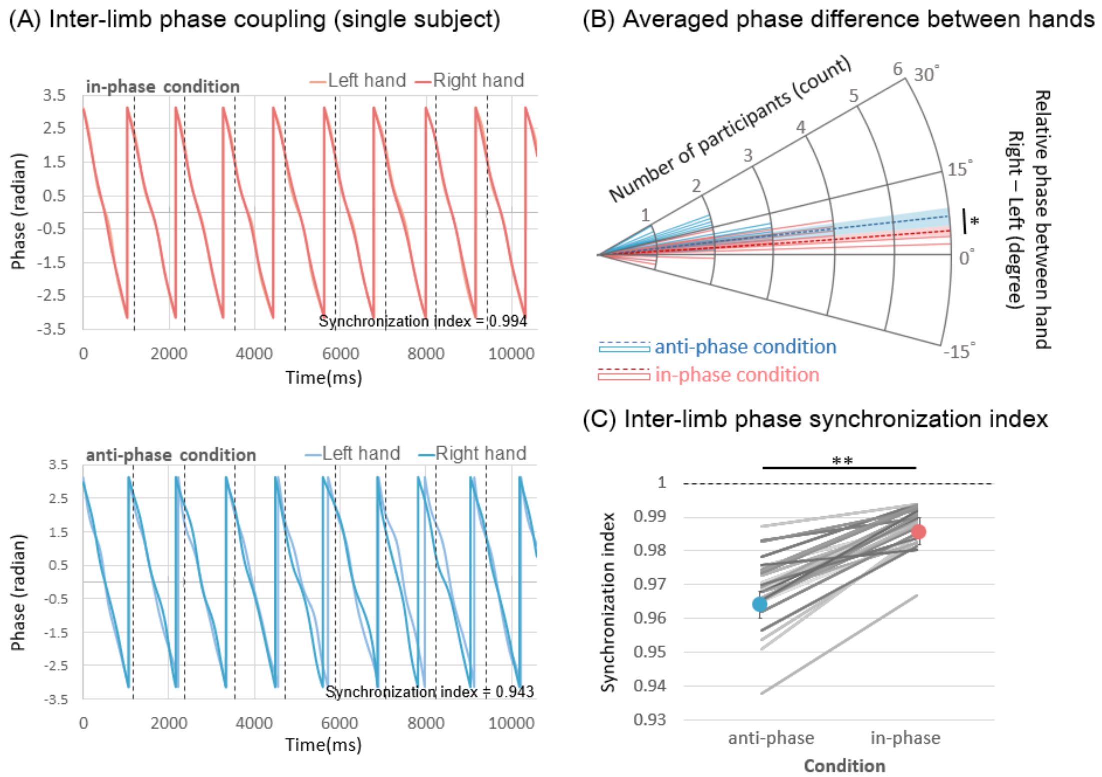


**Figure 3.6. Inter-limb coordination indices.**

(A) An example of phase fluctuation within the trial. (B) Histogram of the phase difference during anti-phase movements and in-phase conditions (solid lines representing single subjects; dotted line±shaded region representing mean±SE). (C) Inter-limb phase synchronization index of anti-phase movements and in-phase condition. Grey lines illustrate the individual performance. *p<.05. **p<.001. Values for anti-phase movements in blue, in-phase movements in red. Values for each participants are shown as single grey lines.

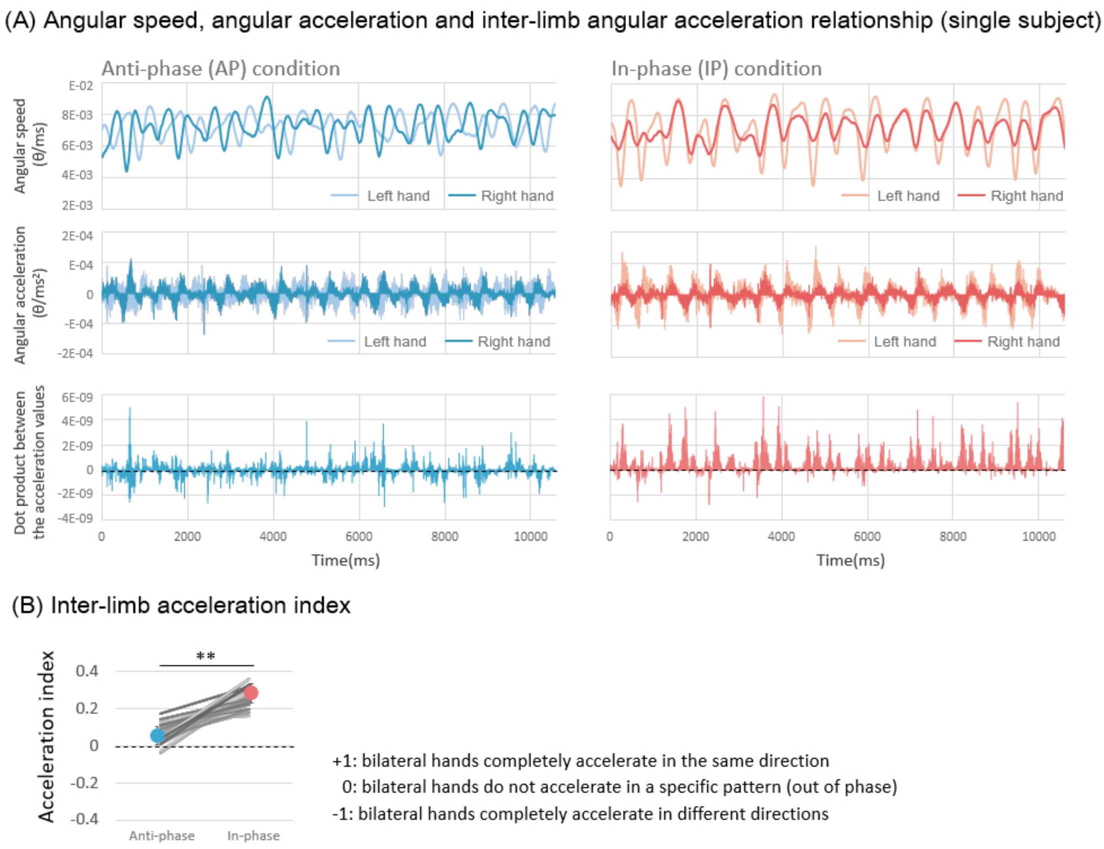


**Figure 3.7. Inter-limb acceleration index.**

(A) An example of angular speed and acceleration fluctuation within the trial (same subject, same trial as Figure 3.6). The first row showed the time-series angular speed data from both hands. The speed changes of both hands are more convergent during in-phase movements, while in anti-phase movements the pattern is random. The second row showed the differentiation of the angular speed, i.e., angular acceleration of both hands. The third row showed the product between the time series acceleration values from left and right hands. (B) Individual and averaged inter-limb acceleration index during anti-phase movements and in-phase condition. **$p<.001$.

## 3.4. Discussion

In this study, we demonstrate differential intra-limb and inter-limb performance during the two basic bilateral coordination patterns. First, in-phase movements are performed with better intra-limb coordination than anti-phase movements (i.e., participants showed lower trajectory variability). This difference was mainly driven by the performance of the non-dominant hand, suggesting that non-dominant hand performance is facilitated during in-phase compared to anti-phase movements. Second, in-phase movements are performed with better inter-limb synchronization and a more convergent speed change profile than anti-phase movements. These results showed that different control processes behind bilateral in-phase and anti-phase movements can be reflected in kinematic profile. Also, in-phase movements might have a beneficial effect on kinematic performance in the weaker (i.e., non-dominant) limb.

We demonstrate kinematic asymmetries between the dominant and non-dominant hands during the control of bilateral movement patterns. Intra-limb performance, in particular trajectory variability and peak speed variability, were both worse in the non-dominant compared to the dominant hand across all conditions. Interestingly, non-dominant hand performance became more consistent and stable during in-phase movements. This result supports the hypothesis that performance of the non-dominant hand is more prone to be affected by task demand during bilateral movements, while the performance of the dominant hand remains stable (Semjen *et al.*, 1995; Byblow *et al.*, 2000). Semjen et al. (1995) found that high-frequency circle drawing movements largely distorted the non-dominant hand trajectory during anti-phase compared to in-phase movements. In addition, there was a higher chance of movement direction reversals happening during anti-phase movements specifically in the non-dominant hand. Our data confirm and extend these results: we found that the non-dominant hand reached better performance during bilateral in-phase movements than anti-phase movements. Our findings are in line with Helmuth and Ivry (Helmuth and Ivry, 1996), who identified a bilateral advantage for timing during finger tapping: lower temporal variability was found during bilateral tapping compared to the unilateral tapping. This observation supports the concept, that in-phase movements have a facilitatory effect on the performance of the “weaker” non-dominant hand, suggesting that a symmetrical movement pattern can improve the temporal stability of the movement. Furthermore, our results demonstrate that this facilitatory effect does not only apply for the temporal, but also for the spatial domain, in a way that the bilateral in-phase advantage can even improve the spatial accuracy. In addition, when estimating the acceleration relationships between hands, our data suggest a temporal advantage for the dominant hand - which is evidenced by the phase lag between hands with the dominant hand in a leading position. Again, this pattern was more prominent in anti-phase movements compared to in-phase movements, which may help confirming that the dominant-hand advantage is more pronounced during anti-phase movements than in-phase movements in the temporal domain (Swinnen *et al.*, 1996; Debaere *et al.*, 2004). However, Franz et al. (2002) reported that not hand dominance but rather movement direction determines which hand leads (Franz *et al.*, 2002). Therefore, the effect of the leading hand might be dependent on the task selection and experimental setup. Taken together, differences in temporal and spatial parameters between the dominant and non-dominant hands decrease during in-phase movements and support the notion that this movement mode represents a basic movement coordination mode with a synergistic control of the hands.

In order to assess synchronization between hands during both bilateral movement modes, we studied the inter-limb phase difference across time series and thereby derived a quantitative index for inter-limb synchronization (Rosenblum *et al.*, 2001). This index quantifies the coupling between the performances of both hands. Our data demonstrate a higher inter-limb synchronization during in-phase movements as compared to anti-phase movements, meaning that the phase relationship in in-phase movements was more stable across time. In order to better understand differences in synchronicity between movement conditions, we also analyzed the speed change relationships between hands. During in-phase movements, acceleration of bilateral arms strongly tended to follow an in-phase relationship, while during anti-phase movements, no systematic relationship between hands was found. Taken together, these results provide evidence that during in-phase movements, bilateral movements are highly synchronized and both arms exhibit convergent speed change profiles. This, in turn, suggests that there is strong bilateral coupling during in-phase movements.

Since the cyclic movements in our paradigm were externally paced by an auditory metronome, we additionally asked whether auditory-motor synchronization might have influenced the differential results of both bilateral movement patterns, as suggested previously (Repp, 2005; Spencer and Ivry, 2007). However, no differences were found for cycle period variability between hands and conditions. Therefore in our paradigm, the variability of auditory-motor synchronization might not affect the outcome of our main kinematic variables that target to differentiate in-phase movements from anti-phase movements.

Our measurements that capture inter-limb acceleration relationship are particularly informative for pointing to different control processes of one or the other bilateral movement mode: the convergent inter-limb acceleration relationship during in-phase movements can be related to the co-activation of the homologous muscle groups (Stedman *et al.*, 1998; Stinear *et al.*, 2001; Shih *et al.*, 2019), which is a result of not only the transcallosal but also the descending fiber structures (Tanji *et al.*, 1988; Cisek *et al.*, 2003; Verstynen *et al.*, 2005; Chiou *et al.*, 2013). It is known that a small proportion of the corticospinal fibers do not cross at the pyramidal decussation, but project to ipsilateral spinal motoneurons (Carson, 2005; Ruddy and Carson, 2013). Since the descending commands from the motor cortex are sent through both crossed and uncrossed corticospinal fibers, the outputs of crossed and uncrossed descending corticospinal projections to the same limb are congruent (synchronous activation of homologous muscle groups in both pathways) and facilitate the desired movement; therefore, a clear pattern that the two hands consistently accelerate at the same time was observed during an in-phase movements. On the other hand, during anti-phase movements, both crossed and uncrossed pathways to the same limb might result in motor output incongruency/ interference (synchronous activation of non-homologous muscles in both pathways). This, in turn, might require more movement speed adjustments that finally leads to a random inter-limb acceleration pattern. The corticospinal structures, therefore, might provide the basis for facilitation or interference between limbs (Jankowska *et al.*, 2006).

## 3.5. Conclusion

From our results in healthy subjects, we confirmed that the circle drawing task engaging both shoulder and elbow joints is capable of capturing the differences between the two fundamental coordination patterns. During in-phase movements, a common neural generator controls movements in both limbs, which results in high inter-limb synchronous movements and an in-phase acceleration profiles between hands. Contrastingly, anti-phase movements are controlled by both hemispheres more independently, which lead to less inter-limb synchronicity. This paradigm thus can be further applied to clinical populations to investigate how neurological diseases affect different coordination patterns.

# Chapter 4. Study II: The effect of aging on bilateral coordination

## 4.1. Introduction

Aging is accompanied by decline in bilateral coordination (Maes *et al.*, 2017). This decline not only undermines independent living, but also predicts future mobility impairment (James *et al.*, 2017). Therefore, a better understanding of age-dependent decline in bilateral coordination is needed to establish early awareness and intervention strategies.

As reviewed in Chapter 1.3.1, previous behavioral studies have shown that aging affects the two basic bilateral movement patterns differently. During in-phase movements, comparable performance was found between young and older adults during in-phase movements (Greene and Williams, 1996; Swinnen, 1998; Serrien *et al.*, 2000; Lee *et al.*, 2002; Serrien *et al.*, 2003; Sparrow *et al.*, 2005). In contrast, during anti-phase movements, older adults exhibited decreased inter-limb phase accuracy and increased variability compared to young adults. The reason that in-phase and anti-phase movements are differently affected in aging could be due to the distinct control processing behind them. Results from neuroimaging studies suggest that in-phase movements are replied on a more left-dominated control (i.e. more activation over the dominant hemisphere compared to the non-dominant hemisphere), while anti-phase movements require control from both hemispheres (similar amounts of activation over the dominant and non-dominant hemisphere) (Jäncke *et al.*, 1998; Serrien *et al.*, 2003; Chen *et al.*, 2005; Maki *et al.*, 2008). Also, previous studies have demonstrated the

Please note that this study has been published as Shih, P.-C., Steele, C.J., Nikulin, V. et al. Alpha and beta neural oscillations differentially reflect age-related differences in bilateral coordination. Neurobiol Aging . 2021 Aug;104:82-91. doi: 10.1016/j.neurobiolaging.2021.03.016.

influence of individual interhemispheric effective connectivity on bilateral coordination (Liuzzi *et al.*, 2011). For example, using dynamic causal modeling, an EEG study has found that older adults expressed larger bidirectional inhibitory connectivity between the two motor cortices during bilateral spatially uncoupled movements, compared to the young adults (Loehrer *et al.*, 2016). However, no individual correlations were found, and this could be because a broader oscillatory frequency range (1-48Hz) were examined, which may potentially diminished the effects in specific frequency bands.

As reviewed in Chapter 1.3.3, a prominent pattern of neuro-oscillatory responses to motor tasks is the modulation of alpha (8-12Hz) and beta (15-25Hz) oscillations (Crone *et al.*, 1998). The task-related power change (TRPow) in alpha usually displays a more non-somatotopical pattern (Crone *et al.*, 1998; Nierula *et al.*, 2013), and has been associated with general task demand (Manganotti *et al.*, 1998; Fink *et al.*, 2005). In contrast, TRPow in beta is more discrete in timing and topography, and is tightly associated with the peripheral muscular activities (Crone *et al.*, 1998; van Wijk *et al.*, 2012). Since neural oscillations in the alpha and beta bands have different physiological meanings, examining the characteristics of both frequency band could help to advance our understanding on the neural mechanism of bilateral coordination and how they are affected by aging.

In this experiment, we combined kinematic measures and EEG to investigate oscillatory processes underlying age-related decline in bilateral coordination. On the behavioral level, we focused on intra-limb and inter-limb synchronization behavior during bilateral movements. We expected to replicate previous findings (Greene and Williams, 1996; Lee *et al.*, 2002; Sparrow *et al.*, 2005), where inter-limb coordination during anti-phase was found to be worse than in-phase movements, and with a more pronounced decline in the older adults. On the neural level, we used EEG to identify the neural mechanisms responsible for the decline of motor performance in aging via the analysis of TRPow in alpha and beta frequency bands. In addition, we examined the information flux between both hemispheres within the two frequency bands using phase slope index (PSI). We hypothesized that age-related coordination decline would be reflected in task-related alpha and beta power changes, and the inter-hemispheric connectivity between the two motor cortices would predict inter-limb synchronization.

## 4.2. Materials and methods

### 4.2.1. Participants

Twenty-three young (group Y; age: 26.3±2.95, 12 women) and twenty-three older adults (group O; age: 69.5±4.96, 12 women) healthy volunteers participated in this study. All participants were right-handed according to the Edinburgh Inventory of Handedness (Y: 89.78±14.78; O: 94.88±11.57, score out of 100) (Oldfield, 1971). The exclusion criteria were: (1) known neurological diseases, (2) visual or hearing defects, (3) professional musical instrument training. Older adults were examined additionally with the Mini-Mental State Examination (MMSE) to exclude the effects of cognitive decline (O: 29.78±0.74, score out of 30). None of the older participants have a score lower than 24 points. All participants were naïve to the experimental purpose. The experiment was approved by the ethics committee of the University of Leipzig, and all participants gave written informed consent to participate in the study according to the Declaration of Helsinki.

### 4.2.2. Experimental procedures

#### *4.2.2.1. Bilateral coordination task*

The experiment was conducted using the KINARM system, as described in Chapter 3.2.2. Figure 4.1A depicts the experimental setup of this experiment. Participants wore an EEG cap, sat on the KINARM chair with arm and neck supports. Both hands held the cylinder grips, and their heads faced the screen, which displayed the paradigm.

To quantify bilateral coordination ability, we used the same circle drawing task, as described in Chapter 3.2.3. Eight conditions, which were classified into four movement patterns, were included in the task (please see Chapter 3.2.3, Figure 3.2): left unilateral movements, right unilateral movements, bilateral anti-phase movements and bilateral in-phase movements. Each trial consisted of a 5-s pre-stimulus phase and 15-s movement phase. A 0.85 Hz-auditory metronome was triggered at the beginning of each movement phase, which also sent out a trial-start marker to the EEG system. During the experiment, participants were instructed to firstly check the upcoming movement condition shown on the screen and then put the corresponding active hand(s) on the starting point(s). The movement phase started 5 seconds after the hands were on the starting points, and participants then had to draw continuous circles in synchrony with the metronome. Importantly, participants were also instructed to focus their eyes on the central fixation cross during the task to reduce head movement and visual attentional bias, since focal attention improves limb movement accuracy (Swinnen *et al.*, 1996). Eye movements were monitored throughout the experiment from the electrooculography (EOG), and participants were reminded after a trial if they moved their eyes to the side for more than twice during the movement phase. Trials with eye movements were documented but not discarded from further analysis (please see

Appendix 2.1). Participants were reminded after a trial if they moved their eyes to the side. Each condition was performed once in a randomized order during each block, and there were ten blocks in each experiment. To reduce muscle fatigue, a 2-min break was introduced between blocks 5 and 6. Before the experiment started, all participants practiced every movement condition once in the order of condition 1-8 (Figure 3.2) as the familiarization session. Therefore, we did not observe a learning effect across the 10 blocks in the experiment (as shown in

Appendix 2.2).

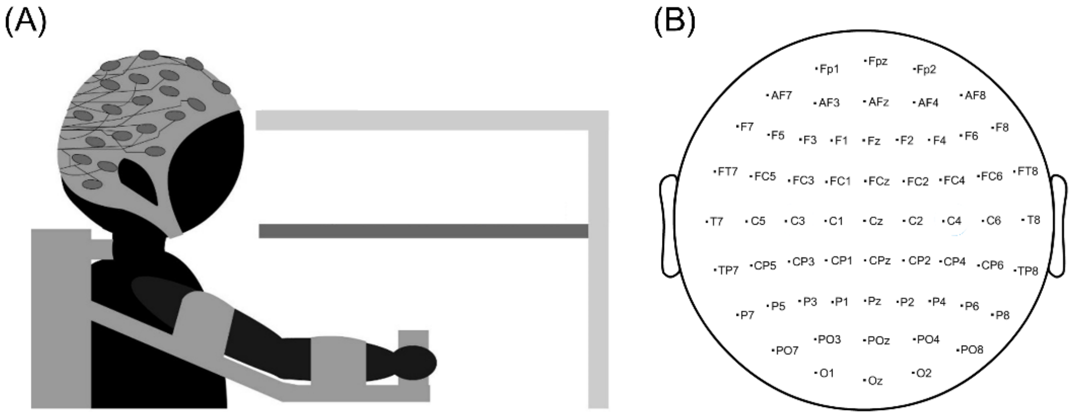


**Figure 4.1. Experimental device for the kinematic-EEG experiment.**
(A) Experimental device. Participants wore an EEG cap and sat inside the KINARM. Their neck and arms were supported by the KINARM, while the hands were holding the cylinder grips. (B) The electrodes configuration of the 59-channel EEG cap.

#### *4.2.2.2. Electroencephalogram (EEG) recording*

During the circle drawing task, EEG was recorded from 59 scalp electrodes mounted in a standard cap (Easycap, Germany) in accordance to the 10-20 system (Figure 4.1B). Two electrodes for EOG were attached on the upper side of the right eye and the lateral side of the left eye to record the vertical and horizontal eye movements. All electrodes were online referenced to the reference electrode on the left mastoid and grounded to the sternum. Data were sampled using the BrainAmp amplifier (Brain Products, Germany) at 1000 Hz with a band-pass analogue filter (0.01 Hz-250Hz). Electrode impedances were kept below 10 kΩ for all participants.

### 4.2.3. Kinematic data processing

Data recorded from KINARM and EEG were both imported into Matlab R2017b (The MathWorks, USA) for further processing. To compare the different bilateral movement conditions, we only considered conditions 5 and 6 (i.e., anti-phase; AP) and conditions 7 and 8 (i.e., in-phase; IP) in the final analysis, which were pooled under each category for analysis.

For kinematic analysis, we used trajectory variability and inter-limb phase synchronization index, which were found to be most efficient in discriminating bilateral anti-phase and in-phase movements in Study 1, to assess intra-limb and inter-limb performance respectively. Both indices were computed once for each trial, and the trial-by-trial results were used for statistical analyses.

#### *4.2.3.1. Intra-limb measure: trajectory variability (TV)*

As presented in Chapter 3.2.4.1, this index was computed as the coefficient of variation of all radii values within each trial. A lower TV represents a more consistent trajectory during the movement, and vice versa.

#### *4.2.3.2. Inter-limb measure: inter-limb synchronization (LimbSync)*

As presented in Chapter 3.2.4.2, this index was based on the classic phase synchronization index (Rosenblum *et al.*, 2001). Please see Eq. 3.1 in page 36 for the equation of the inter-limb synchronization index. This index ranges from 0 to 1. A value close to zero indicates no phase synchronization, while 1 corresponds to perfect phase synchronization.

### 4.2.4. EEG data processing

EEG data recorded from the 59-channels cap was preprocessed using EEGLAB (version 13.6.5b) (Brunner *et al.*, 2013). First, sampling rate was reduced to 250 Hz, and the EEG signal was bandpass-filtered (0.5-45 Hz) using a Hamming-windowed Finite Impulse Response (FIR) filter with a filter order of m = 1500. Channel locations were then imported to the data, and slow drifts were corrected by subtracting the preparation phase as the baseline. Afterwards, manual trial rejection was performed based on visual inspection and experimental notes (e.g. some participants coughed during the movement execution phase; rejection rate: Y = 0.58±1.40, O = 1.30±2.19 trials/person). Noisy channels were excluded from the data (Y = 0.17±0.65, O = 1.13±1.09 channels/person), and then all electrodes were re-referenced to the average reference. Components containing artifacts such as eye movements were visually identified in an independent component analysis (ICA, using the *runica* algorithm) and were removed. Scalp Laplacian using the spline interpolation method (order of splines=4; degree of Legendre polynomial=40; lambda parameter=$10^{-5}$) was performed to minimize volume-conducted potentials and maximize the accuracy of connectivity estimates (Perrin *et al.*, 1989; Cohen, 2014).

After preprocessing, data were band-pass filtered between 8 and 13 Hz (alpha) and 15-25Hz (beta) frequency range using 4th order Butterworth filter. Within each abovementioned frequency band, we performed power analysis (task-related power change) for all electrodes, and then effective connectivity analysis (phase slope index) between C3 and C4 electrodes to address our hypothesis.

#### *4.2.4.1. Task-related power change (TRPow)*

Task-related power change (TRPow), we firstly confirmed that there were no differences in both alpha and beta power amplitude in the preparation phase of anti-phase and in-phase conditions (please see Appendix 2.3 for this statistic). TRPow was calculated as the ratio of the averaged spectral power during the movement period ($Pow_{move}$) compared to the averaged spectral power during the preparation phase ($Pow_{pre}$) expressed as percentage:

$$\text{TRPow} = \left|(Pow_{move} - Pow_{pre})/Pow_{pre})\right| * 100\% \qquad \text{Eq. 4.1}$$

where the movement period contained 15 seconds of the signal from the movement phase, and the pre-movement period contained the last 3 seconds of the signal from the preparation phase. This is to avoid filtering and edge artifacts (Handy, 2005) in our further analyses, and to make sure participants had settled tier movements during the preparation phase. To identify the topographic distribution of each frequency band, the TRPow at each electrode was plotted for each frequency band with spline interpolation using the *topoplot* function of the EEGLAB.

#### *4.2.4.2. Phase slope index (PSI)*

PSI is highly robust against volume conduction, and it allows inference about causal interactions between pairs of neuronal signals. The method has been shown to outperform Granger causality in the detection of directionality in the analysis of data consisting of mixtures of dependent and independent sources (Nolte *et al.*, 2010). The PSI computation was based on the method described in the original paper (Nolte *et al.*, 2008). First, the raw phase slope index between channel *i* and *j* is defined as:

$$\tilde{\Psi}_{\mathrm{ij}} = \widetilde{\mathrm{Imag}}\Big(\sum_{f \epsilon F} C^{*}_{ij}(f) C_{ij}(\mathrm{f} + \delta f)\Big) \qquad \text{Eq. 4.2}$$

where $C_{ij}(f)$ is the complex coherency, $\delta f$ is the frequency resolution, and $F$ is the set of frequencies over which the slope is summed. Second, it is convenient to normalize $\tilde{\Psi}$ by an estimate of its standard deviation:

$$\psi = \tilde{\psi}/std(\tilde{\psi}) \qquad \text{Eq. 4.3}$$

with the standard deviation of $\tilde{\psi}$ being estimated using the jackknife method. This value provides a significance estimate. A positive $\psi$ indicates a stronger possibility for the existence of a net directionality from channel i to j, and vice versa. A PSI value close to zero indicates an evenly balanced lag relationship between channels.

### 4.2.5. Statistical analysis

#### *4.2.5.1. Behavioral measurements*

Single-trial kinematic data were exported from Matlab and imported to Rstudio (version 3.0.2). To examine whether young and older adults groups showed differences in motor performance during unilateral movements, we used a linear mixed model (LMM) approach with the *lme4* (version1.1-18.1) package. Two fixed factors - *Group* and *Hand*, as well as a random intercept for each participant were included in the model. For the bilateral movements, we used the same model structure as for the unilateral movements, but one more within-subject factor – *Condition* (anti-phase or in-phase), was added to the model.

For both unilateral and bilateral movements, the pairwise comparison between the fixed factors were performed using the *emmeans* (version 1.4.1) package with Tukey correction for multiple comparisons. P<0.05 was considered as statistically significant.

#### *4.2.5.2. EEG measurements*

EEG data analyses were performed in Matlab using customized scripts adapted from Cohen (Cohen, 2014) and Nolte and colleagues (Nolte *et al.*, 2008). For the TRPow topography, we used cluster-based statistics (Maris and Oostenveld, 2007). This allowed us to test the main effects of *Group* and *Condition*, as well as the *Group* x *Condition* interaction while accounting for multiple comparisons across the EEG sensors. Following t-tests between each group and condition, neighboring electrodes whose p-values were below 0.05 were formed into clusters. After clustering, we used the Monte Carlo method based on 1,000 permutations to generate a null distribution of the original data. Clusters whose p-values fell below 0.01 (two-tailed) were considered a significant cluster and reported in the results. For the PSI, a 2 x 2 (*Group* x *Condition*) ANOVA F test was used. $P < 0.05$ was considered statistically significant.

#### *4.2.5.3. Associations of behavior and EEG*

To examine the relationship between inter-limb synchronization (LimbSync) and inter-hemisphere directional connectivity (PSI), we built a quadratic mixed effects regression model with the following expression:

$$\mathrm{LimbSync} \sim (\mathrm{PSI} + \mathrm{PSI}^2) * \mathrm{Group} * \mathrm{Condition} + (1|\mathrm{Subject}) \qquad \text{Eq. 4.4}$$

The PSI is a zero-centered index, where a value closer to zero indicates weaker evidence for the existence of interhemispheric directional connectivity, and vice versa. Therefore, we hypothesized a nonlinear relationship between PSI and LimbSync, and thus quadratic terms of PSI were included in the model. The following two steps were performed:

Linear versus quadratic model comparison: before interpreting the result from the quadratic regression, we tested whether the inclusion of the quadratic term substantially improved out-of-sample deviance. This was done by comparing the quadratic model with a reduced model which only included the linear term. We used Bayesian

Informative Criterion (BIC), and only if $BIC_{linear} - BIC_{quadratic} > 10$, which indicates strong evidence (Raftery, 1995), we accepted the quadratic model and interpreted the result from this regression model.

Effect of PSI on LimbSync: we used the *lmer* function to perform the regression, and examined the interaction between the fixed effects (*Group*, *Condition*) to investigate whether the relationship between LimbSync and PSI depended on group and condition. Pairwise comparison was also performed using *sjstats* (version 0.17.1) package in each condition and group to resolve the interaction.

## 4.3. Results

### 4.3.1. Behavioral measurements

Behavioral data at the group level are summarized in Table 4.1.

**Table 4.1. Averaged behavioral results in each group. Data is presented as mean±SD of each group and condition**

| Variables | Older adults | | Young adults | |
|---|---|---|---|---|
| Trajectory variability | Left hand | Right hand | Left hand | Right hand |
| Unilateral | 0.161±0.025 | 0.138±0.021 | 0.158±0.028 | 0.143±0.029 |
| Bilateral AP | 0.186±0.053 | 0.145±0.021 | 0.163±0.025 | 0.154±0.025 |
| Bilateral IP | 0.166±0.023 | 0.137±0.020 | 0.146±0.026 | 0.144±0.028 |
| Synchronization index | Inter-limb measures | | Inter-limb measures | |
| Bilateral AP | 0.910±0.087 | | 0.960±0.012 | |
| Bilateral IP | 0.982±0.006 | | 0.986±0.006 | |

Data is presented as mean±SD. AP: anti-phase movements. IP: in-phase movements

#### *4.3.1.1. Trajectory variability*

We first examined trajectory variability during unilateral movements. The 2x2 LMM revealed a significant interaction between *Group* and *Hand* ($F_{(1,1831)} = 11.973$, p <

0.001), a main effect in *Hand* ($F_{(1,1831)} = 226.486$, $p < 0.001$), but not in *Group* ($F_{(1,45)} = 0.0098$, $p = 0.921$). Pairwise comparisons showed significant differences between non-dominant and dominant hands in both the young (slope = 0.0148, $t_{(48)} = 8.109$, $p < 0.001$) and the older adults (slope = 0.0236, $t_{(48)} = 13.230$, $p < 0.001$). This indicates that for both groups, the non-dominant hand generally showed worse performance compared to the dominant hand. This effect is also stronger in the older adults group, as revealed by the steeper slope.

To investigate bilateral movements, we examined the trajectory variability during in-phase and anti-phase conditions in both groups (Figure 4.2A). The LMM showed no significant three-way interaction ($F_{(1,3707)} = 1.738$, $p = 0.187$), but significant two-way interactions between Group and *Hand* ($F_{(1,3707)} = 93.154$, $p < 0.001$), *Group* and *Condition* ($F_{(1,3707)} = 15.713$, $p < 0.001$), and *Hand* and *Condition* ($F_{(1,3707)} = 19.012$, $p < 0.001$). There were also main effects in *Hand* ($F_{(1,3707)} = 466.223$, $p < 0.001$) and *Condition* ($F_{(1,3707)} = 76.94$, $p < 0.001$), but not *Group* ($F_{(1,45)} = 0.938$, $p = 0.338$). Pairwise comparisons showed significant group differences in trajectory variability of the non-dominant hand ($t = 3.212$, $p = 0.029$) during anti-phase condition, but not in the dominant hand ($t_{(inf)} = -0.134$, $p = 1.000$). Also, there was no significant group differences in the IP performance in both the dominant ($t_{(inf)} = 1.601$, $p = 0.750$) and non-dominant hand ($t_{(inf)} = -0.941$, $p = 0.982$). This indicates that regardless of the group, participants generally increased trajectory variability during the anti-phase condition, and this effect is more pronounced in the non-dominant hand of the older adults.

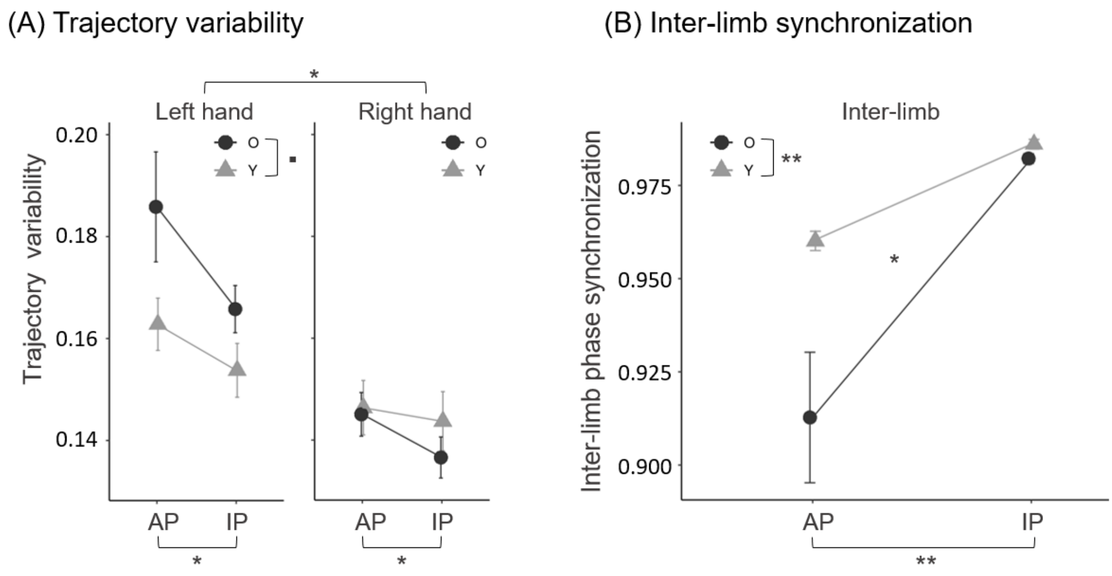


**Figure 4.2. Behavioral performance of young and older adults during bilateral in-phase and anti-phase movements.**

(A) Trajectory variability during the anti-phase and in-phase movements for older and younger adults. (B) Inter-limb synchronization index. Symbol±line=mean±SE. *p < 0.05. **p < 0.001. AP = anti=phase. IP = in-phase. O = older adults. Y = young adults.

#### *4.3.1.2. Inter-limb synchronization*

Figure 4.2B displays the performance of inter-limb synchronization, as measured by the phase synchronization index. The two-way LMM revealed a significant interaction between *Group* and *Condition* (F(1,1831)=53.193, p<0.001), and there were main effects in both *Group* (F(1,45)=9.690, p=0.003) and *Condition* (F(1,1831)=239.384, p<0.001). Pairwise comparisons showed significant differences between groups in the anti-phase (t(1,58)=-5.427, p<0.001), but not in-phase condition (t(1,58)=0.419, p-0.975). Also, differences between the performance during anti-phase and in-phase conditions were larger in the older adults (slope=-0.074, t(1,1831)=-16.272, p<0.001) than in the younger group (slope=-0.026, t(1,1831)=-5.723, p<0.001). These results indicate that aging affected mainly anti-phase movements, while in-phase movements were not significantly affected by aging. The inter-limb phase synchronization index was used later as a response variable for investigating subsequent brain-behavior correlations.

### 4.3.2. EEG measurements

#### *4.3.2.1. Task-related power change (TRPow)*

Before computing the TRPow, we firstly confirmed that there were no differences in both alpha and beta power amplitude in the baseline (preparation phase) between the two movement modes (please see Appendix 2.3). TRPow, as depicted by the percentage of difference between task and pre-stimulus period, showed no main effect between conditions and between groups in the two frequency bands (Figure 4.3). Significant *Group**Condition* interactions were observed in both frequency bands. To resolve the interaction, we performed the paired t-test for each group to confirm the direction of the interaction. Pairwise comparison showed that in the alpha band (Figure 4.3B, left), a cluster over the C4 and CP4 electrodes shows that young adults had decreased alpha power during in-phase compared to anti-phae (AP: -30.00±2.561, IP: -27.46±2.557%, $t_{(44)} = -3.00$, $p < 0.001$), while the older adults have a similar response to in-phase and anti-phase conditions (AP: -31.81±2.664, IP: -33.14±2.215%, $t_{(44)} = 1.55$, $p = 0.134$). In the beta band (Figure 4.3B, right), a cluster over Cz, CPz, C1, and CP2 electrodes revealed decreased power in the older adults during anti-phase compared to in-phase (AP: -31.779±3.471, IP: -29.680±2.959%, $t_{(44)} = -2.486$, $p = 0.02$), while no effect was found in the young adults (AP: -26.479±2.255, IP: -26.899±2.321%, $t_{(44)} = 0.576$, $p = 0.57$). These results indicate differential brain responses to anti-phase and in-phase in the older adults. First, the older adults showed comparable decreases in alpha power during anti-phase and in-phase movement, which is contrary to the performance of the young adults – the decrease of alpha power is smaller during in-phase condition. Second, the result from the beta band shows equivalent decreases in beta power in the young adults, while the older adults showed stronger decreases during anti-phase movements.

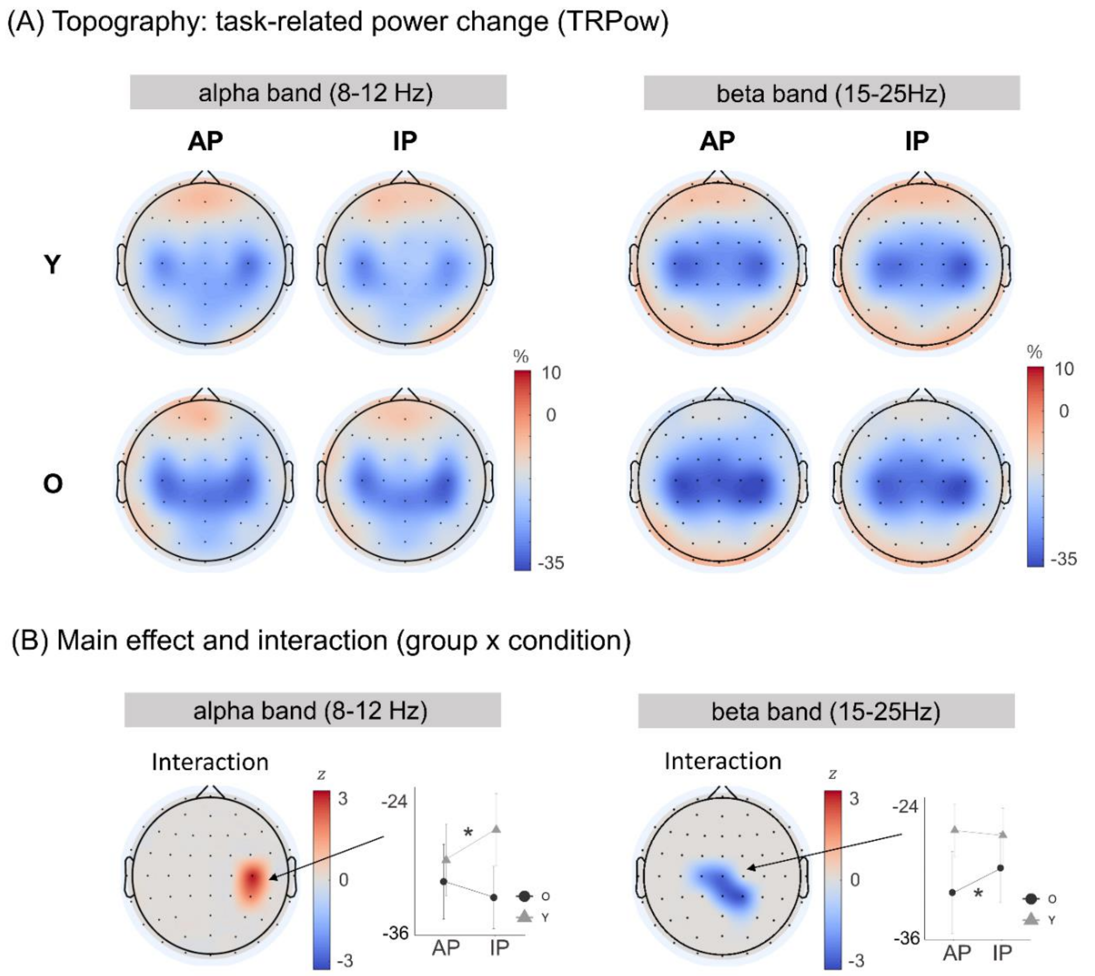


**Figure 4.3. Task-related power change in alpha and beta band.**
(A) Topographical brain maps of TRPow in each condition and group. (B) Significant clusters revealed by statistical analysis. AP = anti=phase. IP = in=phase. O = older adults. Y = young adults.

#### *4.3.2.2. Phase Slope Index (PSI)*

In the alpha band (older adults: AP = 0.186±0.866, IP = 0.235±1.372; young: AP = -0.255±0.751, IP = 0.750±0.913), no interaction ($F_{(1,45)}$ = 0.737, p = 0.395), no main effects in *Group* ($F_{(1,45)}$ = 1.488, p = 0.229) nor *Condition* ($F_{(1,45)}$ = 1.269, p = 0.266) were found. In the beta band (older adults: AP = 0.482±1.101, IP = 0.223±1.296; young: AP = 0.288±1.546, IP = 0.294±1.756), no interaction ($F_{(1,44)} = 0.292$, $p = 0.591$), no main effects in *Group* ($F_{(1,45)} = 0.031$, $p = 0.862$) nor *Condition* ($F_{(1,45)} = 0.265$, $p = 0.610$) were found as well. These results indicate that there is no evidence for differences in PSI in either frequency band between groups and conditions.

### 4.3.3. Associations of behavior and EEG

We performed a regression analysis to examine the association between PSI and LimbSync.

#### *4.3.3.1. Linear versus quadratic model comparison*

In the alpha band, out-of-sample deviance was substantially higher in the quadratic model compared to the linear one ($BIC_{quadratic}$: -267.54, $BIC_{linear}$: -284.38), suggesting that data did not have good fit to the quadratic model. Therefore, the result from the alpha band (Figure 4.4A) was not interpreted. In the beta band, there is strong evidence in favor of the quadratic model ($BIC_{quadratic}$: -321.90, $BIC_{linear}$: -301.68), and a significant quadratic coefficient (Figure 4.4B, regression coefficient = 9.64, $t = 2.812$, $p = 0.006$) was observed. We then further examined the result from this regression analysis.

#### *4.3.3.2. Effect of PSI on LimbSync*

The result of the regression analysis in beta frequency (Figure 4.4B) showed an interaction between *Group* and *Condition* ($t = -4.677$, $p < 0.001$) on response of PSI on

LimbSync. Pairwise comparison revealed significant quadratic effect in anti-phase compared to in-phase condition in both young adult (t = -2.207, p = 0.033) and older adults (t = -2.271, p = 0.028), and a more pronounced effect in the older adults compared to the younger group in anti-phase (t = -3.275, p = 0.0015), but not in-phase (t = -0.330, p = 0.7425) condition. This result indicates an inverted-U relationship between the inter-limb synchronization index and the interhemispheric directional connectivity, and this relationship is more pronounced in the older adults.

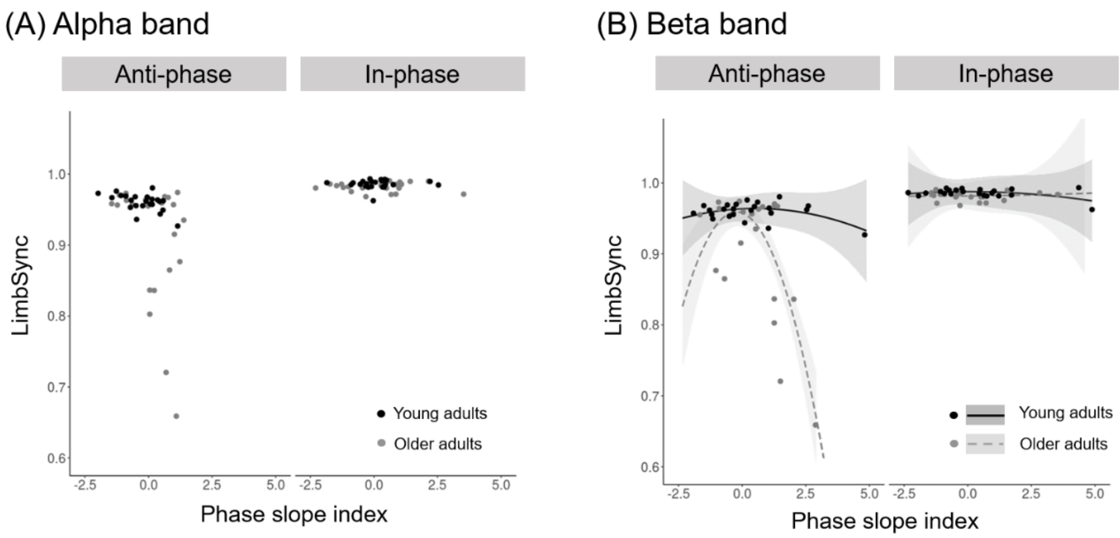


**Figure 4.4. Behavior-brain association during bilateral movements.**

(A) No significant relationship was detected between LimbSync and PSI for the alpha band. (B) Significant quadratic relationship between LimbSync and PSI in the beta band was revealed by a quadratic regression analysis. Notably, in both young and older group, this relationship can be observed in anti-phase condition, but not in in-phase condition. This relationship is more pronounced in the older group. LimbSync = inter-limb phase synchronization.

Notably, during visual inspection, we suspected that the result in Figure 4.4B could be driven by few outliers in the older adults. Therefore, we further examined the stability of our results of the regression model by removing the outliers (please see

Appendix 2.4). We found that after the removal of the two outliers, the quadratic model remained survived, furthermore, the data fitting was even improved. Therefore, the outliers were kept to preserve the variability in performance in the older adults.

## 4.4. Discussion

We investigated behavioral and neural correlates of bilateral coordination decline in aging. First, we corroborated previous behavioral findings by showing age-dependent behavioral changes, specifically during anti-phase movements. Older adults showed lower inter-limb synchronization during anti-phase movements than young, while no significant group differences were found for in-phase movements. Second, we found that alpha and beta oscillations were differently modulated during bilateral coordination in aging: alpha TRPow exhibited similar amount of decreases between the anti-phase and in-phase conditions in older adults, while beta TRPow was reduced more in the anti-phase compared to the in-phase condition. Moreover, we found an inverted-U relationship between interhemispheric directional connectivity in the beta band and inter-limb synchronization during the anti-phase movements in both groups. These results indicate that age-related motor decline in bilateral coordination is differentially reflected in alpha and beta neural oscillation.

### 4.4.1. Aging is associated with performance decreases during anti-, but not in-phase movements

Behaviorally, we first observed from the unilateral condition that the dominant hand performed better than the non-dominant hand, and the differences between hands was slightly larger in the older adults group. This could be an indication that the non-dominant side is more sensitive to age-related decline (Dolcos *et al.*, 2002). When examining the bilateral condition, we found that aging affected mainly anti-phase, but not in-phase movements. First, the circular trajectories of the older adults group showed higher variability than young adults in the non-dominant hand. Based on the performance in the unilateral condition, this could be due to the difficulty of this task for the non-dominant hand. Second, the decrease in bilateral synchronization was observed during anti-phase movements in both groups. Moreover, this decline was especially pronounced in the older adults compared to young adults. This is in line with previous studies (Greene and Williams, 1996; Swinnen, 1998; Lee *et al.*, 2002; Sparrow *et al.*, 2005), which showed that anti-phase movements were more affected by age compared to in-phase movements.

### 4.4.2. Alpha oscillations reflect compensatory activation in the older adults during in-phase movements

We further examined the neuro-oscillatory responses during bilateral movements. In younger adults, task-related power changes in the alpha band over the right (non-dominant) hemisphere were smaller in in-phase compared to anti-phase condition. This modulation is consistent with previous neuroimaging findings (Jäncke *et al.*, 1998; Viviani *et al.*, 1998; Aramaki *et al.*, 2006), that a reduced BOLD signal change over the non-dominant motor cortex was found in in-phase compared to anti-phase movements. Another fMRI study showed a stronger effective connectivity from the left M1 to the right M1 during in-phase finger movements (Maki *et al.*, 2008). These findings highlight a left-dominated motor-cortical control during the in-phase movements in young adults. Our EEG result in the younger group is consistent with this literature. Interestingly, the same observation was not present in our older adults group. Instead, we found that the older adults group showed a similar amount of TRPow over the non-dominant hemisphere when comparing the movement modes. This consequently resulted in a Group-by-Condition interaction in the alpha TRPow, for which the alpha TRPow significantly decreased during anti-phase compared to in-phase movements in the young adults, while no significant differences were detected in the older adults.

Alpha power decrease is related to improving neuronal recruitment of the task-relevant regions (Jensen and Mazaheri, 2010). Therefore, the relative decrease in alpha band power over the non-dominant motor cortex of the older adults might represent a compensatory neuronal activity to maintain behavioral performance during in-phase movements. To confirm this assumption, we performed an additional correlation analysis between TRPow and behavioral performance (please see

Appendix 2.5), and found a trend of correlation. That is, the more the participant showed relatively decreased task-related power change over the non-dominant hemisphere, the better the performance in coordinating the two upper limbs. Since the non-dominant hemisphere is relatively inactive during the in-phase movements in young adults, it becomes an advantage for the older adults to engage this brain region to achieve a good in-phase performance. The compensatory activation in the older adults brain has been shown in other motor tasks (Ward and Frackowiak, 2003; Heuninckx *et al.*, 2008), where the older adults showed higher and more diffusive cortical activity during motor execution. This hyper-activation was also associated with task performance, indicating a compensatory mechanism for the aged brain (Ward and Frackowiak, 2003). Therefore, our results imply that even if the older adults showed no noticeable behavioral deterioration during in-phase movements, it would not necessarily mean that aging does not affect this movement mode. In contrast, the current results suggest that the aging brain develops a compensatory mechanism for the degeneration that is associated with alpha oscillatory activity during the in-phase movements. This result is, however, different from an fMRI study (Goble *et al.*, 2010), which found a compensatory activation in the left hemisphere during anti-phase, but not in-phase movements. However, task difficulty (movement frequency) in their bimanual task was adjusted to the ability of each participant, suggesting that the pattern of compensatory responses in the brain can be depends on the task design, and the two results may not be comparable.

### 4.4.3. Beta oscillations reflect additional sensorimotor processing in the older adults during anti-phase movements

Different from alpha power changes, we observed a Group-by-Condition interaction in the beta power change as in our inter-limb synchronization index. That is, the task-related power change in the beta band over the midline parietal region was stronger in anti-phase compared to in-phase in the older adults group, while the younger group showed no differences between conditions. The amplitude of the TRPow change over the motor and sensorimotor area scales with the motor output variables, such as force output (Boonstra *et al.*, 2007), movement dynamic (Xifra-Porxas *et al.*, 2019) and performance error (Tan *et al.*, 2014). For example, performing dynamic handgrips resulted in more beta desynchronization compared to sustained handgrips in the older adults, suggesting larger beta modulation is needed to reach the muscle contraction threshold in a dynamic movement (van Wijk *et al.*, 2012; Xifra-Porxas *et al.*, 2019). Also, when performing a hand control task, more pronounced decreases in beta power were found in trials with larger errors compared to smaller errors (Tan *et al.*, 2014; Chung *et al.*, 2017). For precise motor control, online somatosensory feedback has to be provided and integrated to the motor system (Perruchoud *et al.*, 2014), and the parietal area seems to be involved in both online motor correction and integrating external feedback (Archambault *et al.*, 2015; Chung *et al.*, 2017). In our experiment, in-phase movements represent a stable condition with better performance, while anti-phase movements represent a more dynamic condition with increasing movement variability. Therefore, the decrease in beta power during the anti-phase movements can be seen as a reflection of additional sensorimotor processing as a consequence of increased online monitoring and corrections during the AP movements.

Interestingly, we did not find any differences in beta TRPow change over the motor cortices between anti-phase and in-phase, even though the relationship between the two motor cortices is crucial for performing successful bilateral coordination movements. Since there is evidence that older adults individuals generate a more bilateral activation pattern during unilateral movements (Ward *et al.*, 2008; Boudrias *et al.*, 2012), failure to suppress the unwanted involvement of the other hemisphere would interfere with bilateral AP movements. Therefore, we examined the relationship between inter-limb synchronization and interhemispheric effective connectivity using PSI to approach this question. We observed that when an individual PSI value is more close to zero, the better the coordination performance, and this relationship is especially pronounced in the older adults. This implies that during anti-phase movements, if one hemisphere is more dominated than the other one, the inter-limb coordination performance would decrease. This is an interesting finding, since another connectivity study (Loehrer *et al.*, 2016) showed that older adults, compared to the young adults, increased bidirectional inhibitory connectivity between the motor cortices during bilateral uncoupled movements. Although no behavior-brain correlation was found in that study, which examined a mixed frequency band (Loehrer *et al.*, 2016), we observed behavioral-brain relationships in our current experiments when examining specifically the beta frequency oscillation. Taken together, stronger interhemispheric inhibition between the bilateral M1s may be the reason why behavioral performance during bilateral anti-phase movements is hampered for individuals with worse coordination performance. Our results not only showed the benefit of inspecting frequency bands with different physiological meanings separately (Meirovitch *et al.*, 2015; Stolk *et al.*, 2019), but also provide potential targets for non-invasive brain stimulation treatments at specific frequency band.

## 4.5. Conclusion

In sum, age-induced bilateral coordination decline is more pronounced in the anti-phase compared to in-phase movements and differential responses of task-related alpha and beta neural oscillations are underlying this phenomenon. Our findings provide new insights into neural mechanisms of age-related decline in bilateral coordination and may foster the development of effective age-specific rehabilitation strategies, such as using non-invasive brain stimulation to target relevant brain areas and specific frequencies.

# Chapter 5. Study III: Effects of lesioned side on bilateral coordination after strokes

## 5.1. Introduction

Although various effective rehabilitation programs have been developed over the past decades, more than half of chronic stroke patients still experience difficulty in achieving daily activities with the upper limbs (Pollock *et al.*, 2014). As reviewed in Chapter 1.4, upper limb impairments can be characterized by decreased moving ability of the contralesional arm and difficulty in coordinating the limbs, both of which often result in reduced quality of life (Broeks *et al.*, 1999; Franceschini *et al.*, 2010). Rehabilitation after stroke has predominantly focused on treating the contralesional arm; however, the coordination between arms that our daily activities are highly dependent on has received less attention (Kantak *et al.*, 2017). Therefore, a better understanding of the characteristics and mechanisms of bilateral coordination impairments after stroke is needed to establish awareness for clinicians and develop effective rehabilitation strategies.

After stroke, patients generally exhibit greater movement variability (Garry *et al.*, 2005) and unsteady force control (Lai *et al.*, 2019) during bilateral movements, regardless of the coordination patterns. Moreover, consistent with findings in healthy adults, stroke patients experienced more difficulty performing anti-phase than in-phase movements (Lewis and Byblow, 2004; Kim and Kang, 2020). However, considering that the two hemispheres are differentially involved in in- and anti-phase movements in healthy adults (as previous shown in Study 2), we would expect that bilateral coordination impairments after left and right hemispheric stroke should show distinct characteristics. In line with this idea, one study found that patients with left hemispheric stroke (LHS) could benefit more from a bilateral training regime than patients with right hemispheric stroke (RHS), hinting that the response to bilateral training is dependent on the lesioned side (McCombe Waller and Whitall, 2005). Another study (Lewis and Perreault, 2007a) found that LHS patients performed in-phase movements more synchronously than those with RHS, as assessed by inter-limb phase synchronization. These studies showed the influence of lesion side in affecting bilateral movements. However, since only inter-limb performance was observed, it is still unclear how intra-limb performance of each limb during bilateral movements is affected after left and right hemispheric strokes. Given that bilateral coordination is controlled by a complex system comprising both intra-limb and inter-limb components (Tseng *et al.*, 2009), a successful bilateral movement requires both coordination between hands and accurate individual hand performance. Therefore, examining between-hand synchronization and individual trajectory control is equally essential for characterizing the impairments.

To determine the causal influence of lesion side on impairments in bilateral movements, we examined inter-limb (inter-limb synchronization) and intra-limb (movement trajectory variability of the contralesional and ipsilesional hands) performance in chronic stroke patients with a left or right hemispheric lesions. This allowed us to characterize the separate impairments of bilateral coordination in left and right hemispheric stroke. We hypothesized that right hemispheric stroke patients would exhibit more impairments in bilateral anti-phase coordination compared to left hemispheric stroke patients, and vice versa in bilateral in-phase movements. We furthermore assessed the individual contributions of the two hands to inter-limb synchronization. This enabled us to use hand performance to infer how stroke affects the differential roles of the two hemispheres in bilateral coordination. Our aim was to provide clinically-relevant insights for the development of more accurately targeted neurorehabilitation while furthering our understanding of the neural control of bilateral coordination.

## 5.2. Materials and methods

### 5.2.1. Participants

The ethics committee of the University of Leipzig approved the study protocol, and participants were given informed consent before their eligibility assessment. Patients were recruited from two sources: the Day Clinic for Cognitive Neurology in University Hospital Leipzig, and advertisements on the local newspaper Leipziger-Volkszeitung. A total of 60 stroke patients were invited and screened between September 2016 and September 2018 for eligibility. The inclusion criteria were: (1) first onset of stroke resulting in hemiparesis; (2) chronic phase after stroke (>6 months from stroke incident); (3) No elbow rigidity (Modified Ashworth Scale, MAS<3). (4) Able to understand and follow the instruction correctly inside the KINARM. The exclusion criteria were: (1) any other kind of systematic and neurological diseases; (2) cognitive deficits (Mini-Mental Scale Examination; MMSE<24); (3) contraindication for MRI; (4) unilateral neglect or other visual impairment.

Eighteen (nine left and nine right hemispheric stroke) patients fit the criteria and were included in the experiment. All patients were right-handers before the stroke. After the patients' recruitment, 18 age- and sex-matched healthy-control adults were identified from the database of the Max Planck Institute for Human Cognitive and Brain Sciences, and participated in the study. The inclusion criteria for the control group were:

(1) right-handedness; (2) no known diseases. Participants were classified into four subgroups: left hemispheric stroke (LHS), right hemispheric stroke (RHS), the control group for the left hemispheric stroke (LHC), and the control group for the right hemispheric stroke (RHC). The demographical data of each patients is shown in Appendix 3.1. The demographical data on the group level is shown in Table 5.1, and the lesion overlap maps of the stroke patients are given in Figure 5.1.

**Table 5.1. Demographic data of the participants in stroke and control groups**

| **Variables/Groups** | **Stroke patients** | | **Healthy controls** | |
|---|---|---|---|---|
| **Group label** | LHS (n=9) | RHS (n=9) | LHC (n=9) | RHC (n=9) |
| Lesioned hemisphere | Left | Right | NA | NA |
| Age | 54.7 ± 14.4 | 60.8 ± 13.3 | 54.7 ± 14.4 | 60.8 ± 13.3 |
| Sex (M/F) | 5/4 | 3/6 | 5/4 | 3/6 |
| Year since stroke | 9.01 ± 5.13 | 5.36 ± 3.17 | NA | NA |
| Stroke type (I/H) | 8/1 | 8/1 | NA | NA |
| Lesion (% of brain volume) | 5.5 ± 7.5 | 9.51 ± 12.4 | NA | NA |
| MMSE | 28.9 ± 1.9 | 29.9 ± 0.3 | 30.0 ± 0.0 | 29.9 ± 0.3 |
| FM-UE | 48.9 ± 11.8 | 41.8 ± 13.9 | NA | NA |
| NIHSS | 2.56 ± 2.30 | 2.77 ± 1.40 | NA | NA |
| MAS (0/1/1+/2) | 1/5/2/1 | 0/6/1/2 | NA | NA |
| Proprioception error (cm) | 5.08 ±4.10 | 5.59 ± 2.35 | NA | NA |

Data is presented as mean±SD of each group. LHS = left hemispheric stroke; RHS = right hemispheric stroke; LHC = left hemispheric control; RHC = right hemispheric control. I = ischemic stroke; H = hemorrhagic stroke. MMSE = Mini-Mental Scale Examination. FM-UE = Fugl-Meyer-Upper Limb Score. NIHSS = National Institutes of Health Stroke Scale. MAS = Modified Ashworth Scale. NA = not applicable.

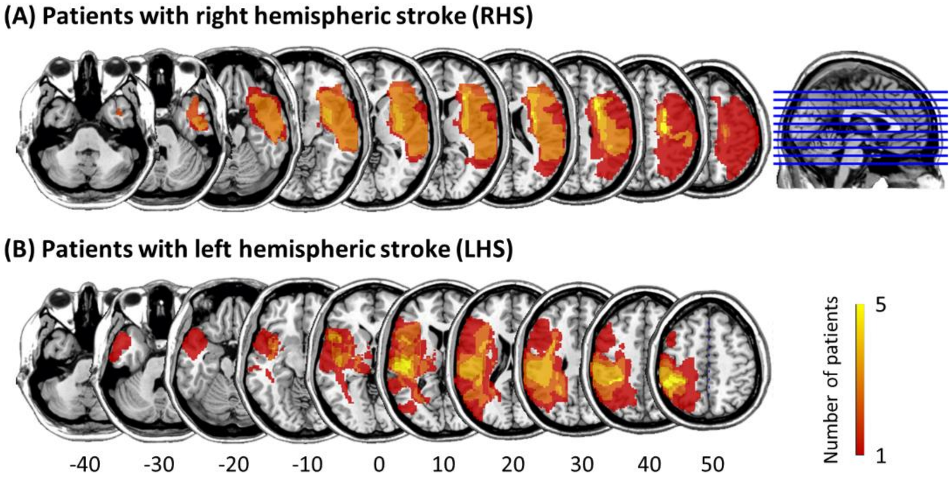


**Figure 5.1. Lesion overlap images.**

(A) Patients with right hemispheric stroke (RHS) and (B) patients with left hemispheric stroke (LHS). The number of overlapping lesions is illustrated by the colorbar.

### 5.2.2. Clinical assessment for stroke patients

For the stroke patients, clinical tests for quantifying motor, sensory, and cognitive impairments were documented during the screening day by a neurologist (BS) and a physical therapist (PCS). Besides the tests used as an inclusion/exclusion criteria (i.e., MMSE, MAS, FM-UE), NIHSS (National Institutes of Health Stroke Scale) and proprioceptive ability of the elbow flexors were also documented. Proprioceptive ability was quantified by the Arm Position Matching test (please see Appendix 3.2) using the KINARM upper limb robotic exoskeleton system (BKIN Technologies, Canada).

### 5.2.3. Device and task

Participants performed the circle drawing task at the KINARM system, as in the previous two studies. Please see the detailed description for the device in Chapter 3.2.2, and the instruction of the task in Chapter 3.2.3.

There were a total of eight movement conditions in the experiment, which were classified into four movement patterns: unilateral movement of the ipsilesional hand, unilateral movement of the contralesional hand, bilateral anti-phase movements, and bilateral in-phase movements. Different from the previous studies, the frequency of the metronome was adjusted to the specific capabilities of the groups in this experiment. A separate pilot experiment was conducted to determine the maximum movement speed for each group that did not include any phase transitions. A phase transition here refers to the observed phenomenon that an anti-phase movements could unintentionally change to an in-phase movement as movement frequency is increased (Haken *et al.*, 1985; Franz *et al.*, 1991). Based on the pilot results, 0.85 Hz was used for healthy controls and 0.75 Hz for stroke patients.

Again, each condition was performed once in a randomized order during each block, and there were ten blocks in each experiment. To reduce the presence of fatigue during the experiment, a 2-min break was set between blocks 5 and 6. Before the experiment started, all participants practiced every movement condition once to become familiarized with the task and testing conditions.

### 5.2.4. Kinematic data recording and processing

During the experiment, participants' hand movements were continuously recorded at a sampling rate of 1000 Hz by the KINARM using Dexterit-E software. Experimental conditions under each category were considered as the same condition in the statistical analysis; for example, condition 5 and 6 are both marked as bilateral anti-phase condition, and conditions 7 and 8 are both marked as bilateral in-phase condition.

To examine task performance during bilateral anti-phase and in-phase conditions (condition 5-8), we computed two indices for each trial to represent intra-limb and inter-limb performance, respectively: (1) trajectory variability and (2) inter-limb synchronization (Shih *et al.*, 2019). For unilateral conditions (condition 1 to 4), only trajectory variability was computed.

#### *5.2.4.1. Trajectory variability (intra-limb performance)*

Trajectory variability quantifies how variable the trajectory of movement is within each trial and for each hand separately. We performed the same procedure as described in Chapter 4.2.3.1. Data was converted from Cartesian ($x$, $y$) to polar coordinates, and the radius ($r$, *distance from the center of the circle*) was extracted from each sample. Trajectory variability was then calculated as the coefficient of variation of all radii values within each trial, for each hand. A lower value represents a more consistent movement trajectory during the task.

#### *5.2.4.2. Inter-limb synchronization (Inter-limb performance)*

Inter-limb synchronization represents how well the two hands were synchronized with each other during bilateral movements. We performed the same procedure as in Chapter 4.2.3.2. This index ranges from 0 to 1, where values 1 corresponds to perfect phase synchronization.

### 5.2.5. Lesion assessment

Structural imaging data were acquired on a 3T MR scanner (Skyra; Siemens, Erlangen, Germany). The scanning sequences included MP2RAGE (FoV = 256 × 256 mm, TR = 5000 ms, TE = 2.9 ms, TI1 = 700ms, TI2 = 2500ms, flip angle 1 = 4°, flip angle 2 = 5°, slice thickness = 1 mm) and FLAIR (FoV = 220 × 220 mm, TR = 10000 ms, TE = 93 ms, TI = 2500 ms, flip angle =180°, slice thickness = 4 mm). Lesions were semi-automatically mapped from the structural images using Clusterize Toolbox (de Haan *et al.*, 2015), and the lesion volume of each participant was calculated within the same toolbox. All lesion maps were normalized to the MNI space to compute the lesion conjunction map (Figure 5.1).

### 5.2.6. Statistical analysis

#### *5.2.6.1. Demographic data*

Continuous demographic data including age, time since stroke, lesion volume, FM-UE, MMSE, NIHSS, and proprioception error between the two stroke groups (RHS and LHS) were compared using two sample t-tests. Ordinal data, i.e. MAS, was compared using ordinal logistic regression.

#### *5.2.6.2. Task performance*

Kinematic data were analyzed with linear mixed-effects models (LMM), which allows better control for random sources of variance without the loss of statistical power resulting from data aggregation across subjects (Baayen *et al.*, 2008). As stroke samples often have high intersubject variability, LMM offers a better approach than univariate

ANOVA or ordinary least squares regression for modeling heteroscedasticity and minimizing the outlier effects from individual subjects.

All mixed-effects analyses were conducted with Rstudio (version 3.0.2) using the *lme4* (version 1.1-18.1) package (Bates *et al.*, 2015) for modeling and the *emmeans* (version 1.4.1) package for pairwise comparison between factors.

<u>Trajectory variability (intra-limb)</u>

To examine whether left- and right-hemispheric stroke affected motor performance differently, we considered *Group* (Stroke or Control) and *Lesioned Hemisphere* (LH or RH) as between-subject fixed effects, with a random intercept for each subject for the unilateral conditions. For the bilateral conditions, we additionally included *Coordinative Pattern* (anti-phase or in-phase) as another between subject fixed effect. For both the unilateral and bilateral movements, pairwise comparisons were performed between *Group* in each *Lesioned Hemisphere* with Bonferroni correction for multiple comparisons. Both contralesional and ipsilesional hand performance were analyzed separately. Importantly, the hands of the control groups were individually matched to the stroke groups. For example, the contralesional hand performance of LHS was compared to the right-hand of the LHC group, while the contralesional hand performance of the RHS was compared to the left-hand of RHC group.

Inter-limb synchronization (inter-limb)

Akin to analyzing trajectory variability in the bilateral conditions, the model for inter-limb synchronization consisted of three fixed factors *Group* (stroke or control), *Lesioned Hemisphere* (left or right), and *Coordinative Pattern* (anti-phase or in-phase), with random intercepts for each participant. Pairwise comparisons were performed between *Group* in each *Lesioned Hemisphere,* Bonferroni corrected for multiple comparisons.

Effects of intra-limb hand performance on inter-limb synchronization

To characterize how the contribution of both hands change in bilateral coordination after left and right hemispheric stroke, we examined the effect of intra-limb (trajectory variability) and inter-limb (inter-limb synchronization) parameters. This analysis aimed at using the behavioral performance to provide evidence on hemispheric contribution during bilateral anti-phase and in-phase movements.

For both bilateral in-phase and anti-phase movements, we first performed regression analyses in the pooled healthy control participants to determine the normative contributions of dominant and non-dominant hands to different bilateral coordination patterns. For each bilateral coordination mode, we built a mixed regression model: *Inter-limb synchronization ~ Trajectory variability * Hand* (dominant or non-dominant hand) + (1|*Subject*) for anti-phase and in-phase conditions, respectively. After establishing the normative relationship, we then examined stroke patients and compared whether this prediction differs between the two stroke groups using the model: *Inter-limb synchronization ~ Trajectory variability * Hand* (contralesional or ipsilesional hand)**Lesioned hemisphere* (LHS or RHS) + (1|*Subject*). In the case of the presence of interaction effects, data was visualized using *interact_plot* function from *jtools* toolbox (version 2.0.3), and pairwise comparisons were performed between *Hand* in each *Lesioned Hemisphere* with Bonferroni correction for multiple comparisons.

## 5.3. Results

### 5.3.1. Demographic data

The levels of impairment in our stroke patients ranged from mild to moderate severity (Table 5.1 for the group summary and Appendix 3.1 for individual data). There were no statistically significant differences in age (t=-0.94, p=0.36), duration of time since stroke (t=-1.82, p=0.09), lesion volumes (t=-0.83, p=0.42), FM-UE (t=1.18, p=0.25), MMSE (t=-1.56, p=0.16), NIHSS (t=-0.27, p=0.80), proprioceptive ability (t=-0.08, p=0.94), and MAS (LR=0.39, p=0.53) between the two stroke groups.

### 5.3.2. Task performance

#### *5.3.2.1. Trajectory variability (intra-limb)*

Data of trajectory variability are summarized in Table 5.2.

**Table 5.2. Average trajectory variability in each group and condition.**

| **Variables** | **Left hemispheric lesion** | | **Right hemispheric lesion** | |
|---|---|---|---|---|
| **Groups** | LHS | LHC | RHS | RHC |
| **Contralesional hand** | Right hand | Right hand | Left hand | Left hand |
| Unilateral conditions | 0.19±0.42* | 0.12±0.03 | 0.19±0.04* | 0.15±0.03 |
| Bilateral anti-phase | 0.21±0.05 | 0.13±0.03 | 0.28±0.08* | 0.18±0.05 |
| Bilateral in-phase | 0.21±0.07* | 0.12±0.01 | 0.23±0.07 | 0.16±0.03 |
| **Ipsilesional hand** | Left hand | Left hand | Right hand | Right hand |
| Unilateral conditions | 0.16±0.03 | 0.13±0.03 | 0.14±0.03 | 0.12±0.02 |
| Bilateral anti-phase | 0.19±0.03 | 0.17±0.06 | 0.18±0.04 | 0.14±0.02 |

| | | | | |
|---|---|---|---|---|
| Bilateral in-phase | 0.17±0.03 | 0.15±0.03 | 0.16±0.04 | 0.13±0.02 |

Trajectory variability is quantified as the averaged coefficient of variation of the circle radii (cm) from each trial. Data is presented as mean±SD of each group and condition. LHS = left hemispheric stroke; RHS = right hemispheric stroke; LHC = left hemispheric control; RHC = right hemispheric control. Please note that, due to handedness, performance of the right hand is generally better than the left hand in the control groups. *p<0.05 compared to the corresponding control group (after corrected for multiple comparisons).

<u>Unilateral movements</u>

Figure 5.2A depicts a representative participant from each group during unilateral circle drawing. Figure 5.2B shows the trajectory variability of the contralesional hand during unilateral condition on the group level. Control participants exhibited lower trajectory variability of the contralesional hand during unilateral movements compared to stroke patients, as revealed by the significant main effect of Group ($F = 23.40$, $p < 0.001$), but not Lesioned Hemisphere ($F = 1.95$, $p = 0.17$) nor Group* Lesioned Hemisphere interaction ($F = 0.96$, $p = 0.33$) in the 2x2 LMM. Figure 5.2C shows the trajectory variability of the ipsilesional hand during the unilateral condition. The statistical results were similar as in the contralesional performance, in that there was a significant main effect of *Group* ($F=8.11$, $p=0.007$), but not *Lesioned Hemisphere* ($F=3.05$, $p=0.09$) nor *Group* Lesioned Hemisphere* interaction ($F=0.13$, $p=0.72$). These results indicate that both stroke groups showed impairment in contralesional and ipsilesional hand movements compared to their respective control groups, and the unilateral performance of patients with left and right lesions were not statistically different from each other.

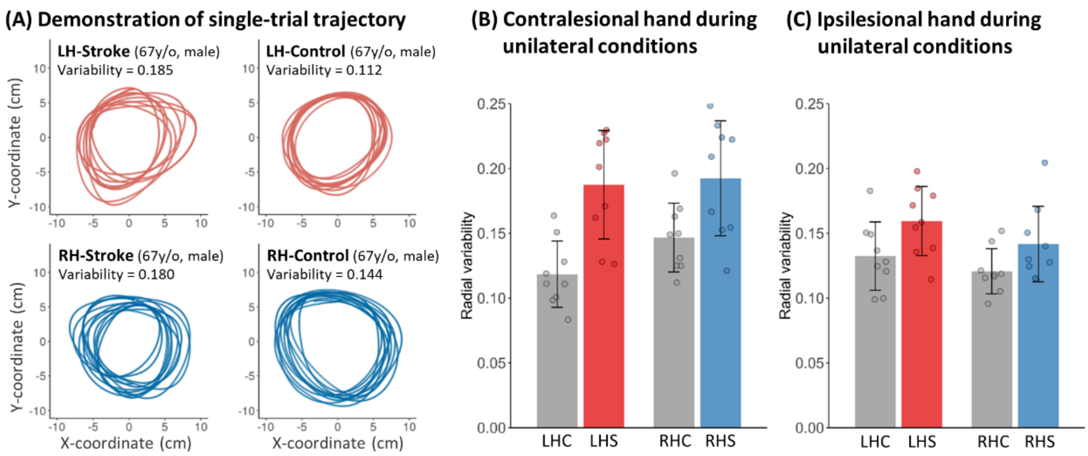


**Figure 5.2. Trajectory variability in the two stroke and two control groups.**
(A) An example trajectory plot of the contralesional arm from one representative participant of each group. (B) Trajectory variability of the contralesional hand during unilateral conditions on the group level. Both LHS and RHS patients showed higher trajectory variability compared to their control groups. (C) Trajectory variability of the ipsilesional hand during unilateral conditions. Stroke patients showed higher trajectory variability compared to their control groups, but no pairwise comparisons survived the correction of multiple comparisons. Translucent points: individual mean data. LHC = Left hemispheric control, LHS = left hemispheric stroke, RHC = right hemispheric control, RHS = right hemispheric stroke. *p<0.05.

<u>Bilateral movements</u>

Figure 5.3A depicts the trajectory variability of the contralesional hand during bilateral anti-phase and in-phase movements. Generally, regardless of stroke or not, participants showed higher trajectory variability during anti-phase compared to in-phase conditions. Also, stroke patients showed higher trajectory variability compared to controls during bilateral movements. However, specifically, LHS patients showed more impairments during in-phase movements while RHS patients showed more impairments during the anti-phase movements. This was revealed by a mixed 2x2x2 LMM, with a significant *Group* Lesioned Hemisphere*Condition* interaction ($F=16.71$, $p<0.001$), and main effects of *Group* ($F = 23.28$, $p < 0.001$), *Lesioned Hemisphere* ($F = 6.80$, $p = 0.01$) and *Condition* ($F = 72.00$, $p < 0.001$). Pairwise comparisons showed significant differences between LHC and LHS in the in-phase ($t = -3.49$, $p = 0.027$) but non-significant (though

borderline) differences in the anti-phase (t = -3.15, p = 0.060) condition. In contrast, RHS patients were significantly impaired in the anti-phase (t = -3.95, p = 0.008) but not the in-phase (t = -2.96, p = 0.09) condition, relative to RHC. Figure 5.3B shows the trajectory variability of the ipsilesional hand. The LMM revealed significant main effects of *Group* (F = 5.35 p = 0.027) and *Condition* (F = 84.07, p < 0.001), but not Lesioned Hemisphere (F = 0.105, p = 0.11). There was also no evidence for a three-way interaction (F = 1.96, p = 0.162). These results indicated that anti-phase movements had higher variability compared to in-phase movements regardless of group. Also, when examining the contralesional hand, bilateral anti-phase movements were found to be more affected in the RHS group, while bilateral in-phase movements were more affected in the LHS group compared to their control groups, respectively.

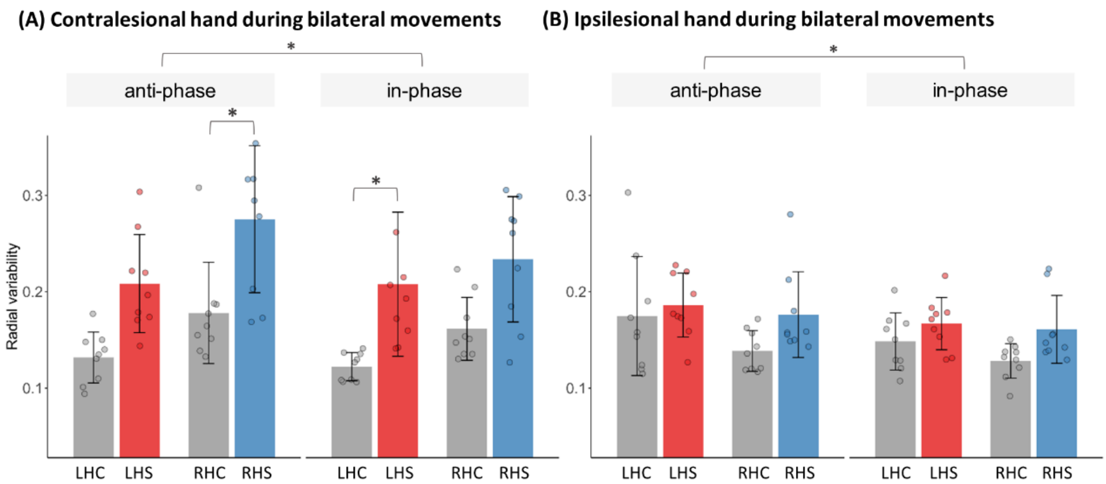


**Figure 5.3. Trajectory variability during bilateral movements.**

(A) Performance of the contralesional hand. Generally, patients showed higher trajectory variability compared to the control groups. Specifically, RHS patients displayed stronger impairment during anti-phase movements, while LHS patients had more impairments during in-phase movements. (B) Performance of the ipsilesional hand. Stroke patients showed higher trajectory variability compare to the control groups, but no significant interaction with the lesion side. No pairwise comparisons survived the statistical threshold after corrected for multiple comparisons. Translucent points: individual mean data. LHC = Left hemispheric control, LHS = left hemispheric stroke, RHC = right hemispheric control, RHS = right hemispheric stroke. *p<0.05.

#### *5.3.2.2. Inter-limb synchronization (inter-limb)*

Figure 5.4 shows the inter-limb synchronization index from each group during bilateral movements. Similar to the trajectory variability, stroke patients generally showed worse performance compared to controls. Moreover, the RHS group had additional impairments during anti-phase movements, as evidenced by a significant three-way interaction ($F = 54.47$, $p < 0.001$) between Group, Lesioned Hemisphere, and Condition. Main effects in *Group* ($F = 5.50$, $p = 0.025$) and *Condition* ($F = 390.23$, $p < 0.001$), but not *Lesioned Hemisphere* ($F = 1.26$, $p = 0.27$) were also observed. Pairwise comparisons showed no significant differences between LHC and LHS in both anti-phase ($t = -0.34$, $p = 1.000$) and in-phase ($t = 1.29$, $p = 0.895$) movements. In contrast for RHS patients, there was a significant difference in the anti-phase ($t = 3.88$, $p = 0.01$), but not in-phase ($t = 1.69$, $p = 0.69$) condition relative to RHC. These results show that regardless of group, both hands were more synchronized during the in-phase compared to anti-phase condition. Also, the stroke groups showed less inter-limb synchronization compared to controls. Most importantly, patients with right hemispheric stroke (RHS) specifically showed impairment in coordinating the two hands during anti-phase movements.

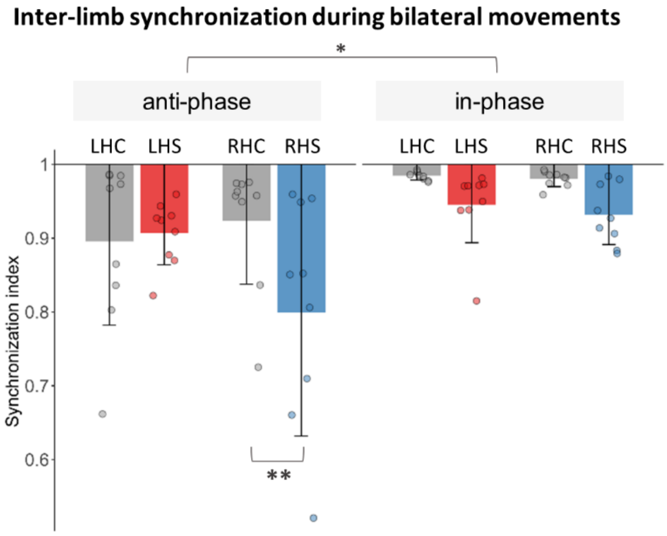


**Figure 5.4. Inter-limb synchronization performance during bilateral movements, quantified using the synchronization index.**

A *Group*Lesioned Hemisphere*Condition* interaction was found. Pairwise comparisons revealed that RHS patients displayed more impairments during anti-phase movements. Translucent points: individual mean data. LHC = Left hemispheric control, LHS = left hemispheric stroke, RHC = right hemispheric control, RHS = right hemispheric stroke. **p<0.01.

### *5.3.2.3. Effects of intra-limb hand performance on inter-limb synchronization*

To understand the contribution of the contralesional and ipsilesional arms on inter-limb synchronization performance, we fit LMM regressions with trajectory variability of the two hands as predictors (*Inter-limb synchronization* ~ *Trajectory variability* * *Hand* * *Lesioned hemisphere* + (1|*Subject*)).

<u>Anti-phase conditions</u>

In anti-phase condition, regression analyses revealed that the performance of the two hands showed similar strength in predicting inter-limb behavior for the healthy control participants as well as the two stroke groups. For healthy controls, the regression model revealed no significant effect of *Hand* (df = 344.62, F = 2.82, p = 0.09, $\beta_{dominant} = -0.553$,

$\beta_{\text{non-dominant}}$ = -0.413). For stroke patients, there were no main effects of *Hand* (df = 314.53, F = 1.96, p = 0.16) nor *Lesioned Hemisphere* (df = 319.16, F = 2.52, p = 0.11), and no *Hand***Lesioned Hemisphere* interaction (df = 314.53, F= 0.002, p = 0.96, $\beta_{\text{RHC, contralesional}}$ = -0.490, $\beta_{\text{RHC, ipsilesional}}$ = -0.274, $\beta_{\text{LHC, contralesional}}$ = -0.350, $\beta_{\text{LHC, ipsilesional}}$ = -0.249).

<u>In-phase conditions</u>

In in-phase condition, regression analyses revealed that in both healthy controls and RHS patients, the performance of right hand, compared to left hand, is a stronger predictor in predicting inter-limb behavior, whilst vice versa in LHS patients.

For healthy controls (Figure 5.5A), the regression model revealed a significant effect of *Hand* (df = 352.28, F = 13.76, p < 0.001) such that the dominant hand ($\beta_{\text{dominant}}$ = -0.386) was significantly better better at predicting inter-limb synchronization compared to the non-dominant hand ($\beta_{\text{non-dominant}}$ = -0.158).

For stroke patients (Figure 5.5B), there was an interaction between *Hand* and *Lesioned Hemisphere* (df = 342.13, F = 5.85, p = 0.016), a main effect of *Hand* (df = 342.13, F = 11.45, p<0.001), but no main effect of *Lesioned Hemisphere* (df = 348.95, F = 0.0001, p = 0.99). Pairwise comparisons revealed that in both stroke groups, contralesional hand performance was a significantly better predictor of the inter-limb synchronization, and that the interaction was driven by stronger prediction in LHS patients ($\beta_{\text{LHS, contralesional}}$ = -0.014, $\beta_{\text{LHS, ipsilesional}}$ = -0.574, t = -2.64, p = 0.009) than RHS ($\beta_{\text{RHS, contralesional}}$ = -0.258, $\beta_{\text{RHS, ipsilesional}}$ = -0.348, t = -2.24, p=0.03). Notably for both the healthy controls and the RHS groups, the right hand (the dominant/ipsilesional hand) was the strongest predictor of inter-limb synchronization. In contrast, for the LHS group, the left hand (ipsilesional) predicted inter-limb performance more strongly.

Taken together, performance of both hands showed similar strength in predicting inter-limb synchronization performance during anti-phase movements in both stroke patients and controls. However, during in-phase movements right hand (dominant hand) performance predicted inter-limb synchronization behavior more strongly than the left hand (non-dominant) in healthy controls. This same effect was found in patients with right-hemispheric lesions, indicating that this mechanism is preserved. However, in stroke patients with left-hemispheric lesions, the prediction was reversed such that left hand (ipsilesional) performance was a stronger predictor of inter-limb synchronization during in-phase movements. These results indicate a reversed pattern in hand contribution in the LHS group.

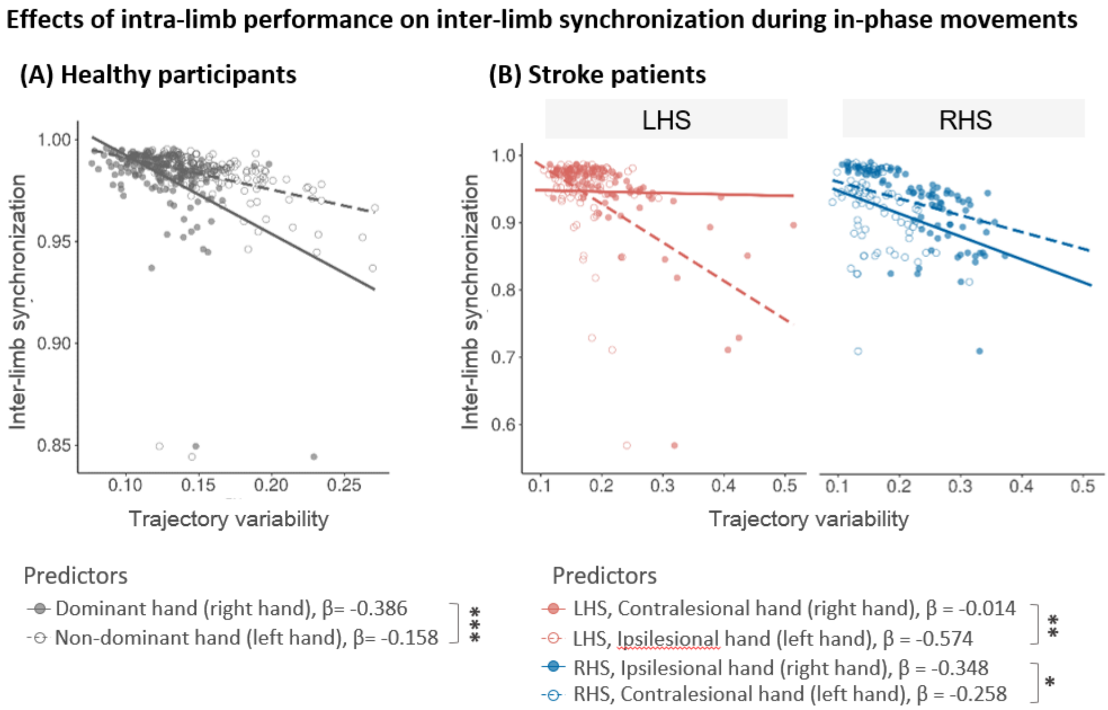


**Figure 5.5. Effects of intra-limb performance on inter-limb synchronization during in-phase movements.**

Each dot represents the performance of each trial in each participant. (A) In healthy controls, the dominant hand was more predictive of inter-limb performance compared to the non-dominant hand. (B) In stroke patients, the paretic hand was a stronger predictor of the change inter-limb performance compared to inter-limb synchronization, which was measured by the synchronization index. L = left hand. R = right hand.

## 5.4. Discussion

This experiment sought to determine the causal influence of stroke lesion side on impairments in bilateral movements. We examined stroke patients with left and right hemispheric lesions as they performed the bilateral circle drawing task, and observed lesioned hemisphere-dependent impairments. That is, patients with right hemispheric lesions showed more impairment in controlling bilateral anti-phase movements, while patients with left lesions were more affected in bilateral in-phase movements. These results suggest that the divergent roles of the both hemispheres during anti-phase and in-phase movements lead to differentially reduced bilateral coordination performance after left and right hemispheric stroke.

First, in the intra-limb assessment (trajectory variability), the RHS group showed pronounced deficits in anti-phase movements, while the LHS group showed slightly more impairment in in-phase movements. Second, in the inter-limb assessment (inter-limb synchronization), the RHS group notably displayed worse coordination ability during anti-phase compared to the LHS group, but did not show significant differences in the in-phase condition: both stroke groups showed only mild impairments in hand-coordination during in-phase movements. These results suggest differential impairments after left and right hemispheric stroke in bilateral coordination. However, could these impairments in bilateral movement be driven by the differential impairments in unilateral movements? As reviewed in Chapter 1.4.1, previous studies have shown that the side of the lesioned hemisphere can lead to distinct motor impairments during unilateral reaching in stroke patients (Sainburg and Duff, 2006; Schaefer *et al.*, 2009). LHS patients showed larger trajectory errors at the early phase of reaching, while RHS patients showed larger error at the final reaching position (Haaland *et al.*, 2004; Mani *et al.*, 2013). 3However, in the current experiment, we did not find differences in impairment levels between LHS and RHS patients when examining the trajectory variability during unilateral movements of both hands. This could be because the current experiment used a rhythmic movement task while previous findings were based on discrete reaching movements. Nonetheless, as there were no differences in impairment levels in unilateral movements between LHS and RHS groups, we can be more confident that the current observations from the bilateral anti-phase and in-phase conditions are specific to bilateral coordination.

### 5.4.1. Left hemisphere stroke leads to specific impairments in bilateral in-phase movements

Why are in-phase movements more affected in the LHS group? Early studies have suggested that the left (dominant) hemisphere plays a major role in organizing coupled bilateral movements, while the right (non-dominant) hemisphere is less so (Jäncke *et al.*, 1998; Serrien *et al.*, 2003). During bilateral in-phase movements the left hemisphere displays larger task-related BOLD signal changes compared to the right hemisphere (Aramaki *et al.*, 2006), and BOLD signal changes in the right hemisphere is causally related to the left one (Maki *et al.*, 2008). This left-dominated response is specific to bilateral in-phase movements, since the two hemispheres show similar task-related BOLD response during bilateral anti-phase movements (Maki *et al.*, 2008). Further supporting this interpretation, TMS pulses applied to the left hemisphere has been shown to interrupt the movements of both hands during bilateral in-phase movements, but not anti-phase movements (Chen *et al.*, 2005). Taken together, these studies provide evidence that bilateral in-phase movements are organized in the left hemisphere. Consistent with this, we found significant impairments in controlling the trajectory of the contralesional hand during in-phase movements in the LHS group. However, when looking at the inter-limb synchronization during in-phase movements, LHS and RHS patients showed similar levels of impairment. One possible reason is that the intra-limb measurement (trajectory variability) is a spatial measure, while the inter-limb measurement (inter-limb synchronization) is a temporal measure. It could be that the impairments are predominantly manifested in the spatial domain. Another explanation could be that while the intra-limb measurement only considered individual limb performance, the inter-limb measurement involved both limbs. Therefore, to resolve the discrepancy between inter- and intra-limb performances in LHS patients, we further examined how the two hands contributed to inter-limb coordination.

Through examining the effects of intra-limb performance on inter-limb performance, we first detected in the healthy controls that the right hand contributed more during the in-phase movements compared to the left hand (Figure 5.5A). This implies a predominant contribution of the dominant side to the bilateral in-phase movements in healthy participants, which is in line with the findings from the neuroimaging studies(Chen *et al.*, 2005; Aramaki *et al.*, 2006; Maki *et al.*, 2008).

In stroke patients (Figure 5.5B), we found that the relative contribution of the hands to the inter-limb coordination is dependent on the side of the lesioned hemisphere. The RHS group, who had no lesions over the left hemisphere, displayed a similar intra/inter-limb relationship as in the healthy participants: right hand (ipsilesional) performance better predicted the inter-limb synchronization. This supports the view that in-phase movements are driven by left (dominant) hemisphere centralized control. However, the LHS group, who had lesions over the left hemisphere, showed a divergent result. We found that the left hand (ipsilesional) performance was a stronger predictor of inter-limb synchronization compared to the right (contralesional) hand. This result is particularly important, as it provides evidence on the primary role of left hemisphere in controlling the in-phase movements.

There could be alternative explanations to interpret the reversed pattern in hand contribution in the LHS group during in-phase movements. For example, it could appear to be a result of switching the preferred hand during daily living from the left to the right one after a left hemispheric stroke. It has been shown that left hemispheric stroke patients generally reduce their usage of the right hand, and use their left hand twice as often as their right (Rinehart *et al.*, 2009). However, if the reversed hand contribution during in-phase movements was truly driven by a shift in hand preference, then we would have also observed the same effect during anti-phase movements, which was not the case. Instead, we interpret this reversal in hand contribution as a result of neural compensation to the damaged left hemisphere. Since the left hemisphere, which plays a leading role for in-phase movements, was impaired after stroke, the right hemisphere could have taken over the responsibility for guiding this movement. This compensatory shift could explain why an increased impairment in inter-limb synchronization was not observed in the LHS group during in-phase movements. However, further neuroimaging studies will need to be performed to confirm this theory.

### 5.4.2. Right hemisphere stroke leads to specific impairments in bilateral anti-phase movements

Contrary to in-phase movements, anti-phase movements require a more balanced relationship between the two hemispheres. Since the bilateral homologous muscles are not activated simultaneously, contralateral movement suppression is needed (Wu *et al.*, 2010). Consistent with this, successful anti-phase movement performance is characterized by bidirectional information flow between the hemispheres in healthy participants (Maki *et al.*, 2008). In the regression analysis, we demonstrated a similar result: for all participants, regardless of group, the two hands similarly predicted the inter-limb synchronization during anti-phase movements. This suggests an equal contribution of the two hands to inter-limb coordination behavior during anti-phase movements, regardless of the stroke side.

We further provide evidence that patients with RHS exhibit greater impairment during anti-phase movements than those with LHS – but what is the mechanism behind it? Previous studies have shown that functional interactions between the hemispheres are more imbalanced in sufferers of RHS than LHS. Greater interhemispheric inhibition (IHI) is directed from the dominant to non-dominant side compared to the other way around (Lewis and Perreault, 2007a) when the muscles are at rest. This means the suppression of contralesional hemisphere activation is more challenging in RHS compared to LHS (Zemke *et al.*, 2003), which results in a more imbalanced interhemispheric relationship. In addition, the right motor cortex has lower capacity to inhibit the left motor cortex than vice versa in healthy right-handers, and this effect becomes larger in RHS patients (Armatas *et al.*, 1994; Netz *et al.*, 1995). However, asymmetries in interhemispheric transfer are also less influential during voluntary muscle activation compared to when muscles are at rest (Lewis and Perreault, 2007a). Therefore, how the individual IHI changed during anti-phase movements in the RHS patients should be confirmed to provide further knowledge on how essential a balanced inter-hemisphere relationship is in maintaining an efficient anti-phase movement.

Greater impairment in RHS compared to LHS patients during bilateral anti-phase movement is in line with both hemispheric specialization theories on open-loop/close-loop and predictive/impedance movement control (Serrien *et al.*, 2006). Evidence from both theories argues that the right hemisphere is specialized for sensory-mediated motor control tasks (Haaland and Harrington, 1989; Sainburg, 2002; Bagesteiro and Sainburg, 2003). Compared to in-phase movements, anti-phase movements are usually performed with more error and variability (Wu *et al.*, 2010). This means that increased attentional and executive control, as well as sensory feedback such as error monitoring are needed during the anti-phase movement (Bangert *et al.*, 2010), suggesting that the role of right hemisphere is essential for movement patterns that require higher sensory demands. Besides the theories developed from upper limbs studies, experiments on lower limbs also showed relevant and interesting findings. For instance, RHS compared to LHS patients showed impaired responses to unanticipated perturbations during standing (Coelho *et al.*, 2019), and more asymmetrical gait pattern during walking (Chen *et al.*, 2014). These results lead to the view that the right hemisphere is more involved in generating reactive muscular responses in the lower limbs (Coelho *et al.*, 2019). It is possible that this implication is transferrable to the upper limbs: the impaired right hemisphere maybe disadvantaged in achieving more complex coordination patterns such as anti-phase movements.

## 5.5. Conclusion

Based on this experiment, we identified the hemispheric specificity of two basic bilateral coordination patterns, and proposed distinct neural mechanisms leading to differential impairments after left and right hemispheric stroke. These findings highlight the importance of developing differential strategies for bilateral coordination training in patients with left and right hemispheric lesions. In Chapter 6.2, the potential rehabilitation strategy based on this project is further discussed.

# Chapter 6. General discussion

In this chapter, I summarize how the results from the three studies together advance our understanding of the neural basis of bilateral coordination and its impairments. Also, I discuss the unique contributions and clinical implications of the current findings. Finally, I close with a discussion on remaining questions and directions for future research.

## 6.1. Summary of research

Our daily activities are highly dependent on effective coordination between the two upper limbs. However, decline in bilateral coordination has been observed in both healthy aging and neurological groups (Pollock *et al.*, 2014; Maes *et al.*, 2017), and have often resulted in decreased quality of life (Broeks *et al.*, 1999; Franceschini *et al.*, 2010). In this dissertation, we performed three studies using behavioral measures, neuroimaging techniques, and lesion models to approach this topic.

In Study 1 (Chapter 3), we examined the two basic bilateral coordination modes – in-phase and anti-phase movements involving shoulder and elbow joints – in thirty healthy young participants. Kinematic measures with high temporal and spatial precision were used to develop intra- and inter-limb parameters to differentiate movement characteristics during the two basic movement modes. Intra-limb measures, such as trajectory variability of each hand, captures the coordination performance within a limb. On the other hand, inter-limb measures, such as phase synchronization between hands, capture coordination performance between limbs. Compared to in-phase movements, we found that participants performed anti-phase movements with worse inter-limb coordination and intra-limb performance of the non-dominant hand. In contrast, the intra-limb performance of the dominant hand was not significantly affected by the two movement modes. We further examined the hand acceleration profile of both hands. Interestingly, during in-phase movements, participants' bilateral hands accelerated and decelerated in an in-phase manner. In contrast, the acceleration and deceleration of the two hands were in a random relationship during anti-phase movements. Taken together, Study 1 confirmed that the current experimental setup is able to differentiate the performance between bilateral in-phase and anti-phase movements engaging multiple joints. Therefore, we used the same paradigm combined with EEG measures to answer the following questions in Study 2: How does aging affect the two bilateral coordination patterns, and what are the underlying neural mechanisms?

In Study 2 (Chapter 4), we combined EEG and kinematic measurements to investigate the effect of aging on the two movement modes by comparing between young and older adults. On the behavioral level, we had the same finding as in Study 1, i.e., both intra-limb and inter-limb coordination were reduced during anti-phase movements compared to in-phase movements, and this reduction was stronger in the older adults. On the neural level, we examined the task-related power change and inter-M1 connectivity in the alpha and beta frequency band. We found larger alpha power decreases over the non-dominant cortical motor area in older adults during in-phase movements, and there was a trend that a larger alpha power decrease is associated with better inter-limb coordination in older adults. Moreover, by examining the inter-M1 connectivity, we found that the decrease in inter-limb coordination during anti-phase movements was predicted by stronger directional connectivity in the beta-band. This effect was observed in both young and older adults, but more pronounced in the older adults group. Our results therefore show that the effects of aging on the two bilateral coordination modes are differentially reflected on the neural level by changes in oscillatory power and interhemispheric directional connectivity. Our findings support the view that aging is more resistant to the decline in bilateral in-phase movements. Since the coordination behavior of bilateral in-phase and anti-phase movements is associated with neural activities in different hemispheres, we performed Study 3 to address the following research question: How does the side of the lesioned hemisphere impact on bilateral coordination?

In Study 3 (Chapter 5), we demonstrated the influence of stroke lesion side on impairments in bilateral movements by testing chronic hemiparetic stroke patients and age- and sex-matched controls. Through examining both intra-limb and inter-limb measures, we found that patients with right hemispheric stroke exhibited greater impairment during anti-phase movements (both intra- and inter-limb parameters) whilst patients with left hemispheric stroke showed greater impairment during in-phase movements (intra-limb parameters only). Though patients with left lesions did not show greater impairment in inter-limb coordination during in-phase movements compared to patients with right lesions, a regression analysis revealed that only patients with left lesions swapped hand dominance during the task. We interpreted this result as a compensatory mechanism whereby bilateral in-phase movements in the left-lesioned group switched from a left-dominated cortical control to a right-dominated cortical control. Findings from this experiment thus provide causal evidence for hemispheric specialization in bilateral movement coordination.

Taken together, this dissertation shows differential neural control processes behind bilateral in-phase and anti-phase movements, and demonstrates how these distinct mechanisms lead to bilateral coordination impairments observed in aging and stroke.

The present results could thus stimulate the development of improved therapeutic strategies to counteract the decline in bilateral coordination, such as differential treatment for patients with left and right hemispheric lesions, or the use of noninvasive brain stimulation at a target hemisphere.

## 6.2. Contributions and clinical implications

A key strength of the current dissertation is the combination of behavioral measures, neuroimaging, and the use of a lesion model to approach our research questions. These methods not only provide information from different perspectives, but also help to demonstrate a causal relationship between brain processing and behavioral performance.

### 6.2.1. Study 1 and Study 2

In the first two studies, we used the circle drawing task involving both shoulder and elbow joints, and found that participants showed worse intra-limb coordination of the non-dominant hand, and worse inter-limb performance during anti-phase than in-phase movements. These results indicated that anti-phase movement is a more challenging movement mode for the human upper extremity, especially for the non-dominant hand. Furthermore, we showed that older adults performed significantly worse than young adults during anti-phase, but not in-phase movements. This implies that behaviorally, aging is more insensitive to the decline of in-phase movements. However, our neural data indicated that even if the older adults did not show significant impairments during in-phase movements, it did not necessarily mean that older adults have no impairments in this movement mode. In fact, we observed that the activity in the right hemisphere might reflect a compensation to age-related coordination decline during in-phase movements. This is shown by the trend of correlation between alpha power decrease in the right hemisphere and behavioral performance during in-phase movements.

These findings have practical implications for movement training in aging. First, we demonstrated that even though the older adults did not show significant impairments in in-phase movements, it is likely to be a consequence of compensatory mechanism in the brain. Therefore, training in the “intact” movements may still be necessary for older adults. Second, our results highlight the role of alpha and beta oscillatory activity in age-related bilateral coordination decline. This provides insight into the development of effective age-specific rehabilitation strategies, such as non-invasive brain stimulation to target relevant brain areas and specific frequencies.

In recent years, non-invasive brain stimulation techniques such as transcranial alternating current stimulation (tACS), transcranial direct current stimulation (tDCS) and TMS have been frequently employed in interventional studies (Reis *et al.*, 2008; Elder and Taylor, 2014). tACS is capable of targeting specific frequency bands to modulate neural oscillations during various task settings (Gundlach *et al.*, 2017; Fresnoza *et al.*, 2018), while tDCS and TMS have been shown to modulate connectivity between hemispheres (Park *et al.*, 2013; Baxter *et al.*, 2017). Considering our findings, interventions such as facilitating brain activity over the non-dominant hemisphere during in-phase movements, or inhibiting excessive inter-hemispheric connectivity from one hemisphere to another during anti-phase movements, could be used as potential treatment strategies to counteract age-related decline in bilateral coordination. It seems very promising, to test this hypothesis in future interventional studies.

### 6.2.2. Study 3

Following the EEG results from Study 2, we expected that left and right hemispheres would be involved differently during bilateral in-phase and anti-phase movements. This hypothesis was confirmed in Study 3 using a lesion model, which may shed light on causal relationship between certain brain areas (in this case, in different hemipsheres) and behavior (Sperber, 2020). Specifically, we found that patients with left hemispheric lesions showed more impairment in bilateral in-phase movements, while patients with right lesions showed more impairments in bilateral anti-phase movements. These findings might have interesting implications for neurorehabilitation strategies.

Bilateral movement rehabilitation approaches, such as Bilateral Arm Training with Rhythmic Auditory Cueing (BATRAC) and Bilateral Arm training (BBT), have shown inconsistent results in longitudinal studies in stroke patients. Although systematic reviews have suggested that these bilateral training regimes may significantly contribute to stroke rehabilitation (Cauraugh *et al.*, 2010; Coupar *et al.*, 2010; van Delden *et al.*, 2012), this could be because these existing bilateral training methods usually employed a mixed protocol that includes both bilateral in-phase and anti-phase movements. Also, most work in this area has not differentiated training for left and right hemispheric stroke patients (Cauraugh *et al.*, 2010). While training to improve bilateral hand usage in daily activities is essential for both patients, our results suggest that specific bilateral interventions should be developed to target specific deficits following left or right hemispheric stroke. For example, after right hemispheric stroke, anti-phase movements are more strongly impaired; therefore, patients would benefit from training that focuses on the simultaneous control of non-homologous muscles. In contrast, the relatively preserved in-phase movements after right hemispheric stroke also means that this movement mode would be a good option for improving timing control, which is important for enhancing the efficiency of daily activities. However, in-phase movements are disturbed after a left hemispheric stroke. Therefore, besides using in-phase movements as a facilitation technique for the contralesional muscles (Summers *et al.*, 2007), this movement mode should be specifically trained to improve coordination between hands. Once patients could manage these two movement patterns in a clinical setting, additional practical programs could be developed to transfer a task from clinical practice to a real-world environment.

## 6.3. Outlook for future research

Although the findings from the current dissertation have advanced our understanding on the neural mechanism behind bilateral coordination and its impairment, some questions remain unsolved. Here, I discuss these questions and propose ways to which they could be addressed in future research.

To begin, we argued in Study 1 and Study 2 that the left hemisphere is predominantly controlling the in-phase movements, while both hemispheres are more equally engaged during anti-phase movements. We further showed in Study 2 and Study 3 that a balanced interhemispheric interaction is key for maintaining the inter-limb synchronization during anti-phase movements. This conclusion, however, was based solely on right-handed participants. Some studies have shown that left-handed and right-handed individuals showed different characteristics in motor control and motor learning (McGrath and Kantak, 2016; Mathew *et al.*, 2019). Left-handers show decreased asymmetrical abilities between the two hands (Mouloua *et al.*, 2018): they display slower dominant hand movement but faster non-dominant hand movement compared to right-handers in reaching tasks. Also, effective connectivity between bilateral hemispheres is reduced in left-handers (Pool *et al.*, 2014). Therefore, it seems possible that the findings in the current dissertation do not generalize to left-handed or mixed-handed individuals, since our results are heavily based on the functional asymmetry between the two hemispheres in right-handers. Given that the asymmetry between hemispheres is reduced in left-handers, the performance between bilateral anti-phase and in-phase movements may be similar. That is because the dominant hemisphere would no longer have the advantage over the non-dominant hemisphere during bilateral movements. Therefore, a possible extension of this dissertation would be to examine the same paradigm on left-handers and mixed-handers to investigate whether the observed behavioral and neural effects in aging and stroke are reduced compared to right-handers.

Relatedly, it would be interesting to investigate whether the differences between anti-phase and in-phase movements are inborn or acquired. From an evolutionary perspective, the advantage of in-phase movements should be a natural phenomenon, since it is based on human neuroanatomy (Sehm *et al.*, 2016). Also, it has been shown that children display mirror movements of the contralateral hand during object manipulation (Licari and Larkin, 2008), and this effect is more pronounced during an unfamiliar task (Mayston *et al.*, 1999). However, the experience and environment in our later age could also contribute to our preference towards specific movement modes. For example, musicians with piano training have been shown to develop weaker inter-hemispheric inhibition, which suggested a more efficient inter-hemispheric communication (Chieffo *et al.*, 2016). Therefore, to further understand whether differences between the two bilateral movement modes are acquired, future studies could investigate professional musicians, especially pianists, who experience training with a lot of different bilateral movements on a daily basis.

Besides the functional perspective, another potential topic to investigate is individual differences in brain structure. In Study 2, we found that effective connectivity between the two motor cortices could explain impairments in anti-phase movements in older adults. Further investigation on structural connectivity could help to explain whether our observation in effective connectivity was driven by structural characteristics or simply functional characteristics. Disentangling the two factors is important, as previous studies employing different measures of white matter structure provided conflicting results regarding their relationship to behavioral performance: For example, a diffusion-weighted imaging study showed that larger corpus callosum (CC) size was negatively associated with bilateral coordination performance in young adults, while it was positively associated with performance in older adults (Fling *et al.*, 2011b). On the other hand, no relationship between fractional anisotropy in the CC and performance in anti-phase movements was observed in another study (Serbruyns *et al.*, 2015). However, a recent paper (Zivari Adab *et al.*, 2020) has shown that fiber density of the CC could be partially mediating the bilateral coordination performance across ages. Therefore, future studies should investigate the relationship between different measures of brain structure and the functional role of interhemispheric interaction in modulating bilateral coordination.

Lastly, in this dissertation, we approached bilateral coordination from a neurophysiological perspective. However, other influences could potentially contribute to our results. For instance, it has been shown previously that the spontaneous preference for symmetrical movements might be purely perceptual, meaning that perceptual inputs and cues can crucially influence movement tendency (Mechsner *et* *al.*, 2001; Müller *et al.*, 2009). Also, it has been shown that the engagement of M1 during motor task is highly modulated by attention (Stefan *et al.*, 2004). With our experimental design, the contribution of perceptual bias has been minimized, since participants were only allowed to focus their eyes on the center fixation cross. Future studies can investigate how perception or attentional bias in aging and stroke affect bilateral movements, which may further provide potential insights on rehabilitation based on a cognitive perspective.

# Chapter 7. Summary of the dissertation

**<u>Zusammenfassung der Arbeit</u>**

Dissertation zur Erlangung des akademischen Grades Dr. rer. med.

Bilateral upper-limb coordination in aging and stroke


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Bilateral upper-limb coordination is an important ability for our living independency, since most of our daily tasks, such as lifting a box or using knife and fork, require the simultaneous use of both arms (Waller *et al.*, 2006). However, bilateral coordination decline has been observed in both healthy aging and neurological groups (Pollock *et al.*, 2014; Maes *et al.*, 2017) , which often results in decreased quality of life (Broeks *et al.*, 1999; Franceschini *et al.*, 2010). Therefore, this dissertation sought to understand the characteristics and mechanisms of bilateral coordination and its impairments.

The two fundamental bilateral movements in human upper limbs, i.e., in-phase (homologous muscles from bilateral arms activate simultaneously) and anti-phase (different muscle groups from bilateral arms activate simultaneously) movements, have been found to show different characteristics in behavioral and neural measurements (Swinnen and Wenderoth, 2004). Behaviorally, anti-phase movements are found to be performed with lower movement accuracy and higher phase variability between hands compared to in-phase movements (Wuyts *et al.*, 1996; Byblow *et al.*, 2000; Pollok *et* *al.*, 2007). On the neural level, fMRI studies demonstrated that the left hemisphere shows larger task-related BOLD signal changes compared to the right hemisphere during in-phase movements (Aramaki *et al.*, 2006), while the BOLD signal changes between the two hemispheres are similar during anti-phase movements (Walsh *et al.*, 2008). These results suggest a left-dominated control of in-phase movements. However, a critical limitation in the literature is the lack of causal evidence supporting hemispherical specialization in bilateral coordination. Therefore, it is unclear whether the observed behavioral differences between anti-phase and in-phase movements were truly due to distinct hemispheric control. Another limitation of the literature is the design of existing paradigms. While most of our daily activities involve movements engaging multiple joints at the same time (Keenan *et al.*, 2006; Murphy *et al.*, 2006), previous studies mostly investigated single joint movements (e.g. index finger tapping, forearm pronation-supination). Contrary to single joint movements, bilateral movements engaging multiple joints require not only inter-limb coordination, but also additional intra-limb coordination. Therefore, it is unclear whether the previous findings from single joint movements could be directly applied to multiple joint movements.

In this dissertation, we used a bilateral coordination paradigm involving both shoulder and elbow joints to investigate the neural mechanisms behind bilateral coordination and its decline. We designed three studies focusing on 1) the differences between bilateral in-phase and anti-phase movements from a human motion perspective, 2) how aging affects different bilateral coordination patterns and its neural correlates, as well as 3) how lesioned hemisphere affects bilateral coordination impairments and whether distinct rehabilitation treatments are needed after a left or right hemispheric stroke.

In Study 1, we examined the two basic bilateral coordination modes, in-phase and anti-phase movements, in healthy young right-handed participants. We used a bilateral circle drawing task involving both shoulder and elbow joints. During the movements, we measured participants' hand positions with high temporal and spatial precision, and developed intra-limb and inter-limb measures to differentiate movement characteristics during the two basic movement modes. For intra-limb coordination, we quantified trajectory variability of each hand during the movements. For inter-limb coordination, we computed the phase synchronization between hands. We found that intra-limb coordination was worse in the non-dominant hand during anti-phase compared to in-phase movements. In contrast, intra-limb coordination in the dominant hand did not differ between anti-phase and in-phase movements. Second, participants showed worse inter-limb synchronization during anti-phase compared to in-phase movements. Moreover, we examined the hand acceleration profile of both hands, and found that participants' bilateral hands accelerated and decelerated in an in-phase manner during in-phase movements. In contrast, the acceleration and deceleration of the two hands were unrelated during anti-phase movements. These inter-limb acceleration profiles support the idea of differential neural mechanisms behind bilateral anti-phase and in-phase movements: during in-phase movements, the hands are governed by a common neural generator, while during anti-phase movements, the two hands are controlled by both hemispheres more independently. Taken together, Study 1 showed that the current experimental setup is able to differentiate the performance between bilateral in-phase and anti-phase movements engaging multiple joints. Therefore, we used the same paradigm combined with electroencephalography (EEG) to examine the presumed decline of bilateral coordination in aging.

In Study 2, we investigated the effect of aging on the two basic bilateral movement modes. We used intra- and inter-limb measures as the behavioral measures, and EEG as a neural measure. Behaviorally, we found that older adults only showed significant impairments in anti-phase movements, but not in-phase movements, compared to young adults. On the neural level, we found that older adults showed different neural responses during anti-phase and in-phase movements compared to young adults. Specifically, during in-phase movements, young adults showed a more pronounced decrease of alpha power (8-12 Hz) over the left compared to the right hemisphere, while older adults showed similar levels of alpha power decrease over both hemispheres. Furthermore, in the older adults, we found a marginal correlation between the change in alpha power over the right hemisphere and the behavioral performance, which indicated a compensatory brain response. As for the anti-phase movements, we found that participants with stronger directional inter-hemispheric connectivity in the beta band (15-25 Hz) showed worse behavioral performance, and this effect was more pronounced in the older adults. This result implies that a balanced inter-hemispheric contribution is essential for executing a successful anti-phase movement. Our findings therefore show that the two hemispheres are differentially involved in the two basic bilateral coordination modes. These different neural characteristics may explain the distinct decline patterns of in-phase and anti-phase movements in older adults. However, causal evidence to support hemispherical specialization is needed to confirm our findings. Therefore, we conducted Study 3, where we used stroke as a lesion model to examine the influence of the lesioned hemisphere on bilateral coordination.

In Study 3, we examined the bilateral coordination ability in patients with left (LHS) and right hemispheric stroke (RHS), as well as healthy controls. Given that healthy young participants show a left-dominant control in in-phase movements in

Study 2 and in the previous literature (Aramaki *et al.*, 2006; Maki *et al.*, 2008), we expected that LHS patients would display a more pronounced impairment of in-phase movements compared to RHS patients. In contrast, since anti-phase movements require a more balanced inter-hemispheric contribution as shown in Study 2, and RHS patients show larger inter-hemispheric inhibition compared to healthy participants and LHS patients (Lewis and Perreault, 2007b), we expected that RHS patients would show more impairment in anti-phase movements compared to LHS patients. As predicted, we found that patients with RHS patients exhibited greater impairment during anti-phase movements (both intra- and inter-limb parameters) and LHS patients showed greater impairment during in-phase movements (intra-limb parameters only). Though LHS patients did not show greater impairment in inter-limb coordination during in-phase movements compared to RHS patients, our regression analysis revealed that only LHS patients swapped hand dominance during the task. We interpreted this result as a compensatory mechanism whereby bilateral in-phase movements in the LHS group switched from a left-dominated cortical control to a right-dominated cortical control. Our findings not only provide causal evidence for hemispheric specialization in bilateral movement coordination, but also characterize the differential impairments in bilateral coordination after a left or right hemispheric stroke.

Taken together, this dissertation highlighted differential neural control processes involved in bilateral in-phase and anti-phase movements, and demonstrated how these distinct mechanisms lead to impaired bilateral coordination in aging and stroke. The present results could therefore advance the development of therapeutic strategies that seek to counteract bilateral coordination decline, such as differential treatment for patients with left and right hemispheric lesions, or the use of noninvasive brain stimulation at a target hemisphere.

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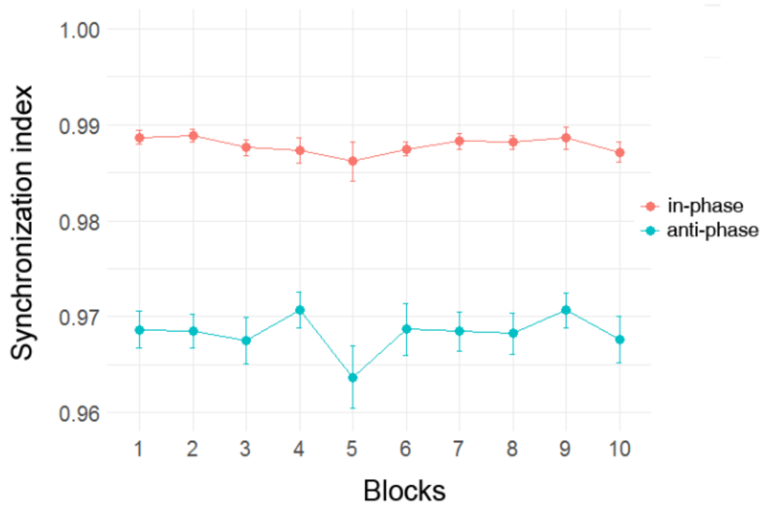
# Appendix

## Appendix 1. Supplementary information for study 1

### Appendix 1.1. Participants' performance across blocks of task execution

We performed one-way repeated-measure ANOVA was used to determine the effect of *Block* on anti-phase and in-phase movements respectively. No learning effects were found across the blocks in both anti-phase ($F_{(9,261)}$ = 1.604, p = 0.114, $\eta^2$ =0.052) and in-phase ($F_{(9,261)}$ = 1.047, p = 0.403, $\eta^2$ =0.035) conditions as shown in Supplementary Figure 1.1.




**Supplementary Figure 1.1. No learning effect on behavioral performance across the experiment.**

For both in-phase (line in red) and anti-phase (line in blue) condition, we did not observe a learning effect across the experiments.

## Appendix 1.2. Centroid offset during the in-phase and anti-phase phase conditions

To examine whether the centroid offset differed between conditions, we performed a two-way repeated measured ANOVA. We found that centroid offset was larger in anti-phase compared to in-phase condition, as well as left hand compared to right hand. Therefore, correction for the centroid offset is necessary before movement phase estimation.

**Supplementary Table 1.1. Centroid offset during in-phase and anti-phase conditions**

| Centroid offset | Left hand | Right hand |
|---|---|---|
| Anti-phase | 0.789±0.1270 | 0.6760±0.1228 |
| In-phase | 0.7273±0.1305 | 0.6591±0.1190 |

Data are shown as mean±SD.

**Supplementary Table 1.2. Statistical results of the centroid offset**

| 2x2 ANOVA | F-value | P-value |
|---|---|---|
| *Condition*Side* | 4.4865 | <0.0360 |
| *Condition* | 13.904 | 0.0003 |
| *Side* | 74.225 | <0.001 |

# Appendix 2. Supplementary information for study 2

## Appendix 2.1. Comparison between trials with and without horizontal eye movements

When participants showed horizontal eye movements for more than twice within a trial, it was documented as a trial with horizontal eye movements. The number of trials with eye movements in each group and condition were summarized in the following tables.

**Supplementary Table 2.1. Performance of trials with and without eye movements in older adults**

| Condition | Anti-phase | | In-phase | |
|---|---|---|---|---|
| Eye movements | No | Yes | No | Yes |
| Number of trials | 18.58±0.67 | 1.42±0.67 | 18.08±2.00 | 1.92±2.00 |
| Synchronization index | 0.911±0.147 | 0.918±0.094 | 0.982±0.012 | 0.983±0.007 |

Data are shown as mean±SD.

**Supplementary Table 2.2. Performance of trials with and without eye movements in young adults**

| Condition | Anti-phase | | In-phase | |
|---|---|---|---|---|
| Eye movements | No | Yes | No | Yes |
| Number of trials | 18.29±1.20 | 1.71±1.20 | 17.99±1.21 | 2.01±1.21 |
| Synchronization index | 0.960±0.018 | 0.963±0.009 | 0.986±0.009 | 0.987±0.006 |

Data are shown as mean±SD.

On average, there were no significant differences in the number of eye-movement trials between *Group* and *Condition* (Pearson's Chi-squared test, X-squared = 1.0506, $p = 0.789$). Nevertheless, we further examined whether the performance of inter-limb synchronization varied between the trials with and without eye movements. Since there were significantly more trials without horizontal eye movements, Welch two sample t-test were used:

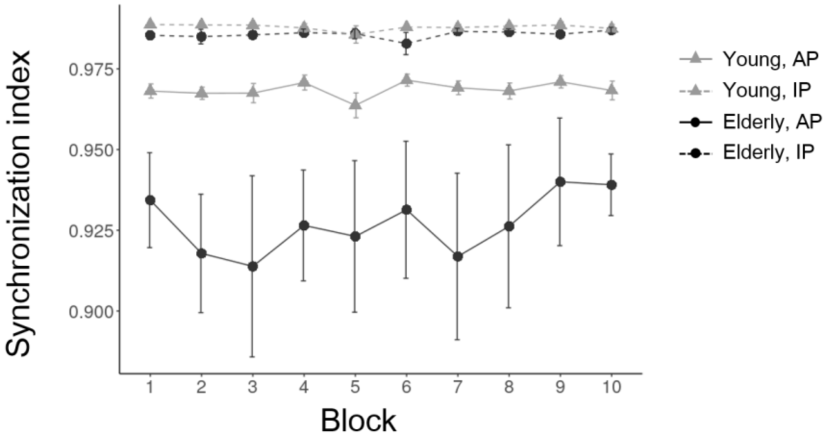
**Supplementary Table 2.3. Comparison between anti-phase and in-phase movement**

| Older adults | Anti-phase | In-phase |
|---|---|---|
| | t = 0.388, df = 19.309, p = 0.702 | t = 1.303, df = 27.958, p = 0.203 |
| Young adults | Anti-phase | In-phase |
| | t = 1.526, df = 27.93, p = 0.138 | t = 0.650, df = 52.207, p = 0.518 |

Since there were no differences in the number of trials with eye movements within each group and condition, as well as no differences in synchronization index between trials with and without eye movements, we did not remove the trials with horizontal eye movements from the final analysis.

**Appendix 2.2. No learning effects in inter-limb coordination behavior were found across the blocks in the experiment.**

We used three-way (*Group*, *Condition*, *Block*) repeated-measure ANOVA to exam whether the inter-limb synchronization index changed across the experiments. As shown in the figure and statistic below, there was no significant interaction between *Group, Condition*, and *Block*, and there was no significant main effect in *Block* as well.




**Supplementary Figure 2.1. No learning effect on behavioral performance across the experiment in both young and older adults.**

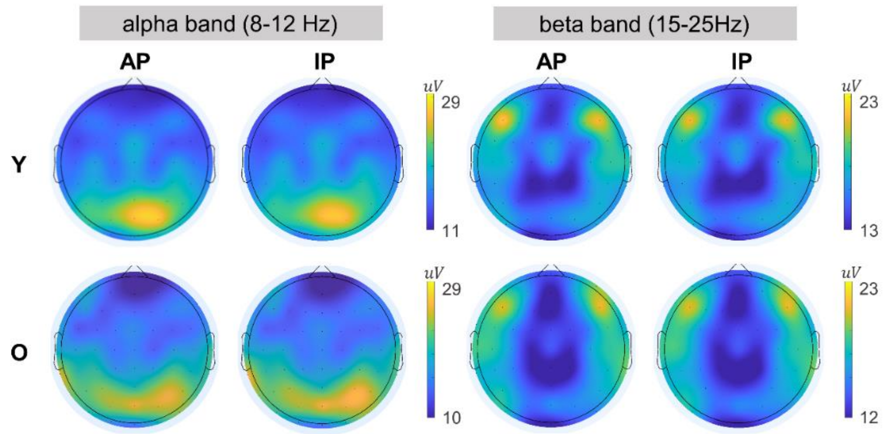
For both in-phase and anti-phase conditions, we did not find learning effects on inter-limb synchronization index across the experiment in both young and older adults,

**Supplementary Table 2.4. Comparison between anti-phase and in-phase movement**

| Linear mixed model | Results |
|---|---|
| *Group * Condition *Block* | $F_{(9,1912)} = 0.293$, $p = 0.976$ |
| *Group * Block* | $F_{(9,1912)} = 0.330$, $p = 0.965$ |
| *Group * Condition* | $F_{(9,1912)} = 37.377$, $p < 0.001$ |
| *Condition * Block* | $F_{(9,1912)} = 0.381$, $p = 0.944$ |
| *Group* | $F_{(9,1912)} = 6.2353$, $p = 0.016$ |
| *Condition* | $F_{(9,1912)} = 151.624$, $p < 0.001$ |
| *Block* | $F_{(9,1912)} = 0.\ 402$, $p = 0.934$ |

## Appendix 2.3. No differences in baseline alpha/beta power amplitudes between AP and IP conditions

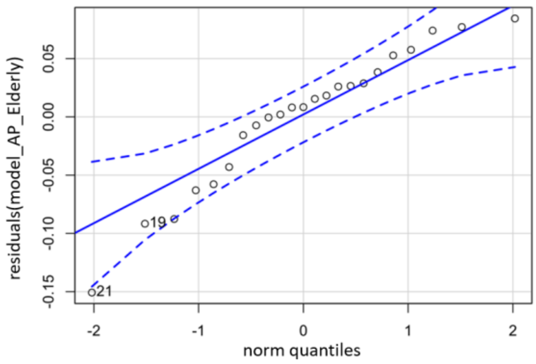
For both alpha and beta power in young and older groups, we used cluster-based statistics to test the main effect in Condition. The significant cluster was defined as two or more neighboring sensors that demonstrated a correlation with $p < 0.05$. No cluster survived the statistical threshold, indicating that there was no significant difference in baseline power amplitude between AP and IP conditions.




**Supplementary Figure 2.2. Alpha and beta power at the preparation phase.**
For both alpha and beta bands, no significant differences between *Group* and *Condition* were observed. Y = young adults. O = older adults. AP = anti-phase. IP = in-phase.

## Appendix 2.4. Normality of the behavior-brain regression model

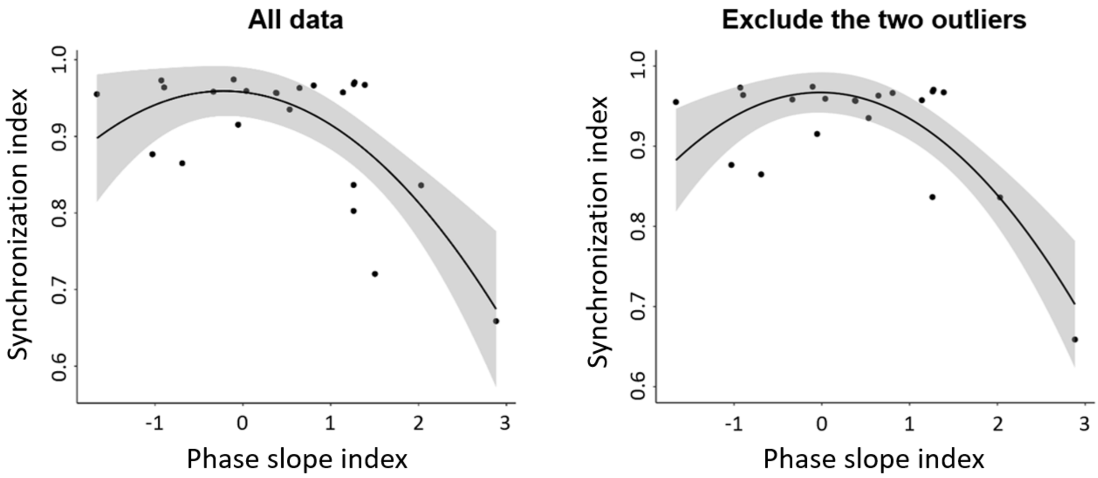
To confirm the stability of the result in Figure 4.4, we firstly checked the homoscedasticity and normality with diagnostic plot and Shapiro-Wilk test to confirm whether the current result was driven by the outliers. Here we specifically displayed the data of the older adults from Figure 4.4B. Data were fitted in the quadratic model (Sync~PSI+PSI^2), and residuals were plotted using qqPlot from the *car* package in R.




**Supplementary Figure 2.3. Q-Q plots for examining the normality of quadratic model.**

The blue line indicates the 95% credible interval. Each hollow circle represents one data point. Two outliers (subject 19, 21) were identified from this inspection.

Most samples lay nicely within the 95% confident interval. Shapiro-Wilk normality test showed the distribution of the data were not significantly different from normal distribution (W = 0.94194, p-value = 0.1978). Sample 19 and 21 were identified as outliers; therefore, we further fitted the model without these two samples to see whether the result stayed.




**Supplementary Figure 2.4. Quadratic models with and without the outliers.**
This figure shows that for both models with or without outliers, the quadratic models are superior to the linear models.

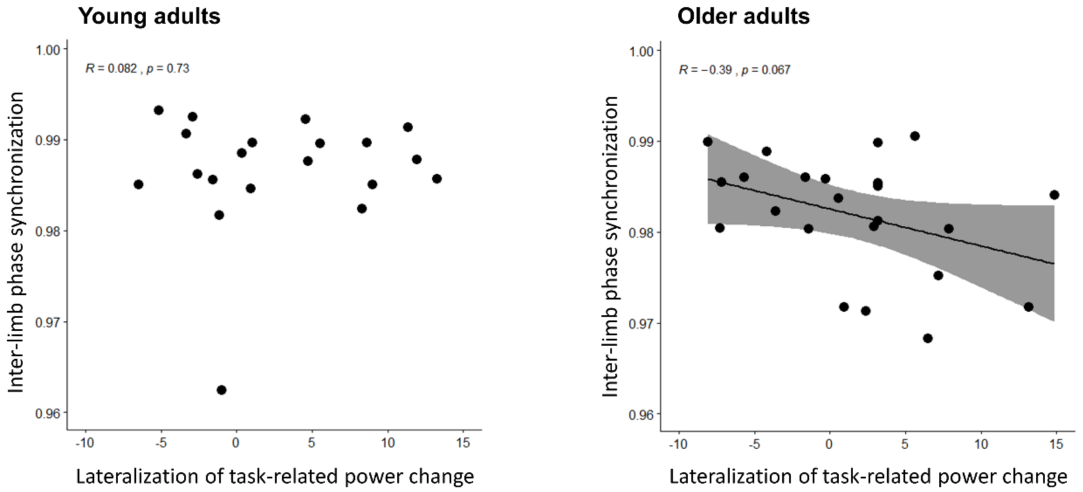
We found that after removing the two outliers, the quadratic model still survived (BIC of linear model= -46.34693, BIC of quadratic model= -59.3335), and the model fitting was superior to the linear model ($F = 20.619$, $p<0.001$). Therefore, the outliers did not affect the current result.

## Appendix 2.5. Correlation between behavioral performance and task-related power change in the alpha band

When examining the task-related power change during in-phase movements (Figure 4.3), we observed that older adults showed larger (more decrease) task-related power change (TRPow) over the right hemisphere compared to the young adults. Since we only observed differences in TRPow but not behavioral performance during in-phase movements at the group level, we interpret this result as a compensatory brain response in older adults. To confirm this assumption, we performed an additional regression analysis to examine whether the task-related power change is related to participants' behavioral performance.

We did not directly take the TRPow from the right hemisphere (C4 electrode) for this analysis. Instead, we took the relative TRPow of the C4 electrode to the C3 electrode to infer how lateralized the brain activity is to the right hemisphere. Therefore, we calculated the lateralization of task-related power change between the left and right motor areas = $TRPow_{C4} – TRPow_{C3}$. If the value = 0, the two hemispheres have equally decreased in task-related power. The lower the value, the more activation is over the right hemisphere compared to the left one.

The lateralization values were correlated with the inter-limb synchronization index using the Pearson correlation. The results are as followed:




**Supplementary Figure 2.5. Correlation analysis: inter-limb synchronization versus alpha power changes between hemispheres.**

This figure shows the correlation between inter-limb synchronization and inter-hemispheric task-related alpha power changes of the (left) young adults and (right) older adults. There is no correlation between the two parameters in young adults, but a trend for correlation in older adults.

For young adults, we did not observe a significant correlation between the lateralization of the TRPow and behavior (R = 0.082, p=0.73). In contrast, for the older adults, we found a trend of correlation (R=-0.39, p=0.067). That is, the more the participant showed relatively decreased in task-related power change over the right hemisphere compared to the left, the better the performance in coordinating the two upper limbs. This analysis provides evidence to support a potential compensatory response of the non-dominant hemisphere activity to behavioral performance.

# Appendix 3. Supplementary information for study 3

## Appendix 3.1. Demographic data of each stroke patients

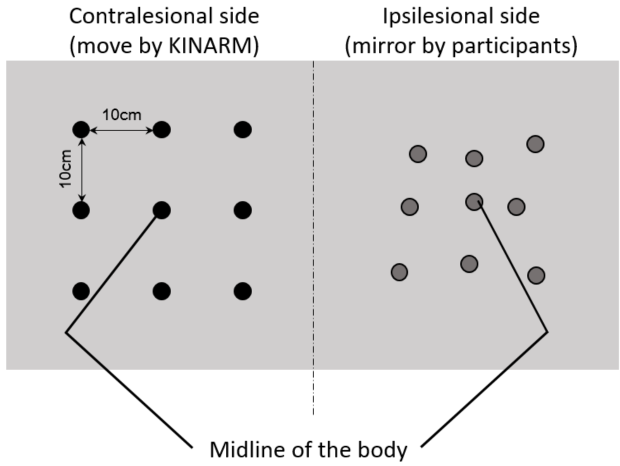
**Supplementary Table 3.1. Demographic data of each stroke participant**

| **Basic characteristics** | | | | **Lesion characteristics** | | | **Clinical examination** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subj | Sex[1] | Age | Onset(yr) | Type[2] | Region[3] | Size(%)[4] | MMSE[5] | NIHSS[6] | FM-UE[7] | FM-UE(A)[8] | MAS[9] | Proprioception[10] |
| Left hemispheric stroke group (LHS) | | | | | | | | | | | | |
| S-04 | M | 60 | 12.08 | H | TH | 2.77 | 30 | 2 | 46 | 26 | 1+ | 12.55 |
| S-05 | M | 32 | 2.42 | I | TH,PO | 0.29 | 30 | 1 | 54 | 27 | 1 | 3.83 |
| S-06 | F | 53 | 5.50 | I | BG | 0.31 | 30 | 2 | 48 | 26 | 1 | 6.03 |
| S-07 | F | 78 | 2.08 | I | MCA | 22.85 | 29 | 3 | 21 | 16 | 1+ | 13.34 |
| S-11 | M | 57 | 8.08 | I | MCA | 11.15 | 24 | 1 | 44 | 24 | 1 | 12.12 |
| S-12 | F | 37 | 2.83 | I | BG | 0.44 | 29 | 4 | 57 | 27 | 2 | 6.98 |
| S-13 | M | 61 | 5.75 | I | MCA | 7.33 | 29 | 5 | 53 | 26 | 1 | 5.44 |
| S-14 | F | 47 | 4.42 | I | MCA | 0.61 | 30 | 4 | 59 | 30 | 1 | 5.98 |
| S-17 | M | 67 | 5.00 | I | MCA | 3.89 | 29 | 3 | 58 | 29 | 0 | 3.87 |
| Right hemispheric stroke group (RHS) | | | | | | | | | | | | |
| S-01 | F | 57 | 8.25 | I | MCA | 18.64 | 30 | 6 | 45 | 26 | 1 | 7.52 |
| S-02 | F | 84 | 3.58 | I | MO | 0.15 | 30 | 2 | 34 | 20 | 2 | 8.74 |
| S-03 | F | 71 | 15.00 | I | MCA | 1.04 | 30 | 0 | 20 | 16 | 1 | 10.04 |
| S-08 | F | 51 | 9.08 | I | MCA | 1.72 | 30 | 0 | 53 | 29 | 1 | 8.15 |
| S-09 | M | 67 | 5.67 | I | MCA | 16.09 | 30 | 1 | 20 | 15 | 1 | 9.90 |
| S-10 | M | 70 | 17.17 | I | MCA | 9.29 | 30 | 2 | 53 | 27 | 1 | 8.90 |
| S-15 | F | 56 | 12.33 | I | IC | 0.20 | 30 | 2 | 53 | 25 | 1+ | 7.82 |
| S-16 | M | 41 | 8.42 | I | MCA | 36.70 | 30 | 6 | 45 | 24 | 2 | 4.28 |
| S-18 | F | 50 | 1.58 | H | BG | 1.80 | 29 | 4 | 53 | 26 | 1 | 5.76 |

[1]Sex: M male, F female. [2]Stroke type: I Ischemic, H Hemorrhage. [3]Lesion locations: BG Basal ganglia, IC Internal capsule, TH Thalamus, PO Pons, MCA Middle Cerebral Artery territory, MO medulla oblongata. [4]Lesion size: percentage to the whole brain volume. [5]MMSE: Mini-Mental State Examination (score 0-30). [6]NIHSS: National Institutes of Health Stroke Scale (score 0-42). [7]FM-UE: Fugl-Meyer assessment for Upper Extremity (score 0-66). [8]FM-UE (A): FM-UE section A for shoulder and elbow (score 0-36). [9]MAS: Modified Ashworth scale, Tri Triceps, Bi Biceps (score 0-4). [10]Propriocepion: assessed by Arm Position Matching task at the KINARM (value: error in hand matching accuracy). Please see Appendix 3.2.

## Appendix 3.2. Proprioception test

We used the Arm Position Matching test provided by the KINARM system to examine participants' proprioceptive ability. Participants sat inside the KINARM, and their visions were blocked. The paradigm is shown in Supplementary Figure 1. The KINARM moved patient's contralesional arm (i.e., the paretic arm of the patients) to a given position, and after the KINARM reach the target, patient was instructed to move the other arm to the mirror-matched position. After completion, the KINARM moved patient's contralesional arm to the next position, and the procedure repeated for 54 times (9 targets, 6 repetitions for each target). Proprioception error was quantified as the mean absolute position error (unit: cm) between the two hands.




**Supplementary Figure 3.1. Arm Position Matching test with nine targets.**

## Appendix 4. Declaration of authenticity

**<u>Erklärung über die eigenständige Abfassung der Arbeit</u>**

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar eine Vergütung oder geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, und dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt wurde. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt an der Entstehung der vorliegenden Arbeit beteiligt waren. Die aktuellen gesetzlichen Vorgaben in Bezug auf die Zulassung der klinischen Studien, die Bestimmungen des Tierschutzgesetzes, die Bestimmungen des Gentechnikgesetzes und die allgemeinen Datenschutzbestimmungen wurden eingehalten. Ich versichere, dass ich die Regelungen der Satzung der Universität Leipzig zur Sicherung guter wissenschaftlicher Praxis kenne und eingehalten habe.

26.November 2020

Pei-Cheng Shih