Investigating the behavioural and neurophysiological underpinnings of a novel bimanual motor learning task



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Abstract

In daily life, we perform many tasks with both hands that require the cooperative and skilled interaction between hands, such as keyboard typing. However, our understanding of the behavioural and neurophysiological underpinnings of how we produce and learn cooperative bimanual skills is sparse.

In this thesis, I addressed this by designing a novel task that measures unimanual as well as different levels of bimanual motor learning. With the novel task, I conducted four independent experiments to answer distinct questions, including characterising learning, and generalisability, as well as understanding learning-related neurophysiological changes using non-invasive brain stimulation and Magnetoencephalography (MEG).

Firstly, I aimed to quantify the learning-related changes of unimanual as well as different levels of bimanual motor learning. Results indicated that the novel task was successfully implemented to characterise learning. Secondly, I investigated if the learning could be modulated with non-invasive brain stimulation using a double-blind sham-controlled study. I replicated the behavioural results of the first experiment, but the applied stimulation did not affect learning the task. Thirdly, I developed different online versions of the task (i.e., training tasks) to measure if this variability across training tasks affected learning and the transfer of learning to multiple transfer tasks. Results indicated that learning depended on the training task, whereas transfer of learning was independent of the training task and depended on the transfer task. Fourthly, I characterised the neural activity of learning the different levels of bimanual interaction with MEG. Results yielded movement-related beta power modulations which were different between the unimanual and bimanual

condition. However, they did not differ between the bimanual conditions and did not change with learning.

Taken together, this work provides new insights into how we produce and learn bimanual skills as the task described here allows for a richer description of bimanual interaction. Testing different versions of the task highlights the complex relationship between learning and transfer of learning. Further, this work contributes to our understanding of the neural underpinnings of unimanual and bimanual movements and give directions for future research.

This thesis is 48,780 words.

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Covid-19 pandemic statement

The Covid-19 pandemic disrupted my studies because the University facilities closed and research requiring face-to-face activities with human participants was paused in March 2020. At this time, I was in my second year as a DPhil student and the majority of my data collection was planned to take place. As a consequence, I stopped collecting data for my research study described in chapter 4 with 55 participants instead of 60 participants. Thus, the number of participants reported in chapter 4 is smaller than originally anticipated due to the start of the pandemic.

In addition, the data of the research study described in chapter 5 was collected during September and November 2020. As research with human participants could not be conducted in person during this time, data was collected solely online.

Further, the start of data collection for the research study described in chapter 6 was significantly delayed. I had anticipated to collect data commencing October 2020. However, only in May 2021, I was able to start data collection with safety procedures in place which I finished in July 2021. As this thesis was handed in in December 2021, data analysis performed in chapter 6 is therefore not as extensive as previously anticipated.

Commencing Michaelmas 2019, I worked as a Junior Dean at St Catherine's College. The role entails to assist the Dean in welfare and disciplinary actions around the College. Due to the pandemic, the role became increasingly challenging as Covid-19 safety procedures had to be implemented and welfare support was increasingly required. The additional challenges arising from to the pandemic affected me and my studies.

Related Publications

The work presented in chapter 3 and 4 has been published in the following peer-reviewed journal article:

Schoenfeld, M. J., Grigoras, I. F., Stagg, C. J., & Zich, C. (2021). Investigating Different Levels of Bimanual Interaction With a Novel Motor Learning Task: A Behavioural and Transcranial Alternating Current Stimulation Study.*Frontiers in Human Neuroscience*, 15.

A subset of the data presented in chapter 5 was submitted by Jade Williams for her FHS project report.

A subset of the data presented in chapter 6 will be submitted by Ipsita Sarkar for her FHS project report.

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List of Abbreviations

ANCOVA . . . Analysis of Covariance

ANOVA . . . . Analysis of Variance

AMI . . . . . Achievement Motivation Inventory

BF . . . . . Bayes Factor

BI . . . . . Blinding Index

CC . . . . . Corpus Callosum

CI . . . . . Confidence Interval

CMC . . . . . Cortico-Muscular Coherence

CTC . . . . . Communication Through Coherence

DBS . . . . . Deep Brain Stimulation

DWI . . . . . Diffusion-Weigthed Imaging

ECG . . . . . Electrocardiogram

EEG . . . . . Electroencephalogram

EOG . . . . . Electrooculogram

ERD . . . . . Event-Related Desynchronisation

ERF . . . . . Event-Related Magnetic Field

ERP . . . . . Event-Related Potential

ERS . . . . . Event-Related Synchronisation

fMRI . . . . . functional Magnetic Resonance Imaging

FOV . . . . . Field of View

GUI . . . . . Graphical User Interface

HPI . . . . . Head Position Indicator

HTML . . . . Hypertext Markup Language

ICA . . . . . Independent Components Analysis

ITI . . . . . Inter-Trial Interval

LCMV . . . . Linearly Constrained Minimum Variance

LTD . . . . . Long-Term Depression

LTP . . . . . Long-Term Potentiation

M1 . . . . . Primary Motor Cortex

MEG . . . . . Magnetoencephalography

MEP . . . . . Motor Evoked Potential

MPRAGE . . Magnetization Prepared Rapid Gradient Echo

MRI . . . . . Magnetic Resonance Imaging

MTurk . . . . Mechanical Turk

OHBA . . . . . Oxford Centre of Human Brain Activity

OSL . . . . . OHBA Software Library

PCA . . . . . Principle Components Analysis

PMC . . . . . Premotor Cortex

RHINO . . . . Registration of Headshapes Including Nose

SMA . . . . . Supplementary Motor Area

SQUID . . . . Superconducting Quantum Interference Devices

tACS . . . . . Transcranial Alternating Current Stimulation

tDCS . . . . . Transcranial Direct Current Stimulation

tES . . . . . Transcranial Electric Stimulation

TMS . . . . . Transcranial Magnetic Stimulation

1 Introduction

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Humans produce countless movements in daily life that require the use of both hands, such as eating with a knife and fork, tying shoelaces or typing on the computer keyboard. Some of these bimanual movements are performed by both hands being used in a similar manner, i.e., requiring equal contributions between hands. Other bimanual movements are performed in a different manner, i.e., requiring unequal contributions between hands. In the example of eating with knife and fork, an unequal contribution between hands is required. Specifically,

one hand is holding the fork and the other is cutting with the knife. Mostly, our hands move seemingly effortlessly: a well-learnt pattern of bimanual interaction is in full operation. This is one of many daily life examples of coordinated and expert bimanual movements, but how are they learned and generated? I aim to shed light on this question in my thesis by investigating the behavioural and neural underpinnings of bimanual motor learning. Studying the basis of bimanual motor learning allows us to understand how humans learn to coordinate actions between their hands. Ultimately, this may be a valuable tool to conceive how these processes change during healthy ageing as well as for developing novel adjunct therapies for rehabilitation after brain injuries such as a stroke.

In this introduction, I will outline the basic behavioural patterns of bimanual interactions and the commonly used tasks to measure bimanual movements and bimanual motor learning. Thereafter, I will then summarise what is known about the neural mechanisms of bimanual movements and bimanual motor learning.

1.1 Bimanual Motor Learning

Skilled coordinated bimanual interactions require extensive training to become proficient (Sailer et al., 2005; Sisti et al., 2011). Motor skills are learned through repetition and training, which result in lasting improvements in speed and accuracy (Willingham, 1998). To train motor skills, specifically bimanual movements, daily life tasks offer a rich variety for experimental manipulations.

Experimentally, conditions can be changed to quantify how participants learn bimanual movements. In this section, I will discuss different tasks that have been used to study bimanual motor learning. Those include, amongst others, finger tapping and flexion/extension tasks, cyclic/rhythmic tasks, and cooperative tasks, see Figure 1.1. Across all tasks, two basic modes of bimanual interactions are used consistently: either equal contributions between hands, i.e., symmetric or

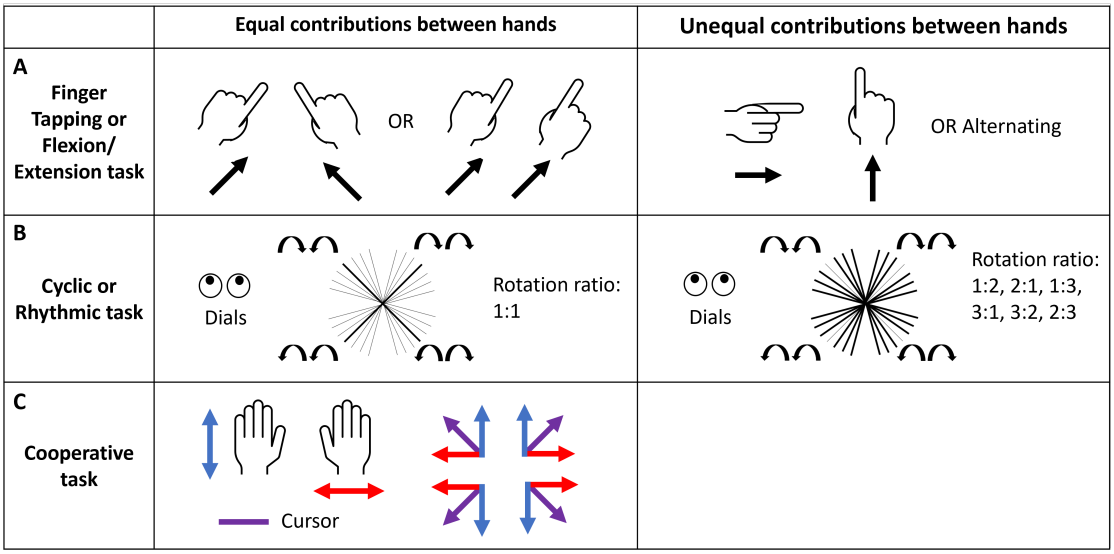


Figure 1.1: Examples of bimanual motor (learning) tasks. (**A**) Finger tapping and flexion/extension tasks have been used to quantify the basic bimanual movements. Equal contributions between hands have been studied with simultaneous (1:1) tapping or flexion/extension of limbs in the same direction (Kajal et al., 2017; Serrien, 2008b). Unequal contributions between hands have been investigated with alternating tapping or flexion/extension of limbs in different directions (Kajal et al., 2017; Serrien, 2008b). The schematic was adapted from Swinnen and Gooijers (2015). (**B**) Sisti et al. (2011) used cyclic movements to assess bimanual motor learning. In their task, a dot was moved on a target line. To move the dot, dials had to be turned in specific rotation ratios requiring equal, i.e., 1:1 rotation ratio, or unequal contribution between hands, i.e., 1:2, 2:1, 1:3, 3:1, 3:2, 2:3 rotation ratios. The schematic was adapted from Sisti et al. (2011). (**C**) Doost et al. (2017) quantified bimanual motor learning in a cooperative task. In the task, the vertical (blue) and horizontal axis (red) were controlled separately to move a cursor (purple) on a complex circuit. To move the cursor required equal contributions between hands. The schematic was adapted from Doost et al. (2017).

mirror-like movements, or unequal contribution between hands, i.e., asymmetric movements. Note that the categories used here are based on Maes et al. (2017) but there are many other ways to categorize bimanual motor (learning) tasks, see Swinnen (2002) and Swinnen and Gooijers (2015) for comparison.

1.1.1 (Sequence) Finger Tapping Tasks

The majority of studies investigating bimanual movements and bimanual motor learning have used simple finger tapping tasks including repetitive finger tapping with simultaneous or alternating tapping (Aoki et al., 2003; Aramaki et al., 2006;

Aramaki et al., 2010; Bangert et al., 2010; Shammi et al., 1998; Takeuchi et al., 2012). Finger tapping tasks thoroughly quantified equal contributions between hands, i.e. simultaneous, mirror-like tapping, or unequal contribution between hands, i.e., tapping in different directions, tapping with different fingers, or alternating tapping between hands, see Fig.1.1A. Some studies have utilized tapping sequences, e.g., similar to playing piano (Schmidt & Lee, 2005). Others investigated bimanual sequences with sequence tapping tasks (Eudave et al., 2017; Kajal et al., 2017; Spirduso & Choi, 1993), sequence learning tasks (Andres et al., 1999; Gerloff & Andres, 2002), as well as sequence learning paired with reaction time tasks (Bhakuni & Mutha, 2015; Boisgontier et al., 2014; Hoff et al., 2015). These tasks were often developed to measure bimanual interaction in combination with neuroimaging techniques, where simple and spatially constrained movements were required, i.e., movements in enclosed spaces like a Magnetic Resonance Imaging (MRI) scanner. Experiments investigating (sequence) finger tapping have advanced the basic understanding of which regions are involved in bimanual interaction and how these regions communicate with each other, as outlined in section 1.2 below. However, the knowledge derived from these studies remains a simplification of bimanual coordination patterns which are artificial and distant to the rich variety of daily life's bimanual interactions and often do not require learning.

1.1.2 Cyclic/Rhythmic Tasks

Continuous movements are defined as those that do not have a clear beginning and end, e.g., where the end of one cycle is the beginning of the next cycle of movement (Bangert et al., 2010). Examples of continuous movements are walking and swimming. To study bimanual movements and bimanual motor learning tasks were used involving continuous movements such as rhythmical finger tapping (Houweling et al., 2010a; Serrien, 2008b; Sommervoll et al., 2011) as well as

rhythmical flexion/extension of fingers and limbs (Gross et al., 2005; Kelso, 1984; Serrien & Brown, 2002), also in combination with force production (Boonstra et al., 2007; Houweling et al., 2008; Leinen et al., 2016) and drawing circles to metronome beating (Dyer et al., 2017; Kelso et al., 1986; Peper et al., 1995; Swinnen, 1998). Typically, cyclic tasks examined either the temporal aspects or the spatial aspects of movements.

The most prominent temporal aspects of cyclic movements are the frequency or rate at which the hands move. One of the first tasks examining the temporal aspects was constructed by Preilowski (1972). In the task, lines had to be drawn in narrow tracks tilted in different angles (90°, 112.5°, 135°, 157.5°, 180°). In order to draw lines, handles built into a X-Y plotter had to be turned. One handle drew horizontal and the other handle drew vertical lines. Thereby, drawing the lines required multi-frequency rotation ratios with equal (1:1) or unequal (1:3, 3:2) contributions between hands. Many studies adapted the original version of the Preilowski task using the original hardware (Fagard et al., 1985), a computer-based Etch-A-Sketch version (Moes et al., 1995; Moore et al., 1995; Neilson & Neilson, 2002), knobs on a response box (Mueller et al., 2009) or button presses (Koeneke et al., 2004). Findings showed faster and more accurate performance in unimanual than bimanual conditions (Fagard et al., 1985; Mueller et al., 2009). Within the bimanual conditions, movements requiring equal contributions between hands were performed more accurately compared to those requiring unequal contributions of hands (Fagard et al., 1985; Mueller et al., 2009). Sisti et al. (2011) adapted the Preilowski task, such that a dot had to be moved along a target line by rotating two dials using left and right index finger and thumb. The authors omitted the unimanual condition, but added more rotation frequencies resulting in seven frequency ratios (1:1, 1:2, 1:3, 2:1, 2:3, 3:1, 3:2) and extended the movement space to four directions (up, down, left, right), Figure 1.1B. Similar to the findings listed above, Sisti et al.

(2011) found that bimanual conditions with equal contributions were easier to perform than unequal contributions. Further, for the rotations requiring unequal contributions between hands, the authors found that with increasing the ratio, i.e., 1:3 and 3:1 in comparison to 1:2, 2:1, 3:2 and 2:3, performance worsened. In other words, the more unequal the rotations across hands, the more difficult they were to perform. In addition, Sisti et al. (2011) could show that the task induced learning-related changes and that the learning-related changes were different for the seven rotations ratios. In particular, the rotation ratio with equal contributions between hands was the easiest to learn indicated by flooring effects after a small number of training sessions. With increasing difficulty of the rotation ratios (i.e., the more unequal they were), learning was more difficult as indicated by the increasing number of training sessions needed to improve performance. Subsequently, this task was used in many of the studies examining the neural underpinnings of bimanual movements and bimanual motor learning as described below (Gooijers et al., 2013; Gooijers & Swinnen, 2014; Rueda-Delgado et al., 2017; Verstraelen et al., 2021).

In addition to cyclic tasks examining temporal aspects, some studies investigated the spatial aspects of cyclic tasks. The most prominent spatial aspects of cyclic movements are amplitude and direction of movements which have been mostly assessed by drawing circles. Thereby, the circles were drawn with either the same amplitude or different amplitudes, i.e., drawing bigger circles in one hand and smaller circles in the other hand (Heuer et al., 2001; Marteniuk et al., 1984; Sherwood, 1994; Spijkers & Heuer, 1995). Studies examining the direction investigated movements performed either in the same or opposite direction (Eliassen et al., 2000; Franz et al., 1996; Swinnen et al., 2001; Swinnen et al., 1998). Varying spatial features led to similar results than varying temporal features (as listed above). Specifically, the production of bimanual equal contributions, i.e., same amplitude or direction, were performed most easily. When performing bimanual movements with unequal

contributions between hands, e.g., different amplitude, the amplitudes grew towards each other and became similar (Marteniuk et al., 1984; Sherwood, 1994). Similar evidence has been generated in which bimanual movements were performed in different directions: a tendency to perform those movements towards one direction was observed (Franz et al., 1996; Swinnen et al., 2001; Swinnen et al., 1998). This suggested that condition-specific effects are similar for cyclic movements regardless of whether the temporal or spatial aspects were varied.

Taken together, findings of the studies using cyclic/rhythmic movements shed light into complex bimanual movements as well as those that required learning. Specifically, those findings provided evidence that unimanual movements are easier than bimanual movements and within the bimanual conditions, equal contributions between hands are easier to perform than unequal contributions. While these studies provided essential insights into the temporal and spatial aspects of rhythmic/cyclic bimanual movement, most daily life bimanual movements are not rhythmic or cyclic by nature. Many bimanual movements require a distinct yet unique cooperative contribution of each hand, such as eating with knife and fork. To advance our understanding of bimanual motor learning to other tasks, in this thesis I therefore wanted to focus on tasks that depend on the cooperative contribution between hands.

1.1.3 Cooperative Tasks

Cooperative movements require a distinct yet unique cooperative contribution of each hand to achieve a goal, such as bottle opening (Maes et al., 2017). Goal directed cooperative bimanual movements are highly understudied although they can provide essential insight into daily life tasks, see for a review Obhi (2004).

Some attempts have been made to develop tasks to investigate goal-directed and cooperative interactions, e.g., in which one hand stabilized the other (Dietz et al., 2015) or in which a cursor had to be navigated across a complex circuit

(Doost et al., 2017). In the study by Doost et al. (2017), the right hand controlled the horizontal displacement of the cursor, and the left hand controlled the vertical displacement. The circuit was tilted in 45° and required equal contributions of both hands to navigate the cursor through the circuit, see schematic in Figure 1.1C.

While the studies mentioned above focused on goal-directed, cooperative and learned bimanual interactions, these tasks required equal contributions of hands and did not compare these to unequal contributions between hands. Investigating both equal and unequal contributions of hands allows for a richer description of bimanual movements and their learning on a behavioural and neural level. In this thesis, I aim to address this by designing a novel task that includes unimanual as well as bimanual motor learning with equal and unequal contributions.

1.1.4 Transfer of Learning

Bimanual motor learning consists not only of the learning process itself, but also the ability to transfer what has been learned to new conditions and task variants. As an example, learning to drive on the right side of the street can be transferred to driving on the left side of the street. Transfer of motor skills is defined as the gain in the capability to respond as a function of practice or experience in one task, i.e., training task, to another task, i.e., transfer task (Schmidt & Young, 1987). One of the first prominent theories of transfer was based on identical elements theory described by Thorndike and Woodworth (1901). The theory states that the higher the level of similarities between tasks, the more transfer occurs, see for a review (Lee, 1988; Magill & Anderson, 2014). More recent transfer theories in motor control and motor learning have focused on generalised motor programs to explain the occurrence of transfer in response to skill learning (Schmidt & Lee, 2005). The theories and tasks used for measuring transfer are fully outlined in chapter 5.

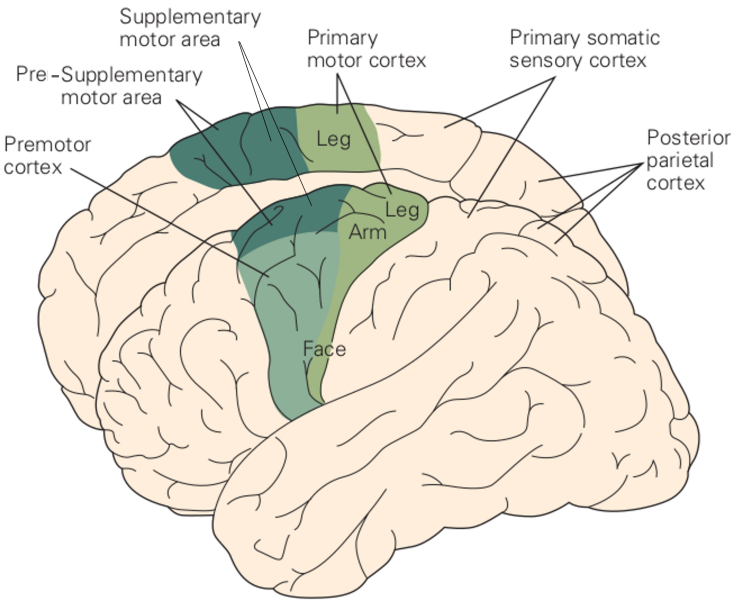


Figure 1.2: Schematic illustration of the motor network associated with bimanual motor learning. It consists of several areas including, amongst others, bilateral primary motor cortices, premotor cortices, and supplementary motor areas. In addition, the cerebellum and subcortical regions such as the basal ganglia belong to the motor network too but are not displayed here for simplicity. Adapted from Kandel et al. (2013).

1.2 Bimanual Motor Learning and the Brain

To perform bimanual movements, the timing and accuracy of muscular activation as well as the interactions between cortical areas of the motor network need to be coordinated precisely (Cardoso de Oliveira et al., 2001).

The motor network associated with bimanual motor movements include, amongst others, bilateral primary motor cortices (M1) for movement execution, supplementary motor areas (SMA) and other premotor areas for movement preparation, basal ganglia for movement initiation and cerebellum for fine-tuning of the movement such as error correction (Gerloff & Andres, 2002; Jantzen et al., 2008; Swinnen & Wenderoth, 2004; Wiesendanger et al., 1996; Wiesendanger et al., 1994), see Fig 1.2. Overall, these brain regions are also important for unimanual movements. However, some animal studies found that specialised populations of neurons in M1 and SMA are only active in bimanual movements (Donchin et al., 1998). Further, depending

on factors, such as environmental information and task demands, complex bimanual motor learning potentially relies on the involvement of an extended network including amongst others sensorimotor cortex, lateral and medial premotor cortex, posterior parietal cortex and cingulate motor cortex (Debaere et al., 2001; Gerloff & Andres, 2002; Kermadi et al., 2000; Koeneke et al., 2004).

1.2.1 Primary Motor Cortex

The primary motor cortex (M1, Broca's area 4) is part of the frontal lobe, bound by the precentral gyrus anteriorly and the central sulcus posteriorly (Pearson, 2000). Layer V of M1 contains axons of specifically large pyramidal neurons that project via the corticospinal tract to the ventral horn of the spinal cord. Those projections connect either directly or indirectly (via interneurons) to pools of motor neurons and enable movement. Due to its direct access to many spinal motor neurons, M1 is considered to be the main site in the human brain for executing voluntary movements. M1 is organised by somatotopic maps. Somatotopic maps were originally discovered by electrical stimulation of patients suffering from epilepsy during open brain surgery (Fulton, 1935; Penfield & Boldrey, 1937; Penfield & Rasmussen, 1950). The stimulation revealed that M1 contains an inverted somatotopic map of the contralateral half of the body with each body part being proportional to the precision of motor control. Specifically, the areas specialised for hands, face, and tongue are disproportionally large. Neuroimaging techniques, e.g., transcranial magnetic stimulation (TMS) and MRI, largely supported these findings (Hluštík et al., 2001), but also highlighted that representations for some body parts appear at multiple locations and overlap with others (Sanes & Donoghue, 2000). Additionally, animal studies indicated that M1 contains a small pool of neurons controlling movement of the ipsilateral side of the body (Kermadi et al., 1998; Tanji et al., 1988) and is highly connected to premotor areas (Kermadi et al., 1998; Luppino et al., 1993; Weinrich & Wise, 1982; Wise, 1985).

In the context of bimanual movements, animal studies have shown that the same neuronal populations in M1 are responsible for uni- and bimanual movements and differ in their activation pattern to enable either uni- or bimanual movements (Donchin et al., 1998; Kermadi et al., 1998). Specifically, single unit recordings from monkeys indicated stronger activation in M1 during bimanual than unimanual movements (Donchin et al., 2001; Donchin et al., 1998). On a macroscopic level, studies in humans come to the same conclusion by showing that brain regions controlling bimanual movements are also involved in unimanual movements. Specifically, these studies found stronger activation in both M1 during bimanual movements than in the contralateral M1 during unimanual movements (Gross et al., 2005; Houweling et al., 2008). Regarding different levels of bimanual movements evidence from single unit recording in monkeys indicated that interhemispheric coupling, i.e., correlation of activity between both M1, is stronger in movements with equal contributions than unequal contributions (Cardoso de Oliveira et al., 2001). Similarly, in a human MEG study, Gross et al. (2005) reported increased activation between left and right M1 for bimanual movements with equal in comparison to unequal contributions (in simple wrist extension and flexion). These results have also been confirmed in finger (sequence) tapping (Houweling et al., 2010a; Kajal et al., 2017; van Wijk et al., 2012) and rhythmic tasks (Rueda-Delgado et al., 2017).

In recent years, M1 is not only seen as the major source of executing voluntary movements, but as an adaptive and dynamic brain region (Bhattacharjee et al., 2021). Most relevant for the scope of this thesis, is that M1 contributes to acquisition of new motor skills as reported by animal (Donchin et al., 1998; Kermadi et al., 1998; Kermadi et al., 2000; Li et al., 2001; Nudo et al., 1996) and human studies (Andres et al., 1999; Zich et al., 2018) investigating unimanual and bimanual motor learning. Further, M1 has shown to increase excitability during bimanual learning measured with TMS (Neva et al., 2012). The few studies investigating bimanual

motor learning in electrophysiology studies reported increased activation in both sensorimotor cortices after learning (Andres et al., 1999; Boonstra et al., 2007). The involvement of M1 in learning new skills implies that M1 is adaptive and facilitates short term and long term changes (Sanes & Donoghue, 1997, 2000). This becomes particular evident when M1 is impaired, e.g., in stroke patients, when motor skills are (re-)learned (Sanes & Donoghue, 2000).

Taken together, M1 is primarily involved in executing uni- and bimanual movements. M1 is not static but a dynamic and adaptive brain region. Since M1 is highly connected to the premotor as well as to parietal and somatosensory areas, M1 converts signals of motor intentions and sensory feedback into movements and enables us to learn new skills.

1.2.2 Supplementary Motor Areas and Premotor Areas

Premotor areas (Broca's area 6) are highly interconnected with M1. These include the premotor cortex (PMC) and supplementary motor cortex (comprising both the supplementary motor area (SMA)-proper and pre-SMA) which are located anterior of M1 not corresponding to specific gyral or sulcal boundaries.

The PMC has been demonstrated to be involved in selecting (Halsband et al., 1993) and preparing voluntary movements (Halsband et al., 1994). Specifically, it has been shown that activity in the PMC increases with movement preparation and decreases after movement execution (Weinrich & Wise, 1982). Further, the PMC can be divided into ventral and dorsal areas which are thought to have distinct roles in preparing and executing movements (Davare et al., 2006; Roland & Zilles, 1996). In addition, some studies suggested that left and right PMC differ functionally, however no consensus has been reached yet (Deiber et al., 1997; van den Berg et al., 2010). For bimanual movements the involvement of the PMC has been reported consistently (Kermadi et al., 2000; Koeneke et al., 2004). In a recent study, it has been suggested

that left dorsal PMC is dominant in motor planning, whereas right dorsal PMC is relevant for fine-tuning bimanual coordination (Verstraelen et al., 2021). However, as this is initial work, further studies need to confirm the role of left and right ventral and dorsal PMC for bimanual movements and bimanual motor learning.

The SMA has been studied intensely and has been shown to be of particular importance for bimanual movements and bimanual motor learning (Brinkman, 1984; Freund, 1990; Stephan et al., 1999). The SMA is located at the medial wall and anterior to the M1 leg area, see Figure 1.2. The SMA has direct connections to the corticospinal tract (Dum & Strick, 1991; Wise, 1996), to motor neurons (Dum & Strick, 1996), and is closely connected to M1 (Luppino et al., 1993) and basal ganglia (Akkal et al., 2007). Both SMAs are strongly interconnected via the Corpus Callosum (Penfield & Welch, 1951; Rouiller et al., 1994). Additionally, the SMA contains a map of the contralateral sides of the body (not as detailed as the motor map in M1) and tends to be recruited with its counterpart on the opposite hemisphere (Immisch et al., 2001; Jäncke et al., 2000a; Sadato et al., 1997). In line with this, electric stimulation of unilateral SMA elicited complex movements of both sides of the body, e.g., stepping (Fried et al., 1991; Penfield & Welch, 1951).

That the SMA seems to be activated with its counterpart on the opposite hemisphere has been one of the reasons why the production of coordinated bimanual movements have been traditionally attributed to the SMA (Dum & Strick, 2002). Anatomical, animal electrophysiology, and lesion data seemed to support this (Brinkman, 1984; Freund, 1990; Rouiller et al., 1994; Stephan et al., 1999; Tanji et al., 1988; Tanji et al., 1987). However, growing evidence from neuroimaging (in humans) and single cell recordings (in animals) did not confirm a specialisation of the SMA in bimanual coordination (Donchin et al., 1998; Immisch et al., 2001; Jäncke et al., 2000a; Sadato et al., 1997). Instead, studies found that the SMA is recruited as a function of task complexity because the SMA is also (although

not to the same extent) involved in unimanual tasks (Sadato et al., 1997) or in the coordination of arm and leg (on the same body site) (Debaere et al., 2001). That the SMA is recruited as a function of complexity would also be consistent with the finding that rhythmic movements with unequal, i.e., rather complex, compared to equal, i.e., less complex, contributions between hands are associated with greater activation in the SMA (Gross et al., 2005; Immisch et al., 2001; Sadato et al., 1997; Ullén et al., 2003). Similarly, studies have also provided evidence that the SMA is playing a key role in learning complex motor skills (Hikosaka et al., 1996; Jueptner et al., 1997); specifically, the SMA shows increased activity with learning (Matsuzaka et al., 1992; Sakai et al., 1998).

Many other aspects of motor control have been attributed to the SMA, see Nachev et al. (2008) for a review. Some of those include movement preparation or planning (Gerloff et al., 1997; Picard & Strick, 1996; Tanji, 1996; Tanji & Shima, 1994) as well as task switching (Jäncke et al., 2000b; Rushworth et al., 2002). The multi-functionality of the SMA indicates that it is involved in 'higher-order' motor control critical for motor learning, i.e., select and execute movement combinations, which holds true for unimanual as well as bimanual motor learning (Gerloff & Andres, 2002; Koeneke et al., 2004).

1.2.3 Basal Ganglia and Cerebellum

The role of subcortical motor areas such as the cerebellum or basal ganglia for bimanual coordination is less well established (Kraft et al., 2007). However, there is evidence to suggest that the basal ganglia and cerebellum play a key role in bimanual movements and bimanual motor learning, as they are part of the motor network and responsible for the smooth execution and learning of skilled movements (Cardoso de Oliveira, 2002; Debaere et al., 2004; Tracy et al., 2001; Ullén et al., 2003).

The basal ganglia are a collection of subcortical nuclei that are part of cortico-subcortical circuits. As such, they directly receive input and project back to cortical regions including sensory, motor, and premotor areas (Alexander et al., 1986; Middleton & Strick, 2000). Basal ganglia are suggested to filter motor plans. Specifically, basal ganglia are thought to suppress neural signals for undesired movements and enhance neural signals for desired movements (Mink, 1996). This also points to a role in motor learning (Marsden, 1982). In particular, evidence suggests the role of basal ganglia in the initiation of voluntary movement by coordinating the timing and the designation of specific muscles (Jueptner & Weiller, 1998; Wichmann & DeLong, 1996). The role of the basal ganglia in bimanual movements does not seem to be different to their role in unimanual tasks (Cardoso de Oliveira, 2002; Kraft et al., 2007).

The cerebellum receives information directly from the spinal cord and from corticospinal axons descending from the cortex. The cerebellum is thought to play a crucial role in movements and motor learning, specifically in adaptation and error correction (Bijsterbosch et al., 2011; Debaere et al., 2004; Schlerf et al., 2012). Cerebellar regions are likely to assist M1 in executing bimanual coordination via indirect connections to (pre)motor regions and thalamus (Matelli & Luppino, 1996; Matelli et al., 1989). Thereby, it is not surprising that the cerebellum also plays a key role in bimanual movements (Debaere et al., 2004; Pollok et al., 2007; Tracy et al., 2001; Ullén et al., 2003). The functional role of cerebellar activity seems to depend more on certain task requirements (Meyer-Lindenberg et al., 2002; Nair et al., 2003; Sadato et al., 1997; Tracy et al., 2001; Ullén et al., 2003). Specifically, cerebellar activation has been found to increase when the coordination demands increase, i.e., when movements are performed with unequal compared to equal contributions between hands and cyclic movement are performed with higher frequency (Debaere et al., 2004). Frequency- and velocity-dependent

activation changes in the cerebellum have been reported for uni- and bimanual movements before (Jäncke et al., 1999; Jenkins et al., 1997; Sadato et al., 1996; Turner et al., 1998). Together, these observations suggest that the cerebellum plays a key role in the timing and coordination of movements with particular focus on adapting and correcting errors.

1.2.4 Corpus Callosum

The corpus callosum (CC) is the largest white matter structure in the brain, consisting of approximately 250 million fibres and connecting brain areas of both hemispheres (Jarbo et al., 2012).

Since the CC connects both hemispheres, the CC plays a key role in bimanual coordination. The role of the CC in bimanual coordination has been primarily studied when the CC was damaged or absent, i.e., in split brain patients. Preilowski (1972) showed that patients generally performed worse than healthy controls when training a complex rhythmic task with both hands. Specifically, for movements with equal contributions between hands, split brain patients struggled to keep both hands in a simultaneous rhythm relying heavily on visual feedback. For a long time, split brain patients were the only cohort in which the influence of the CC on bimanual interactions was studied.

Recently, studies using non-invasive neuroimaging techniques, such as diffusion-weighted imaging (DWI), shed light on the correlation between CC structure and bimanual coordination in healthy cohorts (Gooijers et al., 2013; Johansen-Berg et al., 2007; Sisti et al., 2012). Specifically, Gooijers et al. (2013) demonstrated that when learning a complex rhythmic task, bimanual performance was significantly correlated to the microstructural properties of the primary motor and occipital region of the CC. A review by Gooijers and Swinnen (2014) evaluated the research on linking CC structure to bimanual coordination. They largely confirmed the

importance of CC substructures projecting to premotor and primary sensorimotor areas in bimanual coordination. However, they did not find a more specific link between CC substructures and different levels of bimanual interactions, i.e., equal and unequal contributions between hands. Gooijers and Swinnen (2014) attributed this to age-related as well as training- and pathology-induced changes affecting the individual's CC structure and thereby mediating a link between the CC structure and bimanual coordination. This is in line with findings by Johansen-Berg (2010) demonstrating that the link between the structure of CC with behaviour (other than bimanual coordination) was mediated by genetics and training-induced changes.

Taken together, the CC plays a vital role in bimanual movements and bimanual motor learning as it connects both hemispheres and facilitates inter-hemispheric communication. The specific roles of the CC substructures in the context of bimanual interactions have yet to be determined.

1.3 Communication in the Motor Network

A number of brain areas are involved in generating a rich variety of (learned) bimanual movements. To enable highly diverse movements and enable motor learning, regions of the motor network dynamically modulate their activity as a function of task demand and task features. The change in activity seems to depend on internal factors (e.g., age and expertise level) and external factors (e.g., task complexity and difficulty) (Debaere et al., 2004; Serrien et al., 2007). Neural activity in the motor network is dynamically modulated through temporally aligned neural firing. It is believed that the synchronous rhythms of thousands of neurons passes information across short (i.e., intrahemispheric communication) and long-range communication (i.e., interhemispheric communication, via the CC) (Engel & Singer, 2001; van Wijk et al., 2012). Synchronization is described with an amplitude, frequency, and phase, i.e., as oscillations, Figure 1.3A. Hypothesis about

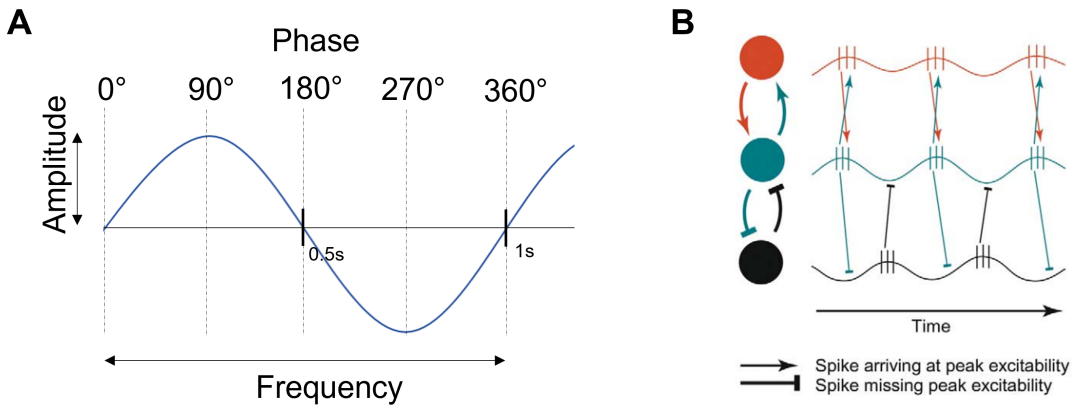


Figure 1.3: Communication in the Motor Network is thought to be mediated via oscillations. **(A)** Amplitude, phase, and frequency of one cycle of an oscillation. **(B)** According to the communication through coherence theory, neuronal groups fire in synchrony and therefore communicate effectively (orange and green). When neuronal groups do not fire in synchrony, they do not communicate effectively (black and green). Modified and adapted from Fries (2005).

the functional role of neural oscillations include, amongst others, the communication through coherence (CTC) theory (Fries, 2005, 2015). According to the CTC theory, neural oscillations in multiple brain regions align in frequency and phase (Fries, 2005, 2015). This alignment, also known as coherence or synchrony, has been proposed to be a central mechanism for inter-regional communication (Fries, 2005, 2015). According to the CTC theory, when aligned (i.e., in synchrony) regions communicate effectively, whereas if they are not aligned (i.e., in de-synchrony) regions do not communicate effectively, see Figure 1.3B. Animal and human work strongly support the CTC theory (Bosman et al., 2012; Womelsdorf et al., 2007). However, there are also limitations to the theory. For instance, the communication between regions is limited physically, e.g., by a conduction delay. Specifically, when two regions are communicating it takes time for a signal to be transmitted from one region to the other. This has important implications for measuring inter-hemispheric communication. I discuss these aspects in the context of bimanual coordination in chapter 4.

1.3.1 Role of Beta Activity

For both movement and motor learning, sensorimotor activity in the beta band is of particular importance for neural communication (Cheyne, 2013; Engel & Fries, 2010; Neuper & Pfurtscheller, 2001). Beta activity ranges from 13-30 Hz and both, spontaneous and task-induced, fluctuations in power (i.e., strength of synchronization) have been reported (van Elswijk et al., 2010). Regarding the task-induced fluctuations, beta power decreases prior to and during movement execution (event-related desynchronisation, ERD) and increases after movement termination (event-related synchronisation, ERS) (Neuper & Pfurtscheller, 2001; Pfurtscheller & Da Silva, 1999). Moreover, beta activity seems to play a role in motor learning, as ERD/S becomes more pronounced with unimanual learning (Tan et al., 2014; Zich et al., 2018). Research on the beta activity in bimanual movements and bimanual motor learning is sparse. However, the evidence from finger tapping, force production or rhythmic tasks supports the hypothesis that beta activity is important in bimanual movements (Gross et al., 2005; Houweling et al., 2008; Rueda-Delgado et al., 2017) and bimanual motor learning (Andres et al., 1999; Boonstra et al., 2007; Serrien & Brown, 2002). Specifically, beta activity has been reported to show condition-specific effects with stronger beta activity in bimanual movements than in unimanual movements (Gross et al., 2005; Houweling et al., 2008). Further, within the bimanual conditions, beta activity was stronger in conditions with unequal compared to equal contributions between hands (Gross et al., 2005; Rueda-Delgado et al., 2017). This was also confirmed in studies measuring the interhemispheric connectivity in the beta band, indicating stronger interhemispheric connectivity between both M1 in bimanual conditions with unequal compared to equal contributions between hands (Serrien, 2008a; Serrien & Brown, 2002; Serrien et al., 2003). In some studies investigating bimanual motor learning, beta activity strengthened with learning (Andres et al., 1999; Boonstra

et al., 2007), however results are inconsistent (Gerloff & Andres, 2002; Houweling et al., 2008) and need further investigation, see chapter 6 for more information. In this thesis, I aim to address this by studying the role of beta activity in bimanual movements and bimanual motor learning.

Beta activity and its functional role has been interpreted in many different ways (Cheyne, 2013). Amongst others, beta activity has been portrayed as epiphenomenal and simply reflecting an idling rhythmic activity that is disrupted before and during, and enhanced after movement (Chen et al., 1998; Gilbertson et al., 2005; Neuper et al., 2006; Pfurtscheller et al., 1996). Further, beta activity has been understood as the representation of the status quo in the motor domain (Engel & Fries, 2010). In a recent review by Barone and Rossiter (2021), the authors followed the status quo hypothesis arguing that beta activity could be an active process functioning as a top-down inhibitory rhythm. Consequently, they interpreted the decrease in beta activity during movements as necessary to release inhibition and initiate a motor plan, and the beta activity after movement (beta rebound) to preserve the motor state from noise (Barone & Rossiter, 2021). Others suggested that beta activity (after movements) might be an indicator of somatosensory processing (Alegre et al., 2002; Baker, 2007; Cassim et al., 2001), or an index of confidence in the prediction of a motor outcome (Tan et al., 2016). However, no consensus has been reached yet. Nevertheless, as outlined above, there is evidence that beta activity is functionally relevant for movements and motor learning. This role is further underlined by clinical studies. For instance, patients with Parkinson's disease suffer from symptoms such as tremor, rigidity, and bradykinesia (i.e., slowness of movement) and freezing of gait (i.e., moments with inability to initiate movements). The symptoms are thought to originate in excessive beta activity in subcortical areas such as basal ganglia (López-Azcárate et al., 2010). Often no other intervention than invasive beta deep brain stimulation (DBS) is available for patients. Further

evidence from stroke patients indicated that beta activity plays a functional role in movements. Specifically, Rossiter et al. (2014b) could show that beta activity during motor performance was significantly weaker in stroke patients in comparison to controls. Similarly, Laaksonen et al. (2012) and Parkkonen et al. (2018) reported that the beta activity after movement (beta rebound) was significantly weaker in the stroke affected hemisphere compared to the healthy hemisphere. These studies point out that impaired motor control is accompanied by impaired beta activity. This emphasized that beta activity might be causally relevant for movements and motor learning and should be a target for neurorehabilitation after stroke. The latter was underlined by Zich et al. (2017) who modulated beta activity in chronic stroke using neurofeedback at home.

In recent years, beta activity has also been interpreted as transient high-power burst events (Jones, 2016; Shin et al., 2017; van Ede et al., 2018). A recent trial by Little et al. (2013) demonstrated major clinical improvements when using DBS specifically during beta bursts (compared to continuous beta DBS). This highlighted the clinical importance of beta bursts. With regard to bimanual movements, it is reasonable to assume that behavioural performance is improved when bursts are coupled across hemispheres, also described as burst coincidence (Tinkhauser et al., 2020). However, research investigating the spatial spread of bursts (Little et al., 2019; Zich et al., 2020) and burst coupling across regions (Seedat et al., 2020; Tinkhauser et al., 2020) has just begun and needs more extensive investigation.

Taken together, it is reasonable to assume that beta activity plays an important role in bimanual movements and bimanual motor learning. In this thesis, I thereby aimed to study the role of beta activity in bimanual movements and bimanual motor learning.

1.3.2 Role of Other Frequencies

Besides the beta frequency band, frequencies at the alpha or mu (8-12 Hz) and gamma (30-100 Hz) band have been shown to be involved in motor tasks. For the scope of this thesis, they are only mentioned briefly. For more information see Nowak et al. (2018) for a review on gamma oscillations, Mierau et al. (2017) on alpha oscillations and Cheyne (2013) for a review on both.

Since their discovery by Hans Berger in 1929, alpha oscillations have been extensively investigated. For (bimanual) movements, alpha/mu and beta activity differ (Debaere et al., 2004; Pollok et al., 2007; Pollok et al., 2005). Further, alpha/mu ERD is spatially more widespread, i.e., to the region somatotopic attributed to the movement than beta activity (van Wijk et al., 2012). So far, the functional role of alpha/mu activity has been interpreted as a correlate for perceptual filtering such as attention (Peylo et al., 2021; Romei et al., 2010) and a general inhibition of task-irrelevant regions (Klimesch et al., 2007; Pfurtscheller et al., 1996). This is in contrast to beta activity which is rather attributed to define movement parameters (such as speed) (Brown, 2000; Rossiter et al., 2014). Therefore, alpha/mu activity seem to play a rather indirect role in movement control, see Mierau et al. (2017) and Klimesch et al. (2007) for a review.

Gamma oscillations in the human motor cortex were first described by Crone et al. (1998) and subsequently confirmed in invasive recordings (Miller et al., 2007; Pfurtscheller et al., 2003; Szurhaj et al., 2005; Szurhaj et al., 2006) as well as Electroencephalography and Magnetoencephalography recordings (Cheyne & Ferrari, 2013; Darvas et al., 2010; Muthukumaraswamy, 2010). The results of these studies are generally in agreement that movement related gamma synchronisation occurs for the duration of the movement and is spatially specific and temporally more congruent than alpha or beta activity (Miller et al., 2009; Muthukumaraswamy, 2010). The functional role of gamma activity is not yet understood. However,

in recent publications the importance of gamma activity (Zich et al., 2021) and theta-gamma coupling (Akkad et al., 2019) for motor learning has been highlighted.

1.4 Bimanual Motor Learning and Neural Plasticity

As stated above, bimanual movements are associated with activation of the motor network. When learning to perform a bimanual task, learning-related changes are associated with changes in the temporal domain in the motor network (Gerloff & Andres, 2002). These learning processes are mainly mediated by neural plasticity. Neural plasticity is defined as the brain's ability to adapt its structure, function and connections in response to experience and other external influences. Neural plasticity is relevant for this thesis for two reasons.

Firstly, neural plasticity plays a vital role for motor learning most likely regulated by neural oscillations (Dayan & Cohen, 2011; Guerra et al., 2019). In particular, it has been shown that cortical excitability is modulated by the early stages of learning, i.e., up to 30 min (Classen et al., 1998; Kleim et al., 2004), whereas motor map reorganization and synapse formation occurred at late stages of learning, i.e., after months and years (Kleim et al., 2004).

Secondly, neuroplastic changes are thought to explain the effects of brain stimulation techniques such as transcranial alternating current stimulation (tACS) (Moliadze et al., 2010; Veniero et al., 2015; Zaghi et al., 2010), see chapter 2 for more information. TACS is a tool used in this thesis aiming to modulate oscillatory activity.

1.4.1 Hebbian Synaptic Plasticity

Neural plasticity is mediated through systematic strengthening of synaptic connections, a process first described by Donald Hebb in 1949. Strengthening of

synaptic transmission is known as long-term potentiation (LTP), while weakening of a synaptic connection is referred to as long term depression (LTD). Both processes depend on the timing of activation between pre- and postsynaptic membrane. If the timing of activation is synchronous, the synaptic connection is strengthened, whereas if the timing of the activation is not synchronous, the synaptic connection is weakened. The results are either in more (LTP) or less (LTD) receptors on the postsynaptic membrane, or in case of LTP even in creation of new synapses or dendritic spines.

Similarly, motor learning depends on plasticity of neurons and circuits within the motor system. LTP-like effects have been shown following motor learning paradigms, including the creation of new synapses and dendritic spines (Hayashi-Takagi et al., 2015; Kleim et al., 2002; Xu et al., 2009). Specifically, plasticity in M1 is likely to occur due to horizontal synapses spanning over the region constructing dynamic motor maps (Huntley, 1997; Jacobs & Donoghue, 1991; Sanes & Donoghue, 2000). The weakening and strengthening of synaptic connections may be a mechanism of optimising neural efficiency for learned movements, thus allowing finer control over movements.

1.5 Aims of this Thesis

Many tasks are available to study bimanual interactions from simple finger tapping to complex coordination paradigms. When coordination patterns become more complex and deviate from simple tasks, they require learning to be performed quickly and accurately. Learning bimanual movements induces learning-related changes in the motor network such as changes in their communication mediated by neuroplastic processes. Since these processes are highly understudied in learning complex cooperative bimanual movements, this thesis aims to investigate their behavioural and neurophysiological underpinnings using a novel task.

Chapter 2 elaborated on the conceptual development and design of the novel task. Further, I discussed different neuroimaging techniques to measure bimanual motor learning, and brain stimulation techniques to modulate bimanual motor learning. I further outlined the use of online experiments and a bimanual competence questionnaire.

In chapter 3, I tested the novel task to characterise the learning patterns for the different levels of bimanual interaction.

In chapter 4, I investigated if the learning-related changes induced by the task could be modulated with non-invasive brain stimulation (i.e., tACS). This question was investigated using a double-blind sham-controlled study.

For chapter 5, I developed an online version of the task to measure how variability in training effected learning and the transfer to different transfer tasks. I used a large sample (N=450) to probe this question with a complex design.

In chapter 6, I aimed to characterise the underlying neural activity of learning the different levels of bimanual interaction with MEG.

Lastly, in chapter 7, I summarised the findings presented in the experimental chapters 3 to 6, stated the key conclusions and gave an outlook for future research.

2 Methods

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2.1 Novel Bimanual Motor Learning Task

To study complex bimanual motor learning, a novel bimanual motor task was designed. The task was developed to capture unimanual learning and different levels of bimanual learning to directly compare equal and unequal contribution of hands (see Figure 2.1). The design was inspired by Doost et al. (2017) who

adapted the unimanual version from Lefebvre et al. (2012).

The task was created to be used in the laboratory and adapted for an online experiment. This section elaborates on the design and structure of the in-lab and online version of the task, followed by the measures of the dependent variables and conceptual choices leading up to the task design.

2.1.1 Task Design and Trial Structure

The task was implemented as a racing game to increase task engagement and commitment as context-dependent effects on motor control have been shown to be important (Steinberg & Vogt, 2015). In the task, a cursor was navigated through a path of six streets tilted in different angles. Cursor movement was enabled using both hands while each hand controlled the movement on the x- and y-axis separately, see Figure 2.1A.

The six streets per path, i.e., one trial, were tilted in different angles and thereby corresponded to different ideal left:right hand ratios, see Figure 2.1A,C. Specifically, in the **unimanual condition** (*Uni*), the 0° and 90° angled streets corresponded to an ideal ratio of 0%:100% between hands and thereby only one hand was needed to navigate the cursor. In the **bimanual equal condition** (Bi_{eq}), both hands were required with an equal contribution, i.e., ideal ratio of 50%:50% between hands, to navigate the cursor on the 45° tilted streets, see Figure 2.1B. In the **bimanual unequal condition** (Bi_{uneq}), both hands were required with an unequal contribution to navigate the cursor, e.g., with an ideal ratio of 25%:75% between hands in streets angled at 22.5° and 67.5°.

For the online version of the task, as described in chapter 5, the set of five streets (0°, 22.5°, 45°, 67.5°, 90°) were extended to different sets of streets with an angular difference of up to 2° between streets, see Figure 2.1A. For the sets of streets with street angles 0°, 22.5°, 45°, 67.5°, 90° ideal hand ratios were identical

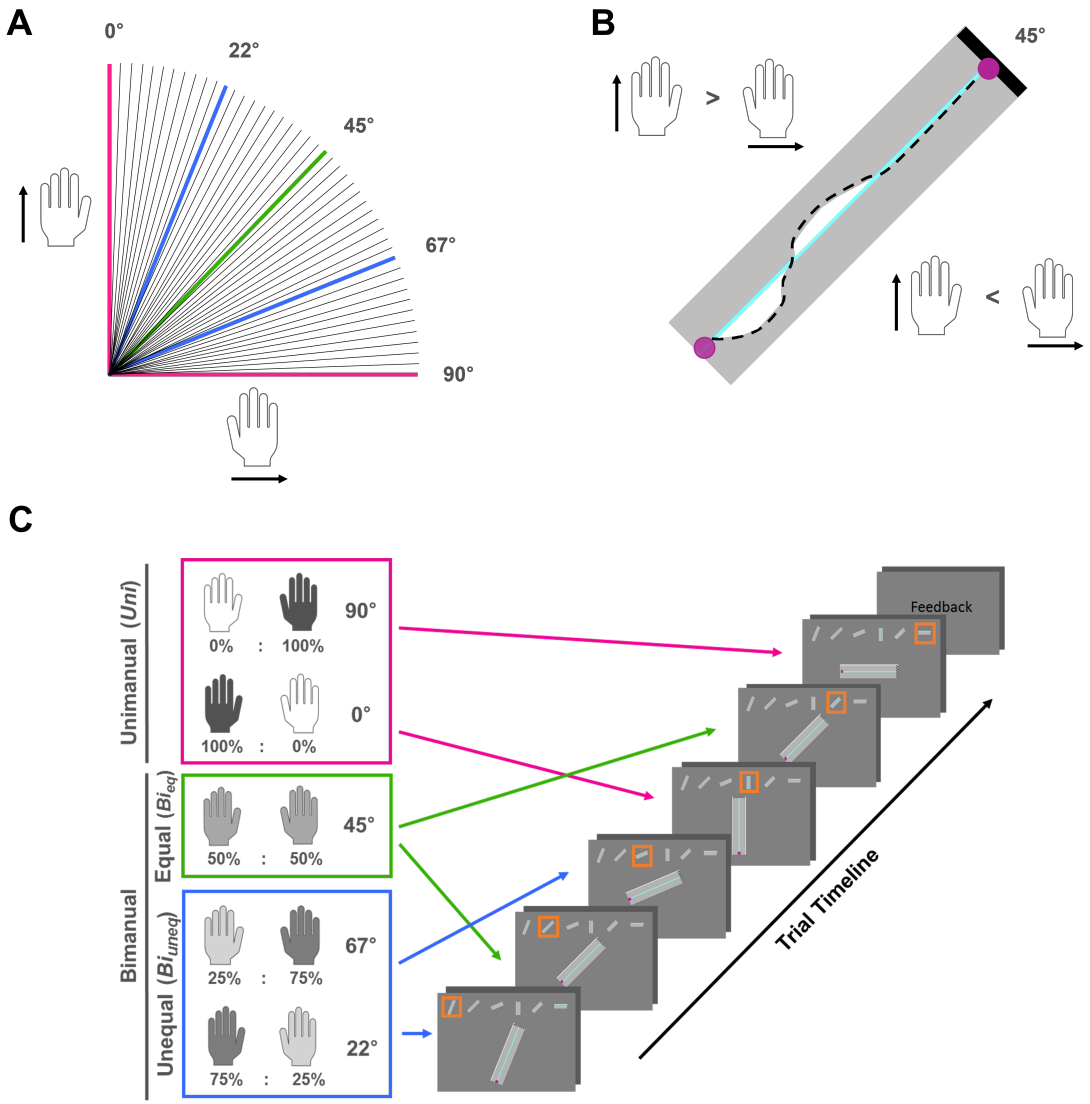


Figure 2.1: Design and structure of the novel bimanual motor learning task. In the task, a cursor had to be navigated across a path of streets in different angles. (**A**) Each hand controlled a different axis on the screen, e.g., left hand controlled upward movement and right hand controlled rightward movement. Street angles were scaled from 0° to 90° with an angular difference of 22.5° for the in-lab version (*Uni*: pink; Bi_{eq}: green; Bi_{uneq}: blue) and up to 2° for the online version (black). The street angles corresponded to specific contributions between hands. (**B**) Specifically, in an angled street of 45°, an equal contribution between hands, i.e., 50%:50%, was required to move the cursor from the starting position to the end of the street. If the contribution between hands was not 50%:50%, the cursor deviated from the midline and was measured as error (white). As an example, the cursor deviated to the left if more force was used in the left hand. Movement time was measured from movement onset to offset, i.e., dashed line from transparent to opaque cursor. (**C**) The task included three levels of bimanual interaction (*Uni*, Bi_{eq}, Bi_{uneq}). Force of one hand (100%:0%) was required for the street with 0° and 90° (*Uni*), an equal amount of force between hands (50%:50%) in the street of 45° (Bi_{eq}) and an unequal amount of force between hands (25%:75%) for the streets rotated in 22.5° and 67.5° (Bi_{uneq}). One trial consisted of six streets and after each path was finished, feedback on movement time and error was presented.

to those in the in-lab version as described above. For other streets, the ideal hand ratios were adapted accordingly. As an example, in the street of 2° and 98° an ideal ratio of 2%:98% between hands was required.

For the in-lab and the online version of the task, the six streets of one path were pseudo-randomized. To ensure similarity in street-to-street transitions, concurrent streets had a minimum angular difference of 22.5° and two unimanual conditions or two bimanual equal conditions did not follow upon each.

Throughout the trial, the whole path was displayed at the top of the screen (if not stated otherwise, see chapter 6). The current street was highlighted by an orange frame and displayed enlarged in the middle of the screen. At the beginning of each street the cursor was at the starting position (i.e., the middle of the width of the street), see also Figure 2.1B. If the cursor hit either side of the street, it was reset to the starting position. When the cursor reached the end of the street (i.e., last 5% of the whole length of the street), the next street started immediately (or with a 5 s inter-trial interval, see chapter 6). After each path was finished, i.e., after six streets, feedback on the performance of this trial (time and accuracy) was provided visually on the screen. The inter-trial interval was self-paced, therefore, participants could decide on their own when to start the next path. The main task in each session, during which subjects learnt to navigate the cursor quickly and accurately along the streets was termed the **training task**.

2.1.1.1 Curved Streets

For the online version of the task, to investigate if learning on the training task transferred to differently shaped streets, curved streets were developed (see chapter 5). Curved streets had the same dimensions, i.e., length and width, as the straight streets. Curved streets had a curvature of 40°, 50° and 55° to allow for upwards and rightwards cursor movement (without backwards movement). Those three curved streets were rotated at 180° to obtain six streets for each trial. The midline of

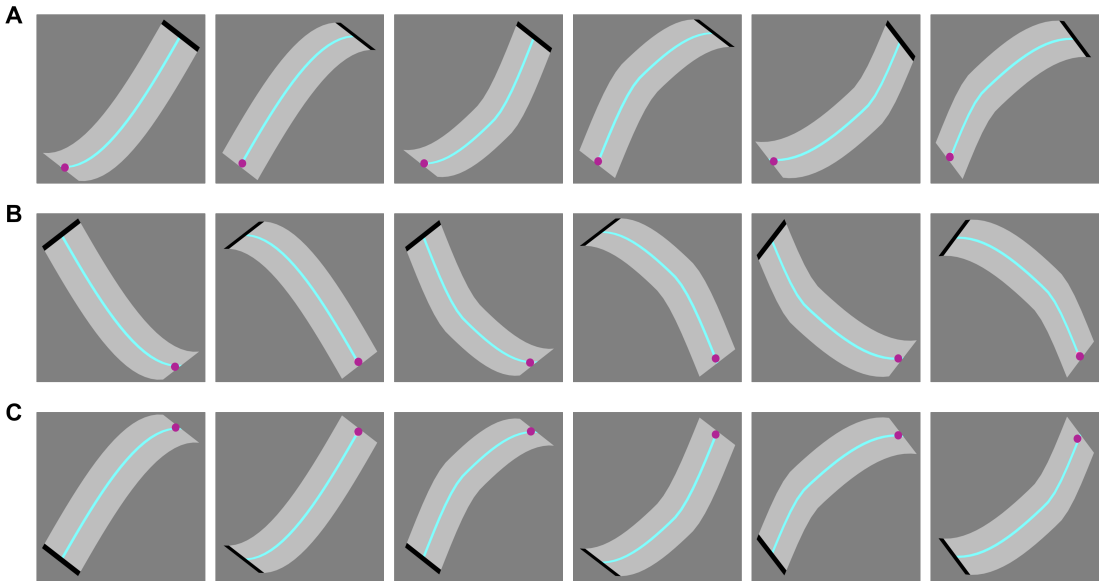


Figure 2.2: Design of the curved streets. Curved streets had the same dimensions as straight streets and were developed with a curvature of 40°, 50° and 55°. The resulting three curved streets were rotated at 180° to obtain six streets for each trial (**A**). Curved streets were mirrored to the left (**B**) as well as to the left and down (**C**) to measure transfer of learning to different movement directions.

the street (ideal line) was parallel and the end of the street (last 5% of the length of the street) was perpendicular to the outer boarders of the streets, as in the straight streets, see Figure 2.2A. To test transfer of motor learning with different transfer tasks, i.e., tasks with increasing difference to the training task, movement directions of the cursor were changed. To enable movement to different directions (left and up as well as left and down), the curved streets were transposed to require movements to the left and up (Figure 2.2B) as well as to the left and down (Figure 2.2C). Specifically, one transfer task tested transfer to curved streets oriented to the same movement direction as straight streets, i.e., right and up (Figure 2.2A). One transfer task tested transfer to curved streets with one movement direction changed, i.e., left and up, (Figure 2.2B). One transfer task tested transfer to curved streets with both movement directions changed, i.e., left and down, (Figure 2.2C). This allowed to test transfer of motor learning to transfer tasks with increasing difference from the training task.

2.1.1.2 Screen and Window Size in the Online Experiment

Computer screens are a variety of different sizes, e.g., 1366 x 768 pixels or 1920 x 1080 pixels, with the most common aspect ratio of 16:9. In-lab, the screen size was fixed to the screen resolution of 1366 x 768 pixels. When conducting experiments online, screen sizes, and therefore the sizes of the study window, i.e., window in which the online study runs, vary between participants (Anwyl-Irvine et al., 2020a). Thus, the optimal units for creating and displaying stimuli are those that scale relative to the different study window sizes, such as height units. Two examples of different study windows sizes are given: With dimensions of a screen with standard 16:9 aspect ratio, the full screen study window ranges from [-0.6667 height units, -0.5 height units] in the bottom left to [+0.6667 height units, +0.5 height units] in the top right. For a standard widescreen (16:10 aspect ratio), the full screen study window ranges from the bottom left [-0.8 height units, -0.5 height units] to the top-right [+0.8 height units, +0.5 height units]. When using height units for creating stimuli, the size of stimuli is automatically scaled relative to the height of the participants' study window (Peirce, 2021). Thereby, height units have a clear advantage over using centimetres or normalised units, as stimuli scale with study window size and remain square (independent of the screen used by the participant).

2.1.1.3 Response Devices

To enable cursor movement in-lab and online, different response devices were implemented. In-lab, bimanual force grippers were used. Online, in the absence of any force grip devices in participant's homes, two keys on the computer keyboard were used. For both force grippers and keys, movement along the x- and y-axis was controlled separately, i.e., one response device (i.e., one key or one gripper) controlled the vertical movement and the other controlled the horizontal movement.

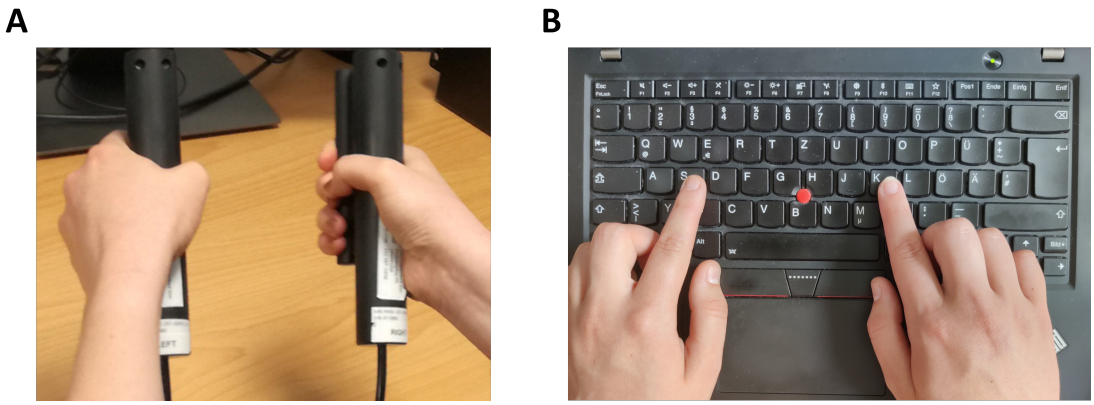


Figure 2.3: Response devices for the task were either force grippers (**A**) or computer keys S and K (**B**).

In-lab, force grippers were calibrated to the participant's maximum force by squeezing the grippers five times as hard as possible. Each gripper was calibrated individually and specifically to the hand holding the gripper. 15% of the participant's maximum force was needed, to enable any movement of the cursor. If participants applied 100% of their maximum force, the cursor would move 25 pixels per refresh rate of the monitor (60 times per second). Participants had to release the force down to 2% of their maximum force between the streets in order to get the next street displayed.

Online, key presses were set on 'K' and 'S' of the computer keyboard. To keep the experience of coordinating both hands and moving the cursor similar to the force grippers, an acceleration rate was implemented. The keys were used with an acceleration rate of 0.001 height units (relative to the height of the study window, see section 2.1.1.2 for more information). Specifically, when holding a key, the cursor would accelerate 0.001 height units per refresh rate of the monitor (60 times per second). This would be at a same rate for x- and y- axis. Therefore, the velocity was relative to the time the key was pressed and would potentiate. Maximum velocity was set to 0.3 height units. If the keys were released, the cursor decreased its velocity gradually in the same rate until it stopped to move.

2.1.2 Conceptual Development

Here, I will focus on the conceptual design of the task, discussing different choices when designing the task.

2.1.2.1 Cursor Movement Design

In the task, a cursor was navigated along a path consisting of six streets. To move the cursor along the street to the end, simultaneous and cooperative contributions between hands were required, i.e., diagonal movement was not possible without the other hand. In order to operationalize cooperation between hands, participants' force was used. Force offered a simple, intuitive way of measuring responses and contribution of each hand in comparison to the other hand. To measure force, response devices such as force grippers offered a continued measurement, e.g., in contrast to a button press (Koeneke et al., 2004). When using key presses in the online version of the task, acceleration was used to mimic a continued movement of the force grippers, i.e., by pressing the keys longer, cursor movement became faster. Measuring a continued movement had the advantage of assessing the processes and dynamics of learning, with particular importance for the MEG data collection, see chapter 6.

Force grippers or accelerated key presses enabled cursor movement within the streets in one plane on the horizontal and vertical axis, e.g., upwards and rightwards. If the cursor hit either side of the street, it was reset to the starting position. An alternative to this would have been to use bi-directional movements. As an example, in a task design with bi-directional movements, one gripper would control upward cursor movement with increasing force, whereby releasing force would lead to downward cursor movement. The other gripper would control rightward cursor movement with increasing force, whereby releasing force would lead to leftwards cursor movement. However, having to adjust the force within one hand instead

of between them, potentially led to error correction in each hand individually, i.e., a within-hand error correction, instead of a between-hand error correction, i.e., adjusting one hand to the other (Diedrichsen, 2007). Thus, potentially, bi-directional movements might not aim at cooperating the force between hands. In contrast, resetting the cursor to the starting position had the advantage of encouraging a strategy of trial-and-error until the optimal contribution of each hand was learned. With the optimal contribution of each hand, the end of the street, i.e., goal, was reached and the next street was displayed. Further, resetting the cursor had the advantage of preventing that the cursor moved outside the street or along the sides of the street to the goal, i.e., reaching the goal without learning the optimal contribution between hands.

2.1.2.2 Trial Structure Design

In the task, the trial structure of six consecutive streets was chosen to avoid memorisation. Motor learning tasks are usually performed with many repetitions to induce learning (Doost et al., 2017; Mueller et al., 2009; Preilowski, 1972). It is likely that these repetitions reinforce learning an association between visual cues, e.g., street angles, and motor commands, e.g., hand ratios. Thus, specific motor memories, rather than generic bimanual motor coordination are learned which has already been recognized by Doost et al. (2017). Therefore, in the task described here, the streets of a path were displayed individually and their order was pseudo-randomized to avoid memorisation. In addition, this trial structure had the advantage of allowing analysis on the trial level, i.e., performance over the six streets per path, and the conditions, i.e., street performance, separately.

The task was implemented as a racing game as context-dependent effects in motor control have been shown to be important (Steinberg & Vogt, 2015). To introduce a feeling of a racing game experience and to increase task engagement, the whole path was displayed at the upper end of the screen. Further, the six streets

per trial were displayed immediately after one another, i.e., when one street was finished and force was released, the next street was displayed promptly. A pause between trials was introduced when feedback was displayed after finishing one trial.

2.1.2.3 Self-Paced Design

Learning complex motor skills necessitate attention (Rowe et al., 2002) and should depict a natural way of transition from trial to trial. Therefore, trial to trial transitions were self-paced without fixed inter-trial-intervals. This assured that no data were lost because participants were simply not ready or paying attention to start the next trial. Further, the self-paced design allowed participants to take a short pause in between trials.

2.1.3 Dependent Variables

For each path (i.e., trial) and street, several dependent variables were measured. Dependent variables were computed online, i.e., during the performance of the task, to provide feedback and offline, i.e., after data collection were finished, for data analysis. To provide feedback, the sum of the whole path was calculated and displayed after each path was finished. For offline data analysis, the calculation was carried out separately for each street and then averaged on different levels, i.e., trial level or condition level as specified in each experimental chapter.

Movement Time

Movement time was defined as the time (in seconds) from movement onset to offset of the cursor. Further, movement time included all resets, i.e., more resets increased movement time, see description of the reset index below. For calculating the movement time for the whole path, the time from movement onset to offset of the cursor of all six streets was summed.

Error

Error was defined as the difference of the cursor from the ideal line (midline of the streets), see Figure 2.1B highlighted in white.

For the straight streets, the error was calculated with Heron's Formula for the area of a triangle:

$$\begin{aligned} s &= \frac{(a+b+c)}{2} \\ A &= \sqrt{s \cdot (s-a) \cdot (s-b) \cdot (s-c)} \\ A\triangle &= \frac{(2 \cdot A)}{a} \\ Error &= RMS(A\triangle) \end{aligned} \tag{2.1}$$

Heron's formula calculates the area of a triangle using the length of the three sides of the triangle. The length of the three sides of the triangle were calculated as follows:

$$\begin{aligned} a &= \sqrt{((End(x) - Start(x)^2) + (End(y) - Start(y))^2)} \\ b &= \sqrt{((ballPos(x) - Start(x))^2 + (ballPos(y) - Start(y))^2)} \\ c &= \sqrt{((ballPos(x) - End(x))^2 + (ballPos(y) - End(y))^2)} \end{aligned} \tag{2.2}$$

For the curved streets, the difference of the cursor from the midline was found with the nearest neighbour, i.e., smallest distance from the midline, using Pythagoras theorem:

$$distance = \sqrt{((ballPos(x) - Midline(x))^2 + (ballPos(y) - Midline(y))^2)} \tag{2.3}$$

For both curved and straight streets, the error was computed at every time point of the street (sampling rate = 60 times per second) and combined across time points using the root mean square. To calculate the error for one path, i.e., one trial, the errors of all six streets were summed up.

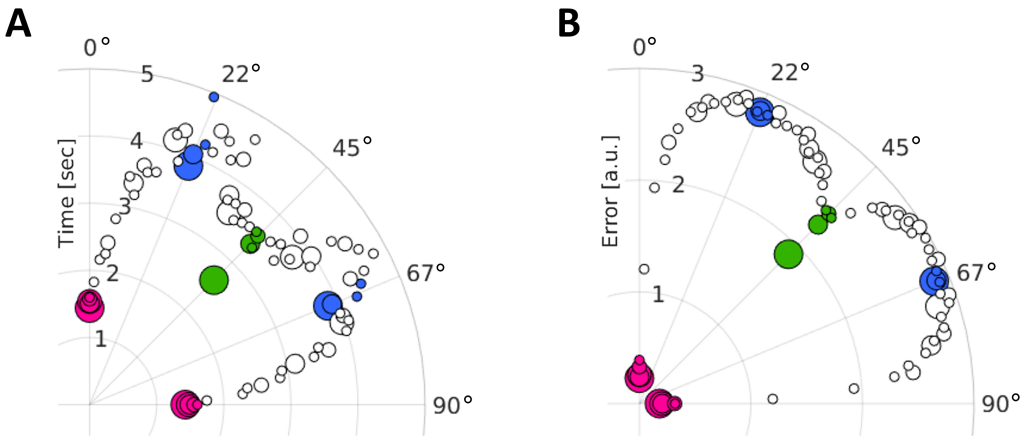


Figure 2.4: Angle difficulty, i.e., performance of each street angle averaged over occurrence and participants (ranging from 0° to 90°) in movement time (**A**) and error (**B**) in the online experiment. Circle colour indicated the street angle (*Uni*: 0°, 90°, pink; Bi_{eq}: 45°, green; Bi_{uneq}: 22.5°, 67.5°, blue; all other angles: white). Circle size corresponded to the occurrence of street angles within one training task, e.g., for the training task with five street angles, the circle size was the biggest (i.e., higher occurrence of each street angle in this training task) in comparison to the training task with 46 street angles with the smallest circle size (i.e., lower occurrence of each street angle in this training task). This figure illustrated the lowest movement time and error (lowest difficulty level) for streets tilted in 0° and 90° (*Uni*) and highest movement time and error (highest difficulty level) for the streets in Bi_{uneq}, tilted in angles ranging from 10° to 40° and 50° to 80°.

Reset Index

In addition, the number of times the cursor was reset to the starting position in each street, was measured independently as the reset index. However, for this data analysis the reset index was included in movement time, i.e., more resets increase movement time.

Denoising Dependent Variables in the Online Experiment

In the online version of the task, data showed systematic inter-trial variance that was not due to learning but due to angle difficulty. As an example, streets angled at 0° and 90° required one finger/key press to navigate the cursor. By nature, those streets were easy to perform and led to low movement time and low error, see Figure 2.4A,B for comparison of street angle difficulty. However, those streets were

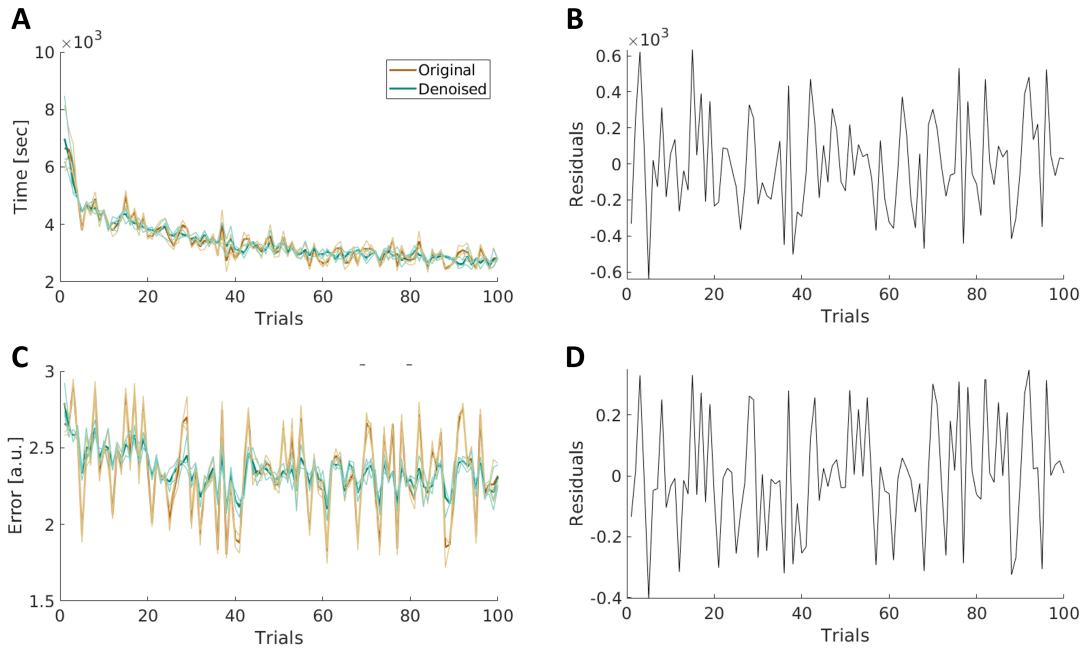


Figure 2.5: Example of the group level performance in one of the training tasks (training task with 15 streets) indicated systematic inter-trial variation in movement time (above) and error (below). (**A,C**) Systematic variations occurred in original group level data (yellow) in each of the three groups that performed the same training task (thin lines) and averaged over those three groups (bold lines). After subtracting the residuals from the original data, data was denoised (green). (**B,D**) Resulting residuals of the fitted linear regression that were subtracted out of single subject data.

not present in each trial (for some training tasks). Therefore, periods of low error and low movement time, i.e., troughs, see Figure 2.5B,D in yellow, systematically occurred in group level data depending on the presence or absence of streets of 0° and 90°. The opposite occurred with streets of the Bi_{uneq} condition. As these streets required an unequal contribution between hands, they were more difficult to perform and led to systematic periods of high error and high movement time, i.e., peaks, see Figure 2.5B,D in yellow, in group level data. To ensure a learning-related effect was measured (and not inter-trial variance), data were denoised.

To denoise data, the difficulty of each trial was weighted by averaging each angle across occurrence and participants. The resulting angle weight was then assigned according to the angle order of each trial. In other words, each trial had a

specific order in which street angles appeared, e.g., 45°,90°,56°,0°,33°,67° and the angle weights were assigned accordingly. The assigned angle weights per trial were averaged which resulted in a trial weight, i.e., trial difficulty. This had the advantage, that a specific weight per trial was given depending on the composition of angles in each trial. Thereby, trial weights accurately depicted the trial's difficulty. With the trial weights and group level performance in movement time and error, a linear regression was fitted (Matlab function fitlm(x,y)) for each training task separately. The resulting raw residuals ($r=y-y_i$) accurately depicted the trial difficulty in each training task and were subtracted from single subject data to denoise data, see Figure 2.5A,C. The advantage of this denoising method was that no data points were lost, and single subject variance remained in the data, see Figure 2.5B,D in green. After denoising, data analysis was carried out as described in chapter 5.

2.2 Online Experiments

Online experiments are gaining increasing attention due to their relative ease and the ability to collect large volumes of data in a short time (Anwyl-Irvine et al., 2020a). While online experiments have been conducted largely in the context of (cognitive) psychology, the field of motor learning has lagged behind. This might be due to the assumption that experimental control is lost in online data collection and that this loss is problematic for kinematic data, as suggested by Tsay et al. (2021). However, first evidence demonstrates close correspondence between the results obtained online with those conducted in the laboratory (Tsay et al., 2021). This was further underlined by studies systematically testing for differences between laboratory and online studies indicating high comparability in terms of precision and accuracy of timings for visual and auditory stimuli or response times (Anwyl-Irvine et al., 2020a; Bridges et al., 2020). To ensure successful online data acquisition three critical components are outlined here: creating, hosting, and recruiting (Sauter et al., 2020).

JavaScript is the programming language of choice to create online experiments. A graphical user interface (GUI) is often provided by platforms like Gorilla, that enables users to drag-and-drop modular components into an experimental sequence. As this only allows simple and often insufficiently flexible experimental designs, a tool for more complex experimental designs is needed. The prime candidate for transition from in-lab to online testing is PsychoPy Builder (Peirce, 2007; Peirce et al., 2019; Peirce & MacAskill, 2018). In order to use PsychoPy for creating online experiments, sections in which Python based scripting are used, need to be rewritten into JavaScript by the experimenter. In PsychoPy builder, the translation from Python to JavaScript is automatically done. This is a big advantage over other experiment builders that either only allow simpler study designs as Gorilla

(Anwyl-Irvine et al., 2020b), or for which the translation into JavaScript is non trivial, e.g., with MATLAB.

In order to host experiments online, many servers and server platforms are available such as Pavlovia, Amazon Mechanical Turk (MTurk) (Crump et al., 2013), Gorilla (Anwyl-Irvine et al., 2020b) and others. Online experiments need to be hosted on a server for the experimental setup and continued maintenance. Using a platform simplifies the hosting process, the automated data storage and the creation of a unique study website link. When choosing a hosting platform, factors to be considered are the cost, flexibility, and ease of use. Commercial services such as Gorilla are generally user-friendly but expensive and only allow use of their own, often inflexible and simplistic experimental builders. Pavlovia is a non-commercial low-cost hosting service that is user-friendly and has a built-in option to link PsychoPy experiments directly to Pavlovia's servers. When experimental code is uploaded as a HTML or JavaScript file to the Pavlovia server, a unique study link is provided from which the study is ran. Pavlovia is connected to a Gitlab repository which allows to manage versions and track issues. Study data, i.e., outcome measures, and logs, i.e., details about time and date of participation, are also saved in the same repository. Therefore, Pavlovia, has significant advantages over other hosting platforms especially when used in conjunction with PsychoPy Builder which is why the experiment described in chapter 5 was hosted on Pavlovia.

In order to recruit study participants, online participant recruitment platforms like Prolific (Peer et al., 2017), MTurk or gorilla (Anwyl-Irvine et al., 2020b) are available. On any of these platforms, the study is distributed to participants that meet inclusion criteria set by the experimenter. For the purpose of chapter 5, Prolific was used due to its transparency, usability, and multiple pre-screening options (Palan & Schitter, 2018). In addition, a study by Peer et al. (2017) showed that Prolific's participants are more honest, more internationally diverse, and less exposed to

common research tasks as compared to participants on other platforms (including MTurk). On Prolific, a link to the study website is provided alongside the study description, and participants use the link to access the study. Prolific will provide only eligible participants with the study link. Upon entering the study website, participants read through the participation information form. This is followed by an online consent form in which participants are presented with a list of statements that need to be ticked. Only participants who give informed consent are able to proceed to the task. Upon completion of the study, the experimenter approves the study performance and participants get paid via Prolific. Participants can withdraw their participation at any time without providing a reason by closing the browser window. Prolific allows pre-screening and provides full anonymity, i.e., each participant has a unique Prolific ID consisting of random numbers and letters. To communicate with participants, messages can be exchanged via the platform. Next to the many advantages listed above, Prolific not only provides a platform to find eligible study participants but verifies and monitors participants study behaviour to ensure data quality, e.g., approved rate of performance in other experiments.

Together, obtaining experiments online require knowledge about advantages and disadvantages of experimental builders for creating studies, of server hosting platforms and of recruitment platforms. Once set up and thoroughly validated, i.e., by piloting instructions, inspecting timing measurements and data quality, online experiments provide a useful tool for collecting large samples of data in a short time.

2.3 Measuring Electrical Properties of the Brain with Electroencephalography (EEG) and Magnetoencephalography (MEG)

Neurons, specifically cortical pyramidal neurons, communicate with each other via continuously changing dendritic currents, i.e., postsynaptic potentials (Baillet et al., 2001; Hämäläine et al., 1993). Those changing currents give rise to an electric and a magnetic field that can be recorded from outside the head (Cohen, 1968).

Electroencephalography (EEG) is a method to measure the electrical properties of the brain. Magnetoencephalography (MEG) is a tool to measure the brain's electromagnetic properties. In contrast to MEG, recording the brain's electrical field with EEG is relatively simple, and has been used extensively in scientific studies and clinical practice since its first description in humans by Hans Berger in 1929.

Recording the brain's magnetic field with MEG is more difficult as the brain's magnetic field strength is about 10 to 100 times smaller than the earth's magnetic fields, meaning that MEG requires a magnetically shielded room (EEG needs only shielding from electric distortions) for recording. The use of MEG was first described in 1968 by David Cohen who quantified the brain's magnetic fluxes with a combination of advanced and already available techniques. Being able to record the magnetic field that neurons induce, advanced the research on the brain's properties significantly. In subsequent years, the quality of MEG recordings was increasingly improved by the development of SQUIDs (superconducting quantum interference devices). When cooled down (-270°) with liquid helium, SQUIDS are extremely sensitive to magnetic field change and thereby enhance the detection of the brain's very small magnetic field. SQUIDs are coupled with superconducting pickup coils, which act like antennae. When a magnetic signal from the brain traverse the coils, it induces current that is then measured by the SQUID and converted into a digital signal.

While in the case of EEG, the electrodes are placed in a cap and onto the scalp, state-of-the-art MEG systems contain sensors in a helmet-shaped dewar and are not attached to the scalp. In the (Elekta) MEG system used to collect the data in this thesis, there are a mix of gradiometers (axial and planar) and magnetometers arranged in whole-head arrays of 306 independent channels, simultaneously sampling at 8 kHz. Gradiometers and magnetometers have different sensitivity profiles. Magnetometers (and axial gradiometers) create a dipolar pattern next to the source and zero right above the source, whereas planar gradiometers are most sensitive right above the source. This means that magnetometers are most sensitive to deep brain sources, while simultaneously being more sensitive to magnetic noise, whereas gradiometers are better at noise reduction. Since the signals recorded by the MEG depend on the location and orientation to neural sources, registration of the participant's head shape and monitoring the head position in the helmet is crucial for good data quality. The head position is usually measured with head position indicator (HPI) coils. The necessity to monitor the participant's head position represents a clear practical difference from EEG, which measures differences of scalar electrical potentials between electrodes attached to the scalp. Although the head's shape and size vary between individuals, in EEG the electrode montages are standardized and scaled to the individual anatomy and with a common nomenclature (Niedermeyer, 2011). As an example, electrodes are usually placed on standard positions on the surface of the head with letters (F: frontal, O: occipital, P: parietal, T: temporal, Z: midline) and numbers (odd numbers left, even number right).

Both EEG and MEG have high temporal resolution in the range of milliseconds. Unlike EEG measures, however, the magnetic fields recorded by MEG pass through dura, skull, cerebrospinal fluid, and scalp relatively unaltered and are thereby less spatially 'smeared', meaning that MEG has a better spatial resolution than EEG. This increased spatial resolution allows for a clearer interpretation of MEG

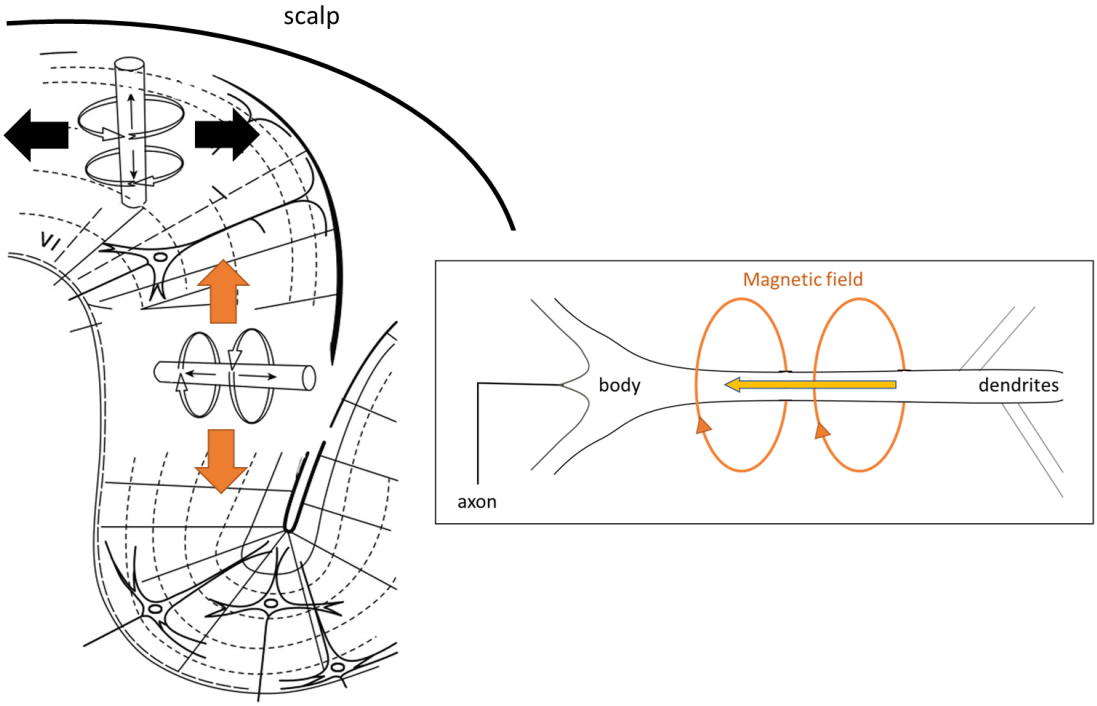


Figure 2.6: Schematic illustration of the relationship between the direction of current and resulting magnetic field in the crown and the sulcus of the cortex. (**Left**) The sources in the sulcus causing tangential fields can be detected with EEG and MEG (orange), whereas sources at the top of the gyrus cannot be detected with MEG but EEG (black). (**Right**) In the idealized pyramidal neuron intracellular current is flowing to the soma. Orange ellipses represent the magnetic field generated by the intracellular current. Adapted and modified from Hansen et al. (2010).

sensor topography in terms of anatomical locations of its underlying brain sources in comparison to EEG (Baillet, 2017).

2.3.1 Biophysical Events Measured with M/EEG

Neurons generate spatially and temporally varying electrical currents. M/EEG signals are thought to reflect mainly the summation of postsynaptic potentials (Baillet, 2017), potentially layer V neurons in the case of MEG (Murakami & Okada, 2006). However, in order to detect a signal with M/EEG a population of approximately 10,000-15,000 cortical neurons need to be synchronized (Murakami & Okada, 2006).

Further, the folding of the cortex and the orientation of neurons with respect

to the skull are of particular importance, see Figure 2.6. MEG is most sensitive to magnetic fields that are perpendicular to the skull, i.e., tangential sources. EEG is sensitive to both perpendicular and tangential neurons and maximally sensitive to radial sources on gyral crowns. Further, MEG primarily detects the magnetic fields induced by intracellular currents, whereas scalp EEG is sensitive to electrical fields generated by extracellular currents. This has significant impacts for measuring specific brain regions.

2.3.2 Beta Peak Frequency Detection with EEG

For the purpose of the thesis, EEG was used to detect participants individual beta peak frequency. Consecutively, brain stimulation application was informed, see chapter 4. To detect the individual's beta peak frequency during an experimental session, i.e., while the participant was present, data collection and analysis pipeline were simple and optimised for its purpose (see detailed description in chapter 4).

In brief, EEG data were collected with a modified Emotiv (www.emotive.com) system (De Vos et al., 2014; Debener et al., 2012; Zich et al., 2015), whereby the original hardware was relocated into a small and light box. The small size of the box meant it could be inserted into a small pocket at the back of an EEG cap. Thereby, the setup was similar to a mobile EEG setup which has shown good data quality (Debener et al., 2012). Additionally, this had the advantage of allowing EEG recording in the brain stimulation laboratory without an electrically shielded room. This practical advantage led to the decision to use EEG instead of other electrophysiological recordings such as MEG.

Data analysis were performed during the experimental session and thereby needed to be relatively fast and simple, i.e., possible to run on a standard laptop in a short period of time. The analysis was conducted using MATLAB (Mathworks Inc., Natick, MA, United States) and EEGLAB14-1-1b (Delorme & Makeig, 2004). Artefacts,

i.e., very high and very low noise and further residual artefacts, were filtered out and data were epoched into segments relative to the movement of the task with baseline correction. To assess the beta peak frequency, time-frequency plots for each of the EEG channels were visually inspected and the frequency with the strongest movement-induced event-related desynchronization was selected. This simplified protocol sufficiently fulfilled the purpose of detecting the beta peak frequency of participants during the experimental session. As EEG was only recorded from three channels on each brain hemisphere, a more extensive data analysis was not feasible.

2.3.3 Source Level MEG Data Analysis

MEG measures the time variation of the magnetic field caused by electrical currents in the brain, i.e., postsynaptic potentials, over the head. These signals can be analysed in many ways and although techniques for MEG data analysis are still emerging, some attempts have been made to standardize state-of-the-art analysis protocols (Gross et al., 2013).

For the thesis, MEG data are analysed at sensor level to evaluate data quality and additionally on source level as source level provides a higher signal-to-noise ratio. Source estimation aims to identify the neural sources, i.e., brain areas, generating the signals recorded by the MEG sensors. However, there are several issues with this approach, referred to as a mathematical 'inverse problem'. First, several configurations of neural sources could generate the same signal (same magnetic field). Second, certain configuration of neural sources will not produce measurable signals, i.e., due to the location and orientation of the source. Third, to measure these large number of signals, only a limited number of sensors is available. Thereby, independent of how high data quality is and how many sensors are used, not all relevant currents in the brain are detectable. Different approaches have been found to overcome the problem, see for a full description Baillet et al. (2001) and Hansen

et al. (2010). To overcome the inverse problem, all source estimation methods need a description of how magnetic fields propagate from the source to the sensors, which is referred to as a mathematical 'forward problem', see for a full description Mosher et al. (1999). In the following, I briefly outline the preprocessing and data analysis steps used for the purpose of this thesis, see chapter 6 for full description as well as parameters and settings.

2.3.3.1 Preprocessing MEG Data

To detect high quality signals, i.e., with a high signal-to-noise ratio, extensive preprocessing steps are necessary to clean MEG data from noise and artefacts (Gonzalez-Moreno et al., 2014). The preprocessing pipeline used was based on the analysis pipeline of Quinn et al. (2018) and is briefly outlined here (see full description, use of software as well as parameter settings in chapter 6). The preprocessing pipeline included the method of maxfiltering which is performed to separate noise occurring from the environment, i.e., noise of the MEG scanner location, from the brain signal. Maxfiltering also corrects for head movement of the participant which was measured with specific coils (HPI coils). Further, data preprocessing included downsampling to reduce computational demands. Thereafter, data were high- and low-pass filtered to remove slow trends and high-frequency noise respectively. Other artefacts were detected automatically with an automatic algorithm ensuring reproducibility and avoiding user bias. This automatic outlier detection used is called the generalised extreme studentized deviate method (Rosner, 1983) and uses the maximum number of outliers limited to 20% of the data. Additional de-noising was performed with an independent component analysis (ICA). In brief, ICA is a model-free technique, i.e., independent of the underlying time-series features such as the task, that decomposes data into additive non-Gaussian subcomponents. Each component explains the data to a certain extent and assumes to be statistically independent from one another. Each component is

displayed as a time series and a spatial map, i.e., topography. Those components with a high correlation with the electrooculogram (EOG), i.e., eyeblinks, lateral eye movements, and electrocardiogram (ECG), i.e., heartbeats, are visually detected as bad components. When detected as bad, those components get rejected from the data, i.e., their time-course is regressed out. For further preprocessing, sensor normalization of Magnetometers and Planar-Gradiometers was performed as the two sensors have different magnitudes. The different magnitudes needed to be normalised to improve later data analysis. To normalize data, the eigenvalue decomposition across sensors was performed and data were divided by the smallest eigenvalue (Woolrich et al., 2011). To ensure that source localisation of the data were comparable across participants, data were projected onto an 8 mm grid using a Linearly Constrained Minimum Variance (LCMV) vector beamformer (Van Veen & Buckley, 1988; Woolrich et al., 2011). Many other approaches, e.g., minimum norm estimates, are available of which each has its advantages and disadvantages (Gramfort et al., 2012; Hauk, 2004; Hillebrand & Barnes, 2005; Lin et al., 2006; Stenbacka et al., 2002; Uutela et al., 1999). The beamforming approach used here discriminates between signals originating from one neural source and those generated elsewhere in the brain. Thus, it assumes that neural activation at each location is independent and uncorrelated to all other locations. These assumptions might not be physiologically possible, as neural sources might be detected by more than one sensor, however, the LCMV beamformer has shown to be a robust measurement even with correlated data (Gross et al., 2001; Van Veen et al., 1997). Further, a parcellation was performed using a customized Desikan-Killiany cortical atlas, see full description in chapter 6. At last, data were epoched (-5 s to 10 s) to the triggers indicating start and end of each trial, e.g., movement onset and movement offset of the cursor in the task. This preprocessing pipeline improved signal-to-noise ratio of data and enabled to perform next analysis steps with high quality data.

MRI Co-Registration

For source estimation, MEG is often combined with magnetic resonance imaging (MRI). This assures that the MEG data are accurately registered to the individual's brain anatomy. This is not trivial, as participants' brain anatomy varies significantly. Registration between structural MRI and MEG data were performed with RHINO (Registration of Headshapes Including Nose) which uses superficial fiducial points as well as additional head shape points that are collected before MEG data collection. As fully outlined in chapter 6, in the MEG experiment described in this thesis, head positions were assessed using five head position indicator (HPI) coils attached to the head of the participant. HPI coil locations, roughly 200 head positions from across the head and three anatomical fiducial locations (nasion, left and right pre-auricular points) were digitalized using a magnetic Polhemus FastTrak 3D system (VT, United States).

To be able to register MEG data to a structural MRI, the scan needs to be a volumetric scan with recognized high neuroanatomic fidelity (such as T1-weighted gradient echo) and a field of view including face, ears, and entire scalp such that an accurate identification of superficial fiducial points is possible (Singh, 2014). In the absence of an individual T1 scan, a MNI152 standard-space T1-weighted average structural template image can be used.

2.3.3.2 Time-Frequency Analysis

Many M/EEG studies extensively studied time-locked-evoked or event-related potentials (ERPs) or magnetic fields (ERFs), see for a review (Schomer & Da Silva, 2012) but are not outlined here. Instead, for the purpose of the thesis, the association between neural oscillations and movements is investigated using time frequency analysis, see chapter 6. Time-frequency analysis is a conventional method to detect the frequency spectrum present shortly before and shortly after a time

period of interest, e.g., movement onset and offset of the task. Thereby, event-related changes, i.e., power changes, can be detected that occur in response to the experimental task. These power changes are not necessarily phase-locked and will not be represented in other measurements, i.e., ERPs or ERFs (Tallon-Baudry & Bertrand, 1999). Thereby, time-frequency analysis is performed to visualize event-related power changes, e.g., event related (de-)synchronization (ERD/S) to provide information about the local distribution in time, frequency, or space. Calculating time-frequency of power can be performed in multiple ways, see for a review Le Van Quyen et al. (2001) and Bruns (2004). For the purpose of the thesis, I used conventional dpss-based multitaper. For each time window the power was calculated, averaged and corrected to a baseline, i.e., before movement onset, see chapter 6 for more information.

2.4 Modulating Brain Activity Using Transcranial Electric Stimulation

Transcranial electric stimulation (tES) is the collective term for a group of non-invasive brain stimulation techniques thought to modify brain activation. TES includes transcranial direct current stimulation (tDCS), alternating current stimulation (tACS) as well as others that are not discussed here, e.g., random noise stimulation. Among tES techniques, tDCS has received the most attention. TDCS involves applying a direct current to the brain and has shown behavioural relevant effects (Paulus, 2011). Only in recent years, tACS has gained increasing attention due to its potential to directly interfere with cortical rhythms, see Antal and Paulus (2013) for a review. In comparison to tDCS, tACS involves applying an alternating current at a certain frequency. TACS is thought to entrain neural oscillations, which has been shown to lead to behaviourally relevant effects, see for a review Herrmann et al. (2013) or Antal and Herrmann (2016). The use of tES, including tDCS and tACS, is safe at low intensities and during or after their application no serious adverse events have been reported (Antal et al., 2017; Nitsche et al., 2003). For the purpose of this thesis, I focus on tACS as this method is particularly well suited to modulate physiologically relevant brain oscillations.

2.4.1 Transcranial Alternating Current Stimulation (tACS)

Generally, it has been argued that if any given oscillations were essential for any cognitive function, this cognitive function should be altered by selectively interfering with the given oscillations (Sejnowski & Paulsen, 2006).

TACS allows to systematically test this hypothesis, as it is thought to modulate spatio-temporal dynamics of neural activity. Specifically, spatial dynamics are targeted via placement of electrodes on the head and temporal dynamics are targeted with specifying waveform parameters such as frequency, phase, or amplitude. By

optimizing stimulation parameters to the spatial and temporal dynamics of ongoing neural activity in the brain, tACS could potentially test causal roles of neural oscillations in behaviour, see for a review Riddle and Fröhlich (2021).

In the past decade, the effects of tACS on sensorimotor and cognitive processes have been systematically tested to demonstrate a causal nature of the oscillation and behaviour relationship. Those include perception (Feurra et al., 2011; Helfrich et al., 2014a; Kanai et al., 2008; Laczó et al., 2012; Neuling et al., 2012), motor (Joundi et al., 2012; Pogosyan et al., 2009; Wach et al., 2013) and cognitive processes (Polania et al., 2012; Santarnecchi et al., 2013; Sela et al., 2012). For the purpose of this thesis, I investigated if tACS can modulate learning-related changes in the bimanual task.

2.4.2 Mechanisms of tACS

TACS involves applying an external sinusoidal current (Antal & Paulus, 2013) and is thought to entrain cortical network connectivity (Antal & Herrmann, 2016; Herrmann et al., 2013). Specifically, the application of tACS is thought to shift the ongoing activity in the brain towards the amplitude, phase, and frequency of the stimulation (all relative to the amplitude, phase, and frequency of the ongoing oscillation) (Ali et al., 2013; Antal et al., 2008; Ozen et al., 2010; Reato et al., 2013; Weinrich et al., 2017), see Figure 2.7. This entrainment effect is maximised when stimulation frequency matches the ongoing neural oscillation (Thut et al., 2011; Zaehle et al., 2010).

Since tACS stimulation is applied in the kHz range, i.e., a relatively weak electric field, the stimulation is thought not to directly interfere with oscillatory activity, but to interfere with the membrane excitability of neurons (i.e., polarization). In this scenario, on the level of the populations of oscillators (as recordable with M/EEG) in-phase adjustment as well as amplitude increase would occur. In vitro and in vivo animal studies have demonstrated that electric fields of sinusoidal

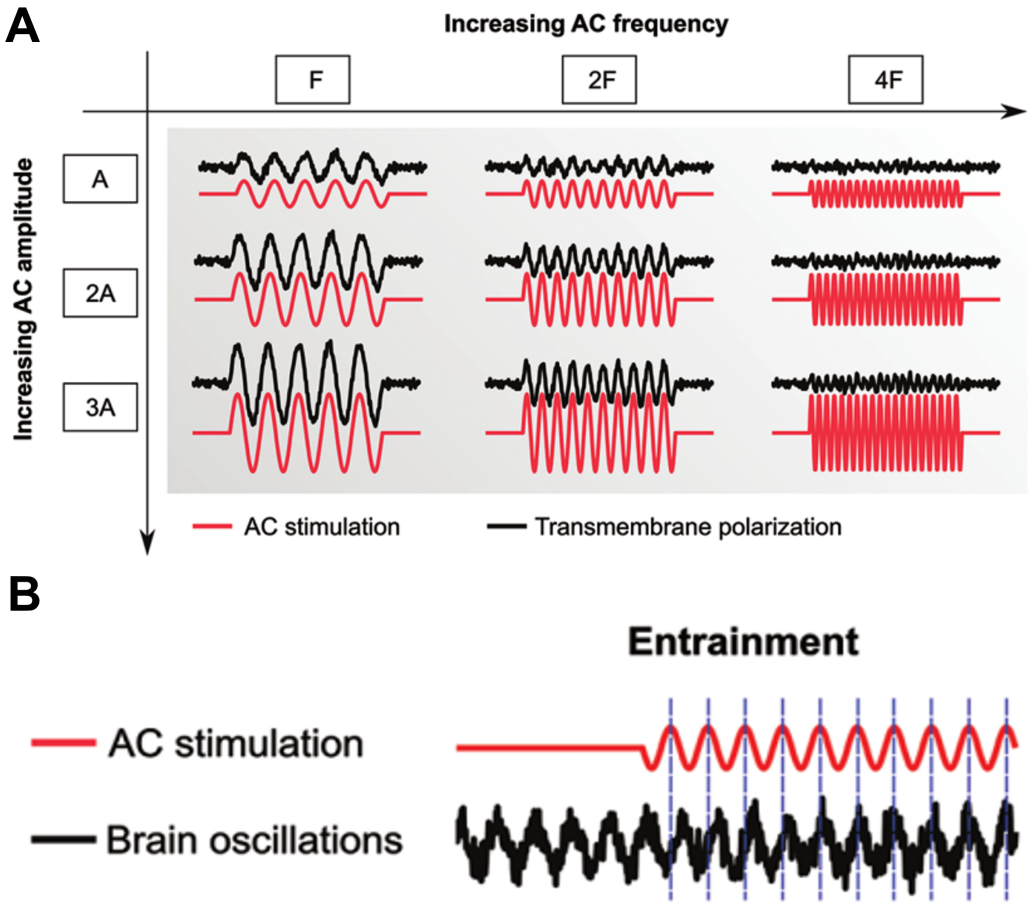


Figure 2.7: Schematic illustration of the effect of tACS on neurons. (**A**) Sinusoidal electrical stimulation (red) modulates the membrane polarization (black). The membrane polarization increases with increasing amplitude (A, 2A, 3A) and decreases with stimulation frequency (F, 2F, 4F). (**B**) The stimulation entrains the oscillations by shifting their phase or modulate its power at the stimulation frequency. Modified and adapted from Reato et al. (2013).

currents generate states of depolarization and hyperpolarization relative to the resting membrane potential (Fröhlich & McCormick, 2010). The polarizing of neurons proportionally increases with the stimulation intensity, see Figure 2.7A. This mechanism is also plausible for the application of tACS in humans which induces oscillations in resting membrane potential towards more depolarized and more hyperpolarized states. Recent studies in humans seem to confirm that tACS modulates behaviour. Concurrent tACS-fMRI approaches have been successful in

providing causal evidence that synchronised power fluctuations contribute to the formation of fMRI-based resting state networks (Bächinger et al., 2017). In line with this, further studies have demonstrated, that tACS changes the connectivity between brain areas (Antal et al., 2008; Weinrich et al., 2017). In addition, although technically challenging, evidence from studies using tACS with concurrent EEG and MEG demonstrated that tACS synchronises cortical oscillators with similar intrinsic frequencies to the entrainment frequency (Helfrich et al., 2014b; Neuling et al., 2015; Soekadar et al., 2013; Witkowski et al., 2016). Similarly, tACS modulated phase coherence between stimulated regions (Helfrich et al., 2014a). Thereby, tACS seem to be the prime candidate to modulate oscillatory activity in the brain and thereby study its link to behaviour.

2.4.3 Stimulation Properties

As tACS has the potential to modulate neural oscillations, maximising the modulation effects by optimally targeting the neural oscillations of interest is essential. In this section, I outline the parameters relevant for the tACS application used in chapter 4.

Frequency

TACS can be applied at a wide frequency range from 5 to 250 kHz. Conventionally, tACS is applied at a frequency known to be relevant for behaviour as informed by electrophysiological recordings, i.e., EEG. As an example, for investigating stimulation effects on motor behaviour, stimulation is usually set at the beta frequency as it is the dominant frequency during movements known from EEG studies (Neuper & Pfurtscheller, 2001; Pfurtscheller & Da Silva, 1999), see full outline in chapter 1. Frequency specific effects have been found to be behaviourally meaningful in human (Feurra et al., 2011; Joundi et al., 2012; Pogosyan et al., 2009), animal (Reato et al., 2013), and simulation studies (Ali et al., 2013; Fröhlich &

McCormick, 2010). Feurra et al. (2011) showed that tACS applied at beta frequency, but not at other frequencies, directly influenced motor cortex physiology. Pogosyan et al. (2009) provided first causal evidence of a link between beta tACS and altered motor behaviour. Specifically, the authors reported that beta tACS applied over the sensorimotor cortex slowed voluntary movement in a unimanual visuomotor task. Similarly, Joundi et al. (2012) and Wach et al. (2013) could show that beta tACS decreased the rate of unimanual force production. Therefore, the choice of stimulation frequency relative to the ongoing oscillations frequency plays a key role in determining the effect of stimulation. This is also emphasized by the finding, that effects of tACS are most pronounced when stimulation frequency matches the ongoing frequency in the brain (Ali et al., 2013; Reato et al., 2013; Schilberg et al., 2018; Thut et al., 2011; Zaehle et al., 2010).

Phase

Some evidence shows that shifting the phase of tACS is behaviourally relevant. In studies by Polania et al. (2012) and Violante et al. (2017), theta tACS was applied to one hemisphere to alter performance in a unimanual reaction time task. The authors reported behavioural performance improved when stimulation was applied in phase synchrony, i.e., 0° phase shift between targeted areas, and declined when stimulation was applied in phase desynchrony, i.e., 180° phase shift between targeted areas (Polania et al., 2012; Violante et al., 2017). Phase synchrony between hemispheres has not been tested to such an extent but first evidence shows that in-phase stimulation, i.e., phase synchrony between hemispheres, at 10 Hz and 20 Hz benefited task switching in a bimanual tapping task (Heise et al., 2019). Helfrich et al. (2014a) could demonstrate that interhemispheric functional coherence was modulated in a phase-specific way when bilateral high-density tACS at 40 Hz was applied with simultaneous EEG recordings. Similar phase-specific effects were shown by Schwab et al. (2019) who applied bihemispheric high definition

alpha tACS. Thereby, modifying the phase of beta tACS by stimulating either in one or between hemispheres, seem to be promising to modulate behaviour. To target a specific phase of tACS, M/EEG data are preferably recorded concurrently (Neuling et al., 2017). While this approach is technically very challenging, it uniquely enables the measurement of tACS-related neural changes during and after stimulation (Kasten & Herrmann, 2019).

Electrode Montage

Conventionally, when investigating the effects of tACS in motor behaviour, the stimulation is applied with two electrodes, one active electrode above M1 and one return electrode on the forehead. When stimulating bihemispherically to measure behaviour in a bimanual task, placing the electrodes is not trivial and might be done with two stimulators. This can be further optimised in combination with differently sized electrodes and high-definition 4-1 montages (Helfrich et al., 2014a) as well as ring electrodes (Heise et al., 2016) as this stimulation is more focal. However, those montages come with their own disadvantages, e.g., amongst others, a significantly weaker electric field over the stimulation target, see Riddle and Fröhlich (2021) for a review. For the purpose of this thesis, I therefore chose a conventional montage with one electrode above the sensorimotor cortex and one above the shoulder on both sides of the body. This required the use of two stimulators each connected to one active and one return electrode resulting in a 4-electrode montage. During piloting, I explored different placements and electrode sizes. The placement above the shoulder was chosen because it minimised the sensation of phosphenes in comparison to other placements, e.g., on the forehead or cheeks. The size of the electrodes was standard 5 x 7 cm. The size was chosen as 3 x 3 cm sized electrodes induced discomfort and pain at the location of the electrodes. Stimulating bi-hemispherically, i.e., between hemispheres, introduced practical challenges as both stimulators had to start simultaneously. Thereby, an external trigger in form of a voltage impulse to

both stimulators started the stimulation. This was implemented with a specific key press on the stimulus computer.

2.5 Questionnaire on Bimanual Competence

In order to compare participant's bimanual proficiency of dexterity between hands, a measure of bimanual competence was implemented. In the absence of standard bimanual proficiency questionnaires, a self-report about a range of bimanual daily life activities was developed for the purpose of this thesis, see Appendix Figure 7.3.4. To assess participant's competence of bimanual daily life activities, participants were asked open questions including a) what sports and hobbies do you perform for which you specifically use both hands, b) do you do any keyboard typing with both hands and/or phone typing with both thumbs, c) do you play musical instruments for which you need both hands, d) do you play video games using joysticks or a controller with both hands. For each of those questions the length of performance was assessed (in years and/or months), the frequency (monthly/weekly/daily) as well as the duration per session (in hours). In order to quantify these qualitative questions, performance was encoded with a simple score from 1 to 3. A score of 1 indicated basic competence of bimanual daily life tasks (one question answered with once a week or less), 2 indicated an intermediate competence (two questions answered with once a week or less) and a 3 indicated an expert competence (two questions answered with more than once a week or more than two questions answered with once a week). The competence score enabled comparison across participants in terms of their proficiency in daily life tasks and made it possible to investigate if the competence had an effect on learning the novel task. However, it must be noted that the competence score was only a self-reported indicator of bimanual competence which was developed in the absence of standardised questionnaires.

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3

Characterising Bimanual Motor Learning with a Novel Task

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3.1 Introduction

Bimanual motor learning has been studied for decades in many different ways, see chapter 1 for a full outline. Mainly, bimanual interaction has been studied using simple finger tapping, e.g., with simultaneous and alternating tapping, flexion and extension of fingers and limbs or tapping in a specific sequence (Andres et al., 1999;

Aoki et al., 2003; Aramaki et al., 2006; Aramaki et al., 2010; Bangert et al., 2010; Eudave et al., 2017; Gerloff & Andres, 2002; Kajal et al., 2017; Shammi et al., 1998; Takeuchi et al., 2012). This gave essential insight into the fundamental principles of bimanual interactions as well as their neurophysiological underpinnings. However, the knowledge derived from these studies remains a simplification of coordination patterns which are artificial, distant to the rich variety of daily life's bimanual interactions and often do not require learning.

The few existing studies examining complex bimanual interactions that require learning have investigated rhythmic or cyclic movements using either rotating levers (Kelso et al., 1986; Sisti et al., 2011; Swinnen et al., 1998) or devices like crank handles (Fagard et al., 1985; Mueller et al., 2009; Preilowski, 1972) to draw on a screen. Specifically, rotation with equal contributions between hands, i.e., rotation patterns of 1:1, as well as unequal contribution between hands, i.e., rotation patterns of 3:1 or 3:2, were quantified (Fagard et al., 1985; Mueller et al., 2009; Preilowski, 1972; Sisti et al., 2011). This gave essential insight into the temporal aspects of rhythmic/cyclic bimanual movements. Specifically, condition specific effects were found with more accurate and faster performance in unimanual than bimanual conditions (Fagard et al., 1985; Mueller et al., 2009). Within the bimanual conditions, the condition requiring equal contributions between hands were performed more accurately compared to conditions with unequal contributions of hands (Fagard et al., 1985; Mueller et al., 2009; Preilowski, 1972; Sisti et al., 2011). Similar to the studies investigating temporal aspects, some studies investigated the production of spatially varying cyclic/rhythmic movements, i.e., by varying amplitude or direction of movements. Studies examining movement amplitude quantified movements requiring equal contributions between hands with drawing circles with the same amplitude. Movements requiring unequal contributions between hands were quantified by drawing bigger circles with one hand and smaller circles with the other hand (Heuer

et al., 2001; Marteniuk et al., 1984; Sherwood, 1994; Spijkers & Heuer, 1995). Other Studies that investigated the movement direction quantified movements that were performed in the same or opposite directions (Eliassen et al., 2000; Franz et al., 1996; Swinnen et al., 2001; Swinnen et al., 1998). Similar to the findings of the temporal aspects of bimanual interaction, the production of spatially varying movements differed across conditions. Specifically, movements requiring equal contributions between hands, i.e., same amplitude or direction, was performed easily, whereas the movements requiring unequal contributions between hands, e.g., differing amplitude or opposite direction between hands, was more difficult to perform (Marteniuk et al., 1984; Sherwood, 1994). This suggested that conditions specific effects replicated over temporally or spatially varying cyclic/rhythmic movements. However, not all our daily life tasks are cyclic or rhythmic by nature. Instead, many tasks that are performed every day require a distinct yet unique cooperative contribution of each hand for goal achievement, such as bottle opening or eating with knife and fork (Maes et al., 2017).

Cooperative bimanual interactions and their learning are highly understudied, see Obhi (2004). Some attempts have been made to develop task designs to investigate goal-directed and cooperative interactions, e.g., in which one hand stabilizes the other (Dietz et al., 2015; Johansson et al., 2006) or in which a cursor had to be navigated across a complex circuit (Doost et al., 2017). However, those studies focused on bimanual interactions requiring equal contributions of hands and did not compare these to unequal contributions between hands. Investigating both equal and unequal contributions of hands allow a richer description of bimanual movements and their learning and provides new insights into how the brain coordinates cooperative bimanual interactions. This could open up new ways to use bimanual motor learning in research of health and disease, as well as research contexts beyond the motor domain.

To advance our understanding of bimanual motor learning, a novel task was designed, as fully outlined in chapter 2. In the task, a cursor had to be navigated on a path with six streets with different angles. Cursor movement was enabled by two hand-held force grippers controlling the x-y-axes separately. The task was designed to capture unimanual learning as well as different levels of bimanual learning to compare bimanual cooperation with equal and unequal contribution of hands. The task was inspired by Doost et al. (2017) who developed their task from the unimanual version of the circuit game used by Lefebvre et al. (2012), to study bimanual motor learning with equal contribution of hands. In this chapter, I aimed to quantify unimanual motor learning and different levels of bimanual motor learning. I hypothesized, the repetitive and extensive training of the novel task would induce learning-related changes in performance. I hypothesized, performance would differ between the three conditions (main effect of condition), that learning-related changes would be evident (main effect of time), and finally that the learning-related changes would differ between the three conditions (interaction between time and condition). Further, I explored whether the bimanual skill acquired in the task was specific to the task or whether it transferred to a transposition of the axes.

3.2 Methods

3.2.1 Participants

Forty right-handed healthy participants (24 females, M=25.3 years, SD=3.55) gave their written informed consent to participate in the study (in accordance with Central University Research Ethics Committee approval, University of Oxford; MSD-IDREC-R61309/RE001) and in accordance with the Declaration of Helsinki. The number of participants was chosen based on experience and on previous studies investigating bimanual motor learning (Doost et al., 2017). Participants were monetarily compensated for their participation. They reported no history



Figure 3.1: Experimental setup. Participants were seated in a comfortable chair in front of the screen with force grippers in their hands.

of neurological or psychiatric disorders and had normal or corrected-to-normal vision. Handedness was assessed with the 10 item Edinburgh Handedness Inventory (Oldfield et al., 1971).

3.2.2 Experimental Design and Procedure

The experiment was conducted in one session, whereby participants were seated in a comfortable chair in front of the computer screen, see Figure 3.1. In the beginning of the session, the novel bimanual motor learning task was performed, as fully described in chapter 2. In brief, participants navigated a cursor across a path of six streets, see Figure 3.2B. The streets were rotated in different angles (0°,22.5°, 45°, 67.5°, 90°). The street angles corresponded to specific force ratios between hands, whereby only the force of one hand (100%:0%) was required for the street angled at 0° and 90° (*Uni*), an equal amount of force between hands (50%:50%)

in the streets angled 45° (Bi_{eq}) and an unequal amount of force between hands (25%:75%) for the streets angled at 22.5° and 67.5° (Bi_{uneq}).

Cursor movement was enabled by two hand-held force grippers, one controlling upward movement and one controlling rightward movement. Force grippers were calibrated to the participant's maximum force by squeezing each gripper five times with maximum force. Each gripper was calibrated individually and specifically to the hand holding the gripper (grippers were not swapped). To enable any cursor movement, at least 15% of the participant's maximum force was needed. If 100% of the force, i.e., maximum force, was applied, the cursor moved 25 pixels per refresh rate of the monitor (60 times per second). The force needed to be released to 2% of the maximum force between the streets in order to get the next street displayed. Movement time and error were measured as dependent variables to quantify the performance in the task, as fully outlined in chapter 2. Further, the reset index was included in movement time, i.e., more resets increased movement time.

At the beginning of the tasks, participant's maximum force was assessed. After calibration, the task was performed with two orientation trials for familiarization, five trials of the transfer task (Transfer Pre), followed by the training task (for 45 min and a minimum of 100 trials) and five trials of the transfer task (Transfer Post), see Figure 3.2A. The transfer task was identical to the training task but was performed with the axes controlled by each hand swapped (transposition task) to assess transfer of learning. Specifically, if the left hand controlled the upward movement in the training task, it controlled the movement to the right in the transfer task and vice versa for the right hand. Which hand controlled upward/rightward movement (hand-axis configuration) as well as which force gripper was in which hand (gripper-hand configuration), e.g., labelled left gripper in the left/right hand of the participant, was balanced across participants.

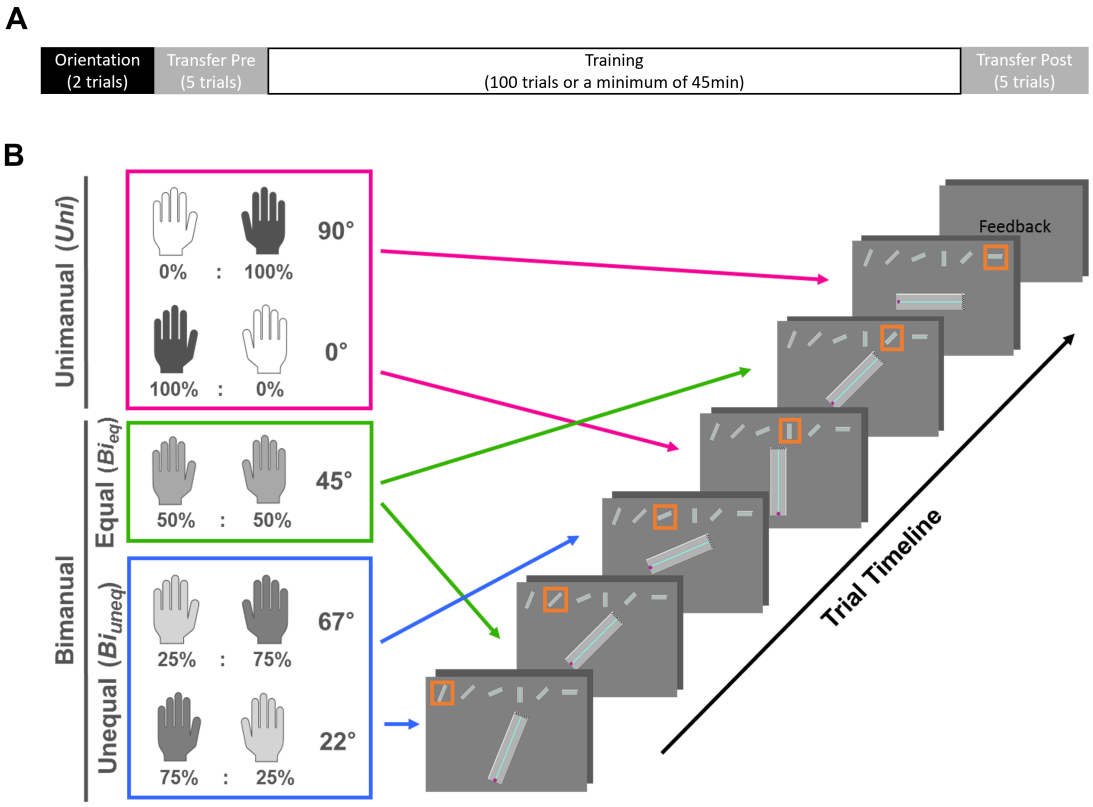


Figure 3.2: Experimental timeline (above) and trial structure (below). **(A)** The novel task consisted of orientation trials, transfer task pre, training task and transfer task post. Training and transfer task were identical but the axes on the screen controlled by each hand were different, i.e., if the left hand controlled the upward movement in the training task, it controlled the movement to the right in the transfer task and vice versa for the right hand. **(B)** One trial consisted of a path of six streets tilted in different angles. The street angles corresponded to specific force ratios, whereby the force of one hand (100%:0%) was required for the street with 0° and 90° (*Uni*), an equal amount of force between hands (50%:50%) in the street of 45° (Bi_{eq}) and an unequal amount of force between hands (25%:75%) for the streets rotated in 22.5° and 67.5° (Bi_{uneq}).

At the end of the session, questionnaires regarding bimanual competence, see Appendix and full description chapter 2, and the short version of the achievement motivation inventory (AMI) were filled in. The AMI is a psychological test inventory with 30 questions measuring different aspects of work-related achievement motivation. The test items were translated from German 'Leistungsmotivationsinventar' (Schuler & Prochaska, 2001).

3.2.3 Data Acquisition

Data were acquired with the Grip Force Bimanual Fiber Optic Response Pad (HHSC-2x1-GRFC-V2, Current Designs Inc, Philadelphia, PA, United States) connected to an electronic interface box (932, Current Designs Inc, Philadelphia, PA, United States). The task was programmed in Matlab (version 9.5.0.944444 (R2018b), The MathWork Inc., Natick, MA, United States), using the Psychophysics Toolbox (version 3.0.14) extensions (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997).

3.2.4 Statistical Analysis

To investigate learning-related changes induced by the novel task, both movement time and error were averaged over the first (trials 1 to 10) and last (trials 90 to 100) ten trials both on the 'trial level' and on the 'condition level'. The trial level comprised the performance of the trial, i.e., mean over six streets. The condition level comprised the performance per condition (*Uni, Bi_{eq}, Bi_{uneq}*), i.e., mean over the two streets of each condition in each trial. Change scores for movement time and error as dependent variables were calculated either as the difference between the first and last ten trials of the training task or as the difference between the pre and post measurement of the transfer task.

At the trial level, learning-related changes were assessed with two paired samples t-tests with the first and last ten trials of movement time and error as dependent variables. Since participants performed the task for 45 min and a minimum of 100 trials, some participants achieved more than 100 trials. Those individually achieved last ten trials ranged from 90-100 to 166-176. To assess an effect of time on task and number of repetitions, two paired samples t-tests compared the last ten trials, i.e., 90 to 100 and individually achieved last ten trials (ranging from 90-100 to 166-176) with movement time and error as dependent variables. To explore a potential trade-off between movement time and error improvements in the training task, a Pearson's

correlation with the change scores of each was performed. To fully investigate which dependent variables were related to the improvement in movement time, a multiple regression with the change scores of error, force, and reset index was conducted.

To explore an effect of achievement motivation on learning, two Pearson's correlations were performed between AMI and changes score, i.e., difference between first and last ten trials, for movement time and error as dependent variables.

To explore whether prior experience with bimanual activities influenced learning the task, two 2 x 3 ANOVAs were conducted with within-subject factors of time (first and last ten trials) and a between-subject factor of bimanual competence (1 Basic, 2 Intermediate, 3 Advanced) for movement time and error as dependent variables.

Next at the trial level, I investigated the transfer of motor skills. To explore whether learning-related changes were similar across the training and transfer task, two 2 x 2 analysis of variance (ANOVAs) were performed with a within-subject factors of task type (training and transfer) and timepoint (before and after learning) with movement time and error as dependent variables. To assess if performance in the transfer task was corresponding to the performance in the training task, two Pearson's correlations were performed with the change score of training and transfer with movement time and error as dependent variables.

At the condition level, the learning-related changes for the different condition were assessed by performing two repeated-measures 2 x 3 ANOVAs with within-subject factors of time (first and last ten trials of the training task) and condition (Uni, Bi_{eq}, Bi_{uneq}) with movement time and error as dependent variables. To evaluate whether learning-related changes differed for the hand-axis configuration, two 2 x 3 x 2 ANOVAs was performed with within-subject factors of time (first and last ten trials of the training task) and condition (Uni, Bi_{eq}, Bi_{uneq}) and a between subject factor of hand-axis configuration (hand-axis configuration 0 or

1) with movement time and error as dependent variables. The same analysis was performed with gripper-hand configuration instead of the hand-axis configuration.

In case of significant effects, post hoc analyses with paired samples t-tests were applied. All reported p-values for t-tests are two-tailed and the significance level was set at $p<.05$ (Bonferroni corrected when appropriate). Statistical analysis was performed using the open-source software JASP (version 0.9.2, JASP Team, 2019).

3.3 Results

3.3.1 Task Induced Learning in Movement Time and Error

Descriptively, both movement time and error were reduced on the trial level, see Figures 3.3A-D. To quantify these learning-related changes, two paired samples t-tests were conducted with the first ten trials and the last ten trials with movement time and error as dependent variables. Results showed a significant reduction in movement time and error (movement time: $t_{1,39}$=8.28, $p<.001$, Cohen's d=1.31; error: $t_{1,39}$=9.03, $p<.001$, Cohen's d=1.43). This suggests learning was induced in both movement time and error, see Figures 3.3 for qualitative (A-B) and quantitative presentation (C-D).

3.3.1.1 Time on Task and Number of Repetitions Were Comparable

The training task was performed for 45 min with a minimum of 100 trials. To investigate if the learning-related changes differed depending on whether trials were calculated based on the time spent on task or number of repetitions performed, the performance of the trials 90-100 with the last ten trials were compared (mean=127.55 trials, SD=24.05, range:90-100 to 166-176). One paired samples t-test was performed for each movement time and error as dependent variables. No significant differences were found (movement time: $t_{1,39}$=0.819, p=.418, Cohen's d=0.13; error: $t_{1,39}$=0.087, p=.931, Cohen's d=0.014) suggesting that time on

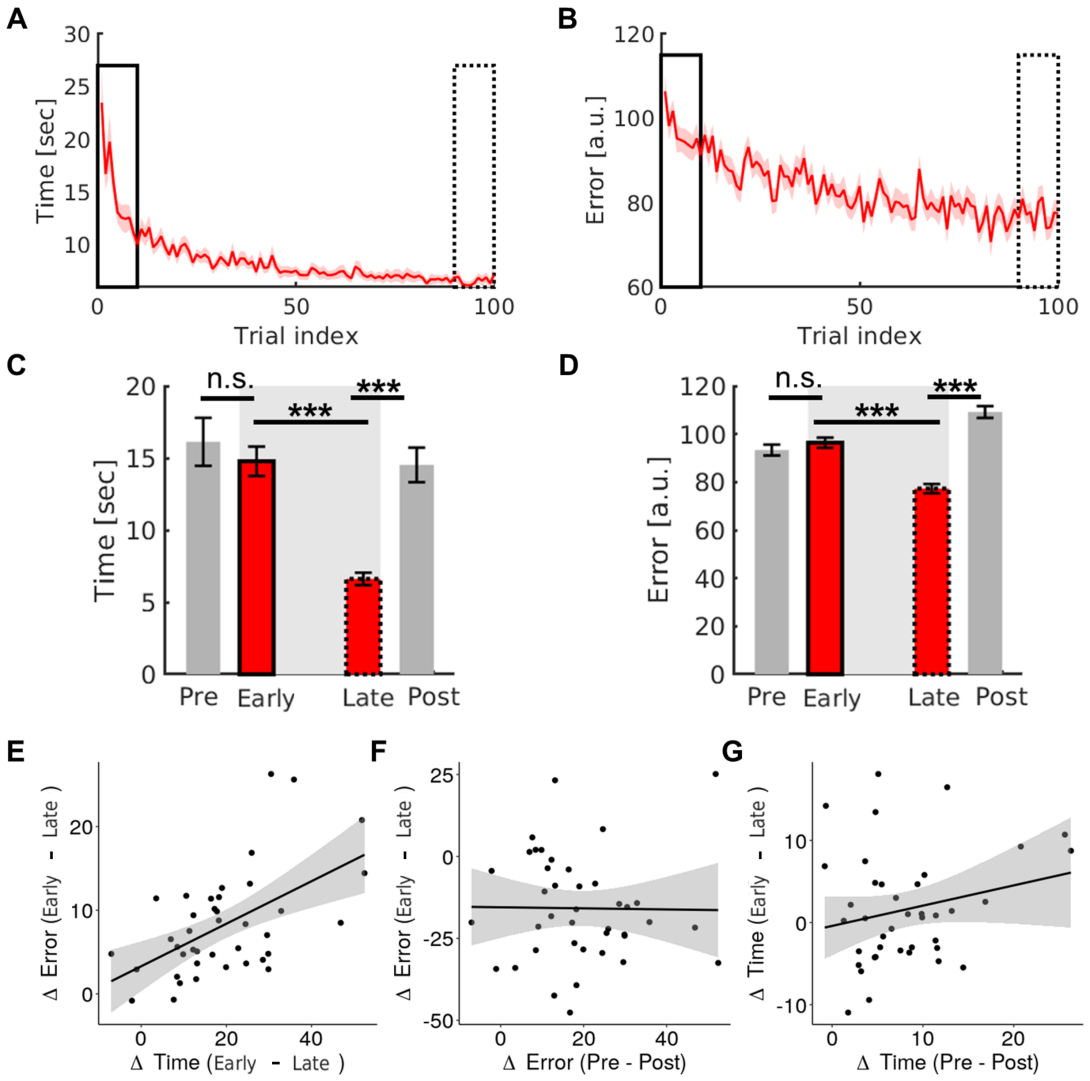


Figure 3.3: Results of the training task (red) and transfer task (grey). (**A, B**) Qualitative presentation of the reduction in movement time (left) and error (right) over the trials of the training task. The frames highlight the first ten (solid frame) and last ten (dashed frame) trials of the training task. (**C, D**) Quantitative presentation of the decrease of movement time and error by comparing the first ten (early) and last ten (late) trials of the training task. The performance in the transfer task conducted before the training task (pre) was comparable with the first ten trials of the training task. The performance in the transfer task conducted after the training task (post) was significantly worse compared to the last ten trials of the training task. (**E**) Significant positive correlation between the change scores (i.e., difference between early and late) for movement time and error yielded no evidence for a trade-off between movement time and error. (**F**) The correlation between the error change scores of training task (i.e., difference between early and late) and transfer task (i.e., difference between pre and post) was not significant which suggested that the performance in training and transfer task did not interact. (**G**) The correlation between the movement time change scores of the training and transfer task was not significant and indicated that the performance in training and transfer task did not interact. Error bars indicate the standard error of the mean. Significance stars *** mean $p<.001$.

task (45 min) and number of repetitions (100 trials) are comparable for this task. For simplicity, the analysis in this experiment was conducted on the number of trials,i.e., 100 trials.

3.3.1.2 No Trade-Off between Movement Time and Error

To investigate whether learning the task were mediated by a potential trade-off between changes in movement time and error, a Pearson's correlation was performed with the change score, i.e., difference between the first and last ten trials of the training task, of movement time and error. This analysis revealed a significant positive correlation (r=.546, p<.001, CI=[.733, .282]) indicating no evidence for a trade-off between accuracy and time when learning the task, see Figure 3.3E.

3.3.1.3 Learning in Movement Time Linked to Error, Force and Reset Index

Due to the design of the task, movement time could be reduced due to fewer errors or with increasing force applied. In addition, movement time entailed the dependent variable reset index, i.e., fewer resets inherently led to decreased movement time.

To explore which components were linked to the reduction in movement time, a multiple regression was conducted with the change score of force, error, and reset index. The overall model explained up to 64% of the variance of movement time changes (*Adjusted* r^2=.64, $F_{3,36}$=24.08, p<.001). The contribution to the overall model was significant for the changes in error (contribution to *Adjusted* r^2=.279, t=2.462, p=.019, CI of unstandardized coefficient=[.022, .224]) and changes in force (contribution to *Adjusted* r^2=.171, t=-3.703, p<.001, CI of unstandardized coefficient=[-.239, -.07]) as well as for the changes in reset index (contribution to *Adjusted* r^2=.19, t=4.528, p<.001, CI of unstandardized coefficient=[-.25, .656]). This suggested that the learning-related changes in movement time were explained by the reduction in error, i.e., participants became more accurate, fewer resets

as well as the increase in force, i.e., participants not only became more accurate, but also used more force to move faster.

3.3.1.4 Learning Did Not Interact with AMI

The AMI was performed to assess participants' achievement motivation (M=6.025, SD=1.609, range:2-9). To explore an effect of achievement motivation on learning, two Pearson's correlations were performed between AMI and changes score, i.e., difference between first and last ten trials, for movement time and error as dependent variables. AMI did not correlate with learning (both p's>.05) suggesting achievement motivation did not interact with learning the task.

3.3.1.5 Learning Did Not Interact with Bimanual Competence

To explore whether prior experience with bimanual activities (M=2.075, SD=0.829, range:1-3) had an influence on learning the task, two 2 x 3 ANOVAs were conducted with a within-subject factor of time (first and last ten trials) and a between-subject factor of bimanual competence (1 Basic, 2 Intermediate, 3 Advanced) for movement time and error as dependent variables. Results revealed no significant main effects or interaction with bimanual competence (all p's>.1) indicating that prior bimanual competence did not interact with learning the task.

3.3.2 Learning Did Not Transfer to Transposing the Hands

To assess a transfer of motor skill, the hands were transposed in the transfer task before (Transfer Pre) and after (Transfer Post) the training task, see experimental timeline Figure 3.2A. To investigate if the learning-related improvements were specific to the hand used or whether they transferred to the transposition task, two 2 x 2 ANOVAs were performed with within-subject factors of task type (training and transfer) and timepoint (before and after learning) with movement time and error as dependent variables, see Figures 3.3C,D. Results revealed a significant main effect

for task type (movement time: $F_{1,39}$=17.71, p<.001, η_p^2=.312; error: $F_{1,39}$=49.681, p<.001, η_p^2=.56), a significant main effect of timepoint in movement time, but not in error (movement time: $F_{1,39}$=36.46, p<.001, η_p^2=.483; error: $F_{1,39}$=0.972, p=.33, η_p^2=.024) and a significant interaction of task type and timepoint (movement time: $F_{1,39}$=26, p<.001, η_p^2=.4; error: $F_{1,39}$=107.683, p<.001, η_p^2=.734).

Post hoc, the significant interaction between task and timepoint was followed up with two paired samples t-tests (Bonferroni corrected). Results revealed that performance during the pre-learning transfer task (Transfer Pre) and the first ten trials of the training task was comparable, as would be expected for a performance prior to learning (movement time:$t_{1,39}$=-0.931, p=.358, Cohen's d=-0.147; error: $t_{1,39}$=1.116, p=.271, Cohen's d=0.177), see Figures 3.3C,D left grey bar. However, performance during the post-learning transfer task (Transfer Post) was significantly worse than in the last ten trials of the training task (movement time:$t_{1,39}$=-7.375, p<.001, Cohen's d=-1.166; error: $t_{1,39}$=-12.462, p<.001, Cohen's d=-1.97), see Figures 3.3C,D right grey bar. This suggested that learning-related changes did not transfer to the transposition task.

3.3.2.1 Learning Did Not Correlate with Transposing the Hands

To investigate if the changes in performance in the training and transfer task interacted (i.e., if learning interacted with the ability to transfer), a Pearson's correlations of the change score of training, i.e., difference between first and last ten trials, and transfer task, i.e., difference between pre and post, was performed once for movement time and once for error as dependent variables (movement time: r=.225, p=.162, CI=[.502, -.093]; error: r=-.013, p=.935, CI=[.299, -.324]). Results showed that learning did not interact with transfer to transposing the hands, as visualized in Figures 3.3F,G.

3.3.3 Distinct Learning Patterns for the Different Levels of Bimanual Interaction

Each trial consisted of six streets, of which two required unimanual (*Uni*) force, two bimanual with equal force (Bi_{eq}) and two bimanual with unequal force (Bi_{uneq}), see Figure 3.2B. Descriptively, the three conditions differed, and they changed differently during learning, see Figure 3.4A,E. To investigate any differences between the learning-related changes across conditions, two 2 x 3 ANOVAs were performed with within subject factors of time (first and last ten trials) and condition (*Uni,* Bi_{eq}, Bi_{uneq}) with movement time and error as dependent variables. Results yielded a significant main effect of time (movement time: $F_{1,39}$=68.61, p<.001, η_p^2=.638; error: $F_{1,39}$=81.55, p<.001, η_p^2=.676, Figures 3.4D,H) and condition (movement time: $F_{2,78}$=52.53, p<.001, η_p^2=.574; error: $F_{2,78}$=1460.82, p<.001, η_p^2=.974, Figures 3.4C,G), as well as a significant interaction between time and condition (movement time: $F_{2,78}$=27.13, p<.001, η_p^2=.41; error: $F_{2,78}$=13.44, p<.001, η_p^2=.256, Figures 3.4B,F). This revealed distinct learning patterns for the three levels of bimanual interaction.

Post hoc, the significant main effect of condition was followed up with three paired-samples t-tests (Bonferroni corrected) for movement time and error as dependent variables. All comparisons were significant (all p's<.001) suggesting the three conditions were distinct, see Figures 3.4C,G.

Further, the significant interaction between time and condition (Figures 3.4B,F) was followed up with three paired-samples t-tests (Bonferroni corrected) comparing the amount of learning between the three conditions using change scores, i.e., difference between first and last ten trials, with movement time and error as dependent variables. Results showed, that for movement time, the learning-related change was significantly larger for Bi_{uneq} compared to Bi_{eq} (p=.003) and *Uni* (p<.001), whereby learning-related change was also larger for Bi_{eq} when compared

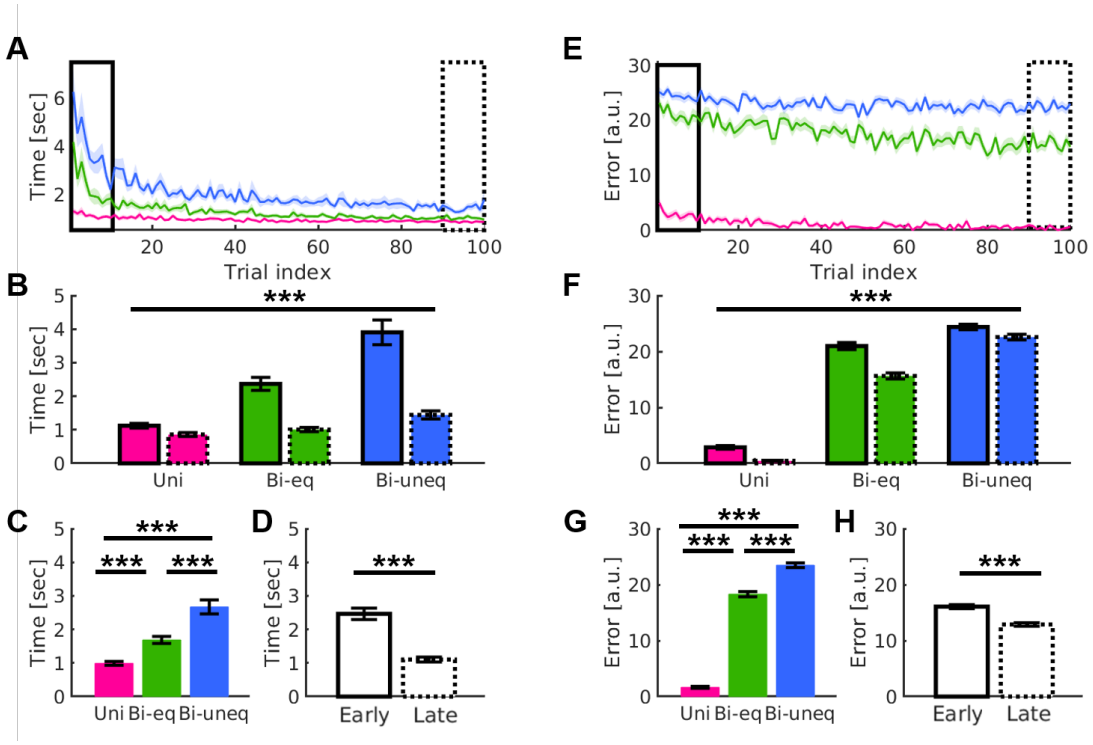


Figure 3.4: Results showed distinct patterns for the three conditions (*Uni*: pink; Bi_{eq}: green; Bi_{uneq}: blue). (**A, E**) Qualitative presentation of the reduction in movement time (left) and error (right) in each condition over the trials of the training task. The frames highlighted the first ten (solid) and last ten (dashed) trials. (**B, F**) Quantitative presentation of the reduction of movement time and error by comparing first ten (early) and last ten (late) trials in each condition (significant interaction of condition x time). Results yielded distinct learning patterns for the conditions. (**C, G**) Comparison of the performance in each condition averaged over time (early, late) suggested that the conditions were distinct (significant main effect of condition). (**D, H**) Comparison of the performance at early and late averaged over conditions indicated a significant difference (significant main effect of time). Error bars indicate the standard error of the mean. Significance stars *** mean $p<.001$.

with *Uni* ($p<.001$). For error, learning-related change was significantly larger for Bi_{eq} compared to Bi_{uneq} ($p<.001$) and *Uni* ($p<.001$), whereby learning-related change did not differ between *Uni* and Bi_{uneq} ($p=.26$).

3.3.3.1 No Effect of Hand-Axis or Gripper-Hand Configuration on Learning-Related Changes

Which hand controlled upward/rightward movement (hand-axis configuration) as well as which force gripper was in which hand, e.g., labelled left gripper in the

left/right hand of the participant, (gripper-hand configuration) was balanced across participants. To investigate if learning across conditions differed for the hand-axis configurations, two 2 x 3 x 2 ANOVAs were performed with within-subject factors of time (first and last ten trials), condition (*Uni,* Bi_{eq}*,* Bi_{uneq}) and a between subject factor of hand-axis configuration (hand axis configuration 0 and 1) with movement time and error as dependent variables. Results showed no significant main effect or interaction with hand-axis configuration (all p's>.1), suggesting that learning the different levels of bimanual interaction did not differ between hand-axis configurations, i.e., which hand controlled upward/rightward movement. The same analysis was performed with gripper-hand configuration. As expected, there was no significant main effect or interaction of gripper-hand configuration (all p's>.1) suggesting that learning the different levels of bimanual interaction was independent of which force gripper was in which hand.

3.4 Discussion

The purpose of this chapter was to quantify learning-related changes of the novel bimanual motor learning task. In line with my hypothesis, the task induced learning-related changes in movement time and error in the absence of a speed-accuracy trade-off and with distinct learning patterns for the levels of bimanual interaction. Against my expectation, the learning-related changes induced by the training did not transfer to transposing the hands. In the following sections those findings are discussed individually.

3.4.1 Learning-Related Changes in Movement Time and Error

The repetitive and extensive training of the task lead to a reduction both in movement time and error in absence of a speed-accuracy trade-off. This is in line with previous motor learning studies reporting performance improvements after

extensive and repetitive training in finger tapping (Andres et al., 1999; Aoki et al., 2003; Aramaki et al., 2006; Aramaki et al., 2010; Bangert et al., 2010; Eudave et al., 2017; Gerloff & Andres, 2002; Kajal et al., 2017; Shammi et al., 1998; Takeuchi et al., 2012) and complex coordination tasks (Doost et al., 2017; Fagard et al., 1985; Mueller et al., 2009; Preilowski, 1972; Sisti et al., 2011). Therefore, in the novel task, movement time and error are estimates to successfully and interchangeably quantify motor learning.

Moreover, the learning-related changes in movement time and error did not differ between the time spent on task and number of repetitions performed. In other words, repeating the task and spending 45 min on the task lead to comparable learning-related changes. In light of using the task in future experiments, either estimate can be used as a termination criterion for the task.

Additionally, the learning-related improvements in movement time were due to increase in force, a reduction error and fewer resets. These findings are consistent with those shown by Doost et al. (2017). The authors reported a link between improvements of their outcome measures of bimanual coordination and a combined measure of speed and accuracy.

Further, I explored whether prior experience with bimanual activities or achievement motivation assessed with the AMI had any influence on the learning ability for the task. However, bimanual activities and achievement motivation did not interact with learning the task.

Overall, the results suggest the task successfully measured motor learning. The design of the task reliably induced learning in the behavioural metrics of movement time and error. The task could open up new ways to investigate bimanual motor learning in the context of health and disease, as well as research contexts beyond the motor domain as discussed below.

3.4.2 Quantifying Learning for the Levels of Bimanual Interaction

Results demonstrated significant differences between the three conditions (*Uni,* Bi_{eq}, Bi_{uneq}). *Uni* was the easiest to perform, followed by Bi_{eq}, and Bi_{uneq} as the most difficult. That unimanual movements show lower movement time and smaller error than bimanual movements is in line with previous reports (Mueller et al., 2009). Mueller et al. (2009) suggested that this pattern of results might be due to the non-skilled and automatic nature of unimanual movements, i.e., equivalent to using the force grippers. That movements with unequal contributions of hands, i.e., Bi_{uneq}, were more difficult than movements with equal contributions of hands, i.e., Bi_{eq}, is consistent with other studies (Fagard et al., 1985; Mueller et al., 2009; Sisti et al., 2011). Specifically, Sisti et al. (2011) outlined that in movements with unequal contribution of hands, the movement of one hand needs to be 'decoupled' from the other. According to the authors, this takes more effort and thereby results in higher errors and increased time. The dissimilarity between equal and unequal contribution between hands is further underscored by theory that movements with equal contributions are preferred, more stable and accurate than those with unequal contributions (Swinnen, 2002; Swinnen & Gooijers, 2015).

Further, results yielded distinct learning patterns for the conditions (significant interaction between time and condition). This is consistent with the study by Sisti et al. (2011). The authors showed that the movement with equal contributions between hands was the easiest to learn indicated by flooring effects after a small number of training sessions. With increasing difficulty of the movements (i.e., the more unequal they were), learning was more difficult as indicated by the increasing number of training sessions needed to improve performance. In the experiment reported in this chapter for movement time, the learning-related changes (i.e., difference between first and last ten trials) ranged from largest in Bi_{uneq}, to Bi_{eq}

to smallest for *Uni*. For error, learning-related changes were largest in Bi_{eq} and comparable in *Uni* and Bi_{uneq}. The unimanual condition showed less learning-related changes in comparison to the two bimanual conditions. This might be due to limited potential for improvement in the unimanual conditions, i.e., floor effect of performance, as the unimanual condition was the easiest to perform (ease of performance). Further, one might argue, that less learning-related changes in the unimanual conditions reflect an ease of learning in the unimanual condition compared to the bimanual conditions. Thus, the one hand squeezes in the unimanual condition did not require the extent of skill learning and interaction between hands compared to the bimanual conditions. Specifically, one might suggest that the learning of the unimanual condition is equivalent to understanding how to use the force gripper, whereby the learning of the bimanual condition comprises the additional component of bimanual interaction. On a more speculative note, the learning-related changes in the unimanual condition might not necessarily be due to improved motor performance, but also due to intrinsic factors. Specifically, over the time course of the task, the performer grows in perceived competence, self-efficacy, and perceived control over the task which have been argued to play a key role in performance improvements (Wulf & Lewthwaite, 2016). Among the bimanual conditions, our results suggested that for movement time learning-related change was larger for Bi_{uneq} than for Bi_{eq}, whereby the opposite pattern was observed for error, suggesting a complex relationship.

Taken together, these results suggest that the task is suitable for quantifying unimanual as well as bimanual motor learning with equal and unequal contribution of hands. The design of the task allowed us to investigate bimanual motor learning with movements that were less artificial and closer to everyday life movements than previous task designs. Therefore, the task allows a richer description of bimanual interaction and bimanual motor learning. Based on this, future electrophysiology

studies can characterise the neural underpinnings associated with learning the different levels of bimanual interaction.

3.4.3 No Transfer of Learning to Transposing the Hands

Against my expectation, the learning-related changes induced by the training task did not transfer to the transposition task. When transposing the hands, performance worsened. Further, no correlation between training and transfer task was found. In the following, the absence of transfer effects is discussed by outlining the relationship between the training task and the transfer task.

The training task consisted of a small number of streets, (N=5, 0°, 90°, 22.5°, 67.5°, 45°) that were repeated many times (range 76-176 trials), as common for motor learning studies (Breslin et al., 2012; Doost et al., 2017; Mueller et al., 2009). However, many repetitions of a small training set might conceivably lead to a memorisation of the streets. Possibly, an association between street angles and required hand ratios were learned, rather than bimanual motor coordination in general. Forming motor memories instead of learning a generic motor skill has been described previously by Doost et al. (2017) and is in line with the Schema theory (Schmidt, 1975, 2003). According to the Schema theory (Schmidt, 1975, 2003), an especial skill is defined as an ability unique to a particular stimulus and is a result of many repetitions (Breslin et al., 2012; Keetch et al., 2005; Schmidt, 1975; Schmidt & Young, 1987; Wulf & Schmidt, 1997). A generic motor skill is acquired when a given movement is abstracted as a movement representation on a higher level, e.g., sequence of individual parts of a movement, relative timing and relative force (Schmidt, 1975, 2003). In other words, in especial skills the memorisation is large and in generic motor skills the memorisation is small. I therefore hypothesize that the training task reinforced an especial skill rather than a generic skill, and that for this training task, the transfer task (transposition) was

too different. In contrast, a training task with more variability (e.g., larger number of streets) might reinforce a more general skill and thus transfer to transposition could be possible, as reported before (Breslin et al., 2012; Czyż & Moss, 2016; Shea & Kohl, 1990; Wulf & Schmidt, 1997).

Conversely, it might also be the case that the transfer task used here was too different from the training task for transfer to occur (Henry & Rogers, 1960; Keele, 1968; Simons et al., 2009). Studies using transfer tasks that are closely related to the training tasks show transfer effects, e.g., when transfer is measured with increased speed, increased distance to a target, or different muscle involved (limb to hand) (Aune et al., 2017; Keetch et al., 2005; Shea & Kohl, 1990; Simons et al., 2009). However, transfer was not observed when training tasks and transfer tasks were rather different, e.g., transfer from tapping to drawing, mismatch between sequences of the movement, reversal of control-display relationship, i.e., transposition (Grafton et al., 2002; Lewis et al., 1951; Robertson et al., 1999). Therefore, amending our transfer task to be closer the training task, e.g., non-trained angles, streets with corners or curves, movement direction of the cursor, might be more likely to yield transfer.

Taken together, the relationship between the training task and the transfer task could be experimentally tested by systematically examining transferability from a set of training tasks (tasks reinforcing especial and generic skill learning) to a set of transfer tasks (with a small or large difference to the training task). I would expect that for training tasks reinforcing generic skills transfer is high for a range of transfer tasks. For training tasks reinforcing especial skills, I would expect transfer to be high for transfer tasks that are close to the training task, but low for other transfer tasks. To shed light onto the relationship between training and transfer, a comprehensive comparison of transfer tasks is needed, ideally in conjunction with varying training tasks. This is crucial to set results of this and other studies into perspective.

3.4.4 Conclusion and Future Directions

The findings of this chapter demonstrated that the novel bimanual motor learning task was successfully validated and is advancing our understanding of bimanual coordination. From here, future electrophysiology studies could characterise intra- and interhemispheric connectivity associated with bimanual motor learning. Ultimately, the understanding of the basis of bimanual motor learning derived from this task has the potential to be of use in a clinical context of stroke and other diseases.

Beyond the research on motor learning, the task could be used in studies investigating task-switching or error-correction. Task-switching is classically studied in cognitive psychology, but understudied in the sensorimotor domain (Monsell, 2003). The novel task can be used to investigate task-switching by evaluating the switching between bimanual coordination patterns, i.e., equal and unequal contribution of hands. This has been previously assessed by Heise et al. (2019) with switching between simultaneous and alternating finger tapping. The novel task would provide insights in switching between complex coordination patterns. In the context of error correction, the novel task offers new research opportunities in the sensorimotor domain. Specifically, while performing the task, the force of each hand is constantly corrected to stay on the midline of the street. To stay on the midline, several strategies can be assessed, i.e., increasing force in one or reducing force in the other hand. Future studies could use the novel task to systematically test strategies for error correction, see for a review Shadmehr et al. (2010).

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4

Modulating Bimanual Motor Learning with Beta tACS

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4.1 Introduction

According to the communication through coherence hypothesis, neural oscillations in multiple brain regions align in frequency and phase, see chapter 1 for more details. This alignment in frequency and phase, i.e., coherence or synchrony, has been proposed to be a critical mechanism for interregional communication (Fries, 2005, 2015). For movements and motor learning, extensive research has demonstrated that neural activity in the beta band (15-30 Hz) is important for neural communication, as neurons desynchronise during movement preparation and execution (ERD) and synchronise after movement termination (ERS) (Neuper & Pfurtscheller, 2001; Pfurtscheller & Da Silva, 1999), see full description chapter 1. In complex bimanual motor learning however, the role of beta activity is not fully understood, see for a review Gerloff and Andres (2002). Evidence from finger tapping, rotation, or flexion and extension, suggests that interhemispheric coherence between left and right M1 in the beta band is present during bimanual movements (Gerloff et al., 1998; Kajal et al., 2017; Serrien & Brown, 2002) and increases with coordinative effort and task demand (Andres et al., 1999; Loehrer et al., 2016). Further, beta activity was reported to be different in movements requiring equal and unequal contributions of hands, whereby equal contributions between hands present lower interhemispheric coherence (Gross et al., 2005; Rueda-Delgado et al., 2017; Serrien, 2008a). This difference is thought to imply that equal contributions between hands require lower effort (Serrien, 2008a), whereas unequal contributions between hands require more effort indicated by increased neural communication (Serrien & Brown, 2002; Serrien et al., 2003). Further, evidence demonstrated that beta activity plays a causal part in learning as ERD were strengthened with unimanual motor learning and the ERS with motor adaptation (Tan et al., 2014; Zich et al., 2018). However, the evidence discussed above does not test the role of beta activity in complex bimanual motor learning. I therefore wanted to test

if frequency and phase alignment between hemispheres improves bimanual motor learning. Specifically, I wanted to test the effects of hemispheric phase synchrony compared to phase desynchrony at the beta frequency on learning equal and unequal bimanual movements. This would allow to directly test the role of hemispheric synchrony of beta activity on bimanual motor learning and thereby give insights into the link between oscillatory activity and behaviour.

In order to modulate phase (de-)synchrony in the beta range transcranial alternating current stimulation (tACS) is the prime candidate, see full description of tACS in chapter 2. TACS is a type of non-invasive brain stimulation applying a weak sinusoidal current to entrain cortical network coherence, see Antal and Herrmann (2016) or Herrmann et al. (2013) for a review. Specifically, the application of tACS is thought to shift the ongoing activity in the brain towards the frequency and phase alignment of the stimulation and thereby change the coherence between brain areas (Ali et al., 2013; Antal et al., 2008; Reato et al., 2013; Weinrich et al., 2017). Thus, tACS provides a tool for investigating the causal role of neural oscillations for behaviour, see Riddle and Fröhlich (2021) for a review. Frequency and phase specific tACS effects have been found before. In terms of frequency specific effects, tACS at the beta frequency has been shown to influence motor performance when applied on one hemisphere, i.e., left sensorimotor cortex (Joundi et al., 2012; Pogosyan et al., 2009; Wach et al., 2013). Specifically, Pogosyan et al. (2009) reported that beta tACS slowed movement in a unimanual visuomotor task. Similarly, Joundi et al. (2012) and Wach et al. (2013) could show that beta tACS decreased the rate of unimanual force production. Further, studies suggested that the effects of tACS are most pronounced when the stimulation frequency matches the natural ongoing frequency in the brain (Ali et al., 2013; Reato et al., 2013; Schilberg et al., 2018; Thut et al., 2011; Zaehle et al., 2010). However, none of those studies investigated the effect of beta tACS on motor learning. Phase-specific tACS effects have been

reported to be behaviourally relevant in studies using theta tACS applied on one hemisphere during reaction time tasks (Polania et al., 2012; Violante et al., 2017). Specifically, behavioural performance improved when stimulation was applied in phase synchrony, i.e., 0° phase shift between targeted areas, compared to phase desynchrony, i.e., 180° phase shift between targeted areas (Polania et al., 2012; Violante et al., 2017). Phase synchrony between hemispheres was investigated by Heise et al. (2019) who examined phase synchrony, i.e., 0° phase shift between hemispheres, with bihemipsheric tACS at 10 Hz and 20 Hz. The authors found beneficial effects of beta tACS on speeding up task switching in a bimanual tapping task. Helfrich et al. (2014a) could demonstrate that interhemispheric functional coherence was modulated in a phase-specific way when bilateral high-density tACS at 40 Hz was applied with simultaneous EEG recordings. Specifically, 0° phase shift between hemispheres enhanced and 180° phase shift between hemispheres impaired interhemispheric functional coherence. Similar phase-specific effects were shown by Schwab et al. (2019) who applied bihemispheric high-definition alpha tACS. Thereby, modifying the phase of beta tACS by stimulating between hemispheres, seems to be promising for modulating learning-related changes in behaviour.

To measure learning-related changes in behaviour, I used the bimanual motor learning with the task described in chapter 2. In the task, three patterns of hand interactions (*Uni, Bi_{eq}, Bi_{uneq}*) were required to move a cursor on streets at different angles. To quantify the performance in the task, movement time and error were measured as dependent variables. As fully outlined in chapter 3, the novel task induced learning-related changes in movement time and error with distinct learning patterns for the conditions (*Uni, Bi_{eq}, Bi_{uneq}*). In this chapter, I aimed to investigate the role of hemispheric synchrony of beta activity while learning the task with in-phase (phase synchrony between hemispheres) and out-of-phase (phase desynchrony between hemispheres) tACS at the individual beta-peak frequency

above both sensorimotor cortices. I hypothesized, in-phase and out-of-phase beta tACS would modulate the learning-related changes of the conditions differently, as previous studies found different beta activity for equal and unequal contributions between hands, i.e., less beta coherence between hemispheres in equal compared to unequal contributions. Specifically, I expected that in-phase stimulation would improve the learning-related changes in Bi_{eq}, whereas out-of-phase would enhance learning-related changes Bi_{uneq} in comparison to sham stimulation. I expected to replicate the findings of the previous experiment in the sham group.

4.2 Methods

4.2.1 Participants

Fifty-five right-handed healthy participants gave their written informed consent to participate in the experiment which was in accordance with the Central University Research Ethics Committee (University of Oxford; MSD-IDREC-R65118/RE001) and in accordance with the Declaration of Helsinki. One participant was excluded from the experiment because no beta peak frequency was detectable. The final sample comprised fifty-four individuals (28 females, M=24.05 years, SD=4.76). In the absence of previous studies on phase-specific beta tACS effects across hemispheres, no effect sizes were available for a power calculation. Participants reported no history of neurological or psychiatric disorders, had no contraindications for brain stimulation and had normal or corrected-to-normal vision. They were monetarily compensated for their participation. Handedness was assessed with the 10 item Edinburgh Handedness Inventory (Oldfield et al., 1971).

4.2.2 Experimental Design and Procedure

To investigate the effect of phase synchrony between hemispheres on bimanual motor learning, the study was conducted with a one session, between-subject,

double-blind and sham-controlled design with three stimulation groups (in-phase, out-of-phase, sham). In the beginning of the session, questionnaires regarding bimanual competence, see Appendix and full description chapter 2, and the short version of the achievement motivation inventory (Schuler & Prochaska, 2001) were filled in, as described in chapter 3. Subsequently, the participant's individual beta peak frequency was assessed with EEG while participants performed simple hand squeezes. The frequency with the strongest ERD above the sensorimotor areas induced by the hand squeezes was set as the stimulation frequency.

Following the assessment of the stimulation frequency, the bimanual motor learning task was performed, see Figure 4.1B, full description of the task chapter 2 and task data acquisition chapter 3. In brief, in the task, one trial comprised a path with six streets in different angles. The street angles corresponded to specific force ratios to navigate a cursor across streets. Thus, the force of one hand (100%:0%) was required on streets tilted in 0° or 90° (*Uni*). The force of both hands with an equal (50%:50%) amount of force (Bi_{eq}) was needed on streets in 45° and an unequal (25%:75%) amount of force between hands (Bi_{eq}) on streets angled at 67.5° or 22.5°.

Cursor movement was enabled with force grippers controlling the x-y axis separately. The force grippers were calibrated to the participants' maximum force prior to the task (see full description of force grippers and force calibration in chapter 2 and 3). To quantify the performance in the task, movement time, i.e., seconds from movement onset to offset, and error, i.e., deviation from the midline, were measured as dependent variables, see chapter 2.

The task was performed with two orientation trials, five trials of a baseline performance and 40 min of training, as based on the findings of the previous experiment described in chapter 3, see Figure 4.1A. To avoid carry over effects from the baseline performance to the training task, the hand-axis configuration was swapped. Specifically, if the left hand controlled the movement to the right

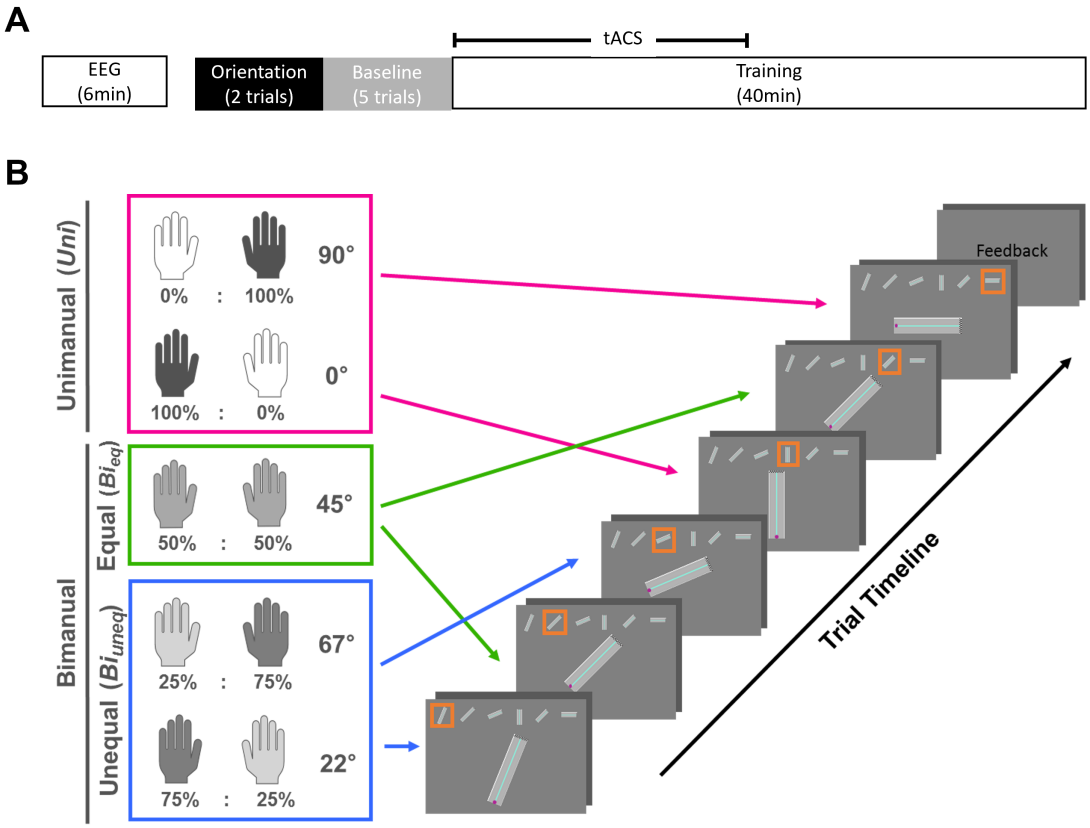


Figure 4.1: Experimental timeline (above) and trial structure (below). (**A**) The task was performed with orientation trials, baseline performance and the training task. Baseline and training task were identical with the hand-axis configuration swapped. Both hand-axis configurations were practised in the orientation trials. (**B**) One trial consisted of a path of six streets all in different angles. The street angles corresponded to hand ratios, whereby the force of one hand (100%:0%) was required for the street with 0° and 90° (*Uni*), an equal amount of force between hands (50%:50%) in the street of 45° (Bi_{eq}) and an unequal amount of force between hands (25%:75%) for the streets rotated in 22.5° and 67.5° (Bi_{uneq}).

at baseline, it controlled the upward movement in the training task and vice versa for the right hand.

Between baseline performance and training task, participants were allocated to one of the three stimulation groups. Beta tACS was applied for 20 min while performing the training task. At the end of the session, participants were asked their guess of stimulation group (sham/active) and certainty estimate on a scale from 1 to 7.

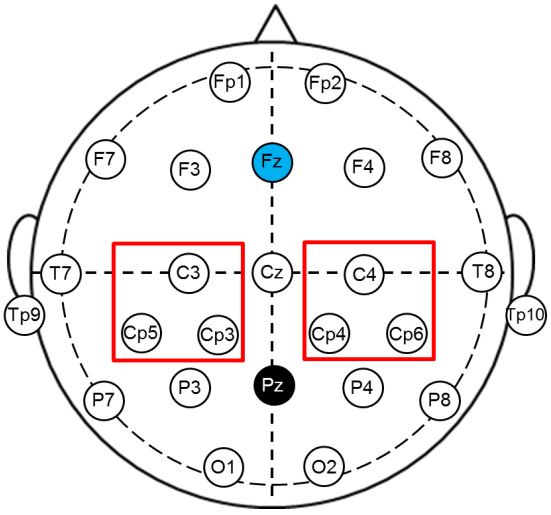


Figure 4.2: Schematic illustration of the EEG electrode positions used for the detection of the individual's beta peak frequency. The EEG data was collected at the 10-20 sites Cp5, Cp3, C3, C4, Cp4, Cp6 as indicated by the red rectangles. The central frontopolar electrode Fz was used as a reference electrode (blue). The central parietal electrode Pz was used as ground electrode (black). The schematic of the 10-20-system was adapted from Easycap (https://www.easycap.de/wp-content/uploads/2018/02/Easycap-10-based-electrode-layouts.pdf).

4.2.3 Data Acquisition

4.2.3.1 EEG Acquisition and Beta Peak Detection

To assess the individual's beta peak frequency, EEG was obtained (6 min) while participants performed simple hand squeezes. Specifically, participants held a squeeze ball in each hand while looking at a fixation cross on the screen. An arrow either pointing to the left or right was presented on the screen for 200 ms, indicating left- or right-hand squeezes. Participants were instructed to perform one hand muscle contraction with maximum force and then immediately relax while otherwise being as still as possible. This was practised before the beginning of the EEG recording and visually monitored by the experimenter. The order of the arrows was pseudo-randomized with a randomized inter-trial interval of 0.25 s, 0.5 s or 0.75 s. The stimuli were presented with OpenViBE Designer, version 2.2.0, Renard et al. (2010).

As also described in chapter 2, EEG data were recorded with a modified Emotiv (www.emotive.com) system (De Vos et al., 2014; Debener et al., 2012;

Zich et al., 2015), whereby the original hardware (128 Hz sampling rate; 0.16 and 45 Hz bandpass) was relocated into a small and light box (49 × 44 × 25 mm; 48 g total weight). The box was inserted into a small pocket at the back of an infra-cerebral electrode cap from Easycap (Easycap, Herrsching, Germany, for reference see www.easycap.de). The EEG data were collected with sintered Ag/AgCl electrodes positioned at the 10-20 sites Cp5, Cp3, C3, C4, Cp4, Cp6 with a central frontopolar electrode, i.e., Fz, as reference and a central parietal, i.e., Pz, as ground electrode. Thereby, data were recorded from three channels above each sensorimotor cortex (6 channels in total over left and right sensorimotor cortex), see Figure 4.2. Data were acquired with OpenViBE Acquisition Server using version 2.2.0, Renard et al. (2010). Data analysis was performed during the experimental session and thereby needed to be relatively simple. Preprocessing included high-pass filtering (5 Hz, finite impulse response, filter order 212) and low-pass filtering (40 Hz, finite impulse response, filter order 44). Subsequently, data were segmented from -2 s to 4 s (relative to the trigger indicating movement onset) and baseline corrected (-1.5 s to 0.5 s). Those segments containing residual artefacts were rejected (EEGLAB functions pop_jointprob.m, pop_rejkurt.m, both SD=3). For the remaining segments, a time-frequency analysis (Morlet wavelet transform, 1 Hz frequency steps) for each of the 6 channels was performed. To assess the beta peak frequency, time-frequency plots were visually inspected and the frequency with the strongest movement-induced event-related desynchronization was selected. The analysis was conducted using MATLAB (Mathworks Inc., Natick, MA, United States) and EEGLAB14-1-1b (Delorme & Makeig, 2004).

4.2.3.2 Beta tACS Protocol and Group Allocation

To ensure the stimulation groups (in-phase, out-of-phase, sham) were comparable, group allocation was carried out in two stages. This had the advantage of minimising variance across groups as accidental difference in pure randomisation cannot be

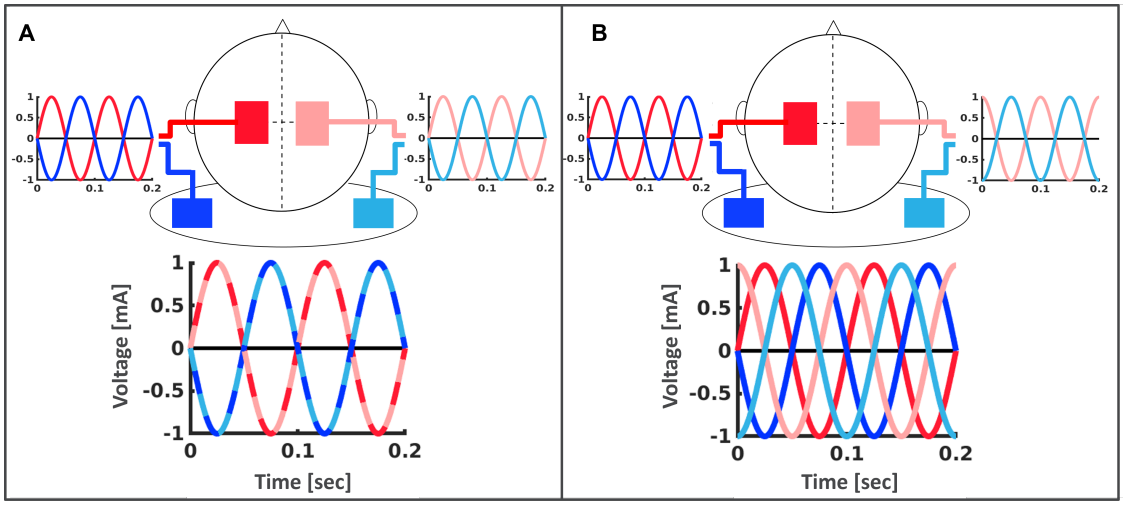


Figure 4.3: Setup for the tACS application with two stimulators (dark and light) which were each connected to one electrode over M1 (red) and one electrode on the shoulder (blue). (**A**) In-phase tACS with 0° phase shift between hemispheres was applied with 0° phase shift in both hemispheres. (**B**) Out-of-phase tACS with 90° phase shift between hemispheres was applied with 0° phase shift in one hemisphere and 90° phase shift in the other hemisphere (the hemisphere receiving 90° phase shift was counterbalanced).

eliminated, as recommended by Sella et al. (2021). The first half of the participants (N=28) was pseudo-randomized across the three stimulation groups. This order was set prior to the beginning of the study with a blinding sheet the researcher did not have access to. The remaining participants (N=26) were allocated to the stimulation groups based on their beta-peak frequency, baseline performance of movement time and error, as well as scores of bimanual competence and achievement motivation (in this order). To assure the double-blinding, the researcher visually inspected all five group allocation parameters and allocated each participant to one out of three blind group labels. A second person translated the blind group label to the real group label based on the number of participants in each group and set the correct stimulation parameters.

After being allocated to groups (N=18 in each group), participants received either sham (3 s of stimulation), in-phase (0° phase shift between hemispheres), or out-of-phase (90° phase shift between hemispheres) tACS, see Figures 4.3A,B. Subgroups controlled for any effects of hemisphere and comprised two subgroups

for out-of-phase stimulation (out-of-phase with the 90° phase shift for the left hemisphere, out-of-phase with the 90° phase shift for the right hemisphere), three subgroups for sham (in-phase sham, out-of-phase sham with the 90° phase shift for the left hemisphere, out-of-phase sham with the 90° phase shift for the right hemisphere), and none for in-phase stimulation.

Subsequently, beta tACS was applied either for 3 s (sham group) or 20 min either in-phase, or out-of-phase with a ramp up and down for 10 s. Each of the two bipolar DC Plus stimulators (NeuroConn, Ilmenau, Germany) administered the stimulation via a pair of conductive rubber electrodes (5 x 7 cm). This resulted in a 4-electrode montage with two stimulation electrodes over M1 (C3/C4) and two reference electrodes over the ipsilateral shoulder (left/right), see Figures 4.3A,B. High-chloride EEG electrode paste was used as a conducting medium and electrodes were fitted with impedances below 5 Ω. Stimulation was applied with an amplitude of 2 mA peak-to-peak (offset at 0) while the training task was performed.

4.2.4 Statistical Analysis

To ensure groups were comparable prior to the experiment, one 1 x 3 Bayesian ANOVA for each group allocation parameter was conducted (beta-peak frequency, baseline performance of movement time and error as well as the scores of AMI and bimanual competence questionnaire). Bayesian ANOVA was chosen for this particular analysis because it had the advantage of testing multiple hypothesis and their likelihood of being true in relation to another. To quantify the ratio of the likelihood of one particular hypothesis to the likelihood of another, the Bayes factor (BF) was calculated, see Lee and Wagenmakers (2013), p.105; adjusted from Jeffreys (1961). Specifically, $\mathrm{BF}_{10} = 10-30$ denoted strong evidence, $BF_{10} = 3-10$ moderate, and $BF_{10} = 1-3$ anecdotal evidence for H_1, while $\mathrm{BF}_{01} = \frac{1}{3}-1$ denoted anecdotal, $BF_{01} = \frac{1}{10}-\frac{1}{3}$ moderate, and $BF_{01} = \frac{1}{30}-\frac{1}{10}$ strong evidence for H_0.

Success of blinding to tACS was evaluated using the index introduced by Bang et al. (2004) once for the sham group and once for the active stimulation groups (out-of-phase, in phase together). If the participant were 50% or less certain, i.e., response 4 or below (of a scale from 1-7), this was coded as a 'don't know' for the blinding indices (BI) calculation. Confidence intervals (CI) were set at 95%. The BI is scaled from -1 to 1, with -1 indicating success of blinding, i.e., more participants mistakenly name the alternative treatment, 0 indicating perfect blinding and 1 indicating complete lack of blinding, i.e., majority of participants guessing correctly.

To investigate tACS-related changes in motor learning, the first ten trials and last ten trials before the end of stimulation were compared, both on the trial level and on the condition level, as described in chapter 3. To test whether beta tACS affected motor learning on the trial level, two 2 x 3 ANOVAs were conducted with a within-subject factor of time (first ten trials and last ten trials before the end of stimulation) and between-subject factor of group (in-phase, out-of-phase, sham) with error and movement time as dependent variables. To assess whether beta tACS affected motor learning differently for the three conditions (*Uni,* Bi_{eq}*,* Bi_{uneq}), two 2 x 3 x 3 ANOVAs were performed with a within-subject factor of time (first ten trials and last ten trials before the end of stimulation) and condition (*Uni,* Bi_{eq}*,* Bi_{uneq}) and a between-subject factor of group (in-phase, out-of-phase, sham) with error and movement time as dependent variables.

Post hoc, a double dissociation of out-of-phase, in-phase tACS and Bi_{eq}, Bi_{uneq} condition was assessed. Therefore, two 2 x 2 x 2 ANOVAs were conducted with time (first ten trials and last ten trials before the end of stimulation) and condition (Bi_{eq}*,* Bi_{uneq}) as within-subject factors and active group as a between-subject factor (out-of-phase, in-phase) with movement time and error as dependent variables. In addition, the influence of the baseline performance was tested by using two baseline adjustment methods as previously suggested by Vickers and Altman (2001) and

Zhang et al. (2014). To adjust for the baseline performance, a change score was calculated, i.e., difference between baseline and training task, and separately, the baseline performance was included as a covariate. The same analysis as described above was performed with both adjustment methods.

In case of significant effects, post hoc analyses with paired samples t-tests were applied with Bonferroni correction for multiple comparisons. All reported p-values for t-tests are two-tailed and the significance level was set at $p<.05$. Statistical analysis was performed using the open-source software JASP (version 0.9.2, JASP Team, 2019).

4.3 Results

The aim of this experiment was to investigate the effects of beta tACS on learning-related changes in movement time and error. Like the experiment in chapter 3, questionnaire outcome measures of bimanual competence and AMI did not interact with learning (all p's$<.05$), but were comparable to the results of this experiment, see Table 4.1.

4.3.1 No Differences Between the Stimulation Groups

To test whether stimulation groups (in-phase, out-of-phase, sham) were comparable at baseline, beta peak frequency, baseline performance of movement time and error as well as scores of bimanual competence and AMI (in this order) were compared. A 1 x 3 Bayesian ANOVA for each parameter was performed, see Table 4.1. Results were in favour of the null hypothesis which suggested no group differences prior to the stimulation.

4.3.2 Blinding Index for the Stimulation Groups

To quantify the success of blinding, the BI was calculated, as previously introduced by Bang et al. (2004). BI was .72 (CI=[.58, .87]) for the active (both in-phase and

Table 4.1: *Results of the five 1x3 Bayesian ANOVAs indicated no group differences.*

Variable	Out-of-phase	In-phase	Sham	Stats
Beta peak (Hz)	19.39+/-3.33 (14-26)	19.39+/-2.35 (16-26)	19.61+/-1.61 (16-22)	BF_{10}=.150
Error (a.u.)	16.13+/-2.38 (11.38-19.62)	16.51+/-2.78 (11.82-23.35)	16.53+/-1.87 (12.7-19.48)	BF_{10}=.162
Movement time (s)	4.24+/-1.49 (2.35-7.12)	4.14+/-1.96 (2.06-9.67)	4.07+/-1.96 (1.85-9.3)	BF_{10}=.149
AMI	5.33+/-1.61 (3-8)	5.72+/-2.24 (1-9)	5.67+/-1.49 (3-8)	BF_{10}=.173
Bim. competence	2.17+/-0.86 (1-3)	2.06+/-0.8 (1-3)	1.78+/-0.81 (1-3)	BF_{10}=.313

out-of-phase) tACS groups and -.056 (CI=[-.38, .27]) for the sham group. This suggested successful blinding for the sham group, but not for the active groups.

4.3.3 Learning-Related Changes in Movement Time and Error but No Effect of the Applied Beta tACS

To test the effect of beta tACS on bimanual motor learning, two 2 x 3 ANOVAs were conducted with a within-subject factor of time (first ten trials and last ten trials before the end of stimulation) and between-subject factor of group (in-phase, out-of-phase, sham) with error and movement time as dependent variables. For both movement time and error, this resulted in a significant main effect of time (movement time: $F_{1,51}$=39.42, p<.001, η_p^2=.436; error: $F_{1,51}$=30.62, p<.001, η_p^2=.375), but not in a significant main effect of group (movement time: $F_{2,51}$=.369, p=.693, η_p^2=.014; error: $F_{2,51}$=0.561, p=.574, η_p^2=.022), or interaction between time and group (movement time: $F_{2,51}$=2.1, p=.133, η_p^2=.076; error: $F_{2,51}$=0.403, p=.67, η_p^2=.016). This suggests that participants successfully learned the task, but the used beta tACS did not modulate the learning, see Figures 4.4A,B.

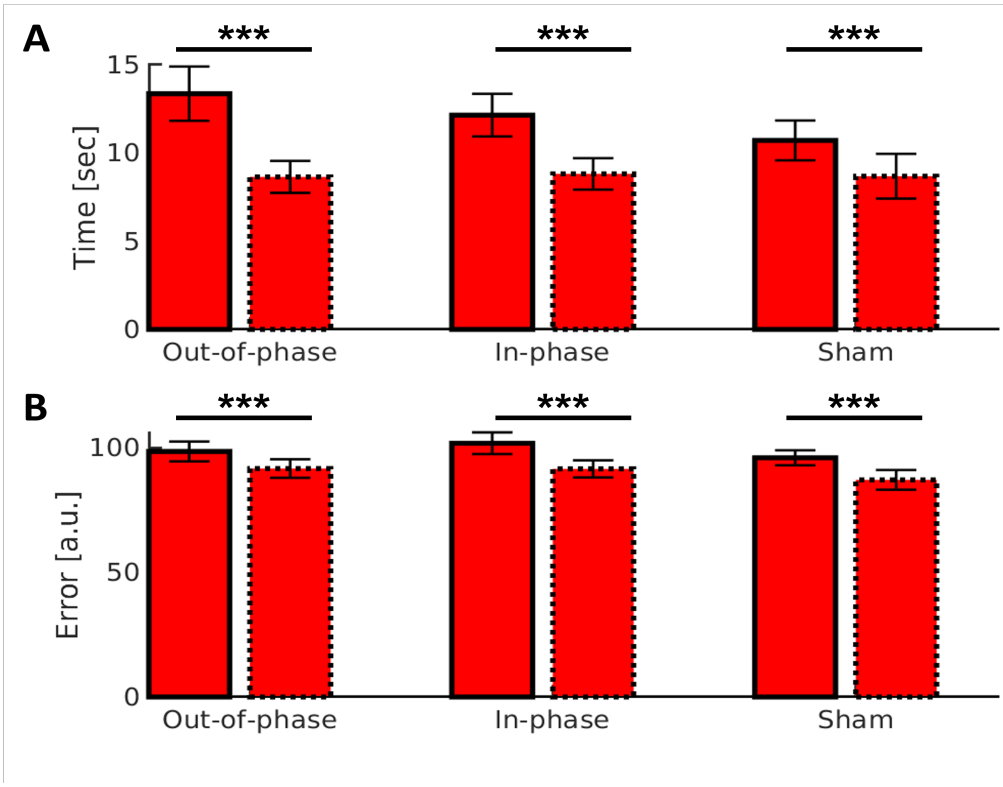


Figure 4.4: Comparison of the first ten (solid frame) and last ten (dashed frame) trials before the end of stimulation for movement time (**A**) and error (**B**) in the out-of-phase, in-phase and sham group (from left to right). Results revealed learning-related changes but the applied beta tACS did not modulate the learning. Error bars indicate the standard error of the mean. Significance stars *** mean $p<.001$.

4.3.4 Distinct Learning Patterns for the Levels of Bimanual Interaction but No Effect of the Applied Beta tACS

To investigate the effect of beta tACS on the different levels of bimanual interaction, two 2 x 3 x 3 ANOVAs were performed with within-subject factors of time (first ten trials and last ten trials before the end of stimulation) and condition (*Uni,* Bi_{eq}, Bi_{uneq}) and a between-subject factor of group (in-phase, out-of-phase, sham) with movement time and error as dependent variables. For movement time and error results yielded a significant main effect of time (movement time: $F_{1,51}$=39.85, $p<.001$, η_p^2=.439; error: $F_{1,51}$=33.05, $p<.001$, η_p^2=.393; , see Figures 4.5F,L), condition (movement time: $F_{2,102}$=79.151, $p<.001$, η_p^2=.608; error: $F_{2,102}$=1330.206, $p<.001$, η_p^2=.963; , see Figures 4.5E,K), and significant interaction between time

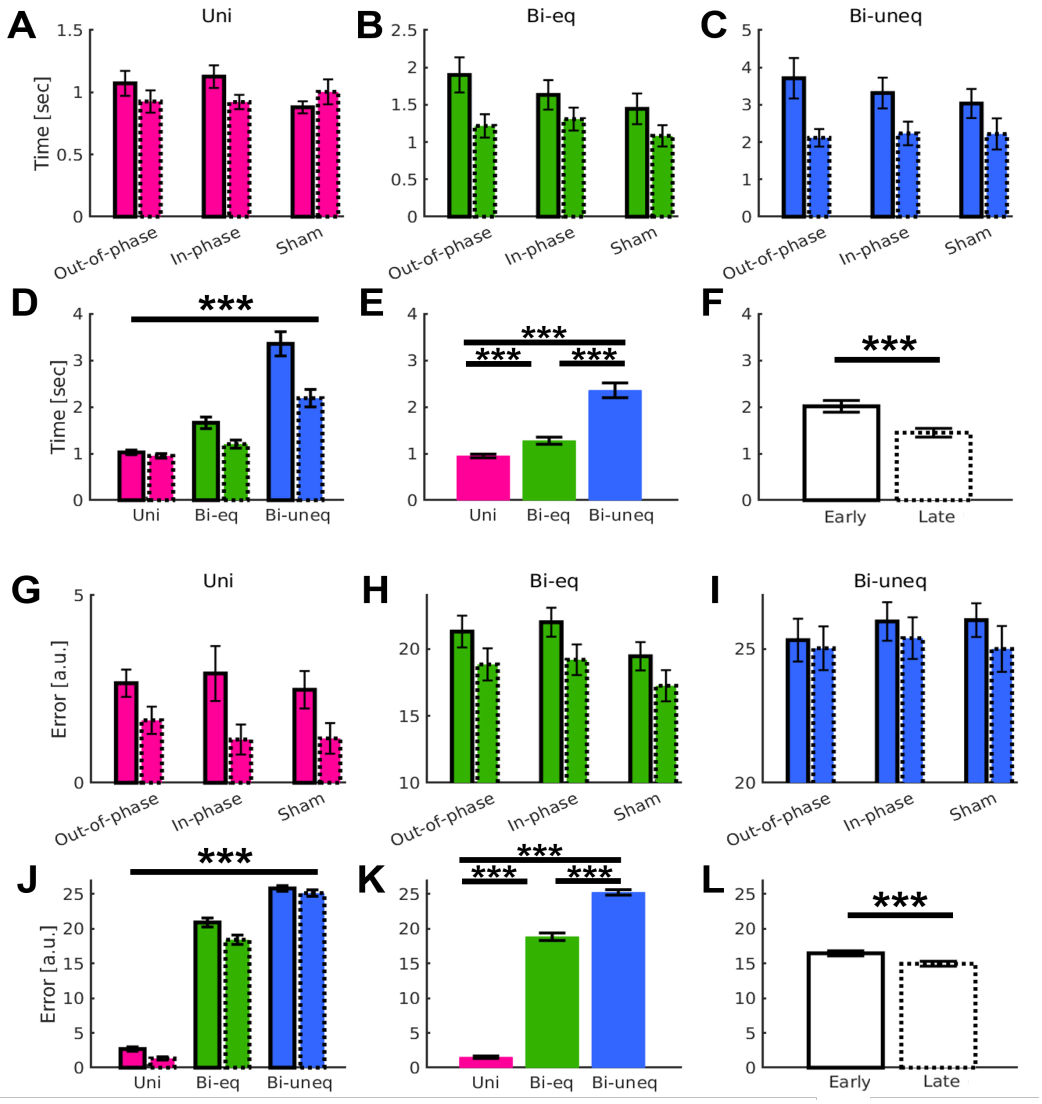


Figure 4.5: Results showed distinct learning-related patterns for the different conditions (*Uni*: pink; Bi_{eq}: green; Bi_{uneq}: blue), but the applied beta tACS did not modulate the patterns in either movement time (**A-F**) or error (**G-L**). This was indicated by the comparison of the first ten (solid frame) and last ten (dashed frame) trials before the end of stimulation for each group (in-phase, out-of-phase, sham) in *Uni* (**A, G**), Bi_{eq} (**B, H**) and Bi_{uneq} (**C, I**) (non-significant interaction between time x condition x group). (**D, J**) Comparison of the first ten (early) and last ten (late) trials before the end of stimulation in each condition averaged over group revealed distinct learning patterns for the different conditions (significant interaction between time x condition). (**E, K**) Comparison of the performance in each condition averaged over time (early, late) and group revealed that the conditions were distinct (significant main effect of condition). (**F, L**) Comparison of the performance at early and late before the end of stimulation averaged over group and condition indicated a significant difference between early and late (significant main effect of time). Error bars indicate the standard error of the mean. Significance stars *** mean $p<.001$.

and condition (movement time: $F_{2,102}$=20.52, p<.001, η_p^2=.287; error: $F_{2,102}$=4.77, p<.011, η_p^2=.085; see Figures 4.5D,J). However, there were no significant main effect or interaction with group (all p's>.1). This suggested that the applied beta tACS did not modulate the distinct learning patterns for the different levels of bimanual interaction, see Figures 4.5A-C, G-I.

To follow up the significant main effect of condition, three paired samples t-tests (Bonferroni corrected) were performed. Results revealed that conditions were distinct (all p's<.001), see Figures 4.5E,K.

To follow up the significant interaction between time and condition (Figures 4.5D,J), change score were calculated, i.e., difference between first and last ten trials of each condition, for movement time and error to compare the amount of learning between the three conditions (Bonferroni corrected). For movement time, the amount of learning was significantly larger for Bi_{uneq} compared to Bi_{eq} and Uni, whereby the amount of learning was also significantly larger for Bi_{eq} when compared with Uni (all p's<.001). For error, the amount of learning was significantly larger for Bi_{eq} compared to Bi_{uneq} (p=.011), whereby the amount of learning did not differ between Uni and Bi_{eq} (p=.076), and Uni and Bi_{uneq} (p=.089).

4.3.4.1 Post-Hoc Analysis

Given the lack of blinding in the active stimulation groups, a double dissociation of out-of-phase, in-phase tACS and Bi_{eq}, Bi_{uneq} condition was assessed. Specifically, two 2 x 2 x 2 ANOVAs were performed with within-subject factors of time (first ten trials and last ten trials before the end of stimulation) and condition (Bi_{eq}, Bi_{uneq}) and a between-subject factor of group (in-phase and out-of-phase group) with error and movement time as dependent variables. Results revealed no significant results with group (all p's>.1). The same applied, when adjusting for baseline performance of the task. Specifically, accounting for the baseline performance by calculating the change score between baseline and training task or including the

baseline performance as a covariate, had no influence on the group effects and resulted in the same non-significant main effect of group or interaction with group.

4.4 Discussion

In this double-blind, sham-controlled study, the novel bimanual motor learning task induced learning by reducing movement time and error with distinct learning patterns for the three conditions. However, against my expectations, in-phase and out-of-phase beta tACS above both sensorimotor cortices did not modulate the learning-related changes.

4.4.1 Replication of Learning-Related Changes with Distinct Levels of Bimanual Interaction

The novel bimanual motor learning task was used to investigate the effects of beta tACS on bimanual motor learning and to explore the effect of beta tACS on learning different levels of bimanual interaction (*Uni,* Bi_{eq}*,* Bi_{uneq}). The results of this experiment demonstrated similar improvements in movement time and error between the sham, in-phase and out-of-phase group, i.e., participants learned the task. Thereby, the results of this experiment replicate the findings of the experiment outlined in chapter 3. In the experiment described in chapter 3, learning was induced over 45 min of training (significant main effect of time) with an effect size of η_p^2=.638 in movement time and η_p^2=.676 in error. This suggested a large effect (>.26 according to Cohen, 1988, pp. 413-414 and Bakeman, 2005). Here, the learning was assessed after 20 min of training. After half the training time, learning was induced across groups with an effect size of η_p^2=.439 in movement time and η_p^2=.393 in error, also indicating a large effect.

Further, results confirmed that conditions were distinct (significant main effect of condition) with *Uni* being the easiest condition, followed by Bi_{eq} and Bi_{uneq}. The findings described in chapter 3 demonstrated this with an effect size of η_p^2=.574 in

movement time and η_p^2=.974 in error. Similarly, the effect sizes of this experiment were η_p^2=.608 in movement time and η_p^2=.963 in error. This indicated a large effect in both original and replicated results. That the unimanual condition was easier than bimanual conditions and that between the bimanual conditions the condition with equal contributions between hands was easier to perform than the condition with unequal contribution between hands, was reported before (Fagard et al., 1985; Mueller et al., 2009; Sisti et al., 2011), see chapter 3 for the full discussion. It seems generally accepted that movements with equal contributions are preferred, more stable and accurate over those with unequal contributions (Swinnen, 2002; Swinnen & Gooijers, 2015).

Additionally, the results of this experiment yielded distinct learning-patterns for the different levels of bimanual interactions (significant interaction between time and condition). In the previous experiment, an effect size of η_p^2=.41 in movement time was reported suggesting a large effect and an effect size of η_p^2=.256 in error indicating a medium effect. Here, the same pattern was found with a large effect in movement time with an effect size of η_p^2=.287 and a medium effect in error with an effect size of η_p^2=.085. The learning-related changes were again largest in Bi_{uneq}, followed by Bi_{eq} and smallest in *Uni* in movement time. In error, learning-related changes were largest in Bi_{eq} and comparable in *Uni* and Bi_{uneq}. Taken together, the findings of this experiment directly replicated previous outcomes in an independent sample, see full discussion of the results chapter 3.

4.4.2 Role of Oscillatory Beta Activity in Bimanual Motor Learning

Beta tACS was applied over both M1 to be stimulated in-phase (synchrony between both hemispheres) and out-of-phase (desynchrony between both hemispheres). I aimed at testing the effects of beta tACS on learning different levels of bimanual interactions. However, against my expectations, the applied beta tACS did not

modulate bimanual motor learning. In the following section, I will discuss several potential explanations for the absence of the hypothesized effect.

One could argue that beta was not the optimal stimulation frequency, as stimulation at 10 Hz benefited task switching in a bimanual tapping task (Heise et al., 2019) and altered motor sequence learning (Schubert et al., 2020). However, sensorimotor beta activity is relevant for bimanual motor control and bimanual motor learning, see chapter 1 for additional information. Although the role of beta activity in complex bimanual motor learning is not completely understood, interhemispheric coherence between both M1 in the beta band is present during bimanual movements (Kajal et al., 2017; Loehrer et al., 2016; Serrien et al., 2002). In addition, beta activity is different between equal and unequal contribution between hands as beta coherence shows lower interhemispheric connectivity in movements with equal contributions compared to unequal contributions (Serrien, 2008a). When applying tACS with concurrent functional Magnetic Resonance Imaging, it has been shown that functional connectivity can be modulated to be in synchrony between hemispheres (Bächinger et al., 2017) and that beta activity can be changed in the targeted area (Weinrich et al., 2017). Together, it is reasonable to expect M1-M1 beta tACS to affect sensorimotor networks, communication and ultimately bimanual motor learning. As this is initial work, the importance of other frequencies cannot be ruled out. Future studies investigating hemispheric synchrony during bimanual motor learning should explore the importance of frequency specificity.

4.4.3 Role of Inter-Regional Delay on Phase Synchrony

Brain hemispheres communicate via the corpus collosum to exchange cognitive and sensory information (Ferbert et al., 1992; Sperry, 1974). This interhemispheric communication has a conduction delay of 27.5-37.5 ms depending on inter-individual differences according to in-vitro measures (Phillips et al., 2015). Non-invasively, with

TMS, it has been suggested that bimanual contractions result in inhibition between hemispheres with an interhemispheric delay of inhibition of 6-30 ms (Ferbert et al., 1992; Fling & Seidler, 2012). During bimanual movements and bimanual motor learning, one would expect that both hemispheres interact most effectively when they synchronize in the same frequency and phase, as discussed in the introduction (Fries, 2005, 2015), and that this interaction is continuous and rapid. Similarly, the nature of the novel task is dynamic as the contribution of both hands might vary to move the cursor as closely as possible along the ideal line. It is reasonable to assume that the interhemispheric communication is thereby similarly dynamic. This might lead to two implications when applying M1-M1 tACS. First, the tACS effect might depend on the conduction delay. Specifically, if one assumes that the hemispheres interact most effectively when in synchrony, the conduction delay hinders an instant arrival of signals. Secondly, the continuous and rapid exchange of information between hemispheres might hinder tACS from effectively entraining the connectivity because the exchange is not entirely in-phase or out-of-phase. Therefore, beta tACS might not be sensitive enough for (de-)synchronization dynamics required for the task, as previously suggested in a study investigating task switching during bihemispheric in-phase tACS by Heise et al. (2019).

4.4.4 Advancing tACS Application

To fully evaluate the potential of stimulation, stimulation parameters can be optimised, e.g., by taking the inter-individual differences across participants into account.

In this experiment, the stimulation frequency was individualised. Individualising the beta peak frequency has been shown to be behaviourally meaningful (Kilavik et al., 2013) and stable between sessions (Espenhahn et al., 2017), but highly variable across participants. This is in line with the findings that the effects of tACS are more pronounced when stimulation frequency matches the natural, individual

frequency (Ali et al., 2013; Reato et al., 2013; Schilberg et al., 2018; Thut et al., 2011; Zaehle et al., 2010) to increase entrainment efficacy (Davis et al., 2012).

In addition to the tACS frequency, phase has been reported to influence performance in unilateral tACS (Polania et al., 2012; Violante et al., 2017), in-phase bihemispheric tACS (Heise et al., 2019) and functional connectivity in a modelling study (Schwab et al., 2019). The importance to stimulate in the optimal to the non-optimal phase was further emphasized in a TMS study by Keil et al. (2014) and Khademi et al. (2018). However, to accurately stimulate tACS in-phase, EEG or MEG is preferably recorded simultaneously (Neuling et al., 2017). While this approach is technically very challenging, e.g., artefact correction, it uniquely enables to measure the extent of tACS-related neural entrainment during and after stimulation.

Conventionally, transcranial electric stimulation is applied with a fixed amplitude, e.g., 1 mA. However, a fixed-amplitude stimulation does not account for inter-individual differences in neuroanatomy, such as skull thickness, which are likely to lead to varying amplitude entering the brain across individuals. To achieve a comparable amplitude at brain level across individuals, stimulation amplitude can be individualised. Indeed, amplitude-controlled stimulation has been described to reduce the variability of current intensities as well as the distribution of the electric field across individuals (Evans et al., 2020). Another way to account for inter-individual differences in tACS is to optimise the electrode montage. Individualising the electrode montage guided by structural Magnetic Resonance Imaging allows to achieve optimised current flow and direction while maintaining a high electrical field intensity above the target area (Lee et al., 2020). This can be further optimised in combination with differently sized electrodes and high-definition 4-1 montages (Helfrich et al., 2014a) as well as ring electrodes (Heise et al., 2016) as this stimulation is more focal. However, those montages come with their own disadvantages, e.g.,

amongst others, a significantly weaker electric field over the stimulation target, see for a review Riddle and Fröhlich (2021). Taken together, optimising the stimulation parameters could help to fully evaluate the potential of bihemispheric stimulation in bimanual motor learning, although their advantages should be balanced against their disadvantages and technical challenges.

4.4.5 Limitations

In this experiment, most participants reported seeing phosphenes during active tACS. Participants were aware that they might see phosphenes depending on their individual reaction to the stimulation, and although sensory side effects like phosphenes are unlikely to hamper the effect of tACS (Schwab et al., 2019), participant's performance might have been influenced indirectly, i.e., attentional bias or discomfort.

4.4.6 Conclusion

Overall, the findings presented in this chapter replicated the findings of the previous chapter in an independent sample. The novel bimanual motor task induced learning with distinct learning patterns for the levels of bimanual interaction. This underscored the successful operationalization of the novel task and its reliable outcomes. However, neither in-phase and out-of-phase beta tACS modulated the learning-related changes. Future electrophysiology studies should investigate the frequency and phase relations underlying complex bimanual motor learning further to put the findings of this chapter into perspective.

5

Variability of Training and Transfer of Learning: An Online Experiment

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5.1 Introduction

Research on motor skill acquisition has a long history of investigating effective ways to structure practice in such a manner that it maximises consistency and accuracy of motor skills. One of the most impressive aspects of motor skill acquisition is that motor skills that have never been trained before can nevertheless be performed, suggesting a transfer of motor skills. Therefore, the practice of motor skills, i.e., training, and their transfer to other motor skills are essential components of motor learning. However, the relationship between training and transfer is not completely understood. Specifically, questions remain about what type of training facilitates transfer, and how related do training task and transfer task need to be to induce transfer. This chapter investigates the relationship between training and transfer of motor skills in the context of complex bimanual motor learning by advancing the novel bimanual motor learning task described in chapter 2.

5.1.1 Variability in Motor Skill Training

One way to investigate the relationship between training and transfer of motor skills, is to increase variability in motor skill training, as suggested in Schema theory by Schmidt (1975). According to the Schema theory, a given motor skill is acquired as an especial or generic skill depending on the training (Schmidt, 1975, 2003). The theory states that a **generic** motor skill is acquired after variable training when a movement is abstracted to a higher level, e.g., in terms of their timing and force (Schmidt, 1975, 2003). As a result, variable training would theoretically prepare better for transfer (Schmidt & Young, 1987; Shea & Kohl, 1990; Shea & Wulf, 2005; Wulf & Schmidt, 1997). Many studies have tested the theory, but results are inconsistent (Schmidt, 2003; Van Rossum, 1990). In contrast, according to Schema theory, an **especial** motor skill is acquired after many repetitions of

constant training and is performed better, i.e., refined, than other movements in response to a specific stimulus (Breslin et al., 2012; Keetch et al., 2005; Schmidt, 1975; Schmidt & Young, 1987; Wulf & Schmidt, 1997). The emergence of an especial skill was reported in basketball (Breslin et al., 2010; Fay et al., 2013; Keetch et al., 2008; Keetch et al., 2005; Stöckel & Breslin, 2013), baseball (Simons et al., 2009) and archery (Czyż et al., 2013; Nabavinik et al., 2018). Especial skills are known to show limited transfer (Keetch et al., 2008; Keetch et al., 2005), however, Shea and Kohl (1991) and Shoenfelt et al. (2002) could show transfer was better after constant training, i.e., especial skill acquisition.

In light of Schema theory, it can be assumed that generic skills emerge when training is variable (Schmidt, 1975, 2003; Van Rossum, 1990), whereas especial skills emerge with constant training (Breslin et al., 2012). Continuously varying motor skill training could help to estimate how specific practice should be to give an advantage of specificity over generalisability and thereby determine transfer of motor skills. The novel task, presented in chapter 2, enables us to vary motor skill training, i.e., to implement either constant or variable training, to reinforce especial or generic skill learning.

5.1.2 Transfer of Motor Skills

In support of the Schema theory, movements that have never been trained can nevertheless be performed, suggesting a transfer of motor skill (Schmidt, 1975). Transfer of learning is defined as the gain in the capability to respond as a function of practice in one task, i.e., the training task, on another task, i.e., the transfer task (Schmidt & Young, 1987). One of most prominent theories of transfer is based on identical elements theory first described by Thorndike and Woodworth (1901) and states the higher the level of similarities, the more transfer occurs, see for a review (Lee, 1988; Magill & Anderson, 2014). Thereby, to investigate the

relationship between training and transfer of motor skills, the transfer task can be varied to increase the difference from the training task.

Transfer tasks that are similar, i.e., have a small difference to a given training task, usually result in transfer effects. Those transfer tasks that resulted in transfer differed from the training task in increased speed, increased distance to a target, different muscles involved, e.g., from lower limb to hand (Aune et al., 2017; Keetch et al., 2005; Shea & Kohl, 1990; Simons et al., 2009). Transfer tasks that are different, i.e., have a large difference to a given training task, usually do not transfer. Those transfer tasks measured transfer from tapping to drawing, with a mismatch between sequences of the movement or a reversal of control-display relationship, i.e., transposition (Grafton et al., 2002; Lewis et al., 1951; Robertson et al., 1999).

In summary, many studies have investigated transfer of motor skills, but transfer has not been assessed with multiple transfer tasks that systematically vary in their difference from a given training task. Systematically varying transfer tasks in their difference from a given training task would allow us to explore how related training task and transfer task need to be to induce transfer, as also suggested by Aune et al. (2017). The novel task, presented in chapter 2 enables us to test transfer of motor skills with multiple transfer tasks by systematically changing the characteristics of the task, i.e., shapes of the streets and movement directions.

5.1.3 Testing the Relationship between Training and Transfer

To shed light on the relationship between training and transfer of motor skills, I systematically tested transfer of motor skills from a set of five training tasks (from reinforcing especial skill learning to reinforcing generic skill learning) to a set of three transfer tasks (from small to large difference to the training task). I hypothesized that learning the training task with more variability would reinforce a generic skill and thus lead to transfer of learning to all transfer tasks, as reported

before (Breslin et al., 2012; Czyż & Moss, 2016; Shea & Kohl, 1990; Wulf & Schmidt, 1997). I hypothesized that learning the training tasks with less variability would reinforce a specific skill and I expected transferability to be high for transfer tasks that have a small difference to the training task but low for other transfer tasks.

5.2 Methods

5.2.1 Participants

A total number of 450 right-handed participants (238 females, M=27 years, SD=5.96) took part in the experiment. Consent was given online and anonymously in accordance with Central University Research Ethics Committee approval (University of Oxford; MSD-IDREC-R61309/RE002). The sample size was estimated with an a-priori statistical power analysis based on data from a pilot study (N=75) comparing the performance in the five training tasks and three transfer tasks over time (interaction between training, transfer, and time, η_p^2=.054). The between-factor comparison was used with the number of groups of 15 and number of measurements of 2. The calculated effect size f was .24 considered to be a medium effect using Cohen's (1988) criteria (>.26 according to Cohen, 1988, pp. 413-414 and Bakeman, 2005). With a correlation between repeated measures=.663, an alpha=.05 and power=.95, the projected sample size needed with this effect size was N=420 (calculated with GPower 3.1.9.4). Thus, the sample size of N=450 used in the present experiment was more than adequate for the main objective of this study.

Data were gathered using Prolific (https://www.prolific.co/). Prolific is a platform for recruiting participants for online experiments, see chapter 2 and Peer et al. (2017) as well as Palan and Schitter (2018) for full description and comparison to other recruitment platforms. On Prolific, eligible participants receive a study invitation and those who access the study first, take part in the study. Eligibility criteria for participants were: (1) age between 18-40 years, (2) no neurological or

psychiatric disorders, (3) no chronic diseases, (4) not on any medication and (5) both hands in good health. Further, eligibility was restricted to fluent English speakers who had an approval rating above 80%, meaning their previous performance in other studies was satisfactory.

5.2.2 Online Data Acquisition: Platforms, Operating Systems and Browsers

All data were collected between September and November 2020. The bimanual motor learning task, described in chapter 2, was translated into the online version with PsychoPy3 v2020.1.3 Builder GUI, a Python based application to design psychological experiments. Running PsychoPy experiments online, requires the generation of an HTML and JavaScript file containing the code describing the experiment. This can be done automatically with PsychoJS, which is a JavaScript based application and the online counterpart of PsychoPy. Therefore, the task was exported to PsychoJS v2020.1 and uploaded to Pavlovia (www.pavlovia.org), an online server hosting the study, see chapter 2 for more information. From there, the online task was run from the browser on participant's computers. This is a common procedure, also described in Anwyl-Irvine et al. (2020a).

The use of devices was restricted to desktop computers or laptops. Operating systems varied between Mac (N=118), Linux (N=12) and Windows (N=320).

The use of a Chrome browser was recommended due to its high temporal accuracy, as previously suggested by Anwyl-Irvine et al. (2020a).

5.2.3 Online Experimental Design and Procedure

5.2.3.1 Training and Transfer Tasks

The study was conducted with a 5 x 3 between-subject design with five training tasks (Train-I, Train-II, Train-III, Train-IV, Train-V) and three transfer tasks (Transfer-S,

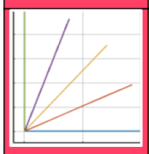
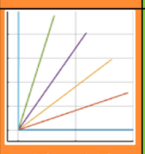
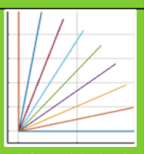
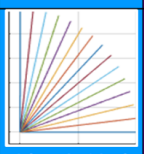
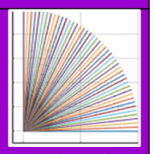
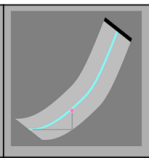
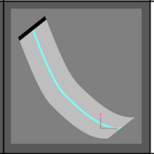
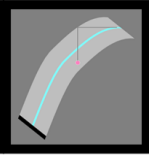
5 x 3 Between-subject design		Training tasks: Train-I	Train-II	Train-III	Train-IV	Train-V	Total N
		 Δ° = 22° N of streets = 5	 Δ° = 18° N of streets = 6	 Δ° = 11.25° N of streets = 9	 Δ° = 6.425° N of streets = 15	 Δ° = 2° N of streets = 46	
Transfer tasks	Transfer-S Δ Small from Train 	I-S	II-S	III-S	IV-S	V-S	150
	Transfer-M Δ Medium from Train 	I-M	II-M	III-M	IV-M	V-M	150
	Transfer-L Δ Large from Train 	I-L	II-L	III-L	IV-L	V-L	150
	Total N	90	90	90	90	90	450

Figure 5.1: The 5 x 3 between-subject design of the online experiment with five training tasks (Train-I, Train-II, Train-III, Train-IV, Train-V) and three transfer tasks (Transfer-S, Transfer-M, Transfer-L) resulting in 15 individual groups (each N=30; I-S, II-S, III-S, etc). The five training tasks (each N=90) varied in their angular difference between streets. Specifically, Train-I had an angular difference of 22° between streets which resulted in five different streets. Train-II comprised an angular difference of 18° between streets resulting in six different streets. Train-III had an angular difference of 11.25° resulting in nine individual streets, whereas Train-IV had an angular difference of 6.425° with 15 streets and Train-V 2° with 46 streets. The three transfer tasks (each N=150) increasingly differed from the training task such that Transfer-S had a small difference to the training task, Transfer-M had a medium difference to the training task and Transfer-L had a large difference to the training task.

Transfer-M, Transfer-L), see Figure 5.1, whereby each participant performed one training task and one transfer task.

Variability in the training tasks (each N=90) was modulated by the angular difference between streets. Specifically, the angular difference between streets linearly varied across training tasks (22°, 18°, 11.25°, 6.425°, 2°). Depending on the angular difference between streets, each training task comprised a different number

of streets. Specifically, Train-I had an angular difference of 22.5° between streets resulting in five different streets with street angles of 0°, 22.5°, 45°, 67.5°, 90°, see Figure 5.1. Train-II consisted of an angular difference of 18° between streets, which resulted in six different streets angles at 0°, 18°, 36°, 54°, 72°, 90°. Train-III had an angular difference of 11.25° between streets, which resulted in nine different streets (0°, 11.25°, 22.5°, 33.75°, 45°, 56.25°, 67.5°, 78.75°, 90°). Train-IV had an angular difference of 6.425° between streets and comprised fifteen streets (0°, 6.425°, 12.85°, ... 90°). Finally, Train-V had an angular difference of 2° between streets with 46 different streets (0°, 2°, 4°, ... 90°).

To test transferability, three transfer tasks additively differed from the training task (each N=150). All transfer tasks were performed on curved streets instead of straight streets, see chapter 2 for conceptual development of curved streets. Specifically, Transfer-S, the transfer task with a small difference to the training task, was performed on curves with the same movement direction as the training task, i.e., upwards and to the right. Transfer-M, the transfer task with a medium difference to the training task, was performed on curved streets with one movement direction changed (upwards and to the left). Transfer-L, the transfer task with a large difference to the training task, was performed on curves with both movement directions changed (downwards and to the left).

The 5 x 3 design resulted in fifteen individual groups (each N=30) consisting of one training task and one transfer task each (I-S, II-S, III-S, IV-S, V-S; I-M, II-M, III-M, IV-M, V-M; I-L, II-L, III-L, IV-L, V-L). As an example, group V-M performed the training task Train-V and transfer task Transfer-M. Group allocation to either of the fifteen groups was done manually by the experimenter. Specifically, after data collection for one group was finished (N=30), the next group was picked pseudo-randomly and the online task was uploaded accordingly. As the study was performed online and with a between-subject design, i.e., participants were

not invited to perform the study again after completing it, the order of group was not expected to affect results.

5.2.3.2 Online Bimanual Motor Learning Task

The in-lab bimanual motor learning task was translated into the online version with the original task design and trial structure. Thereby, a cursor had to be navigated on a path of six streets, see description chapter 2 and Figure 5.2B. The differences between the in-lab and the online version of the task were the variation in angular differences between streets across training tasks and curved streets with different movement directions in transfer tasks. Further, response devices were changed from force grippers to keys 'S' and 'K' on the computer keyboard.

As in the in-lab task, streets in the training task, i.e., straight streets, were rotated in different angles. The angular difference between streets differed across training tasks varying from an angular difference between streets of 22.5° in Train-I to 2° in Train-V between streets, as described above. The street angles corresponded to specific ratios and a specific timing of pressing each key. Specifically, only one key was required in street angles of 0° and 90°, which were present in all training tasks (Train-I to Train-V). Both keys had to be pressed simultaneously in street angles of 45° which was present in all training groups except Train-II, and approximately in Train-V for street angles of 44° and 46°. The rest of the street angles corresponded to more variable ratios and timings to press each key. As an example, on average, a street angle of 2° required to hold key S 98% of the time and key K 2% of the time.

In the transfer task, streets were curved and therefore did not require a specific ratio or timing to press each key but a rather varying ratio or timing of key presses. Therefore, the required hand ratios varied between parts of the curves. The six curves were pseudo-randomized over transfer trials.

Similar to the in-lab version of the bimanual motor learning task, the training task was performed for 100 trials. This led to a varying occurrence of street angles

across training tasks, i.e., in Train-I each street angle occurred at least once in each trial, whereas in Train-V each street angle occurred 1-3 times. Instead of repeating the trials 100 times (100 trials resulted in 600 streets to perform), the street angles could be repeated for a specific number of times (e.g., three times). However, this would lead to a varying number of streets to perform, e.g., resulting in 15 streets in Train-I and 138 streets in Train-V, and thereby to a varying number of trials. I decided against repeating each street angle for the same number of times for the following reasons: First, due to the different amounts of streets to perform, the levels of performance in the training tasks could be attributed to the number of repetitions the performer received, e.g., training on 15 streets in Train-I compared to training on 138 streets in Train-V, as recognized before (Shea & Kohl, 1990, 1991). Thus, comparability across training tasks would be limited. Second, the trial structure and trial design would not be comparable to the in-lab version of the bimanual motor learning task. Thus, a successful translation of the in-lab to the online version of the task could not be assumed. Due to these reasons, I decided to keep the number of trials the same (100 trials) and ensured comparability across training tasks. As a result, the occurrences of street angles varied across training tasks. In Train-I, each street angle occurred at least once in each trial. Additionally, due to the smaller number of street angles (N=5) than streets per trial (i.e., six) one street was duplicated per trial. The duplicated street was randomised, in contrast to the in-lab version in which the 45° was double in one trial. In Train-II, all street angles occurred once in each trial. Due to the bigger number of street angles than streets per trial in Train-III, Train-IV and Train-V, not all street angles were repeated in each trial. However, I ensured that the number of occurrences was comparable across street angles.

Across trials, the order of streets was pseudo-randomized, such that a minimum

of 22.5° angular difference between concurrent streets was assured to avoid street-to-street carry over effects.

Response devices were participant's computer keyboards. The use of a standard QWERTY/QWERTZ keyboard was recommended and restricted to two keys (corresponding to the letters S and K). These keys were selected to avoid that the task was performed with one hand due to their physical distance on a keyboard to one another. The key K enabled cursor movement on the horizontal axis and S on the vertical axis. The movement direction, i.e., upwards or downwards and left or right, was determined by the transfer task and was changed accordingly. The key K and S were used with an acceleration rate of 0.001 height units (units are relative to the height of the study window, see chapter 2 section 2.1.1.2 for more information). Therefore, when holding a key, the cursor would accelerate $\frac{1}{1000}$ height units of the study window per refresh rate of the monitor (60 times per second). This would be at a same rate for the x- and y- axis. Therefore, the velocity was relative to the duration the key was pressed and would potentiate. Maximum velocity was set to 0.3 height units. If the keys were released, the cursor decreased its velocity gradually in the same rate per refresh rate of the monitor until it stopped to move.

Movement time and error were measured as dependent variables to quantify performance, see description in chapter 2.

5.2.3.3 Experimental Timeline

The online study was conducted in one session. After participants gave online consent, they filled in questionnaires of bimanual competence, see Appendix and chapter 2, and achievement motivation (Schuler & Prochaska, 2001), as described in chapter 3. Thereafter, detailed instructions were visually presented. The online task was performed with five trials of the transfer task (pre), followed by 100 trials of the training task and five trials of the transfer task (post), see Figure 5.2A. Before

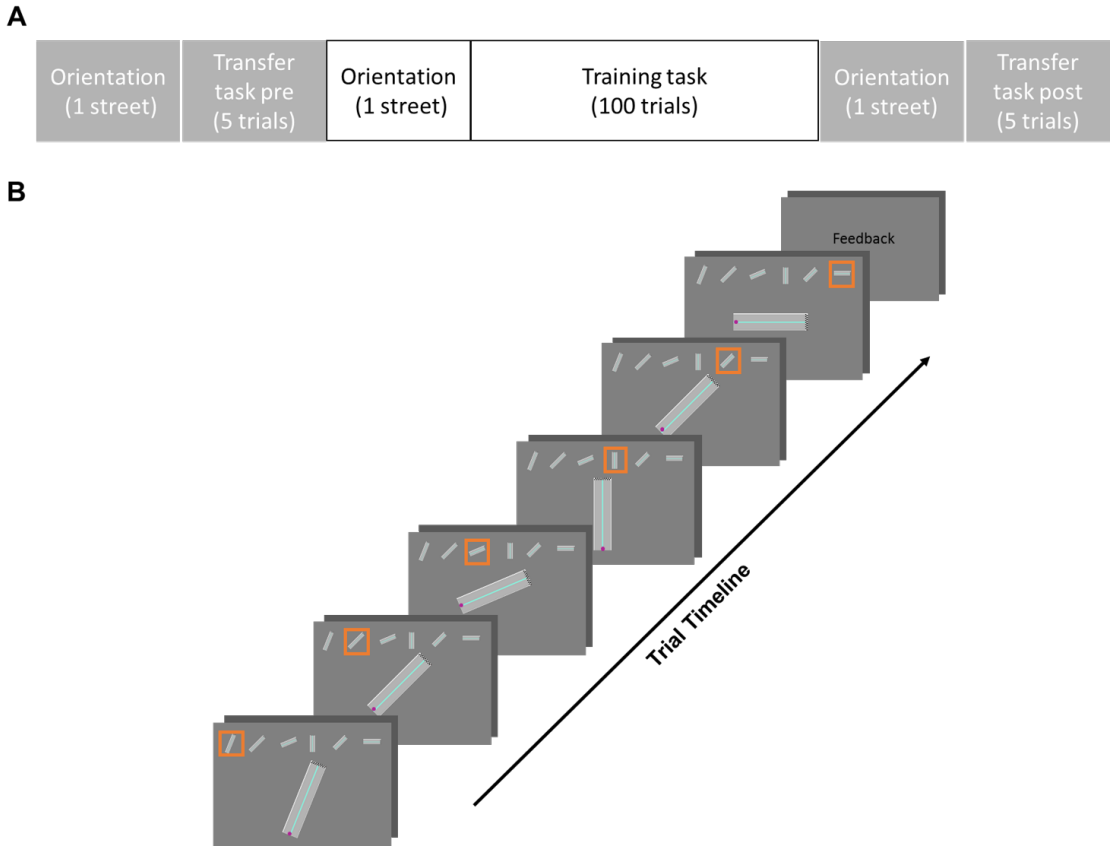


Figure 5.2: Experimental timeline (above) and trial structure (below). (**A**) The task consisted of transfer task pre, training task and transfer task post. Before each transfer task and the training task, one orientation street was presented for familiarization. **(B)** One trial consisted of a path of six streets in different angles. The whole path was displayed at the top of the screen. The current street was displayed enlarged in the middle of the screen end highlighted by an orange frame. At the beginning of each street, the cursor was at the starting position. When the cursor reached the end of the street, the next street started immediately. If the cursor hit either side of the street, the cursor was reset to the starting position. Feedback was given after each trial was finished. The inter-trial interval was self-paced.

each transfer task and the training task, one orientation street was presented for familiarization. Feedback was given on a trial-by-trial basis.

5.2.4 Statistical Analysis

In order to analyse data, some preprocessing, i.e., denoising, was performed as fully described in chapter 2. In brief, the inter-trial variance, i.e., trial difficulty, that systematically occurred on group level data was extracted before learning-

and transfer-related effects were examined. To assess learning-related changes, performance in the first ten (early) and last ten (late) trials of the training task were averaged and compared. To assess transfer-related changes, performance in the five trials of the transfer task before (pre) and after (post) the training task were averaged and compared. Further, to assess the amount of learning and the amount of transfer, change scores, i.e., difference between early and late of the training task and difference between pre and post of the transfer task, were calculated.

To test whether learning and transfer were induced overall, performance in training and transfer at two timepoints was assessed (averaged for all participants). To this end, two 2 x 2 repeated measures analysis of variance (ANOVAs) were performed with a within-subject factors of task type (training and transfer) and timepoint (first and second) once with movement time and once with error as dependent variables. To assess a potential trade-off between movement time and error (also known as speed-accuracy trade-off), a Spearman's correlation was performed with the change score of early and late once with movement time and once with error as dependent variables.

To examine if learning-related changes differed for the fifteen individual groups, performance at early and late were averaged over each of the fifteen individual groups and compared. Two 2 x 3 x 5 ANOVAs were performed with a within-subject factor of time (early and late) and between-subject factors of transfer task (Transfer-S, Transfer-M, Transfer-L) and training task (Train-I to Train-V) once with movement time and once with error as dependent variables.

To measure if transfer-related changes were influenced by the different training tasks, performance at pre and post averaged over each of the fifteen individual groups were compared. Two 2 x 3 x 5 ANOVAs were performed with a within-subject factor of time (pre and post) and between-subject factors of transfer task

(Transfer-S, Transfer-M, Transfer-L) and training task (Train-I to Train-V) once with movement time and once with error as dependent variables.

All data were visualised using Matlab (R2019a version 9.6.0.1174912, The MathWork Inc., Natick, MA, USA). In case of significant effects, post hoc analyses with paired samples t-tests were applied with Bonferroni correction for multiple comparisons. All reported p-values for t-tests were two-tailed and the significance level was set at $p<.05$. Statistical analyses were performed using the opensource software JASP (version 0.14.3, JASP Team 2021).

5.3 Results

5.3.1 Learning in Movement Time and Error Transferred in Movement Time

All participants (N=450) performed a training and a transfer task, see experimental timeline Figure 5.2A. To test whether learning and transfer were induced and to compare the findings of the online experiment to the in-lab experiments, performance in training and transfer at two timepoints was assessed (averaged for all participants). To explore whether performance in the training and transfer tasks changed over time, performance at the early and late timepoints in the training task as well as pre and post timepoints of the transfer task were compared. Thus, two 2 x 2 ANOVAs were performed with within-subject factors of timepoint (first and second) and task type (training task and transfer task) with movement time and error as dependant variables. These analyses revealed a significant main effect of timepoint (movement time: $F_{1,449}$=816.76, $p<.001$, η_p^2=.645; error: $F_{1,448}$=58.47, $p<.001$, η_p^2=.115), a significant main effect of task type (movement time: $F_{1,449}$=1483.08, $p<.001$, η_p^2=.768; error: $F_{1,449}$=1781.14, $p<.001$, η_p^2=.799), and a significant interaction between time point and task type (movement time: $F_{1,449}$=13.62, $p<.001$, η_p^2=.029; error: $F_{1,449}$=144.57, $p<.001$, η_p^2=.244). This suggested that performance in training

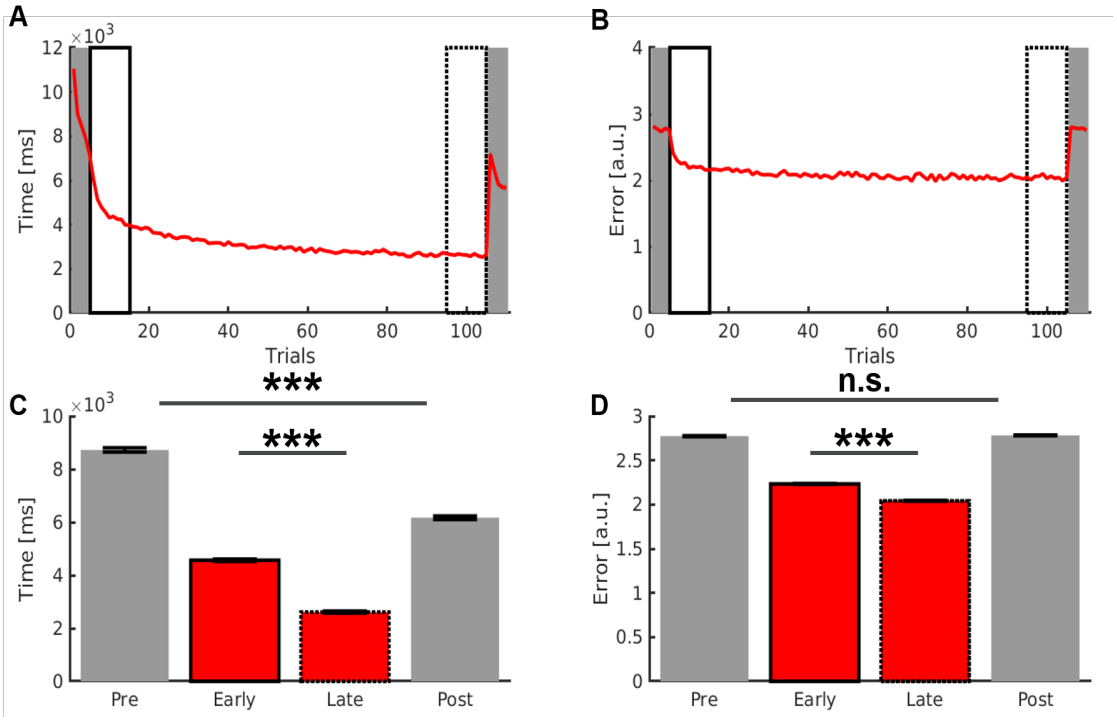


Figure 5.3: Results of the training task and transfer task averaged over all participants (N=450). (**A, B**) Qualitative presentation of the reduction of movement time (left) and error (right) over all trials. The frames indicated the first ten (solid) and last ten (dashed) trials of the training task. The grey background indicated the trials of the transfer task. (**C, D**) Quantitative presentation of the decrease of movement time and error by comparing the first ten (early) and the last ten (late) trials of the training task (red). The transfer task (grey) conducted before (pre) and after (post) the training task showed transfer of learning in movement time but not in error. Error bars indicate the standard error of the mean. Significance stars *** mean $p<.001$.

and transfer changed over time in movement time and error, as visualized in Figures 5.3A-D.

Further, I assessed if learning-related changes were induced by the training overall, irrespective of the training task type, i.e., improvement in performance from early to late. To test this, I performed two paired samples t-tests to compare performance of early and late of the training task with movement time and error as dependant variables. These analyses revealed a significant reduction for both movement time ($t_{1,449}$=34.885, $p<.001$, Cohen's d=1.644) and error ($t_{1,449}$=16.288, $p<.001$, Cohen's d=0.768) suggesting learning was present in both movement time and error, see

Figure 5.3 for qualitative (A-B) and quantitative comparison (C-D) of early and late.

Additionally, I wanted to test if a transfer was induced, regardless of transfer type, i.e., gain of performance, between pre and post. Thus, two paired samples t-test compared performance of pre and post of the transfer task with movement time and error as dependant variables. These analyses demonstrated a significant reduction for movement time but not for error (movement time: $t_{1,449}$=18.253, p<.001, Cohen's d=0.86; error: $t_{1,449}$=-0.587, p=.558, Cohen's d=-0.028). This indicated that learning-related changes only transferred in movement time not in error, see Figure 5.3 for qualitative (A-B) and quantitative comparison (C-D) of pre and post.

5.3.1.1 No Trade-Off between Movement Time and Error

Similar to the in-lab experiments, I wanted to test whether learning the task was mediated by a potential trade-off between changes in movement time and error. To explore a potential trade-off between movement time and error, a Spearman's correlation was performed with the change score, i.e., difference between early and late, of movement time and error. This revealed a significant positive correlation (rho=.138, p=.003, CI=[.227, .046]) indicating the absence of a trade-off.

5.3.2 Learning Differed for the Training Tasks

The online task was designed with a 3 x 5 between-subject design, resulting in 15 individual groups each performing one training task and one transfer tasks, see experimental design Figure 5.2A. To test whether the different levels of variability across training tasks influenced learning in each training task, i.e., learning-related changes differed between the 15 groups, performance at early and late was compared. Due to the randomization and order of the experimental timeline, I expected to see an influence of training task (i.e., difference between the five training tasks) but no effect of transfer task (i.e., difference between the 15 groups) on learning the task. Specifically, before learning the training task, participants had only

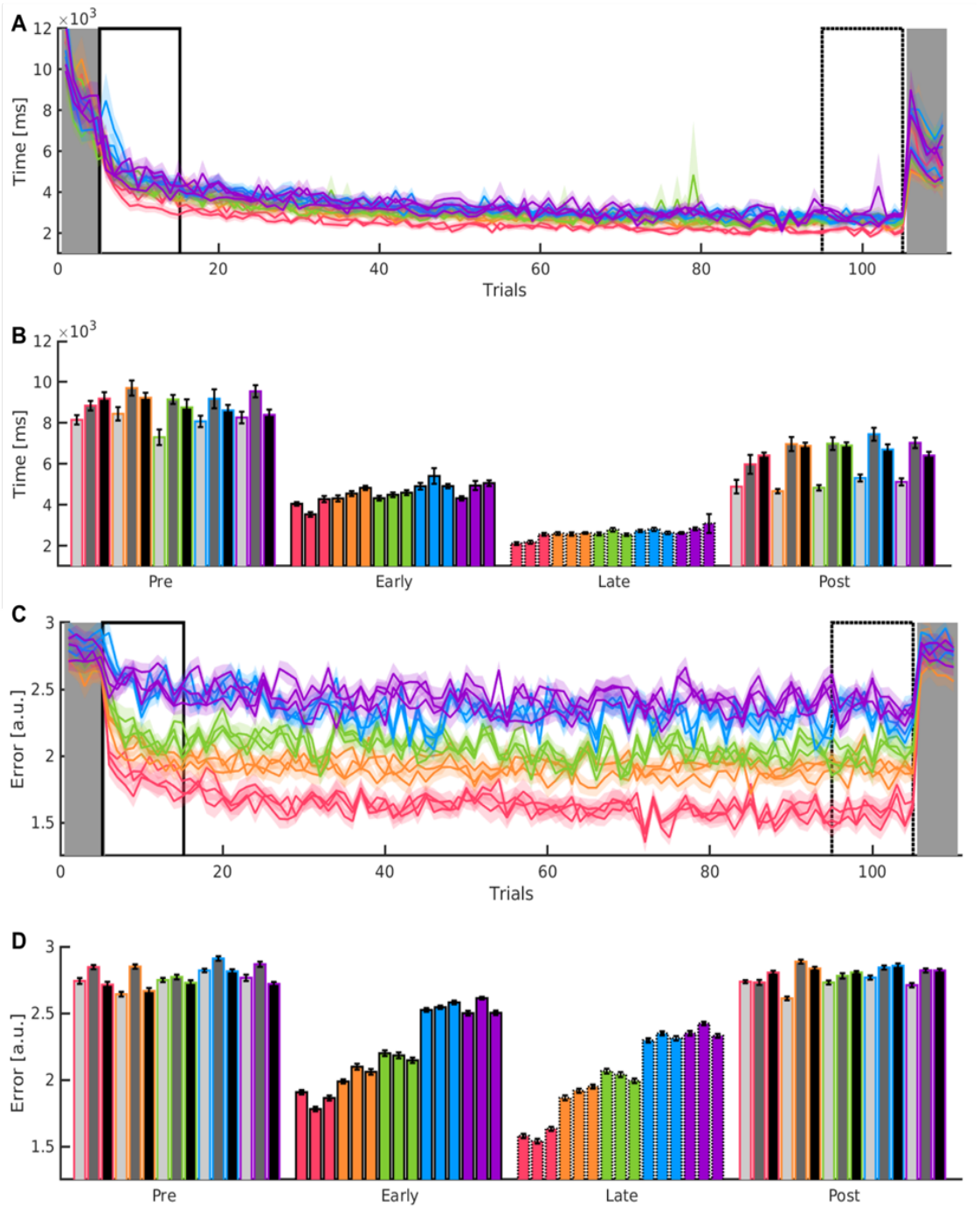


Figure 5.4: Results of the training tasks (Train-I: pink, Train-II: orange, Train-III: green, Train-IV: blue, Train-V: purple) and transfer tasks (Transfer-S: light grey, Transfer-M: dark grey, Transfer-L: black) for each individual group (each N=30). (**A,C**) Qualitative presentation of the performance in movement time (above) and error (below) over all trials. The frames indicate the first (solid) and last (dashed) ten trials of the training task. The grey background indicated the trials of the transfer task. (**B,D**) Quantitative presentation of the performance in the first ten (early) and the last ten (late) trials of the training task and five trials of the transfer task before (pre) and after (post) the training task. Error bars indicate the standard error of the mean.

performed 5 trials of the transfer task, thereby an influence of the transfer task was not expected. In order to tests this, two 2 x 3 x 5 ANOVAs were performed with a within-subject factor of time (early and late) and between-subject factors of transfer task (Transfer-S, Transfer-M, Transfer-L) and training task (Train-I to Train-V) with movement time and error as dependant variables. These analyses indicated a significant main effect of time (movement time: $F_{1,435}$=1259.382, p<.001, η_p^2=.743; error: $F_{1,435}$=273.898, p<.001, η_p^2=.386; Figures 5.5D,I), a significant main effect of training task (movement time: $F_{4,435}$=6.272, p<.001, η_p^2=.055; error: $F_{4,435}$=185.076, p<.001, η_p^2=.63; Figures 5.5C,H) and a significant interaction between time and training task (movement time: $F_{4,435}$=4.238, p=.002, η_p^2=.038; error: $F_{4,435}$=5.542, p<.001, η_p^2=.048; Figures 5.5A-B,F-G). As would be expected, the main effect of transfer task and all other interactions with transfer task were not significant (p's<.01). This suggested a difference between the five training tasks, an overall learning effect, and that learning in the five training tasks was influenced differently over time, indicating different learning patterns for the training tasks, as visualized in Figures 5.5A-B, E-F. As expected, results indicated no influence of the transfer tasks on learning either in movement time or error, see Figures 5.4A-B, C-D for comparison of early and late.

Post hoc, I followed up the significant main effect of training task by calculating the mean performance in each training task over the two time points. To test how the training tasks differed from each other, ten paired samples t-test were performed once for movement time and once for error. Results are displayed in Table 5.1 and 5.2 and suggested a complex relationship between the different training tasks, see Figures 5.5C,H.

To follow-up the significant interaction between time and training tasks and to assess how the learning-related changes, i.e., amount of learning, differed in each training task, change scores, i.e., difference between early and late, were compared,

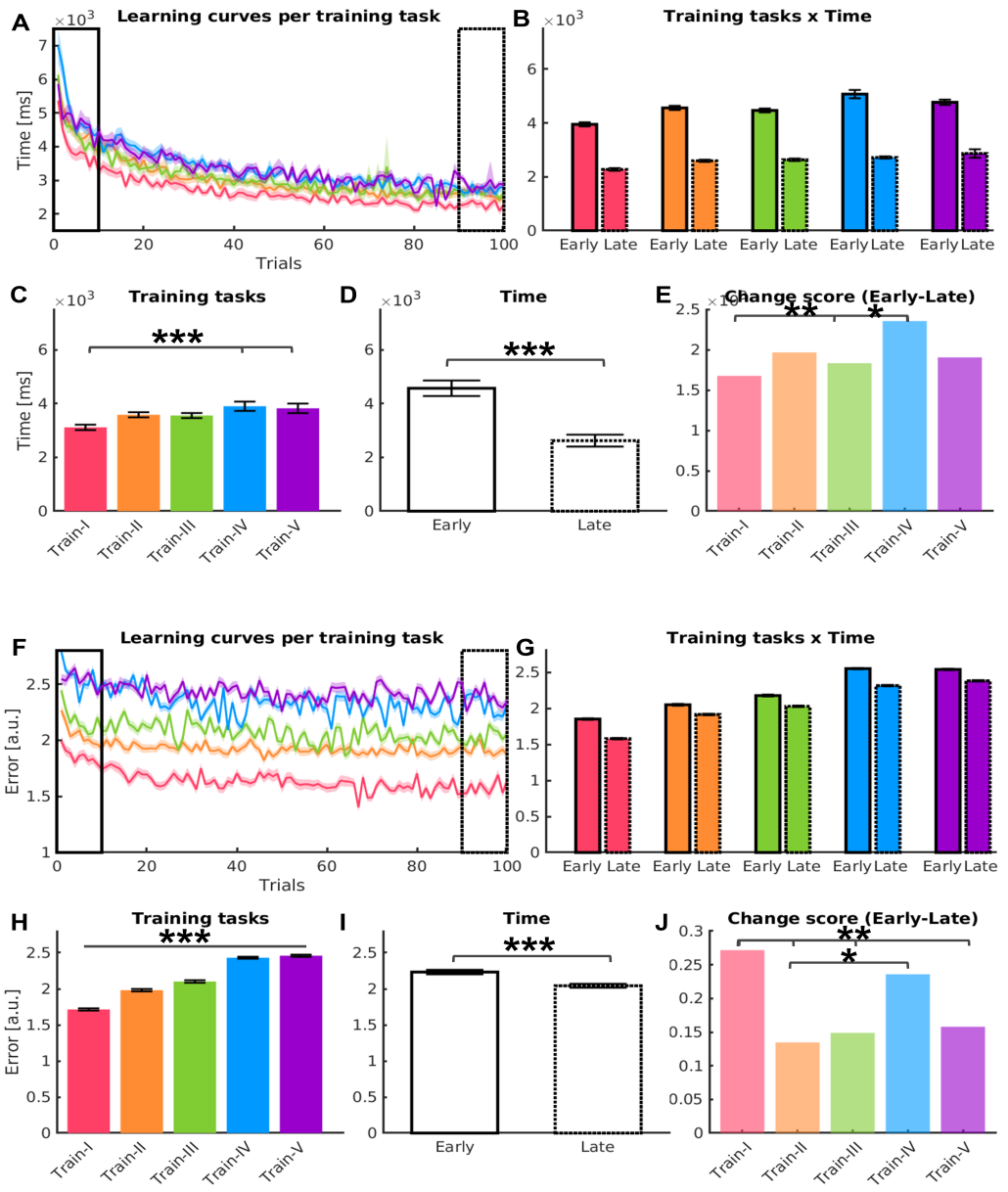


Figure 5.5: Results indicated distinct learning patterns in the five training tasks (Train-I: pink, Train-II: orange, Train-III: green, Train-IV: blue, Train-V: purple; each N=90). (**A, F**) Qualitative presentation of the reduction in movement time (above) and error (below) over the trials of the training task. The frames highlighted the performance in the first ten (solid) and last ten (dashed) trials. (**B, G**) Quantitative presentation of the reduction in movement time and error from the first ten (early) to the last ten (late) trials in each training task (significant interaction of time x training task). (**C, H**) Comparison of the five training tasks averaged over time (early, late) suggested that training tasks were different between each other (significant main effect of training task). (**D, I**) Comparison of the performance at early and late averaged over training task demonstrated that the two time points differed (significant main effect of time). (**E, J**) Illustration of the amount of learning, i.e., difference between early and late, in each training task. Significance stars * mean $p<.05$, ** mean $p<.01$, *** mean $p<.001$. Error bars indicate the standard error of the mean.

Table 5.1: *Post Hoc Comparisons of the Performance in the Training Tasks for Movement Time*

		t	Cohen's d	p_{bonf}
Train-I	Train-II	-1.665	-0.271	.965
	Train-III	-0.901	-0.164	1.00
	Train-IV	-3.902	-0.585	.001
	Train-V	-1.313	-0.185	1.00
Train-II	Train-III	0.765	0.130	1.00
	Train-IV	-2.236	-0.320	.258
	Train-V	0.353	0.048	1.00
Train-III	Train-IV	-3.001	-0.467	.028
	Train-V	-0.412	-0.060	1.00
Train-IV	Train-V	2.589	0.331	.099

Figures 5.5E,J. Thus, ten paired samples t-tests once with movement time and once with error as dependent variables were performed. For movement time, the degree of learning was significantly larger in Train-IV compared to Train-I ($t_{4,445}$=-3.902, p=.001, Cohen's d=0.585) and Train-III ($t_{4,445}$=-3.001, p=.028, Cohen's d=-0.467). The rest of the learning-related changes in each training task was comparable (all p's>.05), as visualised in Figure 5.5E. For error, the amount of learning was significantly larger in Train-I compared to Train-II ($t_{4,445}$=3.797, p=.002, Cohen's d=0.552), Train-III ($t_{4,445}$=3.403, p=.007, Cohen's d=0.508) and Train-V ($t_{4,445}$=3.150, p=.017, Cohen's d=0.428). The rest of the learning-related changes in each training task was comparable (all p's>.05), as visualised in Figure 5.5J.

5.3.3 Transfer Differed for the Transfer Tasks

Before and after learning the training task, each participant performed a transfer tasks, see Figure 5.2A. I hypothesized, learning the training tasks with less variability would lead to transfer to Transfer-S and learning in the training tasks with higher variability would lead to transfer to all other transfer tasks. To examine if learning the training tasks influenced performance in the transfer tasks, the performance at pre and post was compared. Specifically, two 2 x 3 x 5 ANOVAs were performed

Table 5.2: *Post Hoc Comparisons of the Performance in the Training Tasks for Error*

		t	Cohen's d	p_{bonf}
Train-I	Train-II	-8.167	-0.385	$< .001$
	Train-III	-11.860	-0.559	$< .001$
	Train-IV	-21.962	-1.035	$< .001$
	Train-V	-22.807	-1.075	$< .001$
Train-II	Train-III	-3.692	-0.174	.003
	Train-IV	-13.795	-0.650	$< .001$
	Train-V	-14.640	-0.690	$< .001$
Train-III	Train-IV	-10.103	-0.476	$< .001$
	Train-V	-10.948	-0.516	$< .001$
Train-IV	Train-V	-0.845	-0.040	1.00

with a within-subject factor of time (pre and post) and between-subject factors of training task (Train-I to Train-V) and transfer task (Transfer-S, Transfer-M, Transfer-L) with movement time and error as dependent variables. Results indicated a significant main effect of time for movement time but not for error (movement time: $F_{1,435}$=334.645, p<.001, η_p^2=.435; error: $F_{1,435}$=0.352, p=.553, η_p^2=.001; Figures 5.6D,I). Further, results revealed a significant main effect of transfer (movement time: $F_{2,435}$=15.859, p<.001, η_p^2=.068; error: $F_{2,435}$=4.79, p=.009, η_p^2=.022; Figures 5.6C,H) and a significant interaction between time and transfer (movement time: $F_{2,435}$=3.818, p=.023, η_p^2=.017; error: $F_{2,435}$=8.319, p<.001, η_p^2=.037; Figures 5.6A-B, F-G). Against my expectation, the main effect of training and all interactions with training were not significant (p's>.05). This suggested that performance differed in the transfer tasks but the training tasks did not influence the transfer to certain transfer tasks, see Figures 5.4A-B, C-D for comparison of pre and post.

Post hoc, the main effect of transfer task was followed up to assess how the performance in the transfer tasks differed, Figures 5.6C,H. To this end, three paired samples t-test were performed once for movement time and once for error as dependent variables. Results revealed a significant difference between Transfer-S and Transfer-M (movement time: $t_{1,449}$=-5.344, p<.001, Cohen's d=-0.252; error:

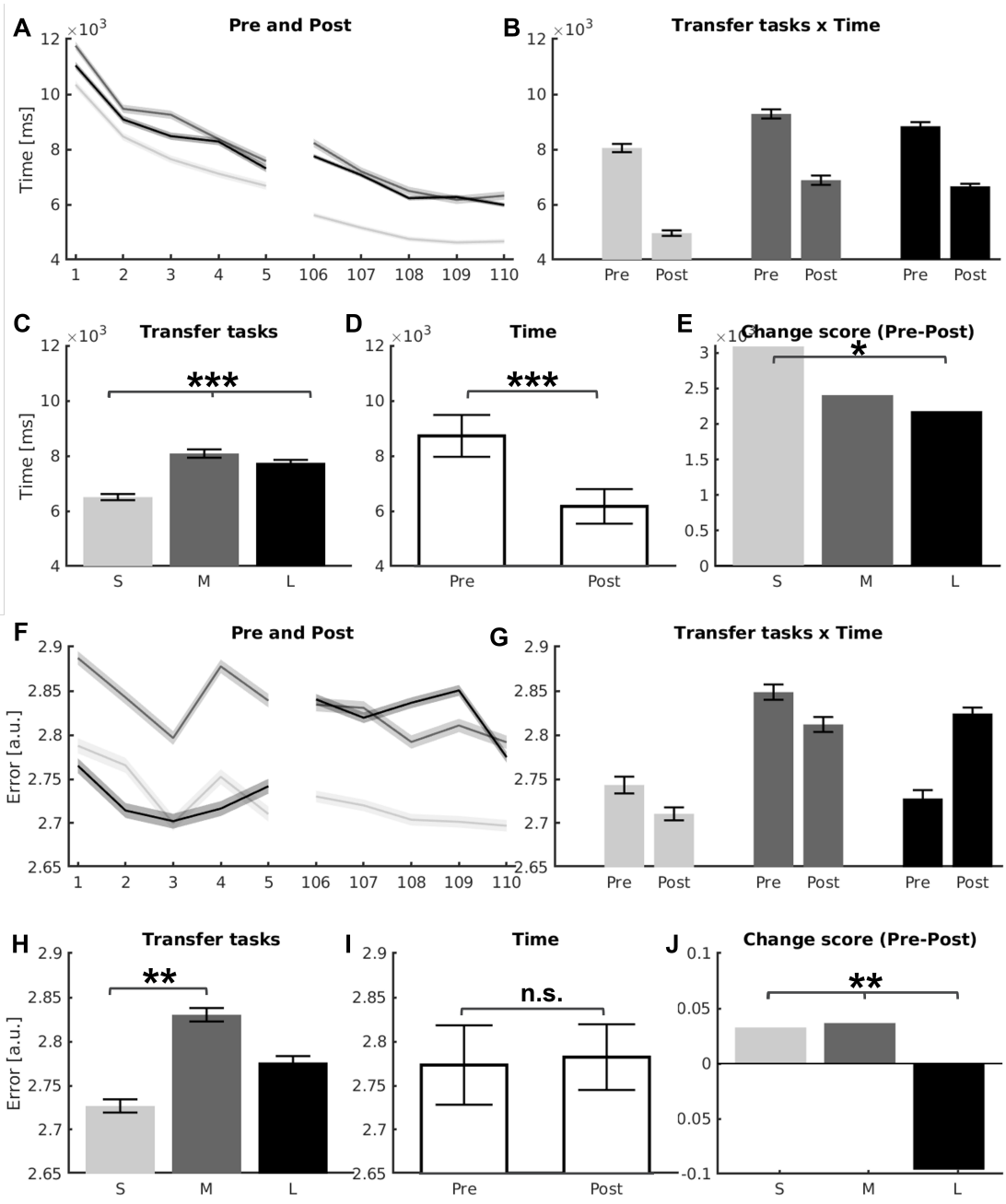


Figure 5.6: Results indicated that transfer effects differed in the three transfer tasks (Transfer-S: light grey, Transfer-M: dark grey, Transfer-L: black; each N=150). (**A, F**) Qualitative presentation of the performance in the five transfer trials before (pre) and after (post) the training task for movement time (above) and error (below). (**B, G**) Quantitative presentation of the performance at pre and post in each transfer task (significant interaction of time x transfer tasks). (**C, H**) Comparison of the performance in each transfer task averaged over time (pre, post) indicated that transfer tasks were different (significant main effect of transfer). (**D, I**) Comparison of the performance at pre and post averaged over transfer task suggested that the time points differed in movement time but not in error (main effect of time). (**E, J**) Illustration of the amount of transfer, i.e., difference between pre and post, in each transfer task. Significance stars * mean $p<.05$, ** mean $p<.01$, *** mean $p<.001$. Error bars indicate the standard error of the mean.

$t_{1,449}$=-3.094, p=.006, Cohen's d=-0.146) and Transfer-S and Transfer-L in movement time but not error (movement time: $t_{1,449}$=-4.213, p<.001, Cohen's d=-0.199; error: $t_{1,449}$=-1.475, p=.423, Cohen's d=-0.07). There was no significant difference between Transfer-M and Transfer-L (movement time: $t_{1,449}$=1.131, p=.776, Cohen's d=0.053; error: $t_{1,449}$=1.619, p=.319, Cohen's d=0.076). This suggested that Transfer-S was different from Transfer-M and Transfer-L but Transfer-M and Transfer-L did not differ between themselves, as visualized in Figures 5.6C,H.

To follow up the significant interaction between time and transfer task and to assess how the amount of transfer differed between the transfer tasks, change scores, i.e., difference between pre and post, were calculated and compared (Figures 5.6E,J). To assess how the amount of transfer differed, three paired samples t-tests were performed once for movement time and once for error as dependent variables. Results revealed that for movement time the amount of transfer was biggest in Transfer-S in comparison to Transfer-L ($t_{2,447}$=2.664, p=.024, Cohen's d=0.316). For error, the absence of transfer was significantly different for Transfer-L in comparison to Transfer-M ($t_{2,447}$=3.605, p=.001, Cohen's d=0.415) and Transfer-S ($t_{2,447}$=3.495, p=.002, Cohen's d=0.382) which showed transfer effects. All other findings were comparable (p's>.05).

5.4 Discussion

The purpose of this experiment was to test the relationship between training and transfer of motor skills. The online experiment obtained a sample of 450 participants in a 5 x 3 between-subject design with five training tasks and three transfer tasks. I observed that the task was both learnable and the skill acquired transferred to a related task. Further, the different training tasks demonstrated different learning patterns. Similarly, the different transfer tasks revealed different transfer patterns, at least for two of the three transfer tasks. However, the relationship between

training and transfer was not as predicted. I hypothesized that training with high variability would lead to greater transfer to all transfer tasks and that training with low variability would only transfer to Transfer-S. In contrast, the results presented here suggested that transfer was independent of the training task and depended on the transfer task itself. Specifically, all training tasks transferred to Transfer-S whereas there was no difference of transfer between Transfer-M and -L which showed little transfer. Together, the results of this experiment indicated a complex relationship between training and transfer of motor skill learning. In addition, I could show that online experiments provide high quality data, strongly suggesting that motor learning studies can be performed online.

5.4.1 Learning-Related Changes in Movement Time and Error Transferred in Movement Time

In this online version of the bimanual motor learning task, practising the training tasks for 100 trials lead to a reduction both in movement time and error on the group level (N=450). This is in line with previous experiments conducted in the laboratory, as described in chapter 3 and 4. Therefore, it can be assumed that the findings of the previous study conducted in the laboratory were successfully translated to the online version of the bimanual motor learning task. This is supported by the previous findings of online experiments, suggesting high quality data in areas of cognitive psychology (Anwyl-Irvine et al., 2020a) and motor learning (Tsay et al., 2021).

After learning the online task, transfer was induced. This had not been shown in the previous experiment reported in chapter 3. In the experiment described in chapter 3, transfer was assessed with a transposition task (i.e., swapping the axis controlled by each hand) which did not lead to transfer effects in movement time or error. As fully outlined in chapter 3, I hypothesized that the training task used in chapter 3 reinforced learning an especial skill and that training and transfer task were too different from each other to induce transfer effects. In contrast, in the present

experiment, transfer was assessed with transfer tasks that differed in the shape of the streets, i.e., curves, and movement directions, i.e., cursor movement was changed to another direction but remained on the same axis (no transposition). Results presented here suggested transfer effects, i.e., reduction from pre to post, but were only significant in movement time not in error. Thereby, the transfer tasks used in this study depicted the relationship between training and transfer better and lead to a fairer transfer in comparison to the previous experiments reported in chapter 3 but grouped over all transfer tasks, transferability was only present in movement time.

Overall, the online experiment led to learning and transfer which demonstrated a successful translation from the in-lab version to the online version of the bimanual motor learning task and suggested a fairer design of the transfer tasks. Further, the results indicate good quality of data of online experiments. Future studies could use this experiment as an indicator that motor learning studies can be obtained online.

5.4.2 Different Learning Patterns for the Different Training Tasks Suggested Especial and Generic Skill Acquisition

In this study, I wanted to test the relationship of training and transfer of motor skills. One way to investigate this relationship, was to test variability of training, i.e., constant and variable practice to reinforce especial or generic skill acquisition. In accordance with that, the five training tasks (Train-I, Train-II, Train-III, Train-IV, Train-V) were designed to continuously vary practice from constant (Train-I, -II) to variable training (Train-III, Train-IV, Train-V). Thus, variability across training tasks was induced by varying the number of repetitions of street angles across training tasks, i.e., in Train-I each street angle occurred at least once in each trial, whereas in Train-V each street angle occurred 1-3 times. At the same time, the number of trials in each training task was the same, i.e., 100 trials.

Results showed that the training tasks differed from each other. Specifically, Train-I showed the lowest movement time and error indicating to be the easiest training task, whereas Train-IV and -V showed the highest movement time and error indicating to be the most difficult training task. The other training tasks, Train-II and Train-III indicated comparable performance in movement time. Similarly, Train-IV and Train-V did not differ significantly from each other in terms of movement time. For error, the level of performance continuously worsened from Train-I, with the lowest error, followed by Train-II, followed Train-III in the middle and Train-IV and Train-V with the highest error. The error in Train-IV and Train-V did not differ significantly. That constant and variable training tasks differ has been reported in unimanual isometric force production (King & Newell, 2013; Shea & Kohl, 1991). This is further underlined by the Schema theory which states that depending on the training task a generic or especial motor skill is reinforced (Breslin et al., 2012; Keetch et al., 2005; Schmidt, 1975; Schmidt & Young, 1987; Wulf & Schmidt, 1997). The differences in the training tasks might also be amplified in the present study because bimanual performance was measured, unlike many other previous studies investigating unimanual force production (King & Newell, 2013; Shea & Kohl, 1991) or unimanual throwing (Shoenfelt et al., 2002). On a more speculative note, Train-I might have had lower error and less movement time than Train-V for the following reasons: Train-I consisted of trials with at least two street angles, i.e., those with 0° and 90° which required one key press and thereby led to low error and low movement time, as also reported in the in-lab version of the task in chapter 3 and 4. In addition, Train-I entailed the street angle of 45° requiring an equal contribution of hands, i.e., simultaneous pressing of both keys. This street angle occurred at least once each trial which also led to low error and little movement time as reported in chapter 3 and 4. In contrast, these three street angles did not appear as often in Train-V. This also holds true when counting in street angles

of 2° and 88° or 4° and 86° which also produced low error and low movement time. Train-V thereby consisted of more street angles that required an unequal contribution between hands than Train-I, which is known to be more difficult to perform than equal contributions between hands, as reported in chapter 3 and 4 as well as in other studies (Swinnen, 2002; Swinnen & Gooijers, 2015).

In addition, previous studies have indicated that learning differs between constant and variable training (King & Newell, 2013; Shea & Kohl, 1990, 1991; Shoenfelt et al., 2002; Wulf & Schmidt, 1997). According to Schema theory, variable training (reinforcing a generic skill) leads to an advantage in learning in comparison to constant training (reinforcing an especial skill) because several variations of the skill are trained (Schmidt, 2003; Schmidt & Lee, 2005; Shea & Kohl, 1990; Wulf & Schmidt, 1997). In line with this, Shea and Kohl (1990) reported that variable practice led to lower errors in comparison to constant practice. In their experiment, variable training entailed practising different unimanual force levels for 289 trials, whereas the constant training consisted of one force level which was trained for 85 trials. However, the authors recognised that their findings might have been due to the different number of repetitions. When they compared training tasks with the same number of repetitions in a follow up experiment, results showed that constant training led to less absolute error, i.e., was performed better, than variable training (Shea & Kohl, 1991). Further, in another task involving basketball free throw, Shoenfelt et al. (2002) reported that constant practice led to lower errors. The authors inferred that due to their experimental task design variable and constant training were more comparable and more consistent and thereby resulted in these outcomes. The benefits of constant practice were underlined by Keetch et al. (2005). They argued that with training the recall schema becomes more refined which is why especial skills, i.e., those that emerge after constant practice, have an advantage over the actions from other movements of the same class (Breslin et al., 2012; Keetch

et al., 2005). In line with this, the results presented in this chapter could show that constant practice led to lower error and less movement time in comparison to variable practice while all training tasks received the same number of repetitions, i.e., 100 trials to perform. Thus, in line with the theory of Keetch et al. (2005), it can be assumed that by design the recall schema was refined in the training tasks with constant practice, i.e., Train-I, Train-II, compared to variable training, i.e., Train-V.

Taken together, the five training tasks were designed to measure constant and variable practice and results strongly suggested that especial and generic skill learning was reinforced, as hypothesized.

5.4.3 Different Patterns of Transfer for the Different Transfer Tasks

Another way to investigate this relationship between training and transfer of motor skills, was to test transferability to different transfer tasks. In accordance with that, three transfer tasks (Transfer-S, Transfer-M, Transfer-L) were designed to increase their difference to the training task.

Results indicated that two of the three transfer tasks differed. Specifically, Transfer-S showed the lowest movement time and smallest error, whereas Transfer-M and Transfer-L were comparable and showed the highest movement time and highest error. Previously, transfer tasks that varied from the training task on the same dimension with only a small difference to the training task showed transfer effects. Those tasks included transfer tasks that had a different amplitude or increased speed in a cyclic rotation task, as well as with increased distance to a target or different muscles involved (from lower limb to hand) when throwing a ball (Aune et al., 2017; Keetch et al., 2005; Simons et al., 2009; Wulf & Schmidt, 1997). These studies tested transferability with one transfer task. However, only by testing transferability with more than one transfer task, it can be demonstrated that transfer is not transfer-task specific and transferability is put into perspective. In

one of the few studies investigating more than one transfer task, Mattar and Ostry (2007) could show that with increasing difference between training and transfer task, the extent of transfer was reduced, i.e., had higher error. Similar findings were shown in the study by Aune et al. (2017), who assessed different transfer tasks with performing the same task with the homologous and non-homologous limbs. Thereby, in the transfer task with a small difference to the training task, transfer was assessed with performing the task with the right shoulder instead of the right index finger (lateral non-homologous transfer). In the transfer task with a bigger difference to the training task, transfer was assessed from one index finger to the other index finger (bilateral homologous transfer) or from left index finger to the right shoulder (bilateral non-homologous transfer). Results indicated that the improvements in the transfer task with a big difference to the training task, i.e., bilateral non-homologous transfer, was smaller than in the other transfer tasks. The improvements in the other transfer tasks, namely between lateral non-homologous and bilateral homologous transfer was comparable. Those effects were seen for both training tasks.

Similarly, the transfer tasks in the present experiment were designed that Transfer-S had a small difference to the training tasks and in line with that showed the lowest movement time and smallest error. Transfer-M and Transfer-L were designed to have a bigger difference to the training tasks and in line with that performance showed the highest movement time and highest error. However, performance in Transfer-M and Transfer-L did not differ. Speculatively, that Transfer-M and Transfer-L had the same level of performance might be due to the fact that only changing the movement direction of one hand interferes with the learned movement direction of the other hand. Specifically, in this scenario, in Transfer-M one hand is faster and more accurate than the other which might induce an unequal contribution between hands. This might be especially plausible with regards to the finding, that unequal contributions are more difficult to perform than

equal contributions between hands, as reported in the previous chapters and in other studies (Swinnen, 2002; Swinnen & Gooijers, 2015). In line with this, Transfer-L potentially was not as difficult because both hands had to learn a new pattern similarly. It is also plausible that Transfer-M and Transfer-L had the same level of performance because in Transfer-M one hand was moving against the reading direction which is more difficult to perform (Mattar & Ostry, 2007).

Taken together, the transfer tasks differed and induced different amounts of transferability, however, not as expected. Although Transfer-M and Transfer-L were designed with additive difficulty, results did not indicate any difference between the two tasks. This further underlined the difficulty of operationalising transfer and designing transfer tasks to ensure a fair comparison between training and transfer task as well as across transfer tasks.

5.4.4 The Role of Variability in Training on Different Transfer Tasks

To test the relationship of training and transfer of motor skills, I tested the transferability of a set of five training tasks to a set of transfer tasks. I expected that training with high variability (Train-IV and Train-V) would induce transfer to all transfer tasks and that training with low variability, i.e., constant training, (Train-I, Train-II, Train-III) would only transfer to transfer task with a small difference to the training task. However, these hypotheses were only partly demonstrated. Training and transfer did not interact. In fact, transfer occurred independent of the training task, and depended on the transfer task. Specifically, transfer generally occurred in Transfer-S whereas there was no difference between Transfer-M and Transfer-L which showed little or the absence of transfer. As outlined above, the results presented in this experiment suggest that the training tasks induced especial and generic skills. In line with our hypothesis, Schema theory predicts that variable training has an advantage over constant training in transfer (Schmidt, 2003; Schmidt & Lee, 2005;

Shea & Kohl, 1990; Wulf & Schmidt, 1997). This was shown in a study by Wulf and Schmidt (1997). The authors compared constant and variable practice on a transfer task which was close to the training task. Their results indicated that transfer effects were larger for the variable compared to constant training group. However, the study only investigated transfer effects with one transfer task which had a small difference to the training. It is therefore difficult to argue that the effect of variable or constant training led to the transfer effects because there is no comparison to other transfer tasks. In contrast, another study which investigated the relationship between training and transfer, showed that in variable training the extent of transfer was no greater than in constant training (Mattar & Ostry, 2007). Similarly, other studies did not find a significant difference in retention tests between the constant and variable training (Shoenfelt et al., 2002). This further underlined the necessity of comparing transferability to multiple transfer tasks in future experiments.

5.4.5 General Limitations of Online Experiments

As in all online experiments, there are certain limitations to performing an experiment online compared to testing in the laboratory. Those limitations include the participant, the equipment (i.e., response devices) available and the environment the experiment is performed in. The limitations regarding the participants refer to the issue that participants might not be who they say they are, i.e., they might not be native English speakers or within the age range the experimenter specified for the experiment. In the experiment presented here, pre-screening options were used to minimise this limitation and Prolific was chosen as a recruiting platform as their participants have been shown to be more honest in contrast to participants on other recruiting platforms (Peer et al., 2017). Another limitation for online experiments is the available equipment that can be used as response devices. In the online experiment discussed here, participants used keys on the computer keyboard

whereas force grippers were used in the in-lab experiment. The comparison between the online and in-lab experiments is thereby limited as they were performed with different response devices. However, it was assured that the experience of the cursor movement was comparable across experiments, e.g., by implementing the acceleration rate when pressing the keys. Further, from the data presented here, results demonstrated a clear learning effect and rather pointed to the fact that regardless of the response devices used in the experiments, the task was learned. Further, in contrast to experiments in the laboratory, the experimenter is not able to control the participants' environment in online experiments. Specifically, the experiment might be performed at various places, e.g., at home or in an office, which might be noisy and distracting, e.g., due to a ringing phone or doorbell. As a consequence, participants' attention is disrupted, participants might take breaks or come back to the study later. However, as the task used here was conceptualised as a racing game and was engaging by design, there were no indication of these limitations in the data. Further, it was monitored how long participants performed the experiment. Once a certain time limit (set by Prolific) was exceeded, the study was stopped. Taken together, there are general limitations in conducting experiments online. However, due to the design of task, there were no indications in the data that any of the limitations resulted in problems.

5.4.6 Conclusion

Taken together, the aim of this experiment was to investigate the relationship of training and transfer of motor skills. The findings of this experiment showed that depending on the training, distinct learning patterns occurred. In addition, results pointed out that transferability did not fully rely on the learned skill, i.e., especial or generic skills, but rather on the transfer tasks that measure transferability. Specifically, independent of the training task, all training tasks transferred to the

transfer task that was closely related to the training task, but not to the other transfer tasks. This, as well as the difficulty of designing transfer tasks, highlights the necessity to test transfer effects with more than one transfer task to put transfer related effects into perspective. Meaning, with only one transfer task, the amount of transfer and relation between training and transfer cannot be fully evaluated.

6

Investigating the Neural Dynamics of Bimanual Motor Learning with MEG

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6.1 Introduction

To produce and learn complex bimanual movements, the temporal coordination of neural activity within the motor network is essential (Cardoso de Oliveira et al., 2001). The motor network involved in bimanual movements includes the bilateral primary motor cortex, supplementary motor areas, and premotor areas (Gerloff & Andres, 2002; Jantzen et al., 2008; Rueda-Delgado et al., 2014; Swinnen & Wenderoth, 2004; Wiesendanger et al., 1996; Wiesendanger et al., 1994) as well as posterior parietal cortex, cingulate motor cortex and others (Debaere et al., 2001; Koeneke et al., 2004), see chapter 1 for more information.

During movement-related activities (i.e., movement preparation, movement execution, movement imagination, etc), dynamics in the beta frequency range (13-30 Hz) are dominant (Neuper & Pfurtscheller, 2001), as fully outlined in chapter 1. Specifically, the event-related desynchronisation (ERD) during movement preparation and movement execution, and the event-related synchronisation (ERS) after movement termination is routinely observed (Pfurtscheller & Da Silva, 1999). In addition, it has been shown that the ERD and ERS are strengthened with unimanual motor learning (Tan et al., 2014; Zich et al., 2018).

Movement-related beta ERD and ERS have been observed for bimanual movements such as flexion and extensions of wrists (Gross et al., 2005), bimanual sequence tapping (Andres et al., 1999) and cyclic/rhythmic tasks (Boonstra et al., 2007; Houweling et al., 2008; Rueda-Delgado et al., 2017). These beta power modulations have been reported to differ between unimanual and bimanual movements (Gross et al., 2005; Houweling et al., 2008). In particular, Gross et al. (2005) found a stronger ERD in bimanual conditions than in a unimanual condition, a finding supported by Houweling et al. (2008). Further, beta power modulations have been shown to differ between bimanual conditions with equal and unequal contributions between hands (Gross et al., 2005; Rueda-Delgado et al., 2017). Specifically,

Gross et al. (2005) showed that movements with unequal contributions induced a stronger ERD than movements with equal contributions between hands. This was confirmed by Rueda-Delgado et al. (2017) when comparing beta activity in complex cyclic movements with equal and unequal contributions. The few existing studies examining bimanual motor learning provided partly contradictory findings for learning-induced changes. Specifically, a stronger ERD/S had been found with learning a bimanual sequence tapping task (Andres et al., 1999) and a rhythmic/cyclic bimanual task (Boonstra et al., 2007). Houweling et al. (2008) and a later report of the same data in Houweling et al. (2010b) found a weakening of ERD/S in both M1 with learning.

Taken together, sensorimotor beta power modulations seem to play a functional role in bimanual movements and bimanual motor learning. However, the current literature lacks studies addressing two important questions: First, the majority of previous studies have either investigated how beta power differed with learning, or how beta power differed between conditions, e.g., comparing performance in unimanual and bimanual conditions. The interaction between the two, i.e., how beta power is affected by learning unimanual and different levels of bimanual interactions, has only been investigated sparsely (Houweling et al., 2008). Second, the main evidence discussed above originates from simplified and artificial movements, i.e., using finger tapping (Andres et al., 1999) or flexion and extension of limbs (Gross et al., 2005). Only a few studies investigated complex bimanual movements. Those that examined complex bimanual movements used cyclic/rhythmic movements with equal contributions between hands and did not compare them to unequal contributions between hands (Boonstra et al., 2007; Houweling et al., 2008), with one exception (Rueda-Delgado et al., 2017). Taken together, the role of beta power in complex bimanual motor learning is not well understood. This chapter is aiming to characterise the neural underpinnings of unimanual and different levels

of bimanual interactions and how these neural underpinnings change with motor learning. To this end, MEG was recorded while the novel task was performed, see full description of the task as well as advantages of MEG in chapter 2.

Based on the results outlined in previous chapters, I expected that the task would, on the behavioural level, induce learning (main effect of time), i.e., faster movement time and reduced error. Further, I expected the different levels of bimanual interaction to differ from each other (main effect of condition) and to yield distinct learning patterns (time x condition interaction). As regards the neural level, I hypothesized that the task would induce an ERD and ERS and that both would be more pronounced with learning (main effect of time). I further hypothesized that the ERD and ERS differed for the levels of bimanual interaction (main effect of condition). Specifically, I expected the ERD and ERS to be stronger in bimanual conditions than in the unimanual conditions. Among the bimanual conditions I expected stronger activity in the bimanual unequal than bimanual equal condition, as shown before (Gross et al., 2005). Further, I explored whether the learning-induced neural changes differ across hemispheres and the levels of bimanual interaction (time x condition x hemisphere interaction).

6.2 Methods

6.2.1 Participants

A total number of 24 right-handed healthy participants (14 females, $M = 23.08$ years, $SD = 3.71$) gave their written informed consent to take part in the study. This was in accordance with Central University Research Ethics Committee approval, University of Oxford (MSD-IDREC-R68649/RE002) and Declaration of Helsinki. The number of participants was chosen based on experience and on another study investigating the neurophysiological underpinnings of different levels of bimanual interaction (Rueda-Delgado et al., 2017). Participants were monetarily compensated.

They reported no history of neurological or psychiatric disorders and had normal or corrected-to-normal vision. Handedness was assessed with the 10 item Edinburgh Handedness Inventory (Oldfield et al., 1971). For one participant no MRI scan could be acquired for safety reasons. Six participants had to be excluded from data analysis due to excessive movement artefacts (one participant), metal-induced artefacts from a retainer in the mouth (four participant) and artefacts resulting from the registration to the individual head anatomy (one participant), leading to low signal-to-noise ratio.

6.2.2 Experimental Procedure

The experiment was conducted as a within-subject design. MEG and MRI (high-resolution T1-weighted images for co-registration of MEG data) were recorded in two separate sessions. The MRI session was conducted for those participants who did not have a high-resolution T1-weighted image in the Departmental database.

The MEG session comprised 6 min of pre-learning resting state, the bimanual motor learning task and 6 min of post-learning resting state, see Figure 6.1A. During the session, participants were comfortably seated in the MEG dewar with their arms rested on a pillow. For the resting state recording, participants were asked to be as still as possible while fixating a white cross on a black background. For the duration of the resting state recordings, the force grippers were placed on the participant's lap. Subjects were then asked to perform the bimanual motor learning task, see full description of the task chapter 2 and task data acquisition chapter 3. In brief, participants navigated a cursor across a path of six streets, see Figure 6.1B. The streets were rotated in different angles (0°, 22.5°, 45°, 67.5°, 90°) that corresponded to specific force ratios between hands. The trial structure, i.e., six streets per trial with feedback presented after each trial, was identical to the experiments described in chapters 3, 4 and 5. In this experiment, an additional 5 s between

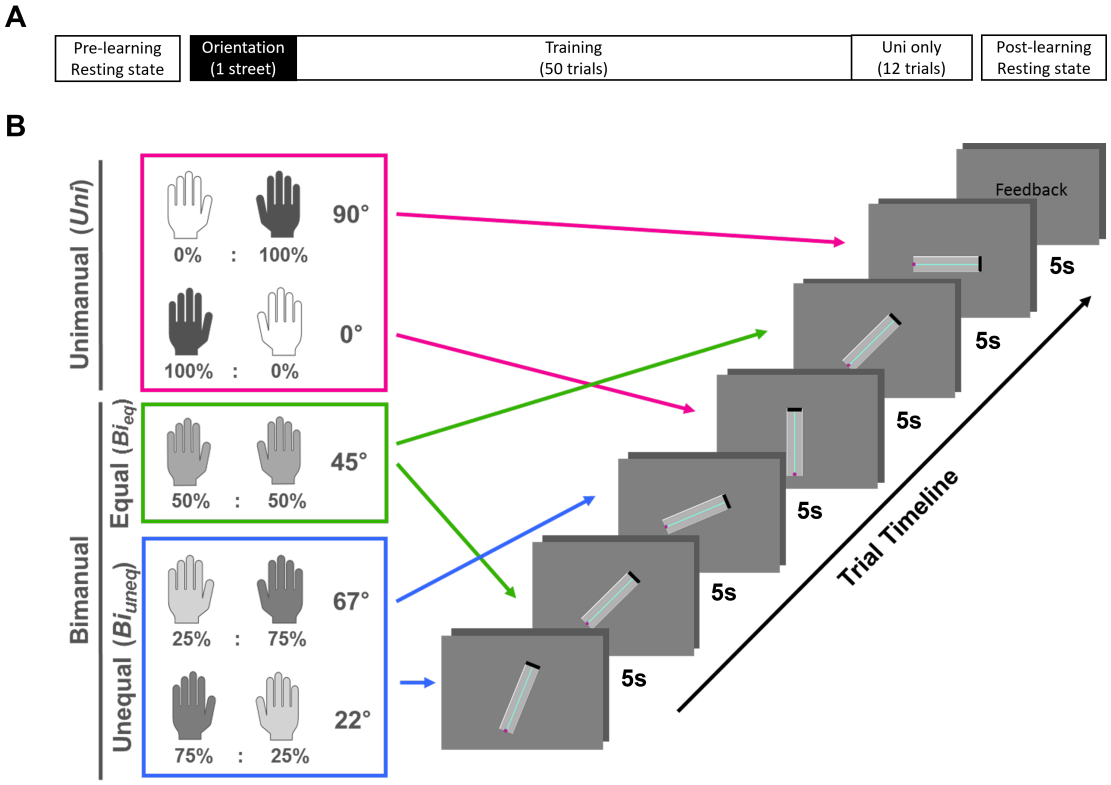


Figure 6.1: Experimental timeline (above) and task design (below). (**A**) The task was performed with one orientation street, followed by 50 trials of the training task and twelve trials of unimanual streets only. Resting state recordings were acquired before learning the task (pre-learning resting state) and after learning the task (post-learning resting state). (**B**) One trial consisted of a path of six streets in different angles. The street angles corresponded to specific force ratios, whereby the force of one hand (100%:0%) was required for the street with 0° and 90° (*Uni*), an equal amount of force between hands (50%:50%) in the street of 45° (Bi_{eq}) and an unequal amount of force between hands (25%:75%) for the streets rotated in 22.5° and 67.5° (Bi_{uneq}). There was an inter-street-interval of 5 s.

streets (inter-street interval) was introduced. The inter-street interval was increased to allow enough time between streets to incorporate the ERS and a baseline period. The duration of the inter-street interval was based on extensive piloting and on previous studies (Rueda-Delgado et al., 2017). In contrast to previous versions of the task, the streets per path were not displayed at the top of the screen. This was amended to avoid that an ERD was induced by movement preparation in the ERS or baseline period (Barrett et al., 1986; Zaepffel et al., 2013).

First, one orientation street for familiarisation was performed. Thereafter, 50

trials of the training task were conducted. Finally, 12 trials (in blocks of 6 trials) with only unimanual streets angled either 0° or 90° were performed, see Figure 6.1A. For the additional unimanual trials participants were instructed which hand was needed before each block of 6 trials and were instructed to keep holding the other gripper in their hand. The additional unimanual trials were implemented as a control condition. Specifically, in the unimanual trials, only unimanual streets were expected, whereas in the trials of the training task unimanual streets were amongst bimanual streets. Hypothetically, the occurrence of unimanual streets in the context of bimanual streets might have induced physiologically relevant motor inhibition (Duque et al., 2017).

As described in the previous chapters, cursor movement was enabled by two hand-held force grippers, one controlling upward movement and one controlling rightward movement (see chapter 2 and 3 for full description of force grippers and force calibration).

On behavioural level, movement time and error were measured as dependent variables to quantify the behavioural performance in the task, as fully outlined in chapter 2. The reset index was included in the movement time, i.e., more resets led to longer movement time.

6.2.3 Data Acquisition

6.2.3.1 MEG Acquisition

Whole-head MEG recordings were acquired in a magnetically shielded room using a 306-channel Triux Neo system from Finnish manufacturer Megin (Megin, Croton Healthcare Company), with one magnetometer and two orthogonal planar gradiometers at each of 102 locations, at Oxford Centre for Human Brain Activity (OHBA). Head position was assessed using five head position indicator (HPI) coils attached to the head of the participant (behind the left and right ear lobe, above the right eyebrow, on the left and right forehead just below the hairline). HPI coil

locations, roughly 200 head positions from across the head and three anatomical fiducial locations (nasion, left and right pre-auricular points) were digitalized using a magnetic Polhemus FastTrak 3D system (VT, United States) before data acquisition. MEG data were sampled at 1000 Hz using a 0.03-330 Hz band-pass filter during digitalisation. In addition, vertical and horizontal electrooculogram (EOG) and electrocardiogram (ECG) were measured to detect eye blinks, horizontal eye movements and heartbeat. Electromyogram was measured above the proximal location of the muscle belly of flexor carpi radialis to record muscle activity. Stimuli were projected (Panasonic PT D7700E, Panasonic, Osaka, Japan) on a 43 x 54.5 cm screen placed 120 cm in front of the participant, with a spatial resolution of 1366 x 769 pixels and a refresh rate of 60 Hz.

6.2.3.2 MRI Acquisition

To create individual head models for the MEG data analysis, a high-resolution T1-weighted image was acquired with a 32-channel head coil using a Siemens 3 Tesla Prisma MRI scanner (Siemens, Erlangen, Germany) at either the Functional Magnetic Resonance Imaging building or at OHBA. A rapid gradient echo (MPRAGE) sequence lasting 8 min was used (time repetition=1900 ms, time echo=3.96 ms, 1×1×1 mm voxel size, field of view=256x256 mm (including nose and ears), slice thickness=1 mm, 192 slices per slab).

To acquire the high-resolution T1-weighted image, participants were comfortably positioned in the scanner. They were instructed to keep their eyes open and move as little as possible for the duration of the scan.

6.2.4 Data Analysis

6.2.4.1 MEG Data Analysis

For this thesis, only the MEG data recorded during the training of the bimanual task were analysed. MEG data analyses were performed using the in-house

OHBA Software Library (OSL: http://ohba-analysisġithubio/osl-docs/, version from November 2019), see Figure 6.2 for analysis pipeline and chapter 2 for additional information. External noise was reduced from MEG data by means of signal-space separation (SSS) and head movements (detected using HPI coils) were corrected, both using a python based Megin MaxFilter tool (ohba_maxfilter_py from http://githubċom/OHBA-analysis/ohba_maxfilter). Continuous data were downsampled to 250 Hz to reduce computational demands. Slow trends, high frequencies and line noise were removed by applying a band-pass (1-100 Hz) and two notch filters (49-51 Hz and 99-101 Hz). Data containing non-stereotypical artefacts were removed by epoching the data into non-overlapping 1 s time windows. Those time windows that contained nonstereotypical artefacts were rejecting using a generalised extreme studentized deviate method (Rosner, 1983) at a significance level of 0.05 with maximum number of outliers limited to 20% of the data. Further denoising was applied with Independent Component Analysis (ICA) using temporal FastICA across sensors (Hyvarinen, 1999). The weights of 62 independent components were estimated and those components that represented stereotypical artefacts such as eye blinks, eye movements, and electrical heartbeat activity were manually identified and regressed out of the data. Data from magnetometers and planar gradiometers were normalized by computing the eigenvalue decomposition across sensors within each coil type and dividing the data by the smallest eigenvalue within each (Woolrich et al., 2011).

For source level analysis (see Figure 6.2 black background), data were co-registered to the individual's T1-weighted structural image. Registration between the standard-space T1-weighted structural image and MEG data were performed with RHINO (Registration of Headshapes Including Nose in OSL) using nose and fiducial landmarks (without extra headshape points) for coregistration and a single shell as forward model. Further, data were projected onto source space using a

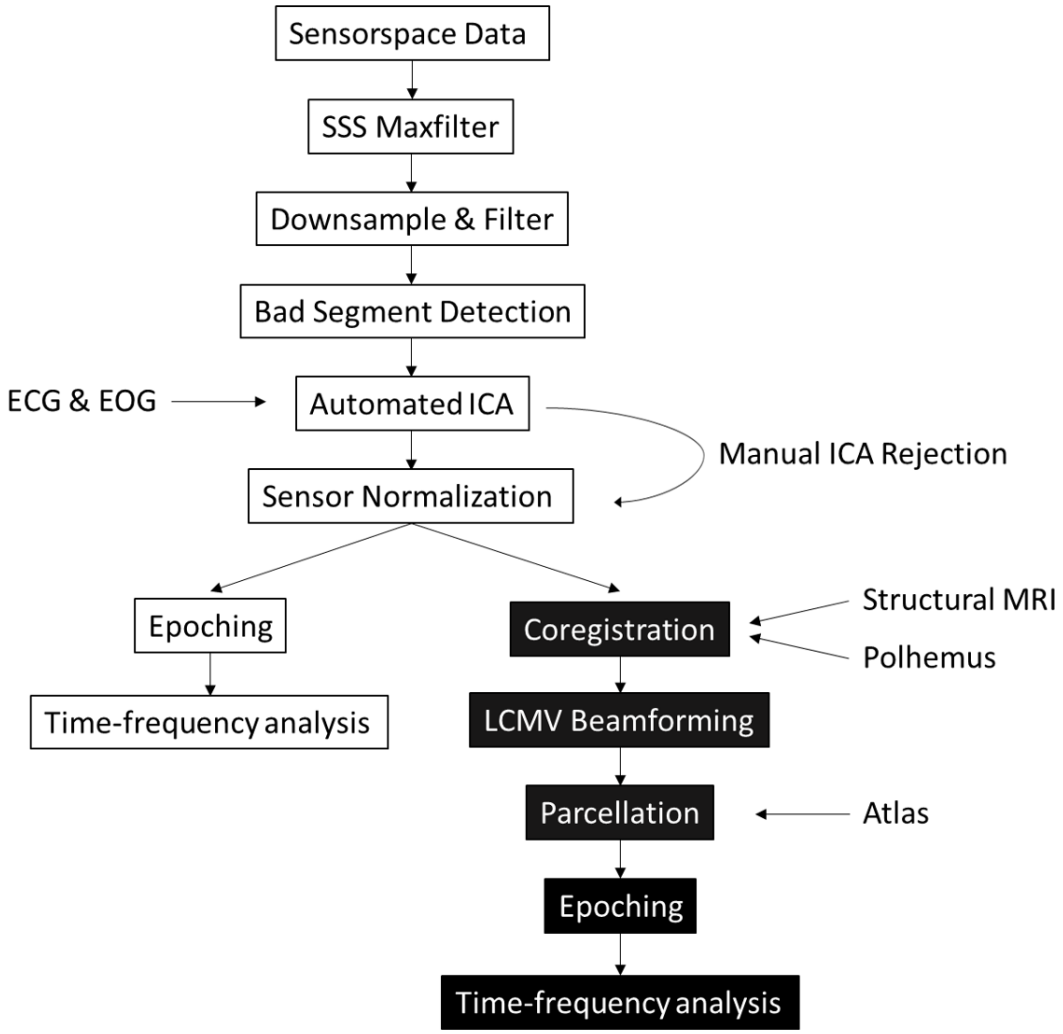


Figure 6.2: Schematic overview of the processing pipeline of MEG data for sensor level analysis (white background) and additional processing steps for source level data analysis (black background). Adapted and modified from Quinn et al. (2018).

Linearly Constrained Minimum Variance (LCMV) vector beamformer (Van Veen & Buckley, 1988; Woolrich et al., 2011). Specifically, beamformer weights were estimated across the 8 mm grid cast within the inner-skull of the T1 image brain resulting in 3559 virtual sensors. A covariance matrix was computed across the whole time-course and was regularized to 50 dimensions using principal component analysis (PCA) rank reduction (Quinn et al., 2018). Parcel-wise time courses were estimated and orthogonalized following the methods in Colclough et al. (2015) and Colclough et al. (2016). A weighted (non-binary) parcellation with 48 cortical

regions was applied (customized from the Desikan-Killiany cortical atlas; N = 92). A single time-course was estimated per node from the first principal component across voxels, with voxel contributions weighted by the parcellation. Parcellation was performed using the ROInets module of OSL. To avoid spurious and artificial correlations between estimated source time-courses, symmetric multivariate leakage correction was applied across the whole network (Colclough et al., 2015). For both sensor and source level analysis, data were epoched (-5 s to 10 s) with regard to movement onset of the cursor in each street.

Time-frequency analysis was applied on sensor and source level to single streets using dpss-based multitaper (steps = 50 ms, time resolution = 400 ms) with a frequency resolution of 2.5 Hz for frequency 5-30 Hz. Segments were baseline corrected (-2 s to 0 s) to the movement onset of each individual street (for both sensor and source level). This procedure results in street-by-street time-frequency decomposition for each sensor (sensor level) and parcel (source level).

To evaluate data quality, spectral-temporal-spatial properties of sensor level data were considered. To assess the time-frequency distributions for each street angle, beta power was averaged over channels, i.e., 12 gradiometer channel pairs above left, and 12 gradiometer channel pairs above right sensorimotor areas as based on Nowak et al. (2017). Further, to evaluate the spatial properties, beta power for each street angle was obtained by averaging over frequency, i.e., 13-30 Hz, and time, i.e., from movement onset to movement offset for ERD and from movement offset to movement offset + 3 s for ERS.

To quantify learning-induced changes, I examined source level data, as source level provides a higher signal-to-noise ratio. For source level, only parcels from sensorimotor areas including left and right Precentral (i.e., M1), Postcentral (i.e., S1), and Paracentral (i.e., SMA) regions, were considered following the Desikan-Killiany atlas (N = 92). The choice of regions was based on the findings from Rueda-Delgado

et al. (2017). Source level data were quantified by averaging beta power over frequency (i.e., 13-30 Hz), time (i.e., from movement onset to movement offset for ERD and from movement offset to movement offset + 3 s for ERS) and space (i.e., across parcels per each hemisphere). In the *Uni* and Bi_{uneq} condition, contralateral and ipsilateral ERD/S referred to the hemisphere contralateral or ipsilateral to the used hand (with more force). In Bi_{eq} condition, the hemispheres were flipped for half of the trials to avoid any systematic bias, i.e., for even trials contralateral refers to the right hemisphere and for odd trials, contralateral refers to the left hemisphere.

6.2.4.2 Statistical Analysis

To investigate learning-related changes induced by the task the mean from the first (trials 1 to 10) and last (trials 41 to 50) ten trials were calculated for each dependent variable separately. On the behavioural level, the dependent variables were movement time and error. On the neural level, the ERD and ERS from source level constitute the dependent variables, as source level provides a higher signal-to-noise ratio. Data were analysed for the performance per condition (*Uni,* Bi_{eq}, Bi_{uneq}), i.e., mean over the two streets of each condition in each trial.

At the behavioural level, learning-related changes were assessed by two repeated-measures 2 x 3 ANOVAs with within-subject factors of time (first and last ten trials of the training task) and condition (*Uni,* Bi_{eq}, Bi_{uneq}) with movement time and error as dependent variables.

At the neural level, task-induced changes were assessed by a repeated-measures 2 x 3 x 2 ANOVA with within-subject factors of time (first and last ten trials), condition (*Uni,* Bi_{eq}, Bi_{uneq}) and hemisphere (contralateral, ipsilateral) once for ERD and once for ERS as dependent variables. In this analysis, the ERD included the duration of movement of the whole streets, i.e., including all resets. However, resets occurred due to the use of incorrect force ratios between hands. Thus, I wanted to test whether the resets prior to finishing the streets contaminated the

ERD. To tests this, post hoc, I re-calculated the ERD from the last reset of each street, i.e., the part of the street performance that led to the successful completion of the street (instead of movement onset) to the movement offset. As above, a 2 x 3 x 2 ANOVA was performed with within-subject factors of time (first and last ten trials), condition (*Uni, Bi_{eq}, Bi_{uneq}*) and hemisphere (contralateral, ipsilateral) with ERD as a dependent variable.

For each condition, I assessed whether beta power (contralateral ERD, ERS) correlated with the behavioural performance (movement time, error). To this end, change scores were calculated, i.e., difference between the first and last ten trials. Four Spearman's correlations were performed between the beta power and behavioural change scores (i.e., ERD-error, ERD-movement time; ERS-error, ERS-movement time).

In case of significant effects, post hoc paired samples t-tests were performed with Bonferroni correction for multiple comparisons. All reported p-values for t-tests were two-tailed and the significance level was set at $p<.05$. Statistical analyses were performed using the opensource software JASP (version 0.14.3, JASP Team 2021).

6.3 Results

6.3.1 Learning Yielded Distinct Levels for the Different Levels of Bimanual Interaction

As hypothesized, the behavioural results were in line with the findings of chapter 3 and 4. In brief, repeated-measures ANOVAs for movement time and error separately demonstrated significant main effects of time and of condition, as well as a significant interaction between time and condition, for both movement time and error, see Table 6.1 and Table 6.2.

Table 6.1: *Results of the 2 x 3 ANOVA with within-subject factors of time (first and last ten trials) and condition (Uni, Bi_{eq}, Bi_{uneq}) with movement time as dependent variable.*

	df	*F*	*p*	η_p^2
Time	1,23	193.984	<.001	.894
Condition	2,46	351.883	<.001	.939
Time * Condition	2,46	193.463	<.001	.894

Table 6.2: *Results of the 2 x 3 ANOVA with within-subject factors of time (first and last ten trials) and condition (Uni, Bi_{eq}, Bi_{uneq}) with error as dependent variable.*

	df	*F*	*p*	η_p^2
Time	1,23	284.153	<.001	.925
Condition	2,46	10041.756	<.001	.998
Time * Condition	2,46	322.680	<.001	.933

6.3.2 MEG Indicated beta ERD and ERS

To evaluate data quality and spectral-temporal-spatial properties, I first examined sensor data. Time-frequency plots indicated a clear ERD and ERS in the beta frequency band from sensors overlying the sensorimotor areas (Figure 6.3). In line with previous studies, the beta ERD started slightly before movement onset, plateaued between movement onset and offset, and terminated after movement offset. Consistent with prior observations, the beta ERS started after movement offset and lasted for roughly 3 s in the streets angled at 0° and 90° and 5 s in the streets angled at 45°, 22° and 67°. In addition, ERD and ERS maps (i.e., beta power averaged over time and frequency across sensors) showed strongest activation over sensorimotor areas, see 6.4 and 6.5. ERD maps showed a bilateral activation for all conditions. In contrast, ERS maps showed lateralised activity for unimanual conditions, i.e., stronger activity in the hemisphere contralateral to the used hand, and bilateral activity for bilateral conditions. Overall, the sensor level analysis confirmed good data quality. To investigate learning-induced changes I went on to look at source level data, as source level provides a higher signal-to-noise ratio.

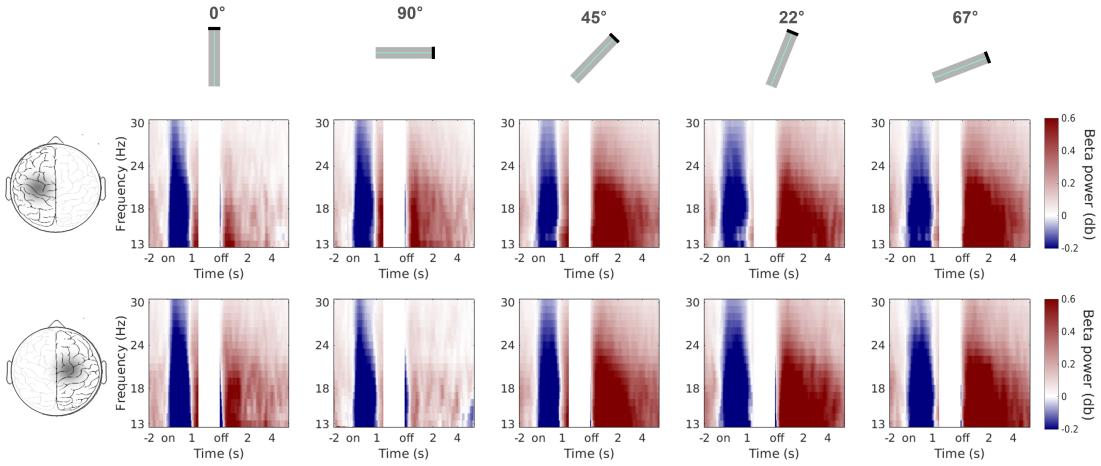


Figure 6.3: Group averaged time-frequency plots for each street angle 0°, 90°, 45°, 22°, 67° (from left to right) and channels above the left (above) and right (below) sensorimotor cortex. Data were averaged over participants (N = 20). As trials differed in length, for visualisation only, data were epoched once to movement onset and once to movement offset, as shown before (Zich et al., 2018). The time between 1 s after movement onset and movement offset was not comparable across trials and participants as indicated by the white bar. The time-frequency distributions suggested an ERD, i.e., power decrease, from movement onset to offset and an ERS, i.e., power increase, after movement offset in the beta frequency range.

6.3.3 ERD Differed in Unimanual and Bimanual Conditions

To quantify whether the ERD differed with learning, different levels of bimanual interaction, and across hemispheres, a 2 x 3 x 2 ANOVA was performed with within-subject factors of time (first and last ten trials), condition (*Uni*, Bi_{eq} Bi_{uneq}), and hemisphere (contralateral, ipsilateral) with ERD as dependent variable. Results revealed a significant main effect of condition ($F_{2,32}$=3.968, p=.029, η_p^2=.199; Figure 6.6D). All other main effects and interactions were non-significant (all p's>.05), see Table 6.3 and Figures 6.6A-C,E,F.

To investigate how the ERD differed across the conditions, three paired samples t-tests were performed (Bonferroni corrected). Results showed that the ERD during *Uni* was significantly stronger than the ERD during Bi_{uneq} ($t_{2,32}$=-2.797, p=.026, Cohen's d=-0.678), all other comparisons were non-significant (p's>.05),

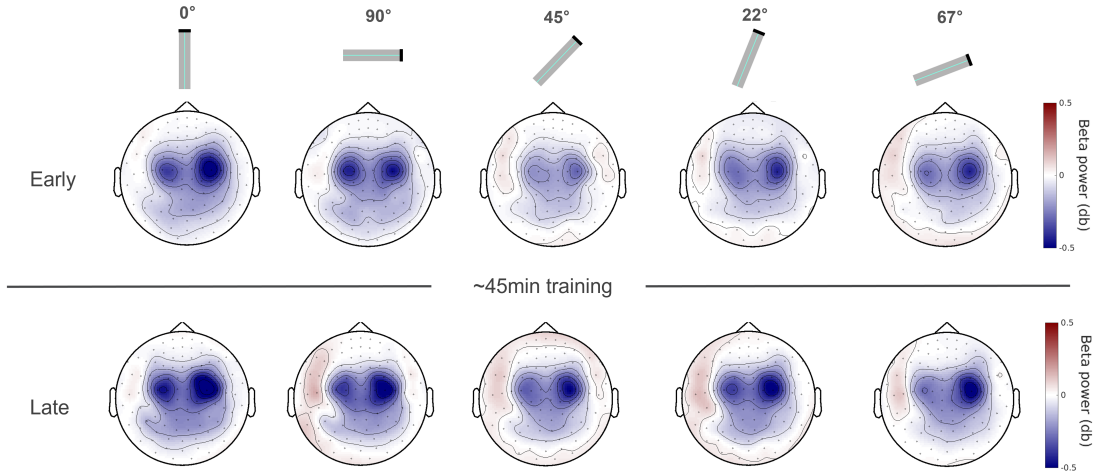


Figure 6.4: Spatial distribution of the ERD averaged across frequency, i.e., 13-30 Hz, time, i.e., from movement onset to offset, and participants (N = 20). This visualisation indicated a bilateral activation pattern for all street angles 0°, 90°, 45°, 22°, 67° (from left to right) at early (above) and late (below) learning.

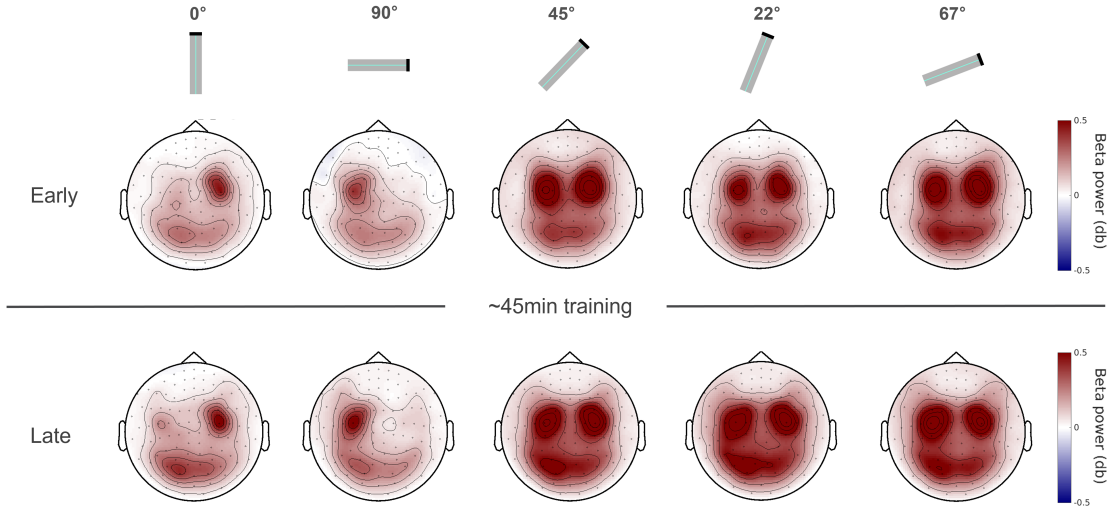


Figure 6.5: Spatial distribution of the ERS averaged across frequency, i.e., 13-30 Hz, time, i.e., from movement offset to movement offset + 3 s, and participants (N = 20). The visualisation indicated a lateralised activation pattern for street angles of 0° and 90° and a bilateral activation pattern for street angles of 45°, 22°, 67° at early (above) and late (below) learning.

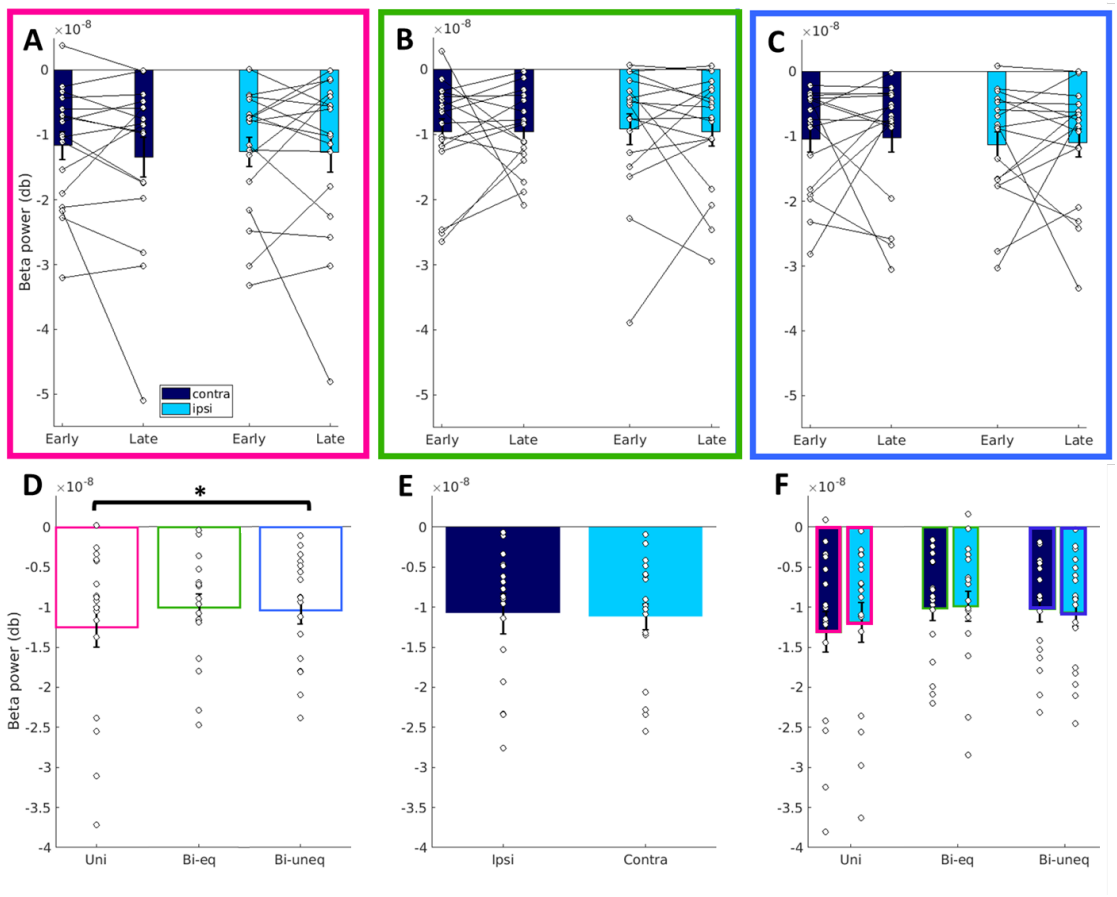


Figure 6.6: Results of the ERD across first ten (early) and last ten (late) trials in the contralateral (dark blue) and ipsilateral (light blue) hemisphere across conditions (*Uni*: pink; Bi_{eq}: green; Bi_{uneq}: blue). (**A-C**) Comparison of the ERD at early and late in the contralateral and ipsilateral hemisphere in *Uni*, Bi_{eq}, and Bi_{uneq} (from left to right) indicated no interaction (non-significant interaction of time x condition x hemisphere). (**D**) Comparison of the ERD in the three conditions averaged over time (early, late) and hemisphere indicated a stronger ERD in *Uni* than Bi_{uneq} (significant main effect of condition). (**E**) Comparison of the ERD in the ipsilateral and contralateral hemisphere averaged over time and conditions indicated no difference (non-significant main effect of hemisphere). (**F**) Comparison of the ERD in the ipsilateral and contralateral hemisphere across conditions averaged over time indicated a similar activation pattern in the hemispheres across all conditions (non-significant interaction between hemisphere and condition). Bars indicated the mean over participants (N = 17). Single subject data was highlighted by circles. Error bars indicate the standard error of the mean. Significance star * mean $p<.05$.

see Figure 6.6D.

To test whether the absence of a significant main effect of time or a significant time x condition interaction was due to the use of incorrect force ratios between hands, a post hoc analysis was performed. Specifically, as described above, the ERD

Table 6.3: *Results of the 2 x 3 x 2 ANOVA with within subject factors of time (first and last ten trials), condition (Uni, Bi_{eq} Bi_{uneq}) and hemispheres (contralateral, ipsilateral) with ERD as dependent variable*

	df	*F*	*p*	η_p^2
Time	1,16	0.020	.890	.001
Condition	2,32	3.968	.029	.199
Hemisphere	1,16	2.631	.124	.141
Time * Condition	2,32	0.433	.652	.026
Time * Hemisphere	1,16	0.912	.354	.054
Condition * Hemisphere	2,32	0.384	.684	.023
Time * Condition * Hemisphere	2,32	0.808	.455	.048

was computed from the movement onset of the cursor. Thereby, the ERD included the performance of the whole street, i.e., all resets of one street. Resets occur due to the use of incorrect force ratios between hands. Therefore, I hypothesized that the use of incorrect force ratios between hands might have contaminated the ERD. To test this hypothesis, I recalculated the ERD, starting from the last reset of the cursor for each street, i.e., the part of the street that successfully led to the completion of the street, and the original analysis (2 x 3 x 2 ANOVA) was repeated. However, this approach was consistent with the findings above: there was a significant main effect of condition ($F_{2,32}$=3.986, p=.028, η_p^2=.199), but all other main effects and interactions were non-significant (all p's>.05). Thereby, the hypothesis that incorrect force ratios between hands could contaminate the ERD to the level that it affects the main effect of time or time x condition interaction was not confirmed.

6.3.4 ERS Differed in Unimanual and Bimanual Conditions and Across Hemispheres

To assess whether the ERS differed with learning, different levels of bimanual interaction, and across hemispheres, a 2 x 3 x 2 ANOVA was performed with within-subject factors of time (first and last ten trials), condition (*Uni*, Bi_{eq} Bi_{uneq}) and hemispheres (contralateral, ipsilateral) with the ERS as dependent

Table 6.4: *Results of the 2 x 3 x 2 ANOVA with within subject factors of time (first and last ten trials), condition (Uni, Bi_{eq} Bi_{uneq}) and hemispheres (contralateral, ipsilateral) with ERS as dependent variable*

	df	*F*	*p*	η_p^2
Time	1,16	0.488	.495	.030
Condition	2,32	28.106	<.001	.637
Hemisphere	1,16	10.545	.005	.397
Time * Condition	2,32	0.012	.988	.000
Time * Hemisphere	1,16	0.025	.876	.002
Condition * Hemisphere	2,32	6.746	.004	.297
Time * Condition * Hemisphere	2,32	2.157	.132	.119

variable. This analysis showed a significant main effect of condition ($F_{2,32}$=28.106, p<.001, η_p^2=.637; Figure 6.7D), a significant main effect of hemisphere ($F_{1,16}$=10.545, p=.005, η_p^2=.397; Figure 6.7E) and a significant interaction between condition and hemisphere ($F_{2,32}$=6.746, p=.004, η_p^2=.297; Figure 6.7F). All other main effects or interactions were non-significant (p's>.05), see Table 6.4 and Figures 6.7A-C.

The significant main effect of condition was followed up with three paired samples t-tests (Bonferroni's corrected) to explore how the ERS differed across conditions. These tests demonstrated a significantly lower ERS for *Uni* than Bi_{eq} ($t_{2,32}$=-6.447, p<.001, Cohen's d=-1.564) and Bi_{uneq} ($t_{2,32}$=-6.538, p<.001, Cohen's d=-1.586), whereas the ERS was not significantly different between Bi_{eq} and Bi_{uneq} (p>.05), see Figure 6.7D.

The significant interaction between condition and hemisphere was followed up three paired samples t-test (Bonferroni corrected) to compare ipsilateral and contralateral ERS for each condition separately. These analyses indicated that during *Uni*, contralateral ERS was significantly stronger than ipsilateral ERS ($t_{2,32}$=4.791, p<.001; Figure 6.7F). In contrast, ipsilateral ERS and contralateral ERS were comparable in Bi_{uneq} ($t_{2,32}$=1.670, p=1.000) and Bi_{eq} ($t_{2,32}$=0.411, p=1.000). This confirms the pattern seen in the sensor level ERS maps: ERS showed a lateralized

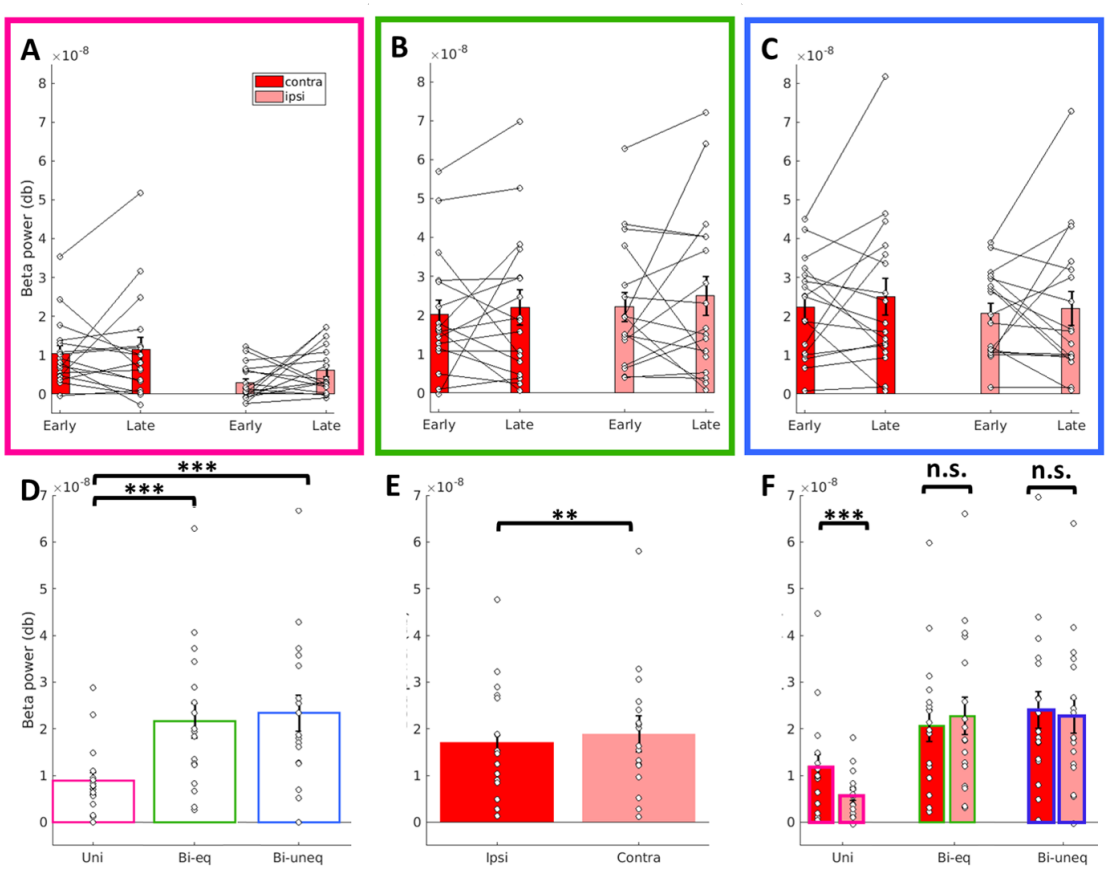


Figure 6.7: Results of the ERS over first (early) and last (late) ten trials, contralateral (dark red) and ipsilateral (light red) hemisphere and condition (*Uni*: pink; Bi_{eq}: green; Bi_{uneq}: blue). (**A-C**) Comparison of the ERS at early and late for the contralateral and ipsilateral hemisphere for *Uni*, Bi_{eq} and Bi_{uneq} (from left to right) indicated no interaction (non-significant interaction of time x hemisphere x condition). (**D**) Comparison of the ERS averaged over time (early, late) and hemisphere indicated a stronger ERS in Bi_{uneq} than *Uni* and stronger ERS in Bi_{eq} and *Uni*. ERS was comparable between Bi_{uneq} and Bi_{eq} (significant main effect of condition). (**E**). Comparison of the ERS in the contralateral and ipsilateral hemisphere averaged over condition and time indicated that the ERS differed in the hemispheres (significant main effect of hemisphere). (**F**) Comparison of the ERS in the contralateral and ipsilateral hemisphere in each condition averaged over time suggested a lateralised ERS in *Uni* and bilateral ERS in Bi_{uneq} and Bi_{eq} (significant interaction of condition x hemisphere). Bars indicated the mean over participants (N = 17). Single subject data was indicated by circles. Error bars indicate the standard error of the mean. Significance stars * mean $p<.05$, ** mean $p<.01$, *** mean $p<.001$.

pattern in the unimanual condition and a bilateral pattern in the bimanual conditions, see Figure 6.5.

6.3.5 ERS and ERD Did Not Correlate with Amount of Learning

For each condition, I assessed whether learning-related changes on the neural level (ERD, ERS) correlated with learning-related changes on the behavioural level (error, movement time). To this end, change scores, i.e., differences between the first and last ten trials were calculated. Four Spearman's correlations were performed for each neural change score with each behavioural change score. Results indicated no significant correlations (p's$>$.01) suggesting that changes in movement time and error did not relate significantly to changes in ERD and ERS.

6.4 Discussion

In this experiment, I aimed to investigate the neurophysiological underpinnings of learning different levels of bimanual interaction. To this end, I recorded MEG data while individuals performed the bimanual motor learning task. Behavioural results indicated that the task was learned with distinct learning patterns for the different levels of bimanual interaction which was consistent with the results reported in the previous chapters, see chapter 3 and 4 for full discussion. Further, results indicated a clear movement-related ERD and ERS in the beta frequency range. ERS and ERD differed for unimanual and bimanual conditions but not within the two bimanual conditions. In addition, the results presented in this experiment did not indicate learning-induced changes in ERD or ERS, and the changes ERS and ERD did not correlate with behavioural findings.

6.4.1 ERD and ERS Differed in Unimanual and Bimanual Conditions

That movement-related ERD and ERS appeared is in line with previous studies investigating unimanual (Sanes & Donoghue, 2000; Zich et al., 2018) as well as bimanual movements and/or bimanual motor learning with M/EEG (Andres et al., 1999; Boonstra et al., 2007; Gross et al., 2005; Houweling et al., 2008; Rueda-Delgado et al., 2017).

In this study, ERD/S indicated condition specific modulations. Specifically, the ERD was stronger in the unimanual condition compared to the bimanual unequal condition and appeared bilateral in all three conditions. For the ERD, condition specific effects have been reported before (Gross et al., 2005; Houweling et al., 2008). Specifically, Gross et al. (2005) found a stronger ERD in bimanual conditions than in a unimanual condition. This finding was confirmed in a force production task (Houweling et al., 2008). That the ERD reported in this chapter showed different condition specific modulations than reported in the literature might reflect the context in which they were measured. Complex movements, as used in this experiment, have been reported to show different beta modulations than simple tasks (Hummel & Gerloff, 2006). Interestingly in this study, the ERD appeared bilateral in all conditions (also in the unimanual condition). As reported intensely over the last decades, unimanual movements are characterized mostly, if not entirely, by a contralateral activation pattern. However, there are studies stating that although unimanual movements are mainly controlled by the contralateral M1, involvement of the ipsilateral M1 is present, too (Alkadhi et al., 2002). A recent meta-analysis on this topic seemed to confirm that unimanual movements involve bihemispheric activation patterns that rather resemble the activation pattern of bimanual movements (Chettouf et al., 2020). The authors outlined that this could be due to the anatomical basis of neurons descending not only to the contralateral but

also to the ipsilateral corticospinal tract (also outlined in chapter 1), see Bundy and Leuthardt (2019) for more information. Further, Chettouf et al. (2020) highlighted that task complexity seems to play a key role in the activation pattern of unimanual movements: with greater complexity, the hemispheres need to communicate more which might be reflected in a decreased lateralisation. Specifically for complex tasks, Chettouf et al. (2020) highlighted the role of the left premotor areas being involved during either left or right hand movements. Premotor areas have been proposed to play an inhibitory role on M1 (Daffertshofer et al., 2005). Its role in unimanual movements originates from the view that unimanual are a special case of bimanual movements, i.e., when only one hand is moved the other is inhibited (Grillner, 2015). The bilateral activation pattern in unimanual movements is thereby thought to reflect inhibitory processes. Thus, there is reason to assume that a bilateral activation pattern is present in unimanual movements. In the experiment presented in this chapter, unimanual movements induced a bilateral ERD. Multimodal approaches examining structural and functional connectivity should investigate the inhibitory and excitatory communication between hemispheres that elicit unimanual movements, as suggested by Chettouf et al. (2020).

In contrast to the ERD, the ERS appeared as hypothesized. The ERS was stronger in the bimanual conditions than in the unimanual condition and was lateralised in the unimanual condition and bilateral in bimanual conditions. Comparison to other studies investigating the ERS is difficult as reports on condition specific modulations of the ERS is sparse. Previous studies found that the ERS in both M1s was unaltered across unimanual and bimanual force production (Houweling et al., 2008) or reaching movements in the context of sensorimotor adaptation (Alayrangues et al., 2019). The absence of condition specific modulations in the ERS might be due to the fact that force production and reaching movements are simple task and again cannot be compared to the complex task used in this experiment without

reservations (Hummel & Gerloff, 2006). However, that the ERS was stronger in the bimanual conditions than in the unimanual condition would be consistent with some of the interpretations on why beta power modulations are stronger in bimanual conditions than in unimanual conditions: First, bimanual movements require the recruitment of additional areas, i.e., enrolment of additional spatially different brain areas, which leads to stronger activation pattern in bimanual compared to unimanual movements (Heitger et al., 2012; Theorin & Johansson, 2007). Second, bimanual movements require an increased communication between motor areas, i.e., an increased temporal information exchange, which leads to an increase in activation (Daffertshofer et al., 2005; Koeneke et al., 2004). That the ERS was lateralised in the unimanual condition and bilateral in bimanual conditions is in line with the interpretation of the functional role of the ERS. Generally, the ERS has been interpreted to play an active role in somatosensory processing (Cassim et al., 2001) such as active immobilisation i.e., reflecting the active termination of a movement (Neuper et al., 2006; Salmelin et al., 1995), as well as evaluating motor error and sensorimotor adaptation (Alayrangues et al., 2019; Shadmehr et al., 2010; Tan et al., 2014; Tan et al., 2016). For the results presented here, these interpretations are also likely and would reflect the condition specific spatial distribution, i.e., the lateralised activation pattern in unimanual movements and bilateral activation patterns in bimanual movements.

Taken together, in the results presented here, I only observed stronger beta power modulations in the bimanual compared to the unimanual condition for the ERS, whereas the ERD was stronger in the unimanual condition compared to the bimanual unequal condition. The ERS appeared lateralised in the unimanual condition and bilateral in bimanual conditions, whereas the ERD appeared bilateral across all conditions. That the ERD and ERS showed different activation patterns might reflect their functional differences, as discussed in the section above. However,

it must be noted, as already pointed out by Rueda-Delgado et al. (2017), there is currently no consensus on how beta power is modulated in unimanual compared to bimanual movements as task designs used to this day vary from each other such that comparison across studies is difficult, see Rueda-Delgado et al. (2014) for review.

6.4.2 ERD and ERS Did Not Differ in Bimanual Conditions

Within bimanual conditions specific beta power modulations have been reported before (Gross et al., 2005; Rueda-Delgado et al., 2017). Specifically, Gross et al. (2005) could show that movements with unequal contributions between hands showed a stronger ERD than movements with equal contributions between hands. This was confirmed in the only study investigating complex bimanual equal and bimanual unequal contributions between hands, i.e., comparing a 1:1 and a 3:2 rhythm (Rueda-Delgado et al., 2017). This difference is thought to imply that equal contributions between hands require lower effort, whereas unequal contributions between hands require more effort indicated by increased neural communication (Serrien & Brown, 2002). Thus, it was reasonable to assume, that differences between the bimanual conditions would occur. However, in contrast to previous findings, the results presented in this chapter did not indicate a difference in ERD/S between the two bimanual conditions Bi_{eq} and Bi_{uneq}. It might be argued that the differences in the two bimanual conditions were absent because in order to navigate through the street, the force ratio between hands needed to be roughly but not exactly, correct. Specifically, as the end of the street, i.e., the goal line, was the width of the street, approximate force ratios between hands could be used to finish one street. One might speculate that ERD and ERS did not differ between Bi_{eq} and Bi_{uneq} because due to the room for error per street (i.e., width of street) the two bimanual conditions were on average too similar. To test this hypothesis, two follow up tests are proposed here. First, data could be analysed specifically

for those streets that were finished with the exact force ratio of 50%:50% for Bi_{eq} and 25%:75% for Bi_{uneq} and tested again. However, this might lead to severe data loss which potentially might differ between the two conditions, i.e., more data loss in Bi_{uneq} as this force ratio was more difficult to achieve (and had to be learned first). Second, to fully evaluate the ERD and ERS patterns for the exact force ratios of Bi_{eq} and Bi_{uneq}, learning the ratios has to be disentangled from producing the force ratios. To disentangle the learning from the force production, I propose to include a control condition in future experiments which tests the simple force production of the ideal ratios. Two bars on the screen (corresponding to the force in each hand) would each have a target line which resembles the exact force ratio for each hand, i.e., 50%:50% and 25%:75%. The participant would be informed how much force they use with lines corresponding to their own level of force (moving up and down depending on their force). They would be asked to hold their force at the target line. This control condition would disentangle the force production of the ratios from learning the ratios as participants are aware of them (due to the visualisation on the screen). Thus, it could be tested more specifically, how beta power is modulated by producing the force ratios of Bi_{eq} and Bi_{uneq}.

Another way to test how beta power is modulated in Bi_{eq} and Bi_{uneq} would be to consider beta power as transient high-power burst events. As fully outlined in chapter 1, beta power is increasingly interpreted as transient beta bursts events and analysed on a trial-by-trial level (Jones, 2016; Shin et al., 2017; van Ede et al., 2018). The richness of the single trial data could infer characteristics of beta power which might be concealed in trial averaged data. Specifically, re-analysing the data presented in this chapter could evaluate beta burst coupling across regions and hemispheres (Seedat et al., 2020; Tinkhauser et al., 2020) also known as burst coincidence, as well as the spatial spread of burst (Little et al., 2019; Zich et al., 2020). This potentially carries more information than the trial averaged beta

power reported in this chapter and allows for a more detailed exploration, i.e., how information exchange is flexibly adapted to enable bimanual movements with equal and unequal contributions. As this approach involved extensive analysis, this was not realizable for the scope of this thesis.

6.4.3 ERD or ERS Were Not Affected by Learning

Against my hypothesis, the results presented in this chapter did not indicate significant learning-induced changes in ERD or ERS. Post hoc, it was tested whether the absence of the learning-induced changes in the ERD (as well as the absence of the interaction with condition) could be due to the use of incorrect force ratios between hands. Specifically, when performing the task, the force ratios between hands are constantly adjusted in order to stay as close as possible to the ideal line of the street. When the force ratio deviates too much from the optimal force ratios, the cursor hits the boundary, and is reset. Hypothetically, the ERD could have been contaminated by incorrect force ratios and resets. To test whether this was the case, post hoc, I re-calculated the ERD from the last reset (instead of movement onset) to the movement offset. Thereby, the ERD only depicted the part of the street performance that led to the completion of the street. However, the results of this post hoc analysis were identical to the original results. This indicated that the absence of the learning effect cannot be attributed to incorrect force ratios between hands.

Previous studies investigating unimanual (Sanes & Donoghue, 2000; Tan et al., 2014; Zich et al., 2018) and bimanual motor learning have reported learning-related power modulations in the beta frequency range (Andres et al., 1999; Boonstra et al., 2007). However, results of previous studies are inconsistent. Specifically, (Andres et al., 1999) described stronger decreases in beta power after uni- and bimanual sequences learning compared to before learning. In a later report of the same

experiment, the learning-induced changes were absent (Gerloff & Andres, 2002). In another study, Boonstra et al. (2007) suggested that beta power modulations were enhanced after learning a bimanual cyclic/rhythmic movement with unequal contributions between hands. Their neural and behavioural changes correlated significantly across trials and within subjects. The opposite was found by Houweling et al. (2008). The authors reported a weaker ERD in both M1 after learning compared to before learning. The authors attributed the weaker ERD in both M1 after learning to the fact that with learning the behavioural task, force production was easier and, thereby, required less attention.

The inconsistent findings listed above point out some aspects to consider for investigating learning-induced changes such as learning strategies and their neurophysiological underpinnings. Recently, Haar et al. (2020) reported opposing changes of the ERS (increase or decrease of ERS) while learning a real-life billiard task. They speculated that these changes potentially reflected different learning strategies. Specifically, Haar et al. (2020) argued that the group with an increased ERS used more error-based motor adaptation, to perform the billiard task. This would be in line with findings of other studies investigating sensorimotor adaptation (Tan et al., 2014; Tan et al., 2016) and error-detection (Alayrangues et al., 2019; Torrecillos et al., 2015). Further, Haar et al. (2020) inferred that the group with an ERS decrease used a strategy of reward-based motor learning, as these ERS changes were in line with those of other studies investigating reward-based motor learning (Kranczioch et al., 2008). That learning strategies influenced the ERS might also be possible for the findings presented in this chapter. Due to the dynamic nature of the task, participants might have used error-based motor adaptation, reward-based learning, or both. However, descriptively the data presented here did not indicate any clear differences in the ERS responses. To test for differences in the ERS, the data would need to be split into groups, i.e., one group with an

increase and another with a decrease in the ERS. However, dividing data into groups to analyse different responses in the ERS would have lacked statistical power due to the number of participants (N=17).

Next to the learning strategies, other aspects to consider when investigating learning-induced changes in ERD and ERS are different stages of learning and their associated neurophysiological underpinnings. According to Halsband and Lange (2006), motor skill learning starts with an initial stage, in which a subject tries to understand the task and explores rules and fundamentals. In the intermediate stage a gradual learning is present, as the motor plan is developed and adapted. In the advanced stage the skill is automatised and the skill is performed rapidly with a minimum of attentional resources. The involvement of cortical areas such as M1, SMA, and PMC differ between the learning stages. Specifically, during initial and intermediate stages of skill learning, activity of the cortical areas is thought to be increased, see for a review Halsband and Lange (2006). Once automated, the activity of cortical areas is thought to decrease back to the early stages of learning. In the experiment presented here, it is highly unlikely that learning the task was at an automated stage, as automation is thought to occur after multiple training sessions (Kleim et al., 2004). In agreement with other studies (Andres et al., 1999; Boonstra et al., 2007), the experiment described in this chapter is likely to be at an initial or intermediate learning stage. Thus, it was reasonable to assume that learning-induced changes in the ERD/S should occur. However, it is not unlikely that learning stages differed across conditions. Specifically, *Uni* was the easiest condition, i.e., equivalent to learning to use the force grippers, and showed floor effects. Thus, learning of the *Uni* condition was potentially at an intermediate stage. In comparison, Bi_{uneq} was the most difficult condition and learning-related improvements did not reach a floor, suggesting that perhaps subjects remained in the initial stage of learning for this condition. In addition, one might speculate

that the time course of learning-induced changes differed across participants, i.e., some participants learned more quickly whereas others learned in the later stages of the experiment. This highlights that comparing the first and last ten trials, as reported in this chapter, might not be sensitive enough to examine learning-induced changes on the neural level and that all time points (all 50 trials) should be considered. Thus, more sensitive analysis approaches should be used that take condition-specific responses and the time course of single subject responses into account. Recently, van Ede et al. (2018) proposed two approaches to enhance sensitivity of data analysis. Specifically, they recommended using Empirical Mode Decomposition which increases the temporal and spectral resolution of data (Huang et al., 1998). Further, van Ede et al. (2018) suggested to use Hidden Markov Modelling in which the time-series, i.e., occurrences and duration, of the data is described in states (Vidaurre et al., 2016). The benefit of this method is that the information about the timing and duration of states is gathered data-driven without making pre-assumptions or constraining the time-series. This is of particular interest in self-paced tasks, as used in this experiment, because timings varied across trials (within participants). Therefore, with Hidden Markov Modelling, the temporal dynamics of learning-induced changes are better depicted, as previously shown by Zich et al. (2018). However, as these approaches involve extensive analysis, they were not realizable for the scope of this thesis. Taken together, considering the aspects listed above, this experiment as well as previous experiments investigating learning-induced changes would jointly benefit from using analysis methods with greater sensitivity. This is particularly evident as most experiments discussed in this chapter have studied ten or less participants. This constitutes a limitation in terms of statistical power. The statistical power of experiments is of concern as they increase the likelihood of false negative or false positive findings and thereby limit the validity of results (Button et al., 2013).

6.4.4 Conclusion

In this chapter, I aimed to investigate the neurophysiological underpinnings of the bimanual motor learning task using MEG. I could show that learning was induced in movement time and error with distinct learning patterns for the different levels of bimanual interaction. This was in line with findings from the previous chapters. Further, I could demonstrate a clear movement-related ERD and ERS in the beta frequency range. The ERD and ERS were different across conditions, but did not change with learning. As this is initial work, future studies should build on this to try to disentangle the neural underpinnings of complex cooperative contributions between hands.

7 General Discussion

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7.1 Summary

The aim of this thesis was to investigate the behavioural outcomes, and neurophysiological underpinnings of bimanual motor learning using a novel task. To this end, a novel task was designed that assessed unimanual and bimanual motor learning with different levels of bimanual interaction. With the task, I performed four independent experiments to answer distinct questions, including characterising learning (chapter 3) and generalisability (chapter 5). I used brain stimulation (chapter 4) and MEG (chapter 6) to understand learning-related neurophysiological changes.

In the first chapter of this thesis, I introduced the concept of bimanual motor learning, its features and neurophysiological underpinnings derived from the literature. I evaluated previous task designs and identified that cooperative contributions

between hands had been highly understudied. Specifically, different levels of bimanual interactions including equal and unequal contributions between hands had not been compared in cooperative tasks. This was also reflected in the studies investigating the neurophysiological underpinnings of bimanual movements and bimanual motor learning. Much is known about how unimanual movements are performed and learned. However, little is known about how movements with equal and unequal contributions between hands are produced and learned. By designing a novel task that allowed for a richer description of bimanual motor learning, the behavioural and neurophysiological underpinnings could be evaluated.

In chapter 2, I reviewed the methods and techniques used in this thesis to characterise bimanual motor learning, stimulate the brain and measure the electrophysiological properties of the brain. Specifically, I described the novel bimanual motor learning task in which a cursor was navigated across a path of angled streets. Each street angle corresponded to specific force ratios between hands which depicted unimanual and bimanual motor learning with equal and unequal contributions. Moreover, I specified the details of how the task was altered for an online experiment to test the relationship between training and transfer of motor learning. I further outlined the use of an online experiment to test complex research questions. I discussed tACS, a non-invasive brain stimulation technique, and their underlying physiological mechanisms to modulate brain activity in the beta band, and thereby potentially modulate bimanual motor learning. In this context, I briefly introduced EEG to assess the stimulation frequency for the application of tACS. This was followed by a description of MEG to examine the neurophysiological underpinnings of bimanual motor learning. In this vein, I discussed the physiological mechanisms supporting EEG, and MEG, as well as the analysis pipelines employed for the data analysis performed in this thesis. Finally, I described the questionnaire used in this thesis which was a self-reported indicator of bimanual competence.

In chapter 3, I investigated behavioural changes of the novel task. I showed that the task induced learning in movement time and error without a speed-accuracy trade-off. In addition, I reported that the different levels of bimanual interactions were distinct and that they yielded distinct learning patterns. However, learning the training task did not transfer to a transposition task, i.e., swapping the axis on the screen controlled by each hand. Therefore, chapter 3 demonstrated that the task is suited to study unimanual and bimanual motor learning with different levels of bimanual interaction. The transfer of motor learning however needed to be investigated further, see below. In the context of other motor learning studies, the contributions of this experiment were twofold: First, the findings presented in this chapter were in line with findings of previous studies quantifying other types of tasks. Thus, this experiment extended what is known about bimanual motor learning to cooperative tasks; a type of task which is highly understudied. Second, previously cooperative tasks had only been investigated with equal contributions between hands. By comparing equal and unequal conditions, the novel task allowed for a richer description of cooperative tasks.

In chapter 4, I examined whether the learning-related changes shown in chapter 3 could be modulated with individualised beta tACS. Specifically, I explored the hemispheric phase (de-)synchrony of bimanual motor learning using in-phase and out-of-phase beta tACS over both sensorimotor cortices. The stimulation frequency in the beta band was individualised using EEG above both sensorimotor cortices. Results indicated that the behavioural findings described in chapter 3 were replicated in an independent sample. However, the beta tACS applied did not have any significant effect on learning the task. These results suggested that bimanual interactions are not solely explained by simple relationships in hemispheric phase (de-)synchrony in the beta frequency range. Specifically, although it was reasonable to assume that beta tACS might affect bimanual motor learning, the

phase (de-)synchrony between hemisphere might be more complex and dynamic (e.g., mediated by the inter-regional delay between hemispheres) and thus, difficult to target with tACS. Apart from the physiological mechanisms, this experiment highlighted the importance of further optimising the application of tACS, e.g., with other electrode montages and amplitude-controlled tACS. Optimisation could reduce inter-individual variations and thus fully evaluate stimulation effects. Taken together, as this experiment was initial work, the findings of this chapter give new directions for future research.

Given that the learning did not transfer to the transposition task in chapter 3, I further investigated the relationship between training and transfer of motor learning in chapter 5. Specifically, I systematically tested the transfer of motor learning from a set of five training tasks to a set of three transfer tasks. Results indicated that depending on the training task, especial and generic skill learning was reinforced. These outcomes were in line with Schema theory stating that variable training reinforces a generic skill, whereas constant training reinforces a especial skill. I further expected that variable training induced transfer to all transfer tasks, whereas constant training only induced transfer to transfer task with a small difference to the training task. Instead, results indicated that transfer was induced for all training tasks when the transfer task was closely related to the training task. This suggested that transfer was independent of the training task and depended on the transfer task. In conclusion, the experiment emphasized the difficulty of designing transfer tasks and the importance of testing transfer with multiple transfer tasks to fully evaluate transfer effects. This not only has implications for studying motor skill learning but also for assessing learning beyond the context of motor skills, e.g., in adaptation or error correction. In addition, the results of this experiment demonstrated a successful translation from the in-lab

version to the online version of the bimanual motor learning task suggesting that motor learning studies can be obtained online with high quality data.

In chapter 6, I investigated the neurophysiological underpinnings of bimanual motor learning using MEG. In line with chapter 3 and 4, the task induced learning with distinct patterns for the different levels of bimanual interaction. Concurrently, a clear movement-related event-related desynchronisation (ERD) and synchronisation (ERS) was observed in the beta band. Further, the ERD and ERS yielded condition specific modulations. Specifically, the ERD was stronger in the unimanual condition compared to the bimanual unequal condition and appeared bilateral across all conditions. The ERS was stronger in both bimanual conditions compared to the unimanual condition and appeared lateralised in the unimanual condition and bilateral in bimanual conditions. Both ERD and ERS did not differ between the bimanual conditions. Further, results did not indicate significant learning-induced changes in either the ERD or ERS. Taken together, these findings provided first insights into the neurophysiological underpinnings of the bimanual motor learning task indicating condition specific effects but no learning-induced changes. Thus, the experiment contributed to our understanding of the neurophysiological underpinnings of performing complex cooperative unimanual and bimanual movements. As this was initial work, the experiment further emphasized to use analysis approaches with greater sensitivity in the future to fully evaluate the temporal dynamics of performing and learning the task. This is particularly evident as there is currently no consensus on how beta power is modulated with learning and across unimanual and bimanual conditions in complex cooperative tasks.

7.2 Main Conclusion

1. The novel task designed for this thesis was successfully implemented and is well suited to characterise unimanual and bimanual motor learning with different levels

of bimanual interaction. Thereby, the design of the task extended the understanding of bimanual motor learning to cooperative tasks and allowed a richer description of cooperative contributions between hands.

2. Testing the relationship between training and transfer of motor learning showed that depending on the training task especial and generic skill learning were reinforced. Transfer of learning was independent of the skill acquired and occurred when training and transfer task were closely related.

3. The used beta tACS did not modulate motor learning in the task. The role of hemispheric phase (de-)synchrony in the beta frequency range might be more complex and needs to be evaluated further.

4. While leaning the task, concurrent movement-related ERD and ERS in the beta band appeared. The ERD was stronger in the unimanual condition compared to the bimanual unequal condition and appeared bilateral across all conditions. The ERS was stronger in both bimanual conditions compared to the unimanual condition and appeared lateralised in the unimanual condition and bilateral in bimanual conditions. In addition, ERD and ERS did not differ across equal and unequal contributions between hands and did not change with learning.

7.3 Future Research

The experiments reported in this thesis raise research questions that could be addressed in future experiments. The research questions listed here could extend the findings of this thesis and explore further implications of the results.

7.3.1 Evaluating Beta Bursts

In chapter 6, movement-related beta activity was investigated and differences between unimanual and bimanual conditions were observed. Within this thesis,

beta activity was quantified as ERD (averaged over time from movement onset to movement offset and over trials) and ERS (averaged over time from movement offset to 3 s after movement offset and over trials). As outlined in the introduction of this thesis, beta activity is increasingly interpreted as dynamic beta bursts events and analysed on a trial-by-trial level (Jones, 2016; Shin et al., 2017; van Ede et al., 2018). Re-analysing the data presented in chapter 6 with this in mind could evaluate beta burst coupling across regions and hemispheres (Seedat et al., 2020; Tinkhauser et al., 2020) as well as the spatial spread of burst (Little et al., 2019; Zich et al., 2020). Combining cooperative bimanual motor interactions and cutting-edge burst analysis could advance our understanding of the communication in the motor network, i.e., how information exchange is flexibly changed to enable highly diverse movements. This might enable new ways to quantify neural communication and ultimately aid clinical application, i.e., in Parkinson's disease or stroke.

7.3.2 Assessing Neural Communication at Different Frequencies

In chapter 4 and 6, I tested the role of beta activity in bimanual motor learning. In recent publications, the importance of gamma activity (Zich et al., 2021) and theta-gamma coupling (Akkad et al., 2019) for motor learning has been highlighted. These approaches could be used to investigate the role of gamma activity and theta-gamma coupling in bimanual motor learning. On the one hand, the data collected in chapter 6, could be re-analysed to investigate the learning-related changes in the gamma frequency band (instead of the beta band) using the analysis pipeline reported in (Zich et al., 2021). Findings would inform if gamma activity differed across the three conditions, i.e., increased with task demands, and if gamma activity changed with learning. On the other hand, brain stimulation techniques such as tACS could be utilized to study the direct link between gamma activity or theta-gamma coupling on bimanual motor learning. As previously shown by Joundi

et al. (2012), gamma tACS increased the rate of unimanual force production (i.e., reaction times were reduced). Similarly, unimanual motor learning improved with theta-gamma tACS (Akkad et al., 2019). A follow up experiment using gamma tACS or theta-gamma tACS could assess whether previous findings regarding the reduced reaction times and improved learning could be replicated in the bimanual motor learning task. Taken together, future work would benefit from looking beyond a single frequency band and investigate learning-related changes in different frequency ranges as well as cross-frequency coupling. Among others, this would shed light on the functional role of theta, beta, and gamma activity, their neurophysiological basis and role in neuroplasticity.

7.3.3 Transfer of Learning

In chapter 5, I investigated the relationship between training and transfer of bimanual motor learning. I found that transfer of learning was independent of the training task but dependent on the transfer task. Possibly, these findings might be generally applicable to all learning tasks and not necessarily be specific to bimanual motor learning. Thus, future research should follow up if the findings of chapter 5 are applicable to research beyond the motor domain, e.g., in adaptation, task-switching or error correction. Similarly to the design used in chapter 5, a large between subject design could be used to systematically test the transferability of skills from a set of several training tasks to a set of multiple transfer tasks. If findings are comparable, potentially, abstract rules or theories could be defined which relate training and transfer tasks and thereby allow to design sensible transfer tasks based on the training task.

7.3.4 Bimanual Learning as a Clinical Tool

As indicated, the experiments presented in this thesis were conducted with samples of young and healthy participants. This allowed to advance the understanding of

how this cohort produces and learns bimanual movements. Bimanual motor learning has been considered a critical marker for functional independence in healthy ageing and as a target for neurorehabilitation after stroke, see Maes et al. (2017) for a review. Thus, the task might be a valuable tool for future research in other cohorts, like older healthy participants as well as clinical cohorts such as stroke patients.

Generally, motor performance has been found to decline with age (Swinnen, 1998) alongside concurrent decline in beta activity in motor performance (Rossiter et al., 2014) and motor learning (Mary et al., 2015). Comparing the performance of younger and older cohorts in the bimanual motor learning task, could assess if the findings outlined in chapter 3 and 4 would replicate in an older healthy cohort or show divergent condition specific effects and divergent learning patterns. Concurrently, using the bimanual motor learning task, it could be tested whether the decline in beta activity seen in older cohorts is also present when learning the task, or whether this pattern could be overcome with time, i.e., learning over multiple training sessions. Thus, assessing the behavioural and neurophysiological underpinnings of the task in an older cohort, would help to understand how these processes change during healthy ageing.

The findings of an experiment with a healthy older cohort could further inform if the task needs to be simplified for use in a clinical cohort such as stroke patients. Stroke leads amongst others to significant impairments in motor ability of the hands, and on the neural level, to a more bilateral recruitment of M1s when using the impaired hand (Ward et al., 2003). With recovery, this tends to revert back to a pattern similar to those reported in healthy controls, i.e., more activation in contralateral M1 (Ward et al., 2004). Usually, rehabilitation interventions aim at recovering the impaired hand alone, i.e., improving unimanual performance. However, many daily life tasks require the cooperative contributions of both hands, providing a rationale to incorporate bimanual movements in rehabilitation

interventions. Moreover, evidence suggests that bimanual training interventions could improve performance in the impaired hand, see Rose and Winstein (2004) for a review. Thus, the use of the bimanual motor learning task might inform or be used as a therapeutic intervention aimed at incorporating the impaired hand by training the cooperative contributions between hands, and potentially, reverting back the bilateral recruitment of M1s when using the impaired hand.

Taken together, examining the behavioural and neurophysiological underpinnings of the task in the proposed cohorts, would have implications for research studying how these processes change during healthy ageing and for developing novel adjunct therapies for rehabilitation after stroke.

Appendix

Sub-ID: Date:

Bimanual tasks in daily life

1. Do you play **sports or hobbies** involving both of your hands (Rugby, Volleyball, sewing, etc)?
    a. If yes, which?

    _____

    b. If yes, since when (in years/months)?

    _____

    c. If yes, how often in the last six months (fortnight/biweekly/weekly/daily)?

    _____

    d. If yes, for how long at once (hours/minutes)?

    _____

2. If you are **typing on a keyboard, or texting on your phone**, do you use both hands/thumbs?
    a. If yes, which?

    _____

    b. If yes, since when (in years/months)?

    _____

    c. If yes, how often in the last six months (fortnight/biweekly/weekly/daily)?

    _____

    d. If yes, for how long at once (hours/minutes)?

    _____

Sub-ID: Date:

3. Do you currently play **videogames** with (a) device(s) involving both of your hands (computer keyboard, controller, joystick)?

    a. If yes, which?

    _____

    b. If yes, since when (in years/months)?

    _____

    c. If yes, how often in the last six months (fortnight/biweekly/weekly/daily)?

    _____

    d. If yes, for how long at once (hours/minutes)?

    _____

4. Do you currently play (a) **musical instrument(s)** involving both of your hands?

    a. If yes, which?

    _____

    b. If yes, since when (in years/months)?

    _____

    c. If yes, how often in the last six months (fortnight/biweekly/weekly/daily)?

    _____

    d. If yes, for how long at once (hours/minutes)?

    _____

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