The relationship between cortical beta oscillations and motor learning

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I, Svenja Espenhahn, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Svenja Espenhahn, November 2017

Abstract

The ability to learn and retain new motor skills is pivotal for everyday life activities and motor rehabilitation after stroke. However, people show considerable individual differences in motor learning. Understanding the neurophysiological processes underlying these individual differences is of significant scientific and clinical importance. At a mechanistic level, oscillations in the beta frequency range (15–30 Hz), fundamental for motor control, reflect underlying cortical inhibitory and excitatory mechanisms. As such, they may provide appropriate biomarkers with which to bridge the gap between cellular and behavioural accounts of cortical plasticity in both healthy and diseased states. This thesis explores the interplay between cortical beta oscillations and individual differences in short-term motor learning within the context of healthy ageing and after stroke.

First, I assess the test-retest reliability of resting and movement-related beta estimates in a group of healthy subjects across several weeks. By demonstrating that EEG-derived power measures of beta activity are highly reliable, I validate the notion that these measures reflect meaningful individual differences that can be utilized in basic research and in the clinic.

Second, I probe the neurophysiological mechanisms underlying natural inter-individual differences in short-term motor learning. I demonstrate comparable motor learning ability between young and elderly individuals, despite age-related alterations in beta activity. Implementing a multivariate approach, I show that beta dynamics explain some of the individual differences in post-training tracking performance.

Third, I extend this line of research by focusing on stroke-related inter-individual variations in motor learning. Employing the same tasks and analyses, I demonstrate preserved, albeit reduced motor learning ability and no aberrant beta activity after stroke. Beta dynamics explained some of the individual differences in stroke patients' performance 24 hours after training, and may thus offer novel targets for therapeutic interventions.

Acknowledgements

Four years have passed since I moved to London and started to pursue my MRC-funded 4-year PhD in Clinical Neuroscience at UCL. During this time, I have had the pleasure of learning from and working with many remarkable people, who have directly and indirectly contributed to my PhD journey. I am truly thankful to all of the people who have made these past 4 years stimulating and enjoyable.

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Abbreviations

ANOVA	ANalysis Of VAriance
ARAT	Action Research Arm Test
AROM	Active Range Of Movement
BB	Baseline Beta
BDNF	Brain-Derived Neurotrophic Factors
BOLD	Blood Oxygenation Level-Dependent
CAR	Common Average Reference
CIMT	Constraint-Induced Movement Therapy
CST	CorticoSpinal Tract
cTBS	Continuous Theta Burst Stimulation
D	Dominant
DLPFC	DorsoLateral Prefrontal Cortex
DMS	DorsoMedial Striatum
DV	Dependent Variable
ECR	Extensor Carpi Radialis
EEG	ElectroEncephaloGraphy
EMG	ElectroMyoGraphy
EPSP	Excitatory PostSynaptic Potential
ERD	Event-Related Desynchronization
ERP	Event-Related Potential
ERS	Event-Related Synchronization
FCR	Flexor Carpi Radialis
FDI	First Dorsal Interossei
FLAME	Fluoxetine for Motor recovery After stroke
FM	Fugl-Meyer
fMRI	Functional Magnetic Resonance Imaging
FSS	Fatigue Severity Scale
ICC	Intraclass Correlation Coefficient

IPSP	Inhibitory PostSynaptic Potential
IV	Independent Variable
KP	Knowledge of Performance
KR	Knowledge of Result
LACI	Lacunar Infarct
LFP	Local Field Potential
LOOCV	Leave-One-Out Cross-Validation
M1	Primary Motor Cortex
MCA	Middle Cerebral Artery
MEG	MagnetoEncephaloGraphy
MEP	Motor-Evoked Potential
MRBD	Movement-Related Beta Desynchronization
MRI	Magnetic Resonance Imaging
MT	Movement Time
ND	Non-Dominant
NFI	Neurological Fatigue Index
NHNN	National Hospital for Neurology and Neurosurgery
NHPT	Nine Hole Peg Test
PCA	Principle Component Analysis
PCA	Posterior Cerebral Artery
PD	Parkinson’s Disease
PIC	Peri-Infarct Cortex
PM	PreMotor
PMBR	Post-Movement Beta Rebound
PPC	Posterior Parietal Cortex
PV	Peak Velocity
RMSE	Root Mean Squared Error
RT	Reaction Time
SART	Sustained Attention To Response Test
SD	Standard Deviation

SEM	Standard Error of the Mean
SICI	Short-interval IntraCortical Inhibition
SMA	Supplementary Motor Area
SNR	Signal-to-Noise Ratio
SPM	Statistical Parametric Mapping
SRTT	Serial Reaction Time Task
SSRI	Selective Serotonin Reuptake Inhibitor
STFT	Short-Term Fourier Transform
SVIPT	Sequential Visual Isometric Pinch Task
t_i	Target position at time i
TF	Time-Frequency
TMS	Transcranial Magnetic Stimulation
TS	Time since Stroke
UL	Upper Limb
VAS	Visual Analogue Scale
W	Width
w_i	Wrist position at time i
A	Amplitude (Distance)

Chapter 1 Introduction

This thesis explores candidate biomarkers with which to bridge the gap between cellular and behavioural accounts of cortical plasticity by investigating the interplay between these neurophysiological markers and individual differences in short-term motor learning in both healthy and diseased states. It builds on a large body of physiological, pharmacological, behavioural and neuroimaging work proposing a role for cortical plasticity in motor skill learning and recovery after stroke. In this chapter, I review and draw together insights from the existing literature, and highlight the translational value of the questions addressed in this thesis. I define key terms that will be used throughout, and present an overview of the following chapters.

1.1 Motor learning: a key feature of human motor control

Successful interaction with the world and other people requires the ability to learn and adapt our motor behaviour to an ever-changing environment. *Motor learning* is the process associated with practice or experience rather than maturation that leads to a fairly permanent change in a person's ability to perform motor skills ("ability to reliably deliver accurate execution" (Kitago and Krakauer, 2013)). These motor skills such as writing, playing an instrument or using a touchscreen require, for example, smooth co-activation of muscle groups into a specific sequence, multi-joint movement synergies, and eye-body coordinated actions (Schmidt, R. A. and Lee, 1999). The goal of motor learning, in general, is to improve performance and acquire new motor skills, which is fundamental to human development. The process itself is dynamic as changes are mostly unpredictable. Thus, it allows an individual to progress from novice to expert in a particular motor skill, and to flexibly maintain motor abilities throughout the lifespan (Schmidt and Wrisberg, 2008a; Willingham, 1998; Wolpert et al., 2011). Consequently, the capacity to (re)learn and retain new motor skills is essential for accommodating neurophysiological changes that often occur gradually with ageing and suddenly following neurological injury. However, daily life experience makes it evident that people show considerable inter-individual differences in their capacity to learn and retain new skills (Frensch and Miner, 1994; Golenia et

al., 2014; Tubau et al., 2007; Unsworth and Engle, 2005; Vegter et al., 2014), possibly due to variations in the structure and function of brain regions involved in motor control (Tamás Kincses et al., 2008; Tomassini et al., 2011). Understanding the neurophysiological processes underlying these differences in the capacity to learn is of significant scientific and clinical importance for improving long-term rehabilitative outcomes in the elderly and patients with brain injury (Stinear, 2010; Ward, 2017).

1.1.1 Motor learning in the lab: motor skill learning vs motor adaptation

In order to study the cognitive processes and neural substrates mediating the ability to learn motor behaviour in the laboratory, a variety of tasks and experimental paradigms have been used. In general, these tasks fall into two categories (for review see (Doyon et al., 2003; Kitago and Krakauer, 2013; Krakauer and Mazzoni, 2011a; Willingham et al., 1989)). The first is *motor adaptation*, in which our capacity to compensate and return to baseline performance following externally induced perturbations (i.e. prisms, rotations, force fields) is tested (**Figure 1.1**A) (Krakauer et al., 2000; Martin et al., 1996; Shadmehr and Mussa-Ivaldi, 1994a). Individuals, in general, rapidly reduce performance errors and once adapted, show 'after-effects' and have to gradually 'de-adapt' their behaviour with practice back to the original state when the perturbations are removed again. Importantly, adaptation does not require the acquisition of new motor synergies. Motor adaptation will not be discussed further here, as it was not used to probe motor learning in this thesis and a comprehensive review of both types of learning would be beyond the scope of this thesis.

The second is *motor skill learning*, the incremental acquisition of sequential movements into well-executed behaviour with lasting improvements beyond baseline performance (**Figure 1.1**B) (Karni et al., 1995; Nissen and Bullemer, 1987). In contrast to motor adaptation, this form of motor learning involves the acquisition of new movement patterns and/or muscle synergies. Thus, the acquisition of motor skill takes longer than adaptation, and sometimes does not reach plateau level for years (i.e. learning to play the violin) (Karni and Sagi, 1993). In both animals and humans, motor skill learning is typically measured by

a reduction in reaction time, the number of errors, and changes in the speed-accuracy trade-off, and/or by a change in muscle activation patterns and kinematics (e.g. (Hikosaka et al., 1995; Reis et al., 2009; Shadmehr and Brashers-Krug, 1997).

In general, motor adaptation and motor skill learning both involve learning novel kinematic and dynamic mappings between motor outputs and sensory inputs, determined by the structure of the task (Wolpert et al., 2011). However, in the case of motor adaptation, these adjustments are mostly temporary, limiting its use in the clinic. In contrast, due to the *durable effects* of motor skill learning, this type of learning plays a central role for post-stroke recovery and has important implications for neurorehabilitation (Kitago and Krakauer, 2013; Krakauer, 2006). Thus, this thesis is concerned with motor skill learning in relation to smooth movements of the wrist.

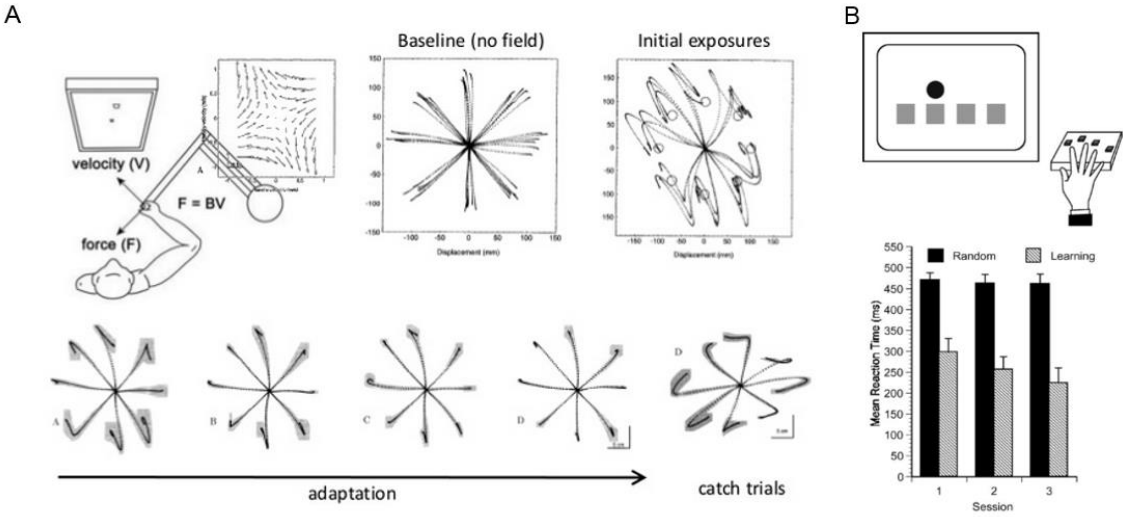

Figure 1.1* | *Schematics of typical motor learning tasks in the lab.
***A**, Motor adaptation task in which subjects perform reaching movements using a manipulandum in a force field. During initial exposure to the force field, movement performance is grossly distorted compared to movement without force field perturbation. With practice, performance within the changed mechanical environment is recovered. **B**, Motor skill learning task in which subjects are cued by a target dot to press a corresponding key with the respective finger. Unknown to the subjects, the location of the target dot is structured according to a repeated sequence. Subjects improve their performance on the repeated but not on the random sequence as indicated by a reduction in mean reaction time. Figure adapted from* (Doyon et al., 2003; Shadmehr and Mussa-Ivaldi, 1994b)*, with permission from Elsevier.*

1.1.1.1 Phases in the process of motor skill learning

The incremental *acquisition* of motor skills follows behaviourally relevant phases. Initially, motor skills develop relatively fast within a single training session (*fast learning*) and later more slowly, with further improvements developing incrementally over multiple training sessions (*slow learning*) (**Figure 1.2**) (for review see (Brashers-Krug et al., 1996a; Doyon and Benali, 2005; Doyon and Ungerleider, 2002b; Doyon et al., 2003; Halsband and Lange, 2006; Luft and Buitrago, 2005; Magill, 2011; Robertson et al., 2004a; Schmidt and Wrisberg, 2008b)). Of note, the relative duration of the fast and slow phases in motor learning is highly task-specific depending on factors such as movement complexity (Dayan and Cohen, 2011). For example, learning a simple key-press sequence could only last minutes, while learning to play the violin may take months, or even years.

However, in order for motor learning to be truly useful, the learned motor skill needs to be retained, following a short or longer time delay, with or without sleep, in which the task is not practised, commonly referred to as *offline learning* (Brashers-Krug et al., 1996b; Doyon and Benali, 2005; Karni and Sagi, 1993; Muellbacher et al., 2002; Robertson et al., 2005; Walker et al., 2002). This process involves the *consolidation* of motor memories, resulting in either a stabilization or enhancement of a motor memory encoded during practice (Hotermans et al., 2006; Robertson et al., 2004a; Walker, 2005). In general, enhancement refers to an increase in performance that exceeds the performance level prior to the time delay.

However, during the initial stages of the consolidation process, motor memories are fragile and susceptible to interference through practice of a competing task within a certain time window. When interference occurs within the first ~6 hours following training, for example due to learning on a competing motor task, the consolidation of the motor memory is disrupted and thus, *retention* is compromised (Brashers-Krug et al., 1996b; Karni and Sagi, 1993; Korman et al., 2007a). Once a motor skill is mastered and the motor memory properly encoded, it can be maintained for long periods of time (long-term retention) and readily retrieved with reasonable performance. An additional interesting concept is the term *transfer* or *generalization* which refers to the ability to apply a motor skill

learned in a specific context to a novel task or context, thereby saving a considerable amount of time and effort attached with the learning process.

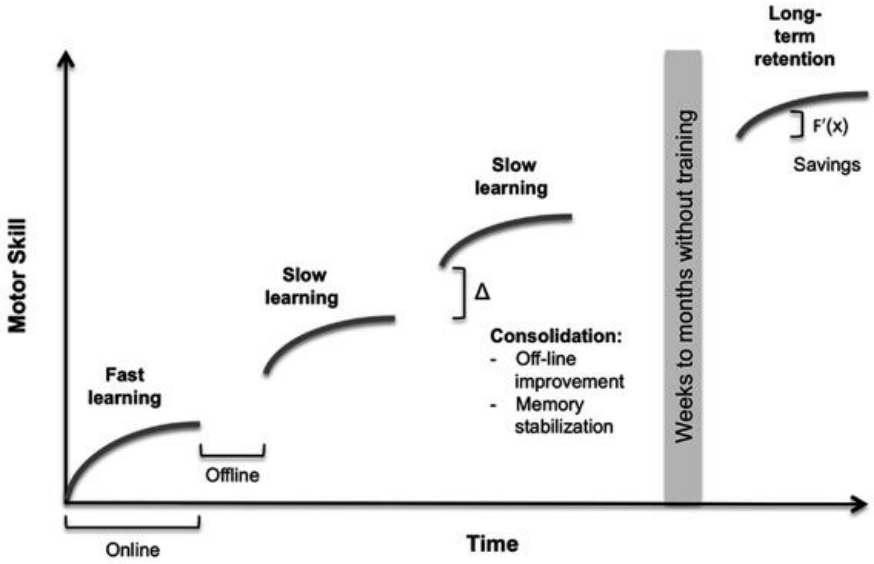

Figure 1.2 | Temporal phases in the process of motor skill learning.
The learning curve illustrates the increase in motor skill with practice over time. Motor skills are initially learned fast during single-session training, and then more slowly over multiple training sessions. Changes in motor skill can occur during training (online) but also after training ended between sessions (offline). Consolidation occurs after practice, incorporating stabilization and offline enhancement of a motor memory. Previous learning manifests in savings, a concept mostly used in the motor adaptation literature, which denotes faster retraining in consecutive sessions. Figure taken (Wessel et al., 2015), with permission from Frontiers.

1.1.1.2 Types of motor skill learning tasks: discrete vs continuous

Many skilled motor behaviours, such as playing the piano or running on complex terrain, consist of a sequence of movements. These motor behaviours can be classified into *discrete* and *continuous* skills (Schaal et al., 2004a). Discrete skills are those in which the movement has a clear beginning and end, such as pressing a key on a keyboard, reaching or grasping. In contrast, continuous motor skills represent cyclical and repetitive movements with no recognizable beginning and end. Examples of continuous skills include swimming, running or performing a tracking task. Of note, discrete movements, due to their rapid nature, are often made without the use of online feedback, while continuous movements involve

the modification/correction of movements while they are being executed using sensory feedback (Schaal et al., 2004b; Seidler et al., 2004).

Most of the studies examining motor skill learning have utilized discrete tasks such as the classical and most established serial reaction time task (SRTT), in which subjects perform a series of button presses (Nissen and Bullemer, 1987; Willingham et al., 1989). Studies employing continuous tasks, commonly utilize continuous tracking tasks, which are characterised by a moving target that subjects attempt to follow with a device (i.e. joystick, computer mouse or other specialised devices) via certain limb movements (Pew, 1974; Shea et al., 2001a; Wulf and Schmidt, 1997). In both paradigms, the subject is often unaware that the sequence of events is not random but consists of a continuous cycle of the same (repeated) sequence embedded in random sequences (implicit learning).
Learning on both tasks is measured as either a reduction in reaction time (i.e. SRT task, **Figure 1.1**B) or an improvement in tracking accuracy (i.e. tracking task). In general, changes in performance are evident for both repeated and random sequences; however, performance on the repeated sequence compared to the random sequence is generally improved. Thus, not only generalized motor components of the task are learned but also characteristics of the specific sequence, which is typically referred to as *sequence-specific learning* (Wulf and Schmidt, 1997).
Awareness about the structured nature of the repeated sequence to be learned has emerged as an influential factor for sleep-dependent memory consolidation as discussed later in section 1.1.1.3. Two types of awareness can be distinguished. If awareness is *explicit*, participants are aware of the task regularities, whereas if it is *implicit*, participants do not have conscious awareness of the task regularities (Willingham, 1998). Few, if any tasks have purely explicit or implicit characteristics (Shanks and St. John, 1994) and thus, the debate about the overlap of implicit and explicit learning remains open.

1.1.1.3 Factors facilitating motor skill learning

The *amount of practice* on a task is generally considered the most important factor for permanent improvements in the ability to perform a motor skill - “practice makes perfect” as the old adage goes. This positive relationship between practice

and skill has been mathematically modelled and referred to as the power law of practice (Newell and Rosenbloom, 1980). Nevertheless, numerous studies have proposed several factors that can facilitate and optimize the learning of motor skills, with a strong emphasis on movement feedback, practice distribution (massed vs distributed practice), scheduling (blocked vs random practice), variation of motor tasks (constant vs variable practice), and sleep (Kitago and Krakauer, 2013; Magill, 2011).

Feedback during a motor task has been shown to modulate motor skill acquisition (for reviews see (Magill, 1994; Schmidt, 1991; Sigrist et al., 2013; Swinnen, 1996). Intrinsic feedback, in the form of sensory-perceptual information that is a natural part of performing the skill, is indispensable for performance and learning. Augmented or extrinsic feedback provides an addition to the normally available task intrinsic feedback. Two types of performance-related information are commonly used: information about the outcome of performing a skill (termed Knowledge of Result, KR) and information about movement characteristics that led to the outcome (termed Knowledge of Performance, KP). Typically, these sources of information are provided after the performance of the skill, but can also be provided during the movement. However, augmented feedback is not necessary for learning and, under certain circumstances, can even be detrimental (i.e. erroneous feedback or concurrent feedback when it distracts attention away from intrinsic feedback), highlighting the necessity of designing valuable feedback in order to motivate, reinforce and speed up learning. Thus, when designing a motor learning experiment, variables such as the type of feedback, which performance-related information to provide, and timing and frequency of feedback need to be considered.

Although practice is the most effective way of improving performance during training, the *structure of practice* influences long-term retention of motor skills. Distributing practice sessions across days, thereby introducing rest periods, has consistently been shown to be beneficial for motor skill learning as compared to massed practice, where learning is crammed into one long session without breaks (e.g. (Arthur et al., 2010; Dail and Christina, 2004; Shea et al., 2000)), for review see (Smith and Scarf, 2017)). This effect termed distributed-practice or spacing effect has been known for more than a century (Ebbinghaus, 1885), with

memory consolidation taking place over periods of rest and sleep between sessions, which is thought to be the mechanism underlying the performance-enhancing impact of the spacing effect. The influence of practice structure on memory consolidation and retention of acquired motor skills also has potential clinical applications for improving neurorehabilitative interventions after brain injury (for review see e.g. (Muratori et al., 2013). Several studies have further shown that introducing *task variability* during practice improves retention (e.g. (Moxley, 1979; Shea and Kohl, 1990; Wulf and Schmidt, 1997)). In addition, practice under interleaved or random practice order degrades performance during the acquisition phase, but it results in superior retention and transfer performance compared to blocked practice schedules. This rather counterintuitive phenomenon is referred to as *contextual interference* (CI), describing the beneficial effect of interference during practice for skill learning (Magill and Hall, 1990; Shea and Morgan, 1979). However, it should be noted that practice under conditions of high contextual interference (i.e. random practice order), where practice takes place on a variety of tasks makes the identification of the cause of performance improvements challenging.

In recent years, a growing literature has suggested that *sleep* plays a crucial role in learning and memory consolidation across a variety of skill domains, with a wide belief that it benefits memory consolidation (for reviews see (Diekelmann and Born, 2010; Stickgold et al., 2001)). Evidence that a night of sleep triggers performance improvements, whereas an equivalent period of wakefulness merely leads to performance stabilization, mainly stems from studies employing explicit motor-sequence learning tasks (Korman et al., 2007; Walker et al., 2002). Notably, the process of sleep-dependent consolidation appears to be reduced with ageing (Brown et al., 2009; Spencer et al., 2007; Wilson et al., 2012), most likely due to age-related changes in sleep patterns (Ohayon et al., 2004). Some studies, however, claim that the observed sleep-dependent performance enhancement is an artefact of the study design and is no longer evident when controlling for confounding factors such as fatigue and reactive inhibition (Brawn et al., 2010; Nettersheim et al., 2015; Rickard et al., 2008).

Notably, sleep does not appear to be beneficial for learning of implicit motor-sequence tasks (Al-Sharman and Siengsukon, 2014; Robertson et al., 2004b;

Siengsukon and Al-sharman, 2011), implying a modulatory effect of an individual's awareness of learning a new skill on the benefits of sleep. The role of sleep in consolidating motor memories further has implications in clinical settings as stroke patients have shown sleep-dependent improvements in motor performance for both implicit and explicit motor learning (Siengsukon and Boyd, 2009, 2008; Siengsukon et al., 2015).

Together, these and other factors should be taken into account when designing learning studies in order to maximise motor learning in healthy adults and, in the context of stroke-related brain damage, may have consequences for movement rehabilitation, which depends on motor learning and consolidation.

1.1.2 Neural correlates of motor skill learning

Over the past few years, a plethora of animal and neuroimaging studies have demonstrated that several brain structures, including *sensorimotor networks* and higher-order associative networks, are critical for the acquisition and/or retention of skilled motor behaviour (e.g. (Dayan and Cohen, 2011; Doyon and Benali, 2005; Doyon and Ungerleider, 2002a; Doyon et al., 2003; Floyer-Lea, 2005; Grafton et al., 1992; Sanes and Donoghue, 2000)). In humans, the neural substrates of the fast and slow components of motor learning have been studied with functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). These methods measure task-related modulations of blood oxygenation level-dependent (BOLD) signals or regional cerebral blood flow (rCBF), thereby providing indirect measures of cortical activity.

In general, these studies revealed increased activity in premotor cortex (PM), supplementary motor area (SMA), parietal regions, striatum, and the cerebellum (Floyer-Lea and Matthews, 2005; Grafton et al., 2002, 1992) and decreased activity in dorsolateral prefrontal cortex (DLPFC), pre-supplementary motor area (preSMA), and primary motor cortex (M1) (Floyer-Lea and Matthews, 2005) during the fast learning stage (Dayan and Cohen, 2011; Halsband and Lange, 2006) (**Figure 1.3**A). Slow learning, over several days or weeks, modulates brain activity in M1 (Floyer-Lea and Matthews, 2005; Karni et al., 1995), primary somatosensory cortex (Floyer-Lea and Matthews, 2005), SMA (Lehericy et al., 2005), and putamen (Floyer-Lea and Matthews, 2005; Lehericy et al., 2005),

which show increased activation, while the cerebellum shows decreased activity (Lehericy et al., 2005) (**Figure 1.3**B). Thus, progression from fast to slow motor skill learning is associated with a shift in brain activity from anterior to more posterior cortical regions, which is thought to reflect the reduced need for the engagement of attentional and control areas (Kelly and Garavan, 2005).

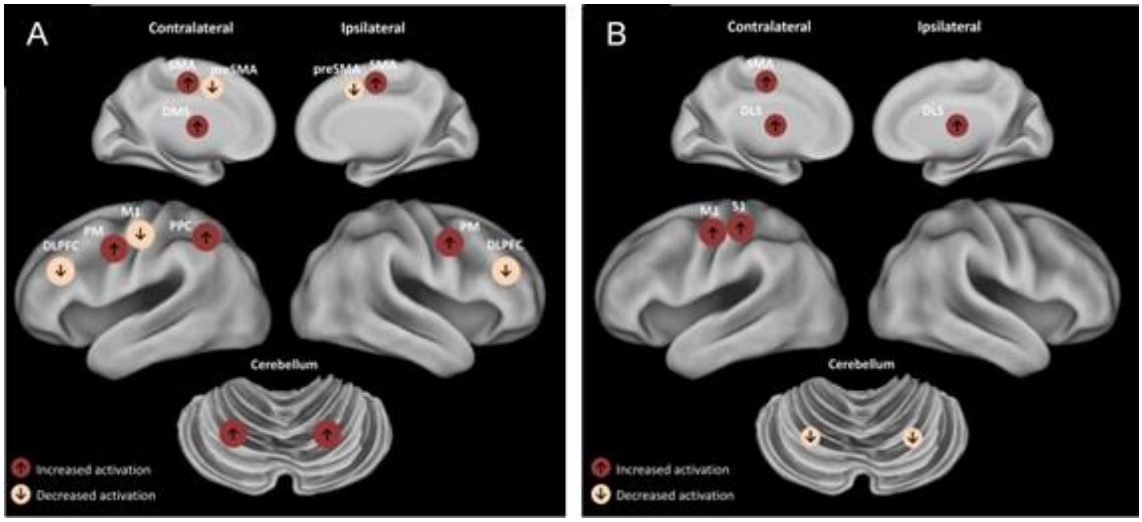

Figure 1.3 | Neural correlates of motor learning in humans.
*Schematic depiction of major brain regions involved in fast (**A**) and slow (**B**) stages of motor learning. The arrows and colours illustrate increases or decreases in particular brain structures based on fMRI and PET findings. DLPFC: dorsolateral prefrontal cortex; M1: primary motor cortex; PM: premotor cortex; SMA: supplementary motor area; preSMA: pre-supplementary motor area; PPC: posterior parietal cortex; DMS: dorsomedial striatum. Figure adapted from (Dayan and Cohen, 2011), with permission from Elsevier.*

Two major models for interpreting the complex pattern of activity have been proposed. The model by Hikosaka and colleagues focuses on the interaction of two parallel loop circuits which are operational in learning spatial and motor features of sequences (Hikosaka et al., 2002). The model proposed by Doyon and colleagues suggests that two distinct cortico-striatal and cortico-cerebellar circuits contribute differentially to motor sequence learning and motor adaptation, respectively, particularly during the slow learning phase (Doyon and Benali, 2005; Doyon and Ungerleider, 2002a). Although the two models propose different patterns of activity, they both affirm that motor skill learning involves interactions

between cortical and subcortical circuits associated with cognitive and control functions, which are important for motor skill learning.

1.1.3 Role of M1 in motor skill learning: acquisition and consolidation

As discussed above, motor learning is associated with activity in a distributed network of cortical structures, including sensorimotor and higher-order associative brain areas. However, non-invasive brain stimulation (NIBS) methods have been used to investigate the functional role of particular brain regions in motor learning, and most have focused on M1, a key structure in the control of voluntary movements. Given this premise and the fact that motor deficits are amongst the most common impairments after stroke-related brain damage, the motor system is the focus of the current work.

Studies employing transcranial magnetic stimulation (TMS) were able to associate different aspects of motor learning with M1, e.g. acquisition and consolidation of motor skills (Muellbacher et al., 2002; Pascual-Leone et al., 1994). For example, synchronous application of single pulse TMS, a procedure that stimulates neurons in a small area underneath the coil, over M1 engaged in thumb abduction learning resulted in enhanced motor memory encoding and longevity (Butefisch, 2004). Importantly, this effect was specific to the synchronous Hebbian stimulation of M1 that drives the training motions and was not evident when TMS was applied between movements.

An influential study conducted by Muellbacher and colleagues further demonstrated that the role of M1 in consolidation can dissociate from initial motor skill acquisition (Muellbacher et al., 2002). By applying repetitive transcranial magnetic stimulation (rTMS), a procedure that interferes with cortical functioning, to M1, they showed that retention of behavioural improvements on a thumb-to-finger opposition task was disrupted when applied immediately after training. The disruptive effect was specific for M1 in a time-dependent manner as rTMS applied 6 hours after practice or to other cortical areas such as DLPFC did not impact retention (**Figure 1.4**). These findings highlight the involvement of M1 during the early stage of motor consolidation. Also, rTMS applied over M1 immediately after practice of a SRTT degrades over-day but not overnight improvements, indicative

of different consolidation processes relating in a different manner to M1 and a role of sleep in rescuing memories (Robertson et al., 2005).

Thus, M1 is a key brain region involved in the acquisition and early consolidation of motor skills and thus, functional reorganization within motor cortical circuitry in association with learning should be evident.

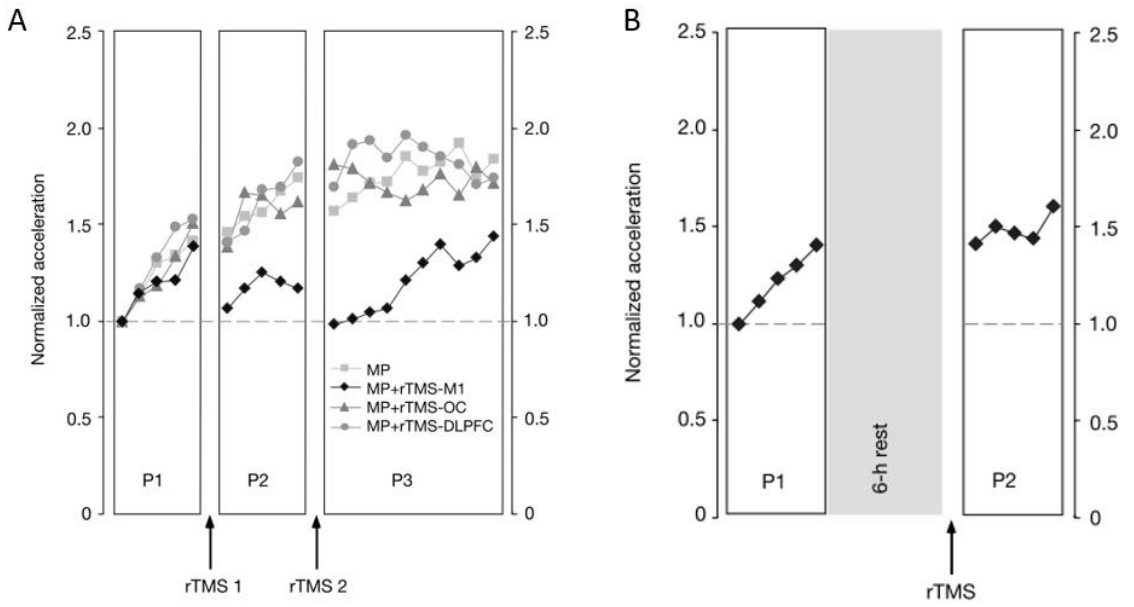

Figure 1.4 | Repetitive TMS over M1 disrupts early motor consolidation. ***A****, Stimulation of M1 (MP+rTMS-M1) but not occipital (MP+rTMS-OC) or DLPFC (MP+rTMS-DLPFC) areas specifically disrupted retention of behavioural improvements on a ballistic pinch task (mean peak acceleration) of practice 1 and 2 (P1, P2). However, motor learning by subsequent practice 3 (P3) was unaffected.* ***B****, Stimulation of M1 when applied 6 hours after practice did not impair retention of a newly acquired skill. MP: Motor practice. Figure adapted from (Muellbacher et al., 2002), with permission from Macmillan Publishers Ltd.*

1.1.3.1 Functional organisation of M1

The primary motor cortex has a complex, interconnected architecture with dynamic properties. It is associated with the regulation of muscle activity and voluntary movement and importantly, is a key contributor in the process of motor learning. Early studies by Penfield and Rasmussen employing microstimulation on the surface of M1 revealed a somatotopically ordered representational map for movements (or muscles), commonly referred to as the 'motor homunculus' (Penfield, W. and Rasmussen, 1950). However, it appears that different body

parts show a distributed representation with extensive overlap, with a system of horizontal connections functionally associating motor cortex neurons into dynamically structured assemblies (Sanes and Donoghue, 2000). These organizational principles of motor representations have important consequences for motor learning as well as recovery after stroke as they provide a basis for *flexible reorganization* of networks as discussed in the next section.

1.2 The interaction of motor learning with brain plasticity

Over the last two decades, neuroimaging and non-invasive brain stimulation in humans coupled with insights from animal studies have demonstrated that the acquisition of motor skills is associated with significant *neural plasticity* within the brain (e.g. (Dayan and Cohen, 2011; Doyon and Benali, 2005)). While previously thought to be a physiologically static organ, these findings have advanced the idea that the neural circuitry as well as the functional properties of neurons within different brain areas are malleable and retain a degree of plasticity throughout life (e.g. (Bavelier et al., 2010; Hensch, 2005)). In particular, changes within M1 have been evidenced to make fundamental contributions to learning and remembering of motor skills. In the following section, I thus focus on plasticity, here defined as "*changes in the strength of synaptic connections in response to either an environmental stimulus or an alteration in synaptic activity in a network*" (Murphy and Corbett, 2009a), within the primary motor cortex in the context of motor learning. Neural plasticity has been shown to be induced not only in response to practice and experience, but also as a result of pathological changes such as stroke, which will be discussed in detail later in this thesis (see section 1.3.2).

1.2.1 Motor learning-related plasticity in M1

The brain's capacity for motor learning induced cortical reorganization of M1 has been observed in various animal models and in humans. Adult rats trained on a prehension task that requires animals to reach for and grasp a food pellet show an expansion of forelimb movement representations (evoked with microstimulation) within motor cortex (Kleim et al., 1998). Similar expansions of finger representations with digit training, at the expense of wrist and forearm representations, were evidenced in squirrel monkeys (**Figure 1.5**) (Nudo and

Milliken, 1996), demonstrating a dynamic relationship between motor skill learning and motor cortical plasticity. It is important to note that reorganization of motor maps is not simply due to repetitive activity of muscle groups involved in movement execution but is specific to the trained task (Kleim et al., 1998; Molina-Luna et al., 2008; Plautz et al., 2000). For example, simple lever pressing in rats (Kleim et al., 1998) and repetitive performance of digit movements (~13,000 movements) in squirrel monkeys (Plautz et al., 2000) was insufficient to drive changes in M1 motor maps.

Consistently, in humans, imaging studies using PET (Grafton et al., 2002, 1992) or fMRI (Karni et al., 1995) and functional testing with TMS (Pascual-Leone et al., 1995, 1994) have demonstrated reorganizational changes in M1 with motor skill learning. Structural changes in grey matter have also been reported in individuals with highly developed motor skills (Draganski et al., 2004). Taken together, these studies imply that changes in motor cortex representations are specific for the trained skill and confined to the cortical area involved in the movement. Understanding the mechanisms that mediate such plastic changes is fundamental in order to exploit the brain’s capacity for learning induced reorganization.

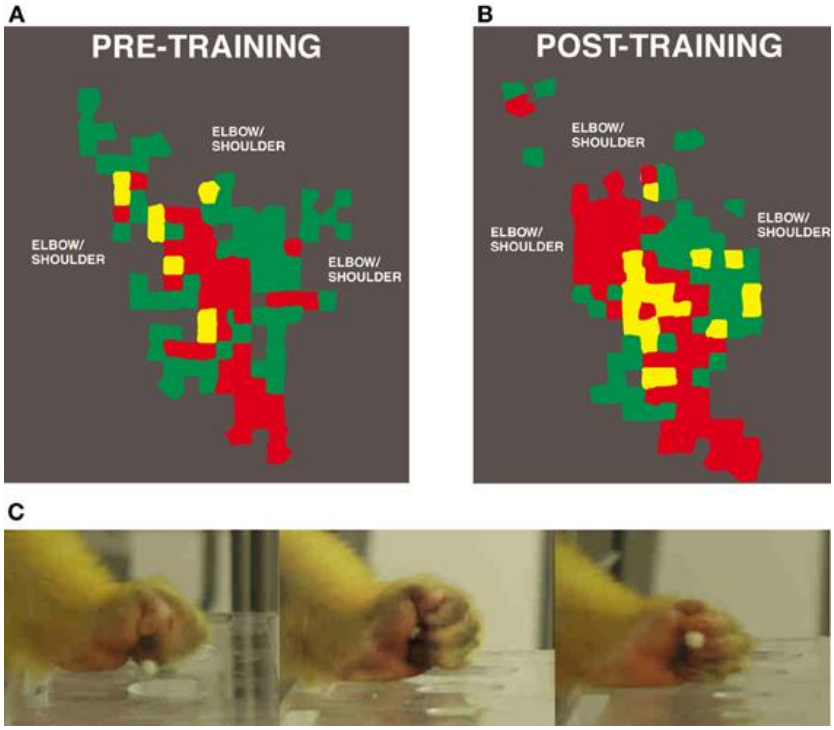

Figure 1.5 | Representational changes in motor maps with skill training. *Motor maps derived before (**A**) and after (**B**) digit skill training show a clear expansion in representational areas of the digit (red) in squirrel monkeys trained on a small well food pellet retrieval task requiring manipulation of 1-2 digits (**C**). Figure taken (Nudo, 2013), with permission from Frontiers.*

1.2.1.1 Mechanisms underlying motor learning-related plasticity

The learning-related reorganization of motor maps in M1 depends on synaptic changes in cortical circuitry such as synaptogenesis and alterations in synaptic strength ((Rioult-Pedotti et al., 1998; Wang et al., 2011; Xu et al., 2009), for review see (Sanes and Donoghue, 2000)). Besides structural changes, alterations in synaptic efficacy of M1 neurons contribute to learning-related reorganization. Consistent with the increase in synapse number, cortical slice preparations obtained from rats trained on a prehension task for 5 days demonstrated long-lasting increases in synaptic strength in layer II-III of rat M1 contralateral to the trained paw (Rioult-Pedotti et al., 2000, 1998). This enhancement in synaptic efficacy was linked to long-term potentiation (*LTP*) and long-term depression (*LTD*)-like mechanisms. LTP and LTD reflect rapid and sustained alterations in synaptic efficacy in response to simultaneous depolarisation of presynaptic and postsynaptic neurons (for review see (Bliss and Lomo, 1973)), obeying Hebbian principles (Hebb's learning rule, "neurons that

fire together, wire together", (Hebb, 1949)). Interestingly, learning-induced LTP is associated with temporary occlusion of the ability to induce LTP in the trained hemisphere (but not in the untrained hemisphere) which is thought to be mediated by the saturation of synaptic modification (Rioult-Pedotti et al., 2007, 2000, 1998). Similar results were obtained in an *in vivo* animal model introduced by Monfils and colleagues (Monfils and Teskey, 2004).

Corroborative evidence that motor skill learning is associated with LTP-like plasticity has been obtained in humans using non-invasive brain stimulation techniques (Cantarero et al., 2013; Rosenkranz et al., 2007; Stefan et al., 2006; Ziemann et al., 2004). These studies provide direct evidence for synaptic modifications in M1 circuitry accompanying acquisition of a new motor skill through mechanisms of motor cortical LTP, and imply that M1 is a dynamic substrate for motor learning (Sanes and Donoghue, 2000).

At the molecular level, substantial evidence supports the idea that the modulation of gamma-aminobutyric acid (*GABA*), the major inhibitory neurotransmitter in the adult brain, is necessary for synaptic changes in M1 associated with motor learning (Clarkson et al., 2010; Hess et al., 1996; Sanes and Donoghue, 2000; Trepel and Racine, 2000). In particular, a decrease in GABAergic inhibitory activity is essential for LTP-like plasticity to occur within M1. For example, focal application of the GABA antagonist bicuculline facilitates LTP-like activity (Castro-Alamancos et al., 1995) and unmasks existing horizontal connections in M1 in animal models (Jacobs and Donoghue, 1991). While a reduction in GABAergic inhibition facilitates the ability to induce LTP-like plasticity, preventing a decrease in GABA prohibits LTP-like plasticity (Castro-Alamancos et al., 1995; Trepel and Racine, 2000), thereby highlighting the importance of the balance between cortical excitatory and inhibitory processes within M1 circuits for motor learning-related plasticity.

Evidence implying that changes in the balance between excitation and inhibition determine motor cortex plasticity in humans comes from pharmacological elevation of GABA levels with lorazepam which results in suppression of use-dependent plasticity in motor cortex (Buetefisch et al., 2000; Pleger et al., 2003). In addition, magnetic resonance spectroscopy (MRS) studies demonstrated a reduction in M1 GABA concentration during short-term learning of a visuo-motor

tracking task, with the decrease in GABA being specific to motor learning and not evident in response to a task without a learning component (Floyer-Lea et al., 2006). Consistent with this role of GABA, individual differences in the responsiveness of the GABA system have recently been linked to the degree to which subjects learnt on a motor sequence task (Stagg et al., 2011a). Specifically, subjects who showed greater learning of the task also showed a greater decrease in their GABA levels in response to M1 stimulation, suggesting that the intrinsic ability to decrease GABA within the cortex is important for the early phase of motor learning and might, at least partly, explain individual differences in the ability to learn new motor skills.

In summary, these findings strongly support the hypothesis that *modulations of GABAergic inhibition* are essential for the induction of motor cortical plasticity observed with motor learning and, therefore represent targets for promoting the capacity for motor learning in the intact brain, and importantly in patients with motor impairments due to brain damage.

1.2.1.2 Non-invasive brain stimulation can facilitate motor learning

As discussed previously (see section 1.1.3), non-invasive brain stimulation methods have been used to explore the functional role of M1 during initial motor learning and consolidation (Muellbacher et al., 2002; Robertson et al., 2005). In addition, cortical excitability and LTP-like plasticity can be modulated using NIBS techniques and thus, may be utilized in order to promote motor skill acquisition and subsequent retention. If the modulation of cortical GABAergic activity is necessary for plasticity and human motor learning to occur, NIBS protocols should modulate learning.

Transcranial direct current stimulation (tDCS) allows the transient modulation of cortical excitability in a polarity-specific manner. Anodal tDCS delivered over M1 has been shown to decrease GABA levels (Stagg et al., 2011a, 2009), thus leading to an increase in cortical excitability and improved performance on a variety of motor learning tasks (Antal et al., 2004; Nitsche et al., 2003; Reis et al., 2009; Stagg et al., 2011a; Tecchio et al., 2010; Vines et al., 2006). In contrast, cathodal tDCS appears to have no effect on learning (Nitsche et al., 2003; Reis et al., 2009). However, the timing of the application of tDCS relative to motor

learning has a differential effect since it exhibits a facilitatory effect only when applied during the motor task. If applied prior to training on a motor task, learning can be unchanged (Kuo et al., 2008) or actually be slowed (Stagg et al., 2011a).

While these studies only investigated the effect of tDCS within a single session, a study by Reis and colleagues demonstrated that anodal tDCS over 5 consecutive days of training on a sequential visual isometric pinch task (SVIPT) resulted in greater motor skill acquisition due to selective enhancement of consolidation (Reis et al., 2009). In addition, enhanced motor skill performance was observed even at 3 months after the end of training (**Figure 1.6**), which may have important clinical implications for long-term functional improvements following rehabilitation. Overall, there is accumulating evidence that tDCS is effective in modulating cortical excitability and therefore, may promote plastic changes associated with motor learning in the healthy brain. The fact that cortical excitatory and inhibitory processes that underlie neuroplasticity are amenable to NIBS highlights that these processes are exciting targets that can promote motor skill acquisition and retention and, in the context of pathology, could promote functional outcomes after stroke, as will be discussed later in this thesis (see section 1.3.4.2).

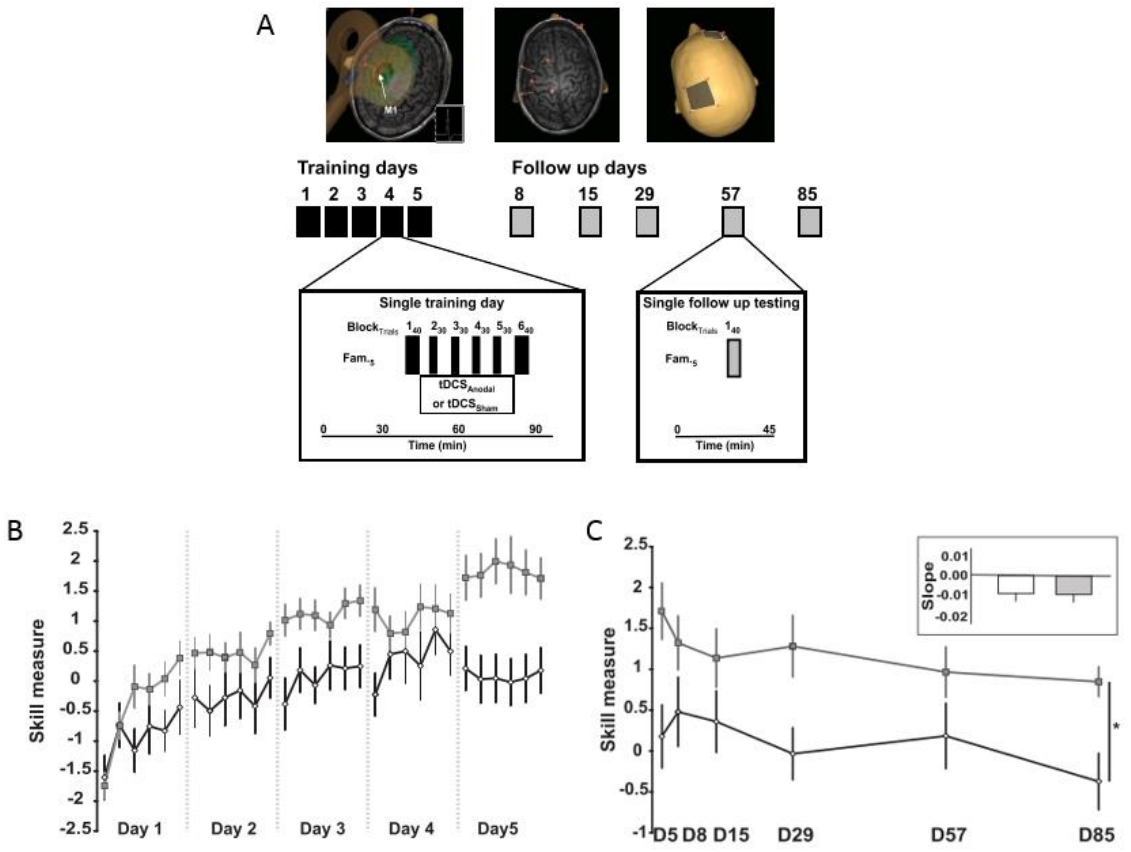

Figure 1.6 | Effect of tDCS on extended time course of motor skill learning. ***A****, The cortical target for tDCS over left M1 was determined using TMS. Subjects trained over 5 consecutive days on the SVIPT, with 20 min of anodal or sham tDCS applied over M1. Retention of skill was tested at 5 follow-up sessions (day 8, day 15, day 29, day 57, and day 85).* ***B****, Learning curves for the sham (white diamond) and anodal tDCS (grey square) groups. While both groups started with comparable skills at the beginning of day 1, the anodal tDCS group showed greater skill acquisition over the course of training than the sham group.* ***C****, Skill remained superior with anodal tDCS (grey square) compared to sham (white diamond) at all time points over a 3-month follow-up period. Figure adapted (Reis et al., 2009), with permission from National Academy of Sciences.*

1.3 Recovery from stroke through plasticity and motor learning

The consequences of *stroke* are often devastating, with the majority of stroke survivors suffering from persistent motor deficits. Stroke recovery is a complex process. A substantial amount of work in animals has been undertaken to elucidate the molecular and cellular events that underlie the profound structural and functional reorganization that occurs during the first weeks and months after focal brain injury (for review see e.g. (Cramer, 2008; Krakauer et al., 2012;

Murphy and Corbett, 2009)). Evidence from these studies suggest a time-limited window of heightened neural plasticity early post-stroke during which most recovery from impairment occurs due to *spontaneous biological recovery* and increased responsiveness to motor training. The presence of a critical period of plasticity thus advocates for the delivery of behavioural training early after stroke, but many stroke patients nevertheless continue to improve in the chronic phase. Post-stroke recovery and rehabilitation rely on mechanisms of learning and neural plasticity (Krakauer, 2006) and thus, understanding the underlying neural processes enabling both, are of great interest for optimizing the timing, intensity and amount of post-stroke rehabilitation in order to maximise patient outcomes (Kitago and Krakauer, 2013; Krakauer, 2006).

1.3.1 The burden of stroke

Stroke is a major *global health problem*, being the second most common cause of death and the leading cause of long-term physical disability worldwide (**Figure 1.7**) (Feigin, 2016; Feigin et al., 2014; World Health Organization, 2010). Although rates of stroke mortality are declining worldwide, a growing number of people will have to cope with the consequences of stroke. Because of this and demographic changes (i.e. ageing of the population and health transitions in developing countries), the global socio-economic burden of stroke is likely to grow in the future, with a predicted rise in stroke survivors from 25 million in 2013 to 70 million by 2030 (Feigin, 2016; Feigin et al., 2014). The majority of strokes are ischaemic in origin and result in sensorimotor impairments. Cognitive impairments are evident as well in patients with stroke. Loss of function is due to death of neurons in the infarcted tissue and cell dysfunction in the surrounding areas. Recovery from stroke is often incomplete, with ~80% of stroke survivors experiencing motor impairments on one side of the body, which leave them incapable of performing daily activities and thus, dependent on others for their care (Langhorne et al., 2009). In particular, recovery of upper limb function is unacceptably poor and a major contributor to reduced quality of life (Kwakkel et al., 2003; Nakayama et al., 1994; Raghavan, 2015). Thus, more effective stroke rehabilitation to maximise recovery and long-term outcomes is an important clinical and scientific goal.

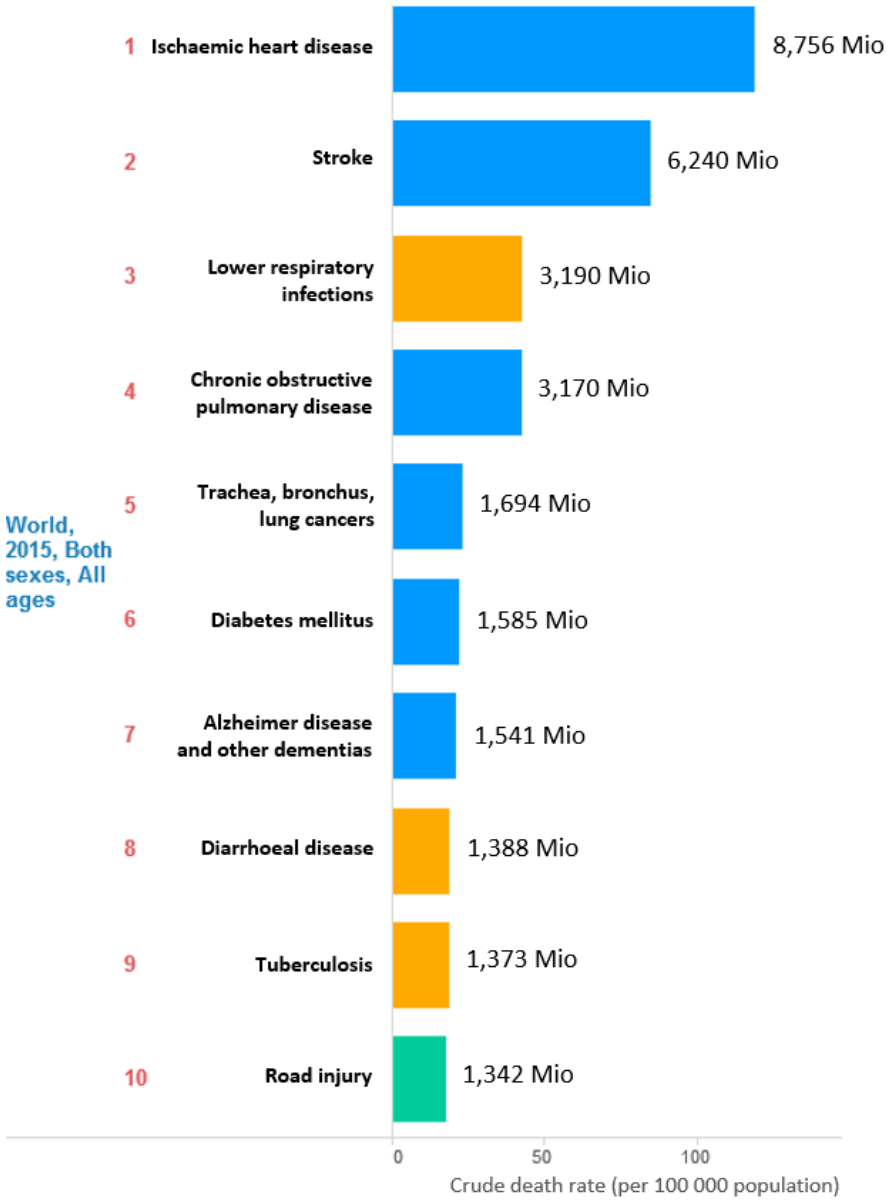

Figure 1.7 | The top 10 causes of death world-wide in 2015.
Stroke is the second most common cause of death after heart diseases, accounting for a combined 15 million deaths in 2015. Cause group: yellow: communicable, maternal, perinatal, and nutritional conditions; blue: non-communicable diseases; green: injuries. Figure taken from (World Health Organization, 2016).

1.3.2 Individual differences in motor recovery after stroke

Motor recovery after stroke, the improvement in movement ability over time, is complex and variable across patients, making accurate *predictions* of motor recovery and treatment response difficult (Prabhakaran et al., 2015; Stinear, 2010). Of note, improvement in movement ability after stroke can be achieved

through either true *recovery* or *compensation*. The first refers to the restitution of the same motor patterns as before injury, while the latter denotes the performance of a movement using alternative motor patterns compared to the pre-morbid state (Levin et al., 2009). For example, a patient with hand weakness can reacquire the ability to use a touchpad through regaining normal movement patterns of the affected hand, through use of alternative muscles of the affected hand, or through learning to use the unaffected hand. Despite differences in the underlying neuronal mechanisms, they both require learning (Kitago and Krakauer, 2013). In this thesis, the term recovery is used without a formal distinction between the mechanisms of true recovery and compensation; however, it is important to note that the motor learning task employed here did not allow for compensation-related improvements.

A commonly cited factor influencing long-term functional recovery is the initial degree of motor impairment, which is quantified by the *proportional recovery rule* (Kwakkel et al., 2003; Prabhakaran et al., 2015). In general, patients with mild-to-moderate deficits are predicted to regain 70 % of their initially lost function by 3 months after stroke, but this proportional relationship does not apply for patients who present with high initial severity. Within this patient subgroup, roughly 50 % of patients have good (proportional) recovery, whereas no substantial recovery is seen in the other half (**Figure 1.8**). The reasons for this clinical phenomenon are unclear, but understanding the underlying neurophysiological processes and identifying factors that are important for recovery would be instrumental in providing novel therapeutic targets for improving post-stroke recovery.

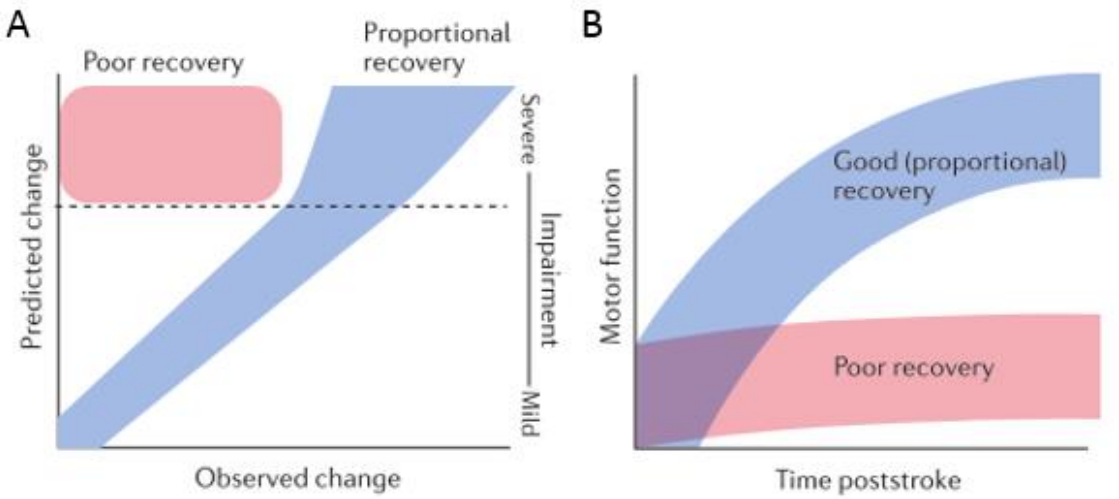

Figure 1.8 | Proportional recovery of motor function after stroke.
A*, Predicted versus observed change in motor impairment at 3 months post-stroke, with patients in the blue area demonstrating proprtional recovery as predicted while recovery of patients in the red area is poor and unpredictable. Patients above dotted line initially show severe levels of impairment. Roughly 50% of patients in this subgroup display good (proportional) or poor recover.* ***B****, Recovery curves of initially severely affected patients (shown in part a above the dotted line) who either recover as predicted (blue) or poorer (red). Figure taken from (Ward, 2017), with permission from Macmillan Publishers Ltd.*

1.3.3 Spontaneous biological recovery: a window of opportunity

Most of the behavioural recovery seen in animals and humans occurs during the first weeks to months after a stroke, during the period of *spontaneous biological recovery*. This time is characterised by rapid, generalized improvement in impairment that is in contrast to the modest functional improvements observed in the chronic phase (Zeiler and Krakauer, 2013). Further, heightened responsiveness to motor training is apparent during this early post-stroke phase, offering a window of opportunity to promote recovery and restore function after stroke (Cramer, 2008; Krakauer et al., 2012; Murphy and Corbett, 2009; Ward, 2017; Zeiler and Krakauer, 2013).

Early evidence of this critical period during which the brain exhibits heightened receptiveness to rehabilitative experience was provided by Biernaskie and colleagues. In their experiment, rats that were given motor training of the affected forelimb early, at 5–14 days post-stroke, displayed significant improvement, while rats given delayed treatment (starting at 30 days post-stroke) exhibited little

recovery (Biernaskie et al., 2004). Although the debate about the optimal timing of rehabilitation continues (Kozlowski et al., 1996; Risedal et al., 1999), these results, together with recent clinical findings (Horn et al., 2005; Salter et al., 2006), lend strong support to the existence of an early post-stroke phase of heightened brain plasticity which interacts with types of behavioural training, and advocates that early initiation of rehabilitation is more effective.

Paradoxically, Zeiler and colleagues demonstrated that experimental induction of a second stroke can reinitiate a critical post-stroke period during which training can support dramatic motor recovery (**Figure 1.9**) (Zeiler et al., 2016). This finding highlights that focal brain damage triggers a series of biological events that create a plastic milieu, which combined with training, enhances recovery. Understanding the biological basis of early post-stroke recovery and its unique interaction with behavioural training is critical as opportunities to augment or prolong spontaneous biological recovery could radically improve recovery.

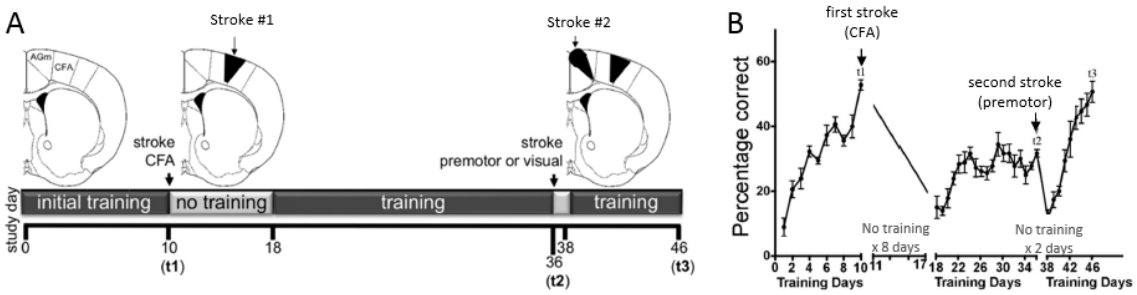

Figure 1.9 | Reinitiation of critical period after induction of second stroke. ***A****, Schematic of experimental timeline.* ***B****, Mice were trained on a prehension task to an asymptotic performance after which a stroke was induced (t1). Intensive training for 19 days was initiated after a 7-day post-stroke delay. A second stroke was then induced in the premotor cortex (t2) and training commenced 2 days later. Notably, recovery was incomplete when training was initiated 7 days after the first stroke. However, training commencing 2 days after the second stroke mediated full recovery from the previous stroke. Figure adapted from (Zeiler et al., 2016), with permission from Sage Publications.*

Based on work in rodents, Murphy and Corbett suggested a simple model for recovery of motor function, with two key elements necessary for the occurrence of spontaneous biological recovery (Murphy and Corbett, 2009). Firstly, recovery requires preserved neural circuitry that routes both sensory and motor signals

during behavioural interventions and thus, allows post-stroke remapping of sensorimotor functions from damaged brain areas to intact tissue. The second part of the model refers to an increase in the potential for plasticity early post-stroke. In the work presented here, I will focus on the second part of the model, the brain's intrinsic capacity to react as a highly dynamic system that changes in response to injury, as discussed next, and experience (see section 1.2).

1.3.4 Plasticity during recovery from stroke

An extensive body of work in animal models of stroke and neuroimaging of humans have provided insight into the molecular and physiological events underlying post-stroke motor recovery. Gradual reorganization of the motor system and recovery of movement after stroke begins early and involves brain regions distant to the damaged site. In animal models of stroke, Nudo and Milliken demonstrated profound reorganization in the damaged hemisphere 3-4 months after focal lesioning of M1 in monkeys, which co-occurred with spontaneous recovery of animals, without any specific training (Nudo and Milliken, 1996). The cortical changes included loss of the areal extend of digit representation adjacent to the insult, and increased adjacent proximal (elbow and shoulder) representations. However, in animals that underwent rehabilitative training with the impaired limb, the shrinkage of the hand representation could be prevented (Nudo et al., 1996b), supporting the functional significance of post-stroke training for cortical reorganization. Again, there is evidence that early training is more effective and that delaying training does not prevent shrinkage of motor maps within the affected M1 (Barbay et al., 2009). Of note, the training consisted of restricting the use of the unimpaired hand, thereby enforcing the use of the affected hand, a therapy commonly known as constraint-induced movement therapy (CIMT) in humans (Wolf et al., 2006).

Over the last 15 years, numerous studies in humans have demonstrated similar reorganisation of motor maps, with shifts in activity to more lateral and posterior regions, which correlates with clinical improvement (Jaillard et al., 2005; Rossini et al., 1998; Traversa et al., 1997a). Using TMS, it has been demonstrated that motor cortex excitability is reduced near the site of stroke injury, and the cortical representation of the affected muscles is decreased (Traversa et al., 1997b).

Together, the above results illustrate that *reorganization* in M1 networks of the affected cortex and beyond occurs in relation to recovery after stroke, however, it remains to be determined whether these new motor maps produce and control movements in the same way as did the damaged region.

Apart from changes in the ipsilesional (affected) hemisphere, increased movement-related activation of the contralesional (unaffected) hemisphere has been shown in human fMRI and PET studies, highlighting an initial pattern of over-activation of motor cortical networks. Over time, this activity normalizes into a more lateralised and 'physiological' activity pattern as the patient recovers motor function (Johansen-Berg, 2002a; Marshall et al., 2000a; Ward et al., 2003a, 2003b). Persistence of contralesional activity in M1 (Carey et al., 2006; Johansen-Berg, 2002b) and secondary motor areas (Ward et al., 2003a) is associated with poor recovery. However, the functional role of more widespread neural activation within the motor cortex network after stroke, being either adaptive or maladaptive, and its contribution to recovery remains controversial (Di Pino et al., 2014; Fridman et al., 2004; Lotze et al., 2006; Murase et al., 2004; Ward and Cohen, 2004).

1.3.4.1 Mechanisms underlying plasticity during stroke recovery

Although some of the spontaneous biological recovery observed after stroke is likely due to resolution of cerebral oedema, resolution of inflammation, and normalization of metabolic disturbances in the acute and subacute phase (Cramer, 2008; Guadagno et al., 2006; Heiss et al., 1998), structural and functional reorganization over the weeks and months following the stroke play a major role. The structural changes that have been observed in animal models of stroke include neuronal growth, synaptogenesis, and the proliferation of dendritic spines in the area adjacent to the lesion, the peri-infarct cortex (PIC), and surrounding areas (for review see e.g. (Carmichael, 2012; Cramer and Chopp, 2000; Cramer, 2008; Murphy and Corbett, 2009)).

In addition to these structural changes, stroke triggers alterations in neuronal excitability through GABA and glutamate signalling (Carmichael, 2012). Immediately after stroke, excitotoxicity mediated by the excitatory

neurotransmitter glutamate contributes to cell death, whereas inhibitory GABAergic signalling can counteract this neurotoxicity (Lai et al., 2014). Thus, this phase is characterised by elevated cortical excitability with deleterious effects. However, the beneficial and detrimental effects of GABA and glutamate signalling seem to reverse after the hyperacute stroke period (up to 3 days post-stroke) (Clarkson et al., 2010). Specifically, changes to the balance between cortical excitatory and inhibitory processes are crucial for the potential for plasticity and may, in the context of stroke, reopen critical periods of heightened plasticity in the adult brain similar to that seen during normal development (Bavelier et al., 2010; Benali et al., 2008). Consequently, interest in assessing cortical excitatory and inhibitory mechanisms as a biomarker of the potential for post-stroke plasticity is growing.

In support of this rational, *in-vitro* and animal work has suggested that reduced GABAergic and increased glutamatergic signalling (Que et al., 1999) leads to expanded and less-specific receptive fields (Alia et al., 2016; Winship and Murphy, 2008), enhanced LTP (Hagemann et al., 1998), facilitation of downstream changes in neuronal structure (Chen et al., 2011), and re-mapping of motor representations to intact cortical areas (Takatsuru et al., 2009). Restitution of neuronal activity induced by stroke-related hyperexcitability has been interpreted as a homeostatic response to injury (Murphy and Corbett, 2009). For example, increased excitatory glutamatergic signalling through AMPA receptors with downstream induction of brain-derived neurotrophic factors (BDNF) is associated with improved recovery in mouse models of stroke (Clarkson et al., 2011). In addition, reduction in GABAergic inhibition is evident in the first few weeks after stroke due to downregulation of GABA receptors (Que et al., 1999) and reduction in inhibitory interneurons (Zeiler et al., 2013). These findings corroborate the idea that homeostatic restitution of neuronal activity (Murphy and Corbett, 2009) is mediated by both increased glutamatergic and reduced GABAergic signalling.

In contrast, recent work suggested that the dominant response to stroke may in fact be excessive peri-lesional inhibition mediated through extrasynaptic GABAergic signalling, which impedes functional plasticity. Interestingly, the administration of an extrasynaptic GABA-receptor inverse agonist (α5IA)

reversed this effect and lead to improved motor recovery (Clarkson et al., 2010; Lake et al., 2015). These findings highlight that the plasticity of the brain that occurs after stroke is important as it may facilitate or hinder recovery of function.

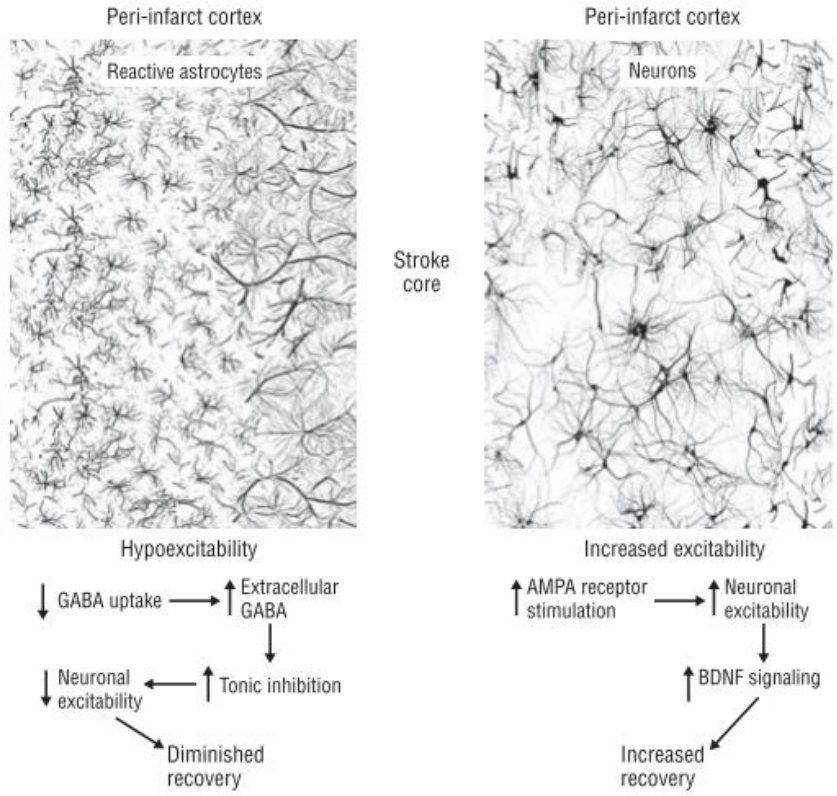

Figure 1.10 | Cortical excitability changes following stroke.
Post-stroke hypoexcitability and hyperexcitability is observed in peri-infarct cortex. Figure taken from (Carmichael, 2012).

In humans, corroborative evidence that GABAergic signalling is one of the key modulators of plasticity has also been obtained using TMS (Swayne et al., 2008), MRS (Blicher et al., 2015), and PET (Kim et al., 2014). These studies mostly report a decrease in inhibitory activity after stroke.

The abundant evidence from animal studies and recent neuroimaging studies in humans clearly suggest that, beyond the hyperacute stroke period, alterations in cortical inhibitory and excitatory mechanisms are important for the potential for plasticity and therefore, represent novel and exciting therapeutic targets for promoting recovery post-stroke. In particular, inhibitory GABAergic and excitatory

glutamatergic signalling is amenable to pharmacological manipulations, thus serving as viable clinical targets for plasticity enhancement.

1.3.4.2 Promoting recovery after stroke in humans

Among the therapeutic strategies under study to enhance functional outcome after stroke in humans are *pharmacological* and *NIBS* modulations, targeting alterations in cortical excitatory and inhibitory processes that underlie post-stroke changes in plasticity. Often, these approaches are used as adjuncts to behavioural training. Studies employing NIBS in combination with motor training demonstrated positive effects on motor recovery (for review see (Hsu et al., 2012; Kang et al., 2016)). For example, applying rTMS to enhance ipsilesional M1 excitability during training on a finger sequence tapping task with the affected hand improved motor learning performance in chronic stroke patients (Kim et al., 2006). In addition, Zimerman and colleagues showed that cathodal tDCS over the contralesional M1 enhanced motor skill learning and overnight retention (Zimerman et al., 2012). However, broad use of NIBS in clinical settings is currently hindered due to inconsistencies in results, which are likely due to methodological differences, and a lack of understanding of the mechanisms of action (Berker et al., 2013; Bonaiuto and Bestmann, 2015).

When it comes to pharmacological manipulations, as of yet, direct clinical application of the GABAergic and glutamatergic manipulations performed in animal models of stroke have not been conducted in humans. Over recent years, there have been increasing reports highlighting the dose-dependent influence of the hypnotic imidazopyridine zolpidem on cortical inhibition mediated by α5-subunit-containing GABA receptors (Prokic et al., 2015). Specifically, low doses of zolpidem augment inhibition, whereas high doses reduce it. *Zolpidem* has been shown to improve functional recovery in animal models of stroke (Hiu et al., 2016), and to improve language, cognitive and motor abilities in single stroke patients (Hall et al., 2010b). However, given the uncertainty about how zolpidem works, and the limited generalizability from single patient data, further research into the mechanism of recovery is needed.

Building on several smaller studies (for review see (Mead et al., 2013)), the *fluoxetine* for motor recovery after stroke (FLAME) study (Chollet et al., 2011) has

generated interest in serotonin-selective reuptake inhibitors (SSRI) for promoting motor recovery. In this placebo-controlled trial, patients within 5–10 days post-stroke were started on a 3-month oral fluoxetine intervention, which lead to improved upper limb recovery (**Figure 1.11**). This study was the first to show that physiotherapy with early fluoxetine administration to moderate-to-severely impaired stroke patients enhances motor recovery after 3 months, although the long-term effects remain unknown. In a mouse model, fluoxetine administration 24 hours after stroke was able to prolong the critical period of post-stoke plasticity, thus maintaining maximal levels of responsiveness to motor training (Ng et al., 2015). This beneficial effect was mediated through the reduction of inhibitory interneuron expression in the intact cortex.

Clearly, plasticity-modifying interventions are a promising treatment strategy with great potential for improving outcomes after stoke. However, clinical trials will only be successful if the biological targets are known and measurable in humans, thus allowing for a mechanistic approach.

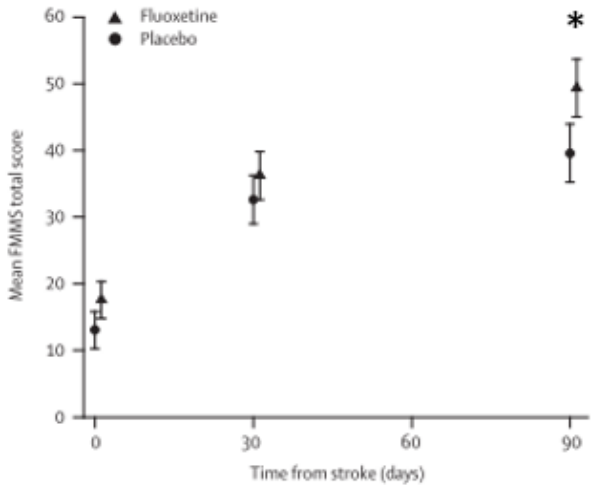

Figure 1.11 | Fluoxetine improves upper limb recovery.
Patients were randomly assigned to fluoxetine (20 mg daily) or placebo for 3 months starting 5–10 days after stroke. All patients had physiotherapy. Upper limb function was evaluated using the Fugl-Meyer motor scale (FMMS). Figure taken from (Chollet et al., 2011), with permission from Elsevier.

1.3.5 Motor learning after stroke

Post-stroke recovery and rehabilitation depend on mechanisms of learning and brain plasticity (Krakauer, 2006). As outlined above, stroke results in major neuroplastic changes at the structural and functional level at the primary site of insult and connected regions. Therefore, it may be expected that learning in individuals with stroke would be altered. Only few studies have examined the motor skill learning capability of individuals after stroke and most have focused on learning with the upper extremities (i.e. (L. a Boyd and Winstein, 2004; Boyd and Winstein, 2006, 2001; Dovern et al., 2016; Hardwick et al., 2017; Orrell et al., 2007; Platz et al., 1994; Pohl et al., 2006; Vidoni and Boyd, 2009; Winstein et al., 1999)). Given the heterogeneity of stroke and the greater movement variability in patients with stroke, it may be difficult to detect specific learning effects in this population. In fact, depending on the lesion location and/or extent, different motor learning aspects could be impaired.

Nonetheless, these few studies have claimed preserved motor skill learning in stroke patients. Winstein and colleagues demonstrated that patients with middle cerebral artery stroke retain the ability to learn with their contralesional (unaffected) arm on an elbow extension-flexion reversal task, however they exhibited lower accuracy and greater variability in their movements compared to healthy controls (Winstein et al., 1999). Using the unaffected arm has the advantage of dissociating an individual's motor learning ability from his/her motor deficits but does not allow the exploration of learning deficits specific for the affected arm.

In addition, Boyd and colleagues revealed implicit motor sequence learning on the SRTT and the continuous tracking task in patients with sensorimotor (Boyd and Winstein, 2001) and basal ganglia stroke (L. A. Boyd and Winstein, 2004), respectively. Interestingly, explicit information interfered with implicit learning regardless of the type of task (continuous versus discrete task) (Boyd and Winstein, 2006).

A more recent study further highlighted that stroke patients with a wide range of impairment were able to learn on a serial voluntary isometric elbow force task using their ipsilesional (affected) arm, however, their overall level of performance achieved through training was still affected by their motor impairment (Hardwick

et al., 2017). Since these findings were derived from patients in the chronic phase of stroke, it is debatable whether well-recovered patients have achieved their level of performance through preserved motor learning or if preserved motor learning is just an epiphenomenon of a well-recovered patient. In addition, the variety of motor tasks employed to assess motor learning deficits in patients, relying on different learning processes and associated with various functional and anatomical brain structures (Kitago and Krakauer, 2013; Krakauer and Mazzoni, 2011b), makes it difficult to synthesize findings across studies. Nonetheless, the above-discussed results provide strong support for *preserved motor learning* capability of individuals' post-stroke, despite abnormal patterns of neural activation and persistent motor impairments that are commonly observed following stroke.

1.4 Bridging the gap: biomarkers of plasticity

As outlined above, mechanisms of learning-related and post-stroke plasticity appear to be modulated by the balance between excitatory glutamatergic and inhibitory GABAergic processes in the brain as demonstrated in animal models. Consequently, these processes represent exciting and novel therapeutic targets. However, animal models have critical limitations and thus, *biomarkers* of cortical excitability in humans are needed to bridge the gap between cellular and behavioural accounts of cortical function and plasticity in both healthy and diseased states. A biomarker is an indicator of disease state that reflects underlying molecular and/or cellular events that are difficult to measure directly in humans (Aronson and Ferner, 2017). Without a valid biomarker that links observed behaviour to underlying biological processes, demonstrating efficacy of therapeutic therapies that aim to promote plasticity is difficult. In the clinical context, an appropriate biomarker would thus improve decision-making about when and for how long plasticity-modifying interventions such as fluoxetine or NIBS should be administered, and which individuals are most likely to respond.

Although behavioural, clinical and demographic measures contribute to predictive models of response to treatment and long-term outcome after stroke, they incompletely characterize inter-individual differences and as such, neuroimaging measures might provide greater insight into the capacity for reorganization (Burke

and Cramer, 2014; Ward, 2017). Several tools have been utilized with the aim of identifying suitable biomarkers in humans (e.g. (Lindenberg et al., 2012; Riley et al., 2011; Saunders et al., 1995; Ward et al., 2003b; Wu et al., 2015)), however, most of these have considerable limitations for studying stroke patients. For example, BOLD fMRI is an indirect measure of neural activity and depends on neurovascular coupling (coupling between neuronal activity, blood flow, and oxygen consumption), which might be altered after stroke (Blicher et al., 2012). The non-invasive method of TMS directly assess cortical excitability and has been extensively used to investigate motor physiology after stroke. However, its reliance on the presence of evoked responses in affected muscles (Motor Evoked Potential, MEP), rather than measurements of spontaneous or task-related brain activity limits, its utility for studying patients with motor paresis (Currà et al., 2002). MRS can measure GABA levels directly, but it is currently unclear how MRS-GABA concentration relates to the pool of GABA available for measurement (i.e. intracellular, extracellular, or synaptic GABA) (Dyke et al., 2017; Stagg, 2014; Stagg et al., 2011b).

Alternative methods are *electroencephalography* (EEG) (Berger, 1929) and magnetoencephalography (MEG) (Cohen, 1972), which directly record the electrical or magnetic field generated by neuronal populations on the scalp surface with millisecond time resolution. The EEG and MEG are very close methodologies, since they both measure the summation of currents of postsynaptic fields from cortical pyramidal cells. Although MEG provides a higher spatial resolution, EEG is a more cost-effective and accessible tool for exploring neuronal mechanisms underlying cognitive and motor processes in clinical populations (Lopes da Silva, 2013). Based on this, the EEG was chosen as the imaging methodology in this thesis, providing surrogate measures of neuronal function. For more details about the principles of EEG acquisition and analysis, please refer to **Chapter 2**.

1.5 Neuronal oscillations as biomarkers

Neuronal oscillations, which are ubiquitous in the brain, have been accepted to be an integral part of neural communication and information processing (Buzsaki, 2006), and their underlying physiological mechanisms are fairly well understood

(Buzsáki et al., 2012). The concept of *neuronal oscillations* is usually credited to Hans Berger, who was the first physiologist to describe the rhythmic fluctuations in the excitability of neurons or populations of neurons in the human brain (Berger, 1929). Oscillatory activity in groups of neurons, as measured by EEG and MEG, generally arises from the feedback interactions between inhibitory interneurons and excitatory pyramidal cells. Simplistically, when a population of pyramidal cells becomes active, they continue to excite each other, resulting in increasing excitation. The inhibitory interneurons within this population also become active and increasingly inhibit the excitatory cells. Eventually the activity of the inhibitory interneurons decreases, allowing pyramidal cells to increase their excitatory activity again. This alternating balance between states of excitation and inhibition is the basic underlying mechanism of a neuronal oscillation (Buzsaki, 2006). Macroscopic EEG and MEG signals reflect a conglomerate of oscillations at different frequencies, which are categorized into characteristic frequency bands, comprising the delta band (δ, 0.5-3.5 Hz), theta band (θ, 4-7 Hz), alpha band (α, 8-12 Hz), beta band (β, 15-30 Hz) and gamma band (γ, >30 Hz), with somewhat arbitrary and variable boundaries. Although these classical frequency bands are still being used, nowadays, functional frequency bands tend to be defined in a data-driven approach (Donner and Siegel, 2011).

Over the last years, a massive upsurge in the interest in neuronal oscillations has demonstrated their task- and state-dependent modulation in a number of cognitive, perceptual, and motor processes (see e.g. (Buzsaki, 2006)). Apart from their well-documented involvement in physiological processes, abnormalities in neuronal oscillations have been reported in various pathophysiological conditions, such as schizophrenia (Uhlhaas and Singer, 2006), Parkinson's disease (Brown and Marsden, 1999; Heida et al., 2014; Heinrichs-Graham et al., 2014; Little and Brown, 2014) and stroke (Rossiter et al., 2014a; Shiner et al., 2015). Consequently, interest in investigating the mechanisms mediating the generation of cortical activity to further our understanding of normal brain functioning and pathophysiology is rising. The work presented in this thesis focuses on neuronal oscillations in the *beta-band frequency* primarily originating from sensorimotor cortex, as these are fundamental for motor behaviour and

control (Engel and Fries, 2010; Pfurtscheller et al., 1996; van Wijk et al., 2012), and potentially for motor recovery after stroke (Ward, 2017, 2015).

1.5.1 Beta oscillations in motor control

Traditionally, early studies have interpreted beta-band activity as a sensorimotor-related phenomenon (Baker et al., 1999, 1997; Murthy and Fetz, 1996; Stancak and Pfurtscheller, 1995), but research has also suggested their role in higher cognitive processing (for review see e.g. (Donner and Siegel, 2011; Engel and Fries, 2010)). Thus, interest in beta oscillations has recently undergone a major renaissance.

Beta oscillations are prominent at rest and characteristically modulated with movement in large parts of the sensorimotor cortex network, with two well-described patterns of movement-related oscillatory dynamics. In particular, prior to and during movement, beta power is suppressed (*Movement-Related Beta Desynchronization*, MRBD) (Pfurtscheller and Berghold, 1989; Salmelin and Hari, 1994; Stancak and Pfurtscheller, 1995). This suppression of beta activity is sustained as long as the effector is moving (Erbil and Ungan, 2007; Stancak and Pfurtscheller, 1995; Wheaton et al., 2009) or as changes in muscle contraction appear (Omlor et al., 2011). Following movement termination, beta power increases above pre-movement levels approximately 0.5 s post-movement (*Post-Movement Beta Rebound*, PMBR) (Jurkiewicz et al., 2006; Pfurtscheller et al., 1998a; Salmelin and R. Hari, 1994; Stancak and Pfurtscheller, 1995).

These spectral characteristics are classically described as event-related desynchronization (ERD) and synchronization (ERS) (Pfurtscheller and Lopes, 1999), and are somewhat spatially distinct, with MRBD typically observed in both contralateral and ipsilateral sensorimotor cortices during unimanual movements, while PMBR typically shows a contralateral preponderance (Salmelin and Hari, 1994; Stancak and Pfurtscheller, 1995). A rather simplistic view on ERD/ERS phenomena is that MRBD indexes activation of sensorimotor cortex (Pfurtscheller and Lopes, 1999) associated with an increase in corticospinal excitability (Chen et al., 1998), while PMBR is thought to reflect a state of active motor cortical inhibition (Solis-Escalante et al., 2012).

Several movement parameters have been shown to modulate the time course of MRBD and PMBR (for review see (Kilavik et al., 2013; Van Wijk et al., 2012)). Strikingly, the beta rhythm also exhibits suppression and rebound-like dynamics during motor imagery (McFarland et al., 2000; Nakagawa et al., 2011), movement observation (Babiloni et al., 2002), passive movement (Alegre et al., 2002), and tactile stimulation (Gaetz and Cheyne, 2006).

Owing to their prominent occurrence at rest, beta oscillations have been postulated to correspond to an 'idling rhythm' of the motor system (Salmelin and Hari, 1994). This theory has been revised with the current view that beta oscillations are associated with the maintenance of the current sensorimotor state, or the 'status quo', at the expense of new movement (Engel and Fries, 2010; Jenkinson and Brown, 2011). In support, inducing beta synchrony with 20 Hz transcranial alternating-current stimulation was shown to slow volitional movements (Joundi et al., 2012; Pogosyan et al., 2009). This effect was shown to be specific for the beta-band, as entrainment with 5 Hz oscillations did not suppress movement. Similarly, Gilbertson and colleagues demonstrated a slowing of movement when it was initiated during spontaneous burst of beta oscillations in the ongoing resting-state activity (Gilbertson et al., 2005a). Although these findings establish a causal link between beta oscillatory activity and concurrent motor behaviour, their distinct modulation by a variety of functional processes explain why their functional role is still debated (Engel and Fries, 2010; Jenkinson and Brown, 2011; Pfurtscheller et al., 1996).

1.5.2 Generation and modulation of beta oscillations: GABA linkage

Studies in animals and humans suggest that beta oscillations are the summed output of excitatory glutamatergic pyramidal cells temporally aligned by inhibitory GABAergic interneurons (Jensen et al., 2005; Murakami and Okada, 2006; Yamawaki et al., 2008). As such, they are dependent on the balance between excitatory and inhibitory processes within these neuronal circuits (Buzsaki, 2006; Murakami and Okada, 2006; Yamawaki et al., 2008) and may reflect the potential for both local and network plasticity (Traub et al., 2004).

Recent modelling and in vitro work in combination with pharmacology have shown that beta oscillations are generated in deep cortical layer V of sensory and

motor cortex and were robust to various neurotransmitter blockers. Notably, administration of the GABA-A receptor blockers such as bicuculline (Roopun et al., 2006) and pictotoxin (Yamawaki et al., 2008) resulted in abolished beta oscillations (**Figure 1.12**). These findings in animal slices suggest that the cortical networks supporting beta oscillations in M1 critically depend on GABAergic signalling. While this work provides strong evidence for the dependence of beta oscillations on GABAergic mechanisms, it did rely on pharmacologically induced excitatory drive, a condition that may not be reproduced in vivo.

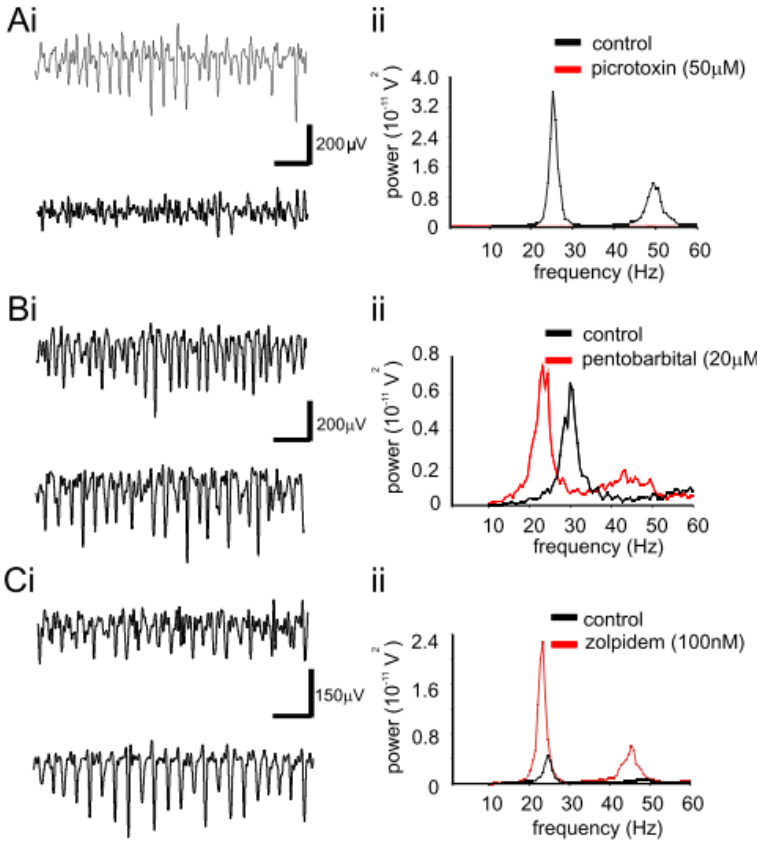

Figure 1.12 | Pharmacologically induced beta oscillations depend on GABA. *Oscillations in the beta-band were elicited in animal slices by co-application of kainic acid (glutamate receptor agonist) and carbachol (muscarinic receptor agonist). Properties of M1 network oscillations were then examined using pharmacological manipulations at GABA receptors. Extracellular voltage recordings and associated power spectra showing the effects of picrotoxine (**A**), pentobarbital (**B**), and zolpidem (**C**). While beta oscillations were abolished by the GABA-A receptor antagonist picrotoxine, pentobarbital and zolpidem modulated beta oscillations, indicating their dependence on GABAergic signalling within M1 networks. Figure taken from (Yamawaki et al., 2008), with permission from Elsevier.*

Pharmacological studies in humans however, have further linked cortical GABA levels to properties of beta oscillations. For example, diazepam (Baker and Baker, 2003a; Hall et al., 2011, 2010a), a GABA agonist (phasic), and tiagabine (Muthukumaraswamy et al., 2013), a GABA reuptake inhibitor (tonic), both enhanced resting beta power and levels of MRBD, whereas PMBR was only increased by tiagabine. Furthermore, administration of benzodiazepine reduced the frequency of beta oscillations concurrent with an increase in beta power (Jensen et al., 2005).

In contrast to the pharmacological results, TMS-EEG studies have linked MRBD to increased sensorimotor cortex excitability which is thought to be mediated by downregulation of GABAergic activity (Aono et al., 2013; Takemi et al., 2013). Specifically, MRBD during motor imagery was associated with increased corticospinal excitability, as indexed by TMS-induced MEPs, which appeared to be mediated by reduced GABAergic activity, as measured by short-interval intracortical inhibition (SICI). These somewhat contradicting results with regard to the relationship between the magnitude of MRBD and levels of GABAergic inhibition are likely due to the different methodological approaches used in these studies.

Using MRS and MEG, Gaetz and colleagues related M1 GABA concentration with PMBR power (Gaetz et al., 2011). Together, there is growing evidence linking beta synchrony and GABAergic inhibition and thus, beta oscillations could serve as biomarkers of net inhibitory and excitatory mechanisms in human cortex.

The potential of beta oscillations as biomarkers of cortical excitatory and inhibitory mechanisms is further affirmed by findings in stroke patients. For example, persistent elevated low-frequency oscillations were associated with poorer recovery after stroke (Laaksonen et al., 2013). Further, a weaker beta rebound in the ipsilesional (affected) hemisphere in response to tactile finger stimulation, reflecting increased motor cortex excitability, was associated with good recovery in patients with stroke (Laaksonen et al., 2012). Finally, in a single stroke patient, pharmacological reduction (using zolpidem) of elevated perilesional theta and beta oscillations led to clinical improvement (Hall et al., 2010b). Since the change in neuronal oscillations matched the clinical improvement, this finding is

particularly interesting as it further highlights the potential of beta oscillations as biomarkers of excitatory and inhibitory processes that can be utilized to demonstrate efficacy of therapeutic therapies.

1.5.3 Alterations in beta oscillations

Cortical beta oscillations are thought to be fundamental for motor behaviour and control, and alterations in these oscillations are a candidate mechanism for movement pathologies. While changes in beta oscillatory activity have been observed in a number of settings, not all of them are representative of a pathological state.

1.5.3.1 Alterations in beta oscillations with ageing and motor learning

Normal development and ageing are characterized by significant alterations in beta oscillatory activity. For example, Rossiter and colleagues showed that ageing was associated with greater resting beta power and stronger MRBD (Rossiter et al., 2014b) and argued, in line with previous animal and pharmaco-MEG studies, that these changes reflect increased inhibitory activity and therefore, potentially reduced potential for plasticity in the elderly. Similarly, during typical development from child to adolescent, the magnitude of MRBD and PMBR increases (Gaetz et al., 2010), suggesting a maturational process of motor cortical inhibition. As such, these measures may be implicated in the processes governing motor learning in children and adults, and help predict recovery of motor function following stoke.

Although, associations between beta oscillations and motor performance suggest a crucial role in brain function, their role in motor learning is not well established. Few studies have reported changes in beta oscillations in the context of motor learning. In these studies, greater MRBD (Boonstra et al., 2007; Houweling et al., 2008; Pollok et al., 2014) and PMBR (Mary et al., 2015) after compared to before training was linked to better performance on unimanual and bimanual motor learning tasks. The authors argued that these changes in beta power might represent neurophysiological markers of plasticity processes taking place during motor learning as discussed in section 1.2. Similarly, changes in beta power at

rest and during movement were reported in healthy controls after training on a reaching task, but such changes were markedly reduced in patients with Parkinson's disease, suggesting abnormal plasticity processes in pathology (Moisello et al., 2015).

Recent studies employing continuous theta burst TMS (cTBS), known to modulate plasticity (Huang et al., 2005) and cortical excitability, have demonstrated concurrent changes in beta oscillations (McAllister et al., 2013; Noh et al., 2012). Interestingly, in the study by McAllister and colleagues, only 50% of participants displayed an inhibitory after-effect following cTBS and a concurrent increase in spontaneous beta power, while non-responders did not display either changes in cortical excitability nor beta oscillations (**Figure 1.13**) (McAllister et al., 2013). This finding is of particular interest as the observed variability may be related to GABAergic processes underlying the presence of beta oscillatory activity and as such, might account for individual differences in response to cTBS that could become clinically significant in the context of pathology.

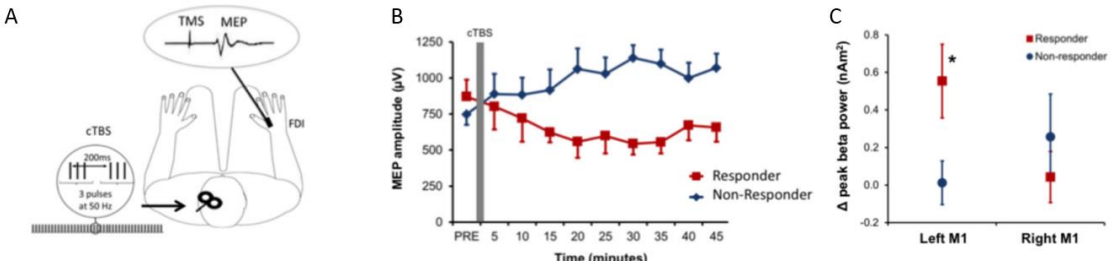

Figure 1.13 | Effect of cTBS on cortical excitability and M1 beta power.
A*, Continuous theta burst stimulation was applied over M1 and cortical excitability was determined from motor-evoked potentials in first dorsal interossei (FDI) muscle.* ***B****, Only 50 % of participants demonstrated inhibitory after-effects following cTBS as evidenced by a decrease of cortical excitability in these responders (red).* ***C****, Spontaneous beta oscillatory activity was concurrently increased in responders while non-responders lacked changes in beta power (calculated as the differences between mean beta power in pre- and post-TBS recordings). Figure adapted from (McAllister et al., 2013).*

1.5.3.2 Alterations in beta oscillations in pathology

In contrast to normal beta oscillations, altered beta activity is a signature of pathology in movement disorders such as Parkinson's disease (PD) (Brown,

2007; Doyle et al., 2005; Heinrichs-Graham et al., 2014; Little and Brown, 2014), cerebral palsy (Kurz et al., 2014), dystonia (Crowell et al., 2012), and stroke (Rossiter et al., 2014a; Shiner et al., 2015). In PD patients, abnormal beta oscillations have been observed in the basal ganglia (Kühn et al., 2004) and motor cortex (Heida et al., 2014; Heinrichs-Graham et al., 2014), and are associated with the loss of voluntary movement, including bradykinesia. Treatments that alleviate motor symptoms, like dopaminergic medication (L-DOPA) (Hall et al., 2014) and deep brain stimulation (DBS) (Kühn et al., 2008) also reduce the power of beta oscillations. Besides excessive resting beta oscillatory activity, it was recently observed that Parkinson's disease patients also exhibit reduced MRBD (**Figure 1.14**) (Heinrichs-Graham et al., 2014).

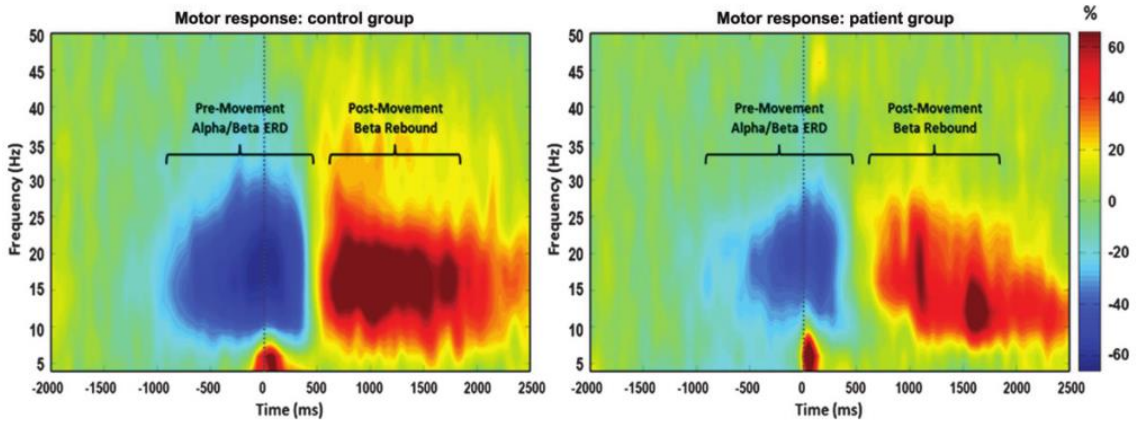

Figure 1.14* | *Reduced beta desynchronization in Parkinson's disease.
Average time-frequency spectrograms show the typical pattern of movement-related beta desynchronization (MRBD, blue colour), followed by a post-movement beta rebound (PMBR, red colour) during a hand movement task for healthy control (left panel) and PD patients(right panel). However, these responses were clearly diminished in PD patients. Spectral power is expressed as percent difference from baseline (-2 to -1.2 s relative to movement onset at 0 s). Figure taken from (Heinrichs-Graham et al., 2014), with permission from of Oxford University Press.

In chronic stroke patients, aberrant sensorimotor cortex beta power during movement has recently been shown (Rossiter et al., 2014a). In this study, MRBD, but not PMBR, was found to be significantly reduced in patients compared to healthy controls. Further, patients with greater impairment had lower MRBD in contralateral M1. Whilst stroke patients and PD patients have very different

pathologies, they both share the feature of reduced MRBD in M1 in conjunction with deficits in motor control. Thus, it may be that both patient groups are unable to modulate beta-band power, which results in abnormal inhibition of behavioural changes. These findings highlight the functional role of beta oscillations for motor behaviour and are in line with the proposed 'status quo' hypothesis of beta synchrony maintaining the current sensorimotor state while compromising flexible motor control (Engel and Fries, 2010).

1.6 Thesis overview

To summarise, this thesis explores the interplay between spectral characteristics of beta oscillations, as candidate biomarkers of cortical inhibitory and excitatory mechanisms, and individual differences in short-term motor learning. In a series of experiments, I seek to understand the neurophysiological processes underlying an individual's ability to learn and retain new motor skills in the context of healthy ageing and after stroke. Specifically, this thesis aimed to address the following principal research questions:

1. How does natural inter-individual variation in cortical beta oscillations seen with ageing relate to a person's ability to learn and retain new motor skills? Which spectral characteristics of beta oscillatory activity – resting or movement-related (dynamic) – are linked to individual differences in motor learning?
2. How are stroke-related changes in beta oscillations associated with a patient's ability to relearn motor skills? Which spectral characteristics of beta oscillatory activity after stroke – resting or movement-related (dynamic) – are linked to individual differences in motor learning?

Understanding the relationship between cortical beta oscillations and individual differences in motor learning may offer novel targets for therapeutic interventions designed to promote rehabilitative outcomes after brain injury.

In **Chapter 2**, I discuss the neurophysiological correlates underlying the EEG signal, some considerations with regard to its acquisition, and provide an overview of the principles behind time-frequency analysis.

In **Chapter 3**, I introduce the methodological techniques implemented and summarise the experimental considerations made in the design of the motor tasks used in this thesis. Specifically, I describe the development of a novel instantiation of the continuous tracking task so that it was possible to promote optimal learning across healthy ageing adults and stroke patients.

In **Chapter 4**, I focus on the test-retest reliability of beta oscillatory estimates, which are used in the following experimental chapters. I introduce EEG-derived measures of resting and movement-related beta activity and demonstrate their highly reliable nature across several weeks, a prerequisite for exploring the longitudinal relationship between beta oscillatory activity and individual variation in the capacity to learn a new motor skill.

In **Chapter 5**, I combine neuroimaging and motor learning in 40 healthy ageing adults to characterise the influence of natural inter-individual variations in beta-band activity on motor learning ability during a continuous tracking task. Using the standard measures of resting and movement-related beta activity introduced in the previous chapter, I explore their respective relation with an individual's ability to learn and retain new motor skills.

In **Chapter 6**, I focus on individual differences in motor learning in a clinical population of stroke survivors. Specifically, I use the same motor tasks and the same analysis pipeline to assess the impact of stroke on the relationship between beta activity and motor learning in 18 chronic stroke survivors.

Finally, in **Chapter 7**, I draw together the key findings from the different lines of research presented in this thesis, discuss the implications of this work for basic and clinical research, and outline some limitations and future directions.

1.7 Acknowledgement of contributions

I gratefully acknowledge Joern Diedrichsen's assistance in developing the motor learning task employed in **Chapter 5** and **Chapter 6**. I thank Archy de Berker for his guidance during coding and technical testing of the motor tasks used throughout **Chapter 4, Chapter 5**, and **Chapter 6**. I also thank Holly Rossiter and Bernadette van Wijk for providing guidance and supervision in EEG data analysis throughout **Chapter 4, Chapter 5**, and **Chapter 6.** I am grateful for Nellie Redman's support during testing in **Chapter 5**. Lastly, I gratefully acknowledge Fatima Jichi for her statistical support in sample size calculation.

Chapter 2 Acquisition and analysis of EEG signals

In the last years, our understanding of brain-behaviour relationships has dramatically improved due to advances in non-invasive brain imaging techniques. Human brain imaging techniques typically are categorised into *metabolic-based* (i.e. mainly fMRI and PET) and *electrophysiological-based* (i.e. mainly EEG and MEG) approaches, which allow the assessment of brain activity during performance of a task with varying spatial and temporal precision. Electrophysiological techniques are generally considered to have excellent temporal resolution but relatively poor spatial sensitivity, while metabolic techniques are assumed to have high spatial resolution, but rather poor temporal precision. As such, the use of a brain imaging tool depends on its suitability to address the research question, for example if the research question asks 'where in the brain a task-related process occurs', metabolic techniques are the optimal imaging modality. On the other hand, brain imaging techniques with high temporal resolution are invaluable and exceptional tools for the study of complex, dynamic cognitive and motor processes that occur within tens to hundreds of milliseconds. Since EEG was the chosen brain imaging tool to address the research questions of this thesis, in this chapter, I will specifically discuss the neurophysiological events that underlie the generation of the EEG signal, highlight advantages and limitations of employing this imaging technique in healthy and patient populations, and provide an overview of the principles behind EEG time-frequency analysis, including preprocessing and signal decomposition using the powerful wavelet transform employed in the work presented in this thesis. Please refer to **Chapter 3** for specific details regarding the implemented EEG data analysis pipeline used in the subsequent chapters.

2.1 Neurophysiological basis of EEG

EEG uses electrodes placed on the scalp to record the summed excitatory and inhibitory postsynaptic potentials of populations of neurons, most likely pyramidal cells, which are aligned parallel to each other and perpendicular to the cortical surface. The synchronous activity of approximately 10,000–50,000 neurons within this spatial organization then generates an electrical field that is powerful

enough to be picked up by means of electrodes from the scalp (Lopes da Silva, 2011; Murakami and Okada, 2006).

When neurotransmitters activate ion channels on the cell membrane of these neurons, either generating an excitatory or inhibitory postsynaptic potential (EPSP, IPSP), intra- and extracellular currents flow, creating an electrical field surrounding the neurons. For example, influx of positive ions into the cell (mostly Na^+ and Ca^+) creates an excitatory postsynaptic potential and an extracellular 'sink' (lack of positive ions in extracellular medium), with a concurrent redistribution of ions within the neuron leading to an outward flow of ions, creating an extracellular 'source' (excess of positive ions in extracellular medium) at the level of the soma. These synaptic actions thus result in dipolar sink-source configurations that generate time-varying electrical currents surrounding the neurons (**Figure 2.1**A) (Buzsaki, 2006; Nunez and Srinivasan, 2006).

In accordance with Maxwell's equation for electromagnetism, the electrical fields simultaneously create magnetic fields. These electric and magnetic fields form the building blocks of EEG and MEG signals, respectively (Buzsáki et al., 2012; Lopes da Silva, 2013, 2011). The direction of the electrical current flow is important as EEG and MEG vary in terms of their sensitivity towards the dipole orientation. Whereas EEG can detect both tangentially and radially oriented sources, MEG is mainly sensitive to tangentially oriented sources which protrude outside the head (**Figure 2.1**B) (Ahlfors et al., 2010; Cohen and Cuffin, 1991).

To reach the head surface, the neuronal signals need to travel through electrical tissues with different conductive properties (e.g. cerebrospinal fluid, skull and scalp). Unlike the EEG signal, which is attenuated and distorted by these various electrical tissues, the magnetic field measured by MEG passes through these tissues unimpeded (Lopes da Silva, 2013; Nunez and Srinivasan, 2009).

In summary, EEG measures the super-position of electric postsynaptic activity of populations of pyramidal cells that travels to the head surface due to volume conduction.

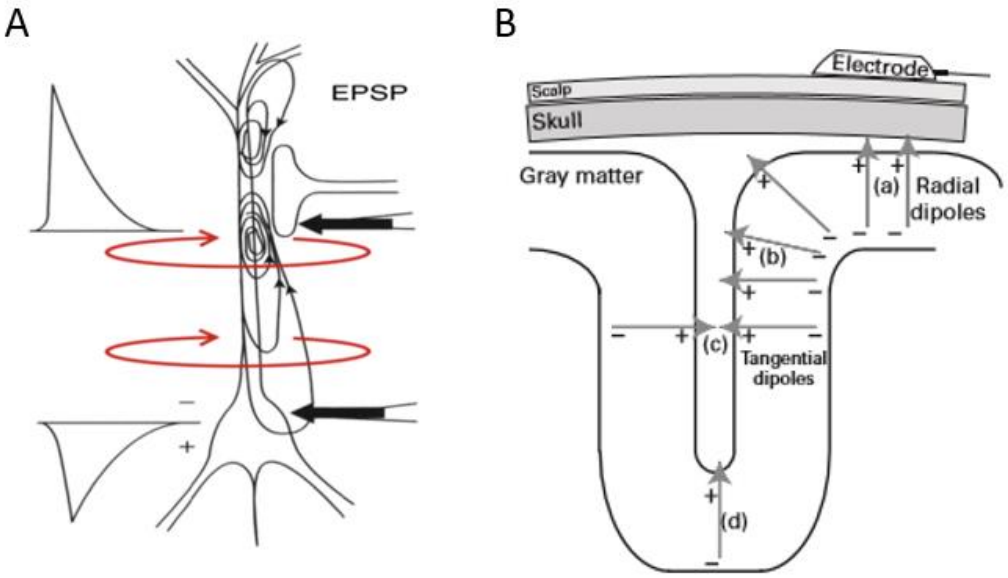

Figure 2.1* | *Schematic of electrical fields generated by cortical neurons. ***A****, An idealized pyramidal cell showing the patterns of intra- and extracellular current flow caused by activity at an excitatory synapse. An excitatory postsynaptic potential (EPSP) is associated with the generation of an active current sink in the extracellular medium next to the synapse. The current that flows in at the synaptic side is compensated by currents flowing in the opposite direction (passive source) at the level of the soma. This dipolar sink-source configuration around the neurons is reflected in local field potentials (LFPs). The electrical current flow also generates a magnetic field (red ellipse).* ***B****, Different dipole orientations with respect to the skull contribute differentially to EEG and MEG signals. While EEG is sensitive to both radial (a) and tangential (b) dipoles, tangential diploes (b) will contribute the strongest signal to MEG. In addition, electrical fields can cancel each other out or only contribute a weak signal to the EEG if the dipoles are on opposing sides of the sulcus (c) or are further away from the recording electrode (d). Figures taken from* (Cohen, 2014; Lopes da Silva, 2013)*, with permission from Elsevier.*

2.1.1 Advantages and limitations of EEG

Among the existing non-invasive brain imaging techniques for the study of human brain function, electrophysiological techniques such as EEG and MEG are classically considered to possess excellent temporal resolution, but a relatively poor spatial sensitivity (**Figure 2.2**). The high *temporal precision* in the millisecond range allows capturing very fast and complex dynamic changes in brain activity that occur with neurocognitive processes. In contrast, techniques such as fMRI that rely on indirect measures of hemodynamic response do not

provide the necessary fine temporal resolution, being roughly 2-3 orders of magnitude slower than electrophysiological responses (Cohen, 2014). Further, the voltage fluctuations measured by EEG are *direct* reflections of well-understood neurophysiological mechanisms that give rise to population-level oscillations (Buzsaki, 2006). By comparison, metabolic techniques such as BOLD-fMRI only indirectly measure neural activity and rely on a complex relationship between neuronal metabolism and changes in cerebral blood flow at a local level (Buxton and Frank, 1997; Logothetis, 2003; Ogawa et al., 1992). For example, the neurovascular response measured in fMRI occurs a couple of seconds after the preceding neuronal activity, resulting in lower temporal precision of techniques relying on these hemodynamic responses. Another reason why electrophysiological tools are advantageous for studying neurocognitive processes is that they provide *multidimensional* data, with at least four dimensions: time, space, frequency, and power (strength of activity in specific frequency band) and phase (timing of activity). This multidimensionality provides exceptional possibilities to better understand the complexity of brain processes by employing analyses that are motivated by known neurophysiological mechanisms.

While electrophysiological tools possess multiple advantages, their use in research studies where precise functional localization is important is limited due to the relatively poor spatial sensitivity. As discussed above, the neuronal signal recorded by electrodes at the scalp is distorted by the inhomogeneity of various resistive layers of the head. Consequently, the recorded signal at each electrode is a volume conduction-induced mixture of the underlying brain sources, resulting in deteriorated spatial resolution. *Volume conduction* has a stronger influence on electrical fields measured with EEG than magnetic fields recorded with MEG. This physiological phenomenon forms the basis of different mathematical approaches that vary in their complexity, and physiological and physical assumptions, with the aim of modelling the electrical sources based on the potential distribution recorded on the scalp (Lopes da Silva, 2011; Nunez and Srinivasan, 2009). Another limitation of EEG is that it is difficult, albeit not impossible, to record activity from sub-cortical structures such as the thalamus, basal ganglia, or

hippocampus. This is due to the exponential decrease of electrical field strength with distance between the source and the recording electrode.

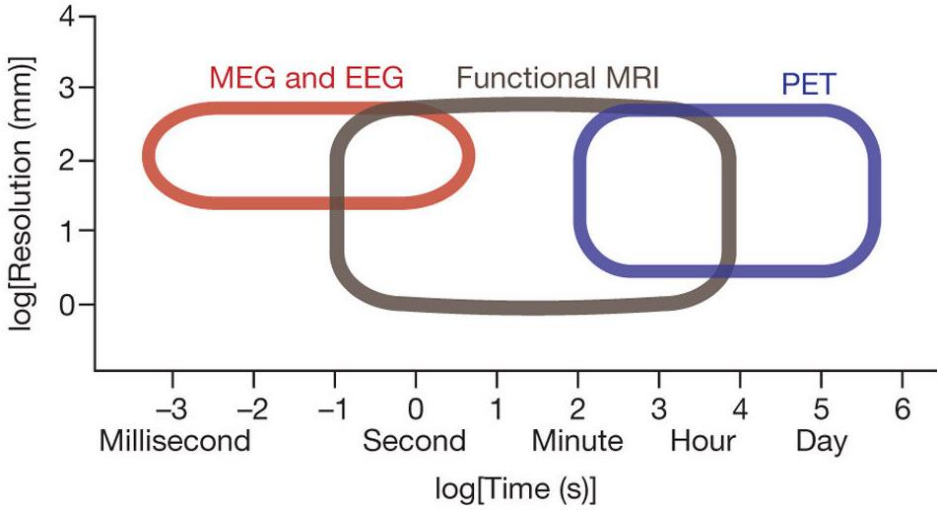

Figure 2.2 | Two-dimensional comparison of human brain imaging tools. *Metabolic and electrophysiological brain imaging techniques differ in their spatial and temporal resolution. Figure taken from (Meyer-Lindenberg, 2010), with permission from Macmillan Publishers Ltd*.

Despite these limitations of electrophysiological techniques, they are powerful tools with excellent temporal resolution and offer many advantages over metabolic techniques. For example, EEG and MEG do not expose participants to high-intensity magnetic fields or radioisotopes as in fMRI or PET, thus allowing the inclusion of participants with metal implants in their body.

2.1.1.1 Benefits of EEG over MEG

Whilst EEG and MEG are very similar and essentially record similar neurophysiological properties, EEG has several practical advantages over MEG. In contrast to MEG, which requires magnetically shielded rooms and intensive and expensive maintenance, EEG is portable and can easily be transported to another lab or hospital, making it an accessible imaging tool that can also be used for bedside examinations of brain function. In addition, EEG is less sensitive to movements due to the direct contact between the electrode and the scalp, and is more cost-effective than MEG or other techniques. For these reasons, EEG is an ideal tool for exploring brain function in healthy and clinical populations and is a

promising tool for the identification of widely available and cost-effective biomarkers of cortical function.

2.2 Considerations for high-quality EEG recordings

“There is no substitute for clean data” (Luck, 2005) and as such, acquiring high-quality EEG data is the first crucial step for scientific investigations. Like other brain imaging techniques, EEG is susceptible to various forms of noise (i.e. biological/subject-related or technical), which represent challenges for analysis and interpretation of EEG data. In order to deal with and reduce noise, and thus ensure optimal data quality, several technical and practical considerations can be applied, both at the time of EEG recording and during data pre-processing. For example, the quality of the EEG system and set-up, the experimental design, the preparation of the subject, and general acquisition settings are some of the factors that should be taken into account (Gross et al., 2013) and some are outlined next.

Since EEG measures the difference of electrical potential (typically in microvolts, μV) between each scalp electrode and a reference electrode, this reference should ideally be unaffected by brain activity, because any activity present in the reference electrode, including noise, will be reflected as activity in the scalp electrodes. Typically chosen reference electrodes are averaged mastoids, vertex or ear lobes (Luck, 2005). In addition, a ground electrode prevents the accumulation of static charge (Picton et al., 2000), preventing noisy signals in the EEG.

Standard EEG systems comprise 32 or 64 electrodes whereas technological advances have brought about high-resolution EEG caps that can include up to 256 electrodes. While more electrodes are useful to increase the signal-to-noise ratio (SNR) and to perform source reconstruction analysis to localise various EEG components, practical considerations such as preparation time and data storage need to be taken into account. Specifically, most EEG caps require the application of electroconductive gel to form a physical bridge between the skin and the recording electrode, reducing the electrical impedance. As such, preparation time increases as a function of the number of electrodes and can be

problematic for studies of challenging populations such as children and patients. Since high impedances distort the EEG signal, it is desirable to obtain homogenous impedance values ideally below 5 kΩ across the electrode montage (Luck, 2005; Picton et al., 2000). Asking subjects to wash their hair and to avoid hair spray or gels, and the use of abrasive skin preparation pastes and conductive gels help to record a clean EEG signal.

The positioning of electrodes on the scalp is important because different lobes of cerebral cortex are related to different brain functions. The standard method for electrode placement is the international 10–20 system (Jasper et al., 1958), which positions electrodes relative to landmarks, the nasion, inion, and pre-auricular points. This system ensures that results of an EEG study can be replicated by other laboratories and allows consistent electrode placement in the case of long-term monitoring.

Another factor is the sampling frequency/rate, which determines the temporal resolution of the EEG data and needs to be sufficiently high to capture the frequencies of interest in the respective study. Typically, the sampling rate should be at least twice the highest frequency of interest (Nyquist theorem, (Srinivasan et al., 1998)), however, in practice more data points per oscillation cycle increase SNR and thus, allow for better high-frequency activity estimation. Obtaining a satisfactory SNR requires the recording of a sufficient number of trials, taking into account exclusion of trials due to subject-related (i.e. eye-movements, sweating) and technical (i.e. line noise, impedance fluctuation) artefacts. In general, the number of trials depends on how big the observed effect is, how reliable the EEG dynamics under investigation are (for example see **Chapter 4**), and the specific analyses that will be performed. Again, a practical consideration in this regard is that participant's vigilance may not remain constant with many trial repetitions and that long EEG recordings may not be tolerated by every subject population.

2.3 Analysis of EEG signals in the time-frequency domain

EEG data comprise the volume-conducted summation of neural synchrony within and among neural assemblies and thus, provide an opportunity to translate the neurophysiological mechanisms that modulate these oscillations to human EEG studies, and to gain new insights into the neuronal underpinnings of sensory,

perceptual, motor and cognitive processes, as well as their pathologies. The recorded EEG signal, expressed as a time series, is suitable for a variety of analyses, including event-related potentials (ERPs) analysis and time-frequency (TF) analysis. While ERPs are simple and fast to compute, and their peak amplitudes and latencies provide insight into the nature and timing of neural events underlying discrete sensory and cognitive processes (Luck, 2005; Makeig et al., 2004), ERP averaging filters out most of the dynamic and multidimensional activity in the EEG signal. For example, oscillations at various frequencies represent multiple co-occurring and interacting neural processes in the brain that do not have a representation in the ERP.

Hence, *time-frequency analysis* approaches can capture many different aspects of the EEG signal by decomposing it into time-locked magnitude and phase information for each frequency. As such, this approach offers a more refined and detailed investigation of the brain's event-related oscillatory activity, with changes in EEG power being interpreted in terms of changes in the underlying neural synchrony, as exemplified by the concepts of event-related synchronization and desynchronization (ERD/ERS) (Pfurtscheller and Aranibar, 1977; Pfurtscheller and Lopes, 1999).

Interest in the field of time-frequency dynamics is proliferating due to ample opportunities for exploratory data analysis, however, the large number of analysis methods used to process EEG data, and their complexity, presents a problem for the development of unified analysis environments. For example, time-frequency transformation methods include the short-term Fourier transform (STFT) (Gabor, 1946), continuous or discrete wavelet transform (Daubechies, 1992; Mallat, 1989), and Hilbert transform (Lyons, 2004), which are all based on linear convolution. A comprehensive survey of the various time-frequency decomposition methods is beyond the scope of this thesis, but fortunately these methods tend to return similar results (Le Van Quyen et al., 2001), so I will focus on time-frequency decomposition using the continuous Morlet wavelet transform, as implemented in SPM and employed in the work presented here.

2.3.1 Pre-processing of EEG signals

Before subjecting recorded EEG signals to advanced time-series data analysis and statistical analysis, a number of critical pre-processing steps are usually applied in order to attenuate noise retained in the data, without losing valuable information contained in the signal. Although it is crucial to obtain clean high-quality data by minimizing biological and technical noise during EEG data acquisition (as outlined above), the EEG signal inevitably represents a mixture of signal and noise. Therefore, in order to make inferences about true task-related activity changes, rather than noise, different pre-processing strategies need to be applied, however no standardized procedure exists. Since the choice of transformations applied to the data generally depend on the type of advanced data analysis and their tolerance to noise, here, only the commonly applied pre-processing steps are briefly outlined (Cohen, 2014).

Due to the complex interaction between bad electrodes and referencing, the first step generally involves the removal or interpolation of bad electrodes prior to re-referencing and further pre-processing steps. Filtering the EEG data using high-pass, low-pass and notch filters removes high frequency artefacts (i.e. due to muscle contraction or aliasing), low-frequency drifts (i.e. due to sweating or drifts in electrode impedance), and electrical line noise typically occurring at 50 Hz or 60 Hz. Since the EEG signal is usually recorded at a high sampling rate, but most research focuses on frequencies typically below 100 Hz, next the signal is downsampled in order to save processing time and disk space. It is important to point out that it is essential to perform downsampling after filtering with regards to the Nyquist theorem (Srinivasan et al., 1998).

Investigating task-related changes in the EEG requires epoching of continuous data around triggers that mark particular experimental events (time = 0). For time-frequency-based analyses, the length of the epochs should be longer than the analysed time period in order to provide “buffer zones”, which can later be removed. These buffers avoid edge artefacts in the wavelet analysis that result from applying filters to sharp edges, such as the first and last points of the EEG epochs (Cohen, 2014).

Finally, artefacts in individual trials should be detected and removed by means of visual inspection or automatic detection procedures. Rejecting EEG trials with artefacts larger than a preset value is the most commonly used automatic method in research settings. While automatic procedures are fast and free of user bias, they only work efficiently for well-known artefacts. As such, visual inspection of the data should be performed independent of whether automatic artefact rejection approaches are employed in order to ascertain robust performance of the applied automatic method (Gross et al., 2013). It is common for EEG studies to monitor behavioural and physiological events during the recording and as such, this information can additionally be used to guide the identification and removal of artefacts based on i.e. task performance, electromyography (EMG) or oculomotor activity. Since trial rejection can lead to large amounts of useful information being discarded, it once again stresses the importance of minimizing noise during the time of recording to ensure optimal data. Another strategy that can be applied uses signal-processing techniques to deal with artefacts, especially those that arise from eye movements and blinks, while preserving the EEG signal. These artefact correction methods rely on linear transformation or regression techniques (Ille et al., 2002; Schlögl et al., 2007; Wallstrom et al., 2004).

2.3.2 Time-frequency analysis using wavelet transform

Once the EEG signal has been pre-processed, the signal can be spectrally decomposed using a variety of transformation methods that extract two characteristics of the sine wave at a given frequency: *magnitude* and *phase*. This is accomplished by convolution, a windowed transformation centered on an EEG segment that multiplies the raw data. In general, a sliding time window is employed in order to characterize changes in the time-frequency representation of power. This can be done either with a time window that has a fixed length, or decreases in length with increased frequency. The latter principle underlies the class of frequently applied continuous wavelet transforms, which are advantageous since they allow flexible optimization for either high frequency resolution or time resolution (Cohen, 2014).

Wavelets are a waveform of limited duration that have an average value of zero and which are computed by multiplying an envelope function (e.g. Gaussian

function) with a complex oscillation. One common type of biologically plausible wavelet is a Morlet wavelet that has the largest magnitude at the centre time point and tapers off to zero at both ends. Morlet wavelets are well suited for localizing frequency information in time, but have a poorer frequency resolution. This illustrates an important property of wavelets and other common decomposition methods, which strike a compromise between time and frequency resolution (**Figure 2.3**). It is common practice to use fewer cycles of the wavelet for lower frequencies and more cycles for higher frequencies (e.g. (Le Van Quyen et al., 2001)). Regardless of the decomposition method applied, the resulting magnitude and phase characteristics of EEG oscillations for every trial, time point, frequency and electrode are extracted and can be used to calculate numerous measures that describe different aspects of dynamic brain function. Additionally, the application of source localization methods to temporal dynamics of spectral power reveals the source of oscillatory activation

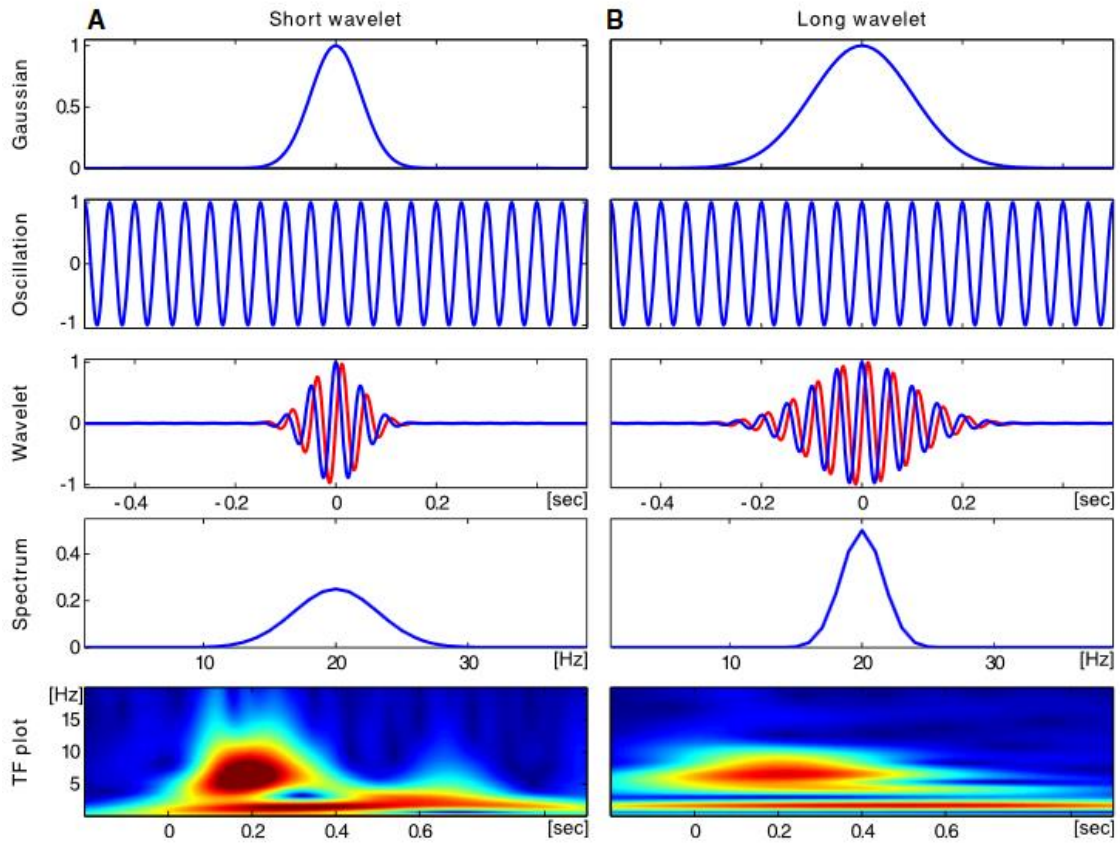

***Figure 2.3* | *Trade-off between time and frequency resolution*.**
Spectral decomposition of EEG/MEG signals represents a trade-off between precision in the time and frequency domain. In general, the larger the time window used for time-frequency estimation, the greater the frequency resolution but at

*the expense of poorer time resolution. Wavelets (third row) are generated by multiplying a Gaussian (top row) with a short (**A**) or long (**B**) duration with a complex oscillation (second row).Convolving an ERP with the wavelet, then results in the time-frequency spectrogram (bottom row) with different time and frequency resolutions depending on the length of the Gaussian. Figure taken from (Herrmann et al., 2014), with permission of Springer.*

2.3.2.1 Time-frequency power

The power of an oscillation refers to the amplitude or height of the sine wave's peak. Since time-frequency power obeys a 1/f scaling, whereby power at high frequencies has a much smaller magnitude than power at lower frequencies (Linkenkaer-Hansen et al., 2001), raw event-related power is not the most informative. In order to observe event-related changes in the EEG signal, power is typically normalized with respect to a pre-event baseline. Several baseline normalization methods are commonly used, such as simple baseline subtraction, decibel conversion or expressing power in percentage relative to a baseline. While different baseline transformations yield similar results, they are not identical and express power on different scales (i.e. logarithmic vs linear). The normalized power is then averaged across trials. Two types of signal power can be distinguished based on their phase-relationship to the stimulus. While *evoked power* refers to changes in oscillatory power that are phase-locked to the stimulus onset, *induced power* is not. To estimate evoked power, the signal is averaged across trials prior to time-frequency analysis, whereas the estimation of induced power requires that time-frequency decomposition is performed first for each trial first and the ensuing power is then averaged (David et al., 2006).

Besides power, other measures can be derived such as phase-locking factor (PLF) (Lachaux et al., 1999), which provides information regarding the phase angle consistency of oscillations with respect to an event's onset, or coherence, which refers to the coupling of frequency spectra between EEG channels as a proxy of the brain's regional and interregional connectivity.

Chapter 3 Methods

In this chapter, I introduce the methodological techniques implemented in this thesis to investigate the oscillatory correlates of individual differences in learning and retention of newly acquired motor skills. I outline the temporal structure of the studies, how the applied methods were developed and summarise the experimental considerations that were made.

3.1 Experimental design

In order to interrogate the neurophysiological processes underlying an individual's ability to learn and retain motor skills, it was necessary to establish that EEG-derived beta oscillatory measures are stable over time, validating the notion that these measures reflect meaningful individual differences. Since the reliability of EEG-derived measures might vary as a function of frequency band, brain region and type of task (Friedrich et al., 2013; Krause et al., 2001; Neuper et al., 2005), I firstly established the intra-individual reliability of beta oscillatory measures for the specific motor task applied (**Chapter 4**). For this purpose, I repeatedly tested healthy subjects on a simple motor task (see section 3.2.3 for details) over a period of approximately 12 weeks. The time interval between sessions varied from one week for the first five sessions to six weeks between the fifth and sixth EEG session. By using variable time intervals between EEG sessions (**Figure 3.1**), it was possible to test for a systematic influence of interval length (i.e. 1 week, 2 weeks, 5 weeks) on test-retest reliability, which is of relevance for studies designed to test longitudinal changes in clinical and non-clinical populations or therapeutic interventions.

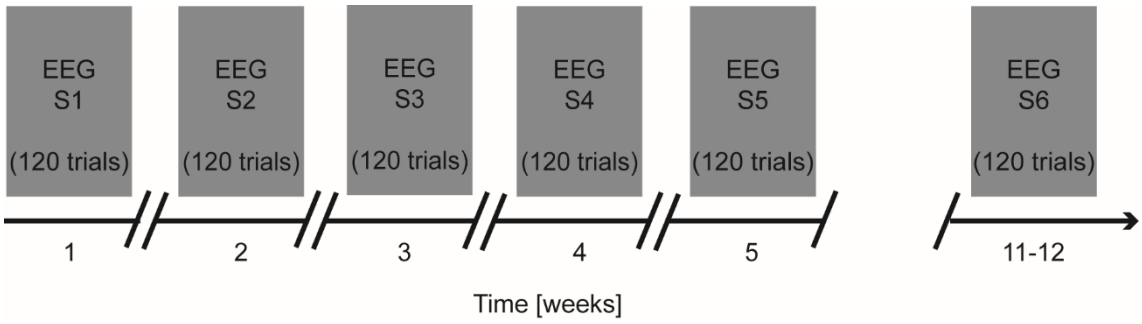

Figure 3.1 | Timeline of experiment in Chapter 4.
Subjects' EEG was repeatedly recorded over six sessions during the performance of the simple motor task. The time interval between sessions varied from one week for the first five sessions (S1–S5) to six weeks between the fifth and sixth EEG session (S6).

In **Chapter 5** and **Chapter 6**, I then combined neuroimaging and motor learning in order to probe the link between beta oscillatory activity and the degree to which individuals learn and retain newly acquired motor skills in the context of healthy ageing and after stroke. Specifically, subjects underwent short-term training on a motor learning task (see section 3.2.2 for details), and were subsequently retested for their ability to retain the acquired motor skill following a short or longer time delay: 45–60 min (retest1 on day 1) and 24 hours (retest2 on day 2) after initial training. Fatigue or boredom associated with practice can temporarily depress performance (Adams, 1961; Brawn et al., 2010; Rickard et al., 2008; Schmidt and Wrisberg, 2008b), resulting in an underestimation of the actual level of learning. Thus, the purpose of the retest1 session was to allow any temporary effects that the training session might have created to dissipate, thus only leaving the fairly *permanent learning effects*. The purpose of the retest2 session was to additionally allow motor memory consolidation to occur and thus, assess *retention* of the previously acquired motor skill after a night's sleep.
Electroencephalography (EEG) recorded during the performance of a separate motor task, not used during training, was used to assess beta oscillatory activity before (Pre), immediately after (Post1) and 24-hours after (Post2) the initial training phase (**Figure 3.2**). This experimental design enabled investigating whether (i) pre-training or (ii) post-training beta oscillatory activity is associated with individual differences in short-term motor learning behaviour. By recording beta oscillatory activity during the performance of a separate task, not used for

training, but which employed comparable motion features, it was possible to investigate the generic properties of brain activity and their relation to motor learning.

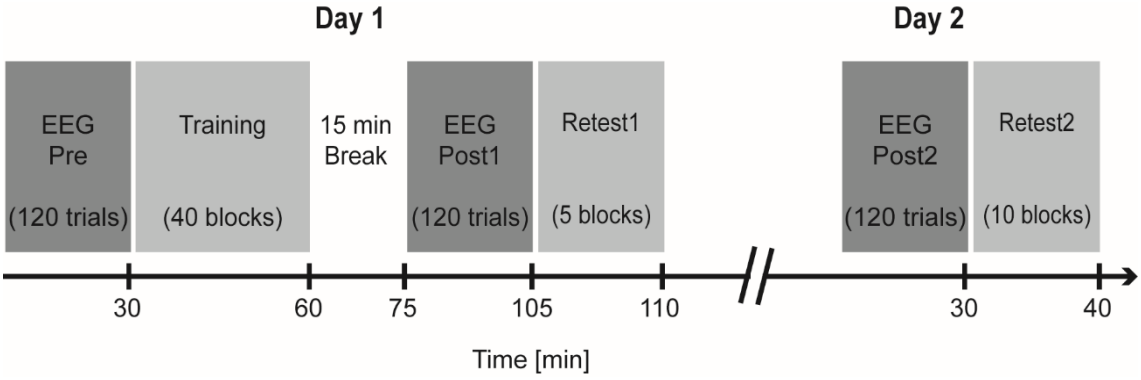

Figure 3.2 | Timeline of experiments in Chapter 5 and Chapter 6.
EEG was recorded during the performance of a simple motor task before (Pre) and at two time points after the training phase (Post1 and Post2). Performance on the motor learning task was retested after a time delay on the same day (retest1 on day 1, 45–60 min after initial training) and the following day (retest2 on day 2, 24-hours after initial training).

3.2 Motor tasks

For the purposes of this thesis, it was necessary to design two motor tasks, one that assayed an individual's motor learning capacity (**Chapter 5** and **Chapter 6**), and one that elicited reliable EEG-derived beta oscillatory dynamics (**Chapter 4, Chapter 5** and **Chapter 6**). For **Chapter 5** and **Chapter 6**, employing principles from previous motor learning studies (e.g. (Al-Sharman and Siengsukon, 2014; L. a Boyd and Winstein, 2004; Boyd and Winstein, 2006; Pew, 1974; Shea et al., 2001b; Siengsukon and Boyd, 2009; Wulf and Schmidt, 1997)), I developed a novel instantiation of the continuous tracking task. Specifically, the motor learning task required subjects to perform wrist flexion and extension movements in order to continuously track a target moving along a smooth trajectory on a fixed arc at an individually adjusted velocity. For **Chapter 4**, **5**, and **6**, I developed a separate simple motor task that required subjects to perform visually cued wrist flexion and extension movements to engender strong, reproducible movement-related beta dynamics. In order to allow for greater motor improvements with training, both motor tasks were performed with the non-dominant (**Chapter 4** and **Chapter 5**) or contralesional (affected) hand (**Chapter 6**). All tasks were presented using my

own custom written software routines in Matlab (version R2013b; The MathWorks, Inc., Natick, MA, USA).

3.2.1 Apparatus

As dexterous movements are often impossible for people with upper limb (UL) impairment, and might be compromised with healthy ageing (Martin et al., 2015), I chose to implement motor tasks that employed wrist movements with reduced dexterity demands compared to finger movements (i.e. more gross than fine movements). By implementing an instrumented wrist rig with a built-in potentiometer, developed by a group in Southampton (Burridge et al., 2009; Turk et al., 2008), it was possible to record the angular displacement around the wrist joint in the horizontal plane (maximum range 180°, 90° into flexion and extension, respectively). Throughout all experiments, subjects were seated in front of a computer monitor (41 x 25 cm) with their non-dominant hand or contralesional (affected) hand rested in the moulded splint of the wrist rig (**Figure 3.3**). The wrist rig's cuff was inflated to a comfortable level, and the forearm strapped to a cushioned arm support with the shoulder joint in a neutral position and the elbow joint angle between 80°–90° of flexion. This set-up prevented hand and arm movement during the experiments, thus ensuring that movements were restricted to the wrist.

Wrist angular displacement was sensed by the potentiometer, fixed with its axis coaxial to the axis of rotation of the wrist joint. A displacement of 0° indicated a neutral position of the wrist, with the hand being in the same plane as the forearm. The angular position of the wrist was continuously sampled at 100 Hz via a data acquisition box containing A/D and D/A converters (USB-1408FS and USB-1608FS, respectively, Measurement Computing, Norton, MA, USA) and sent via an optical USB link (Rover 200, Amplicon, Brighton, UK) to the computer for storage and display. The subject's angular position of the wrist was continuously displayed on the computer monitor (refresh rate 60 Hz) as a cursor in the form of a red circle – hereafter referred to as "*wrist cursor*". Flexion movement of the left wrist moved the wrist cursor to the right, while wrist extension caused the cursor to move left and vice versa.

On the first day of each experiment presented in this thesis, subjects performed at least three maximal active flexion and extension movements to define their active range of movement (AROM) around the wrist joint. From this, the maximum flexion/extension position and the mid-point of the AROM (in degrees) of each subject were used as start and/or target positions in the motor tasks (see section 3.2.2 and 3.2.3 for more details). This procedure controlled for natural and stroke-related differences in subjects' mid-point and movement range (i.e. stroke patients are more likely to be more in flexion and show smaller AROM compared to healthy adults) and ensured maximal muscle function when the joint was in neutral, mid-range position (Saladin, 2004). In addition, it allowed subjects to familiarise themselves with the wrist rig.

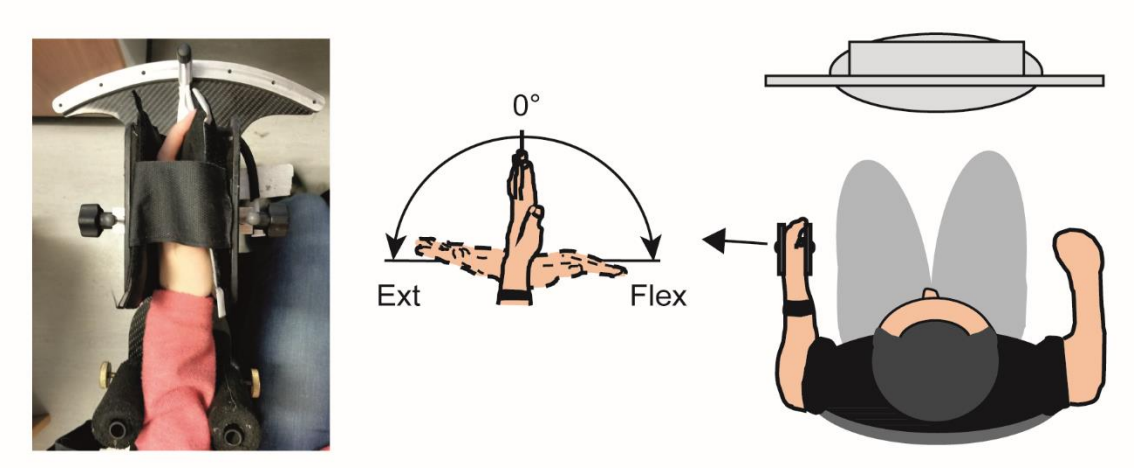

Figure 3.3 | Experimental set-up used during all motor tasks.
The non-dominant/affected hand was rested in the moulded splint of the instrumented wrist rig, which restricted movements to flexion and extension around the wrist joint while subjects sat in front of a computer monitor. The forearm was strapped to a cushioned arm support to reduce movements of other UL joints. The angular position of the wrist was continuously displayed on the computer monitor in form of a red circle.

3.2.2 Continuous tracking task to assay motor learning

In order to assay an individual's ability to learn and retain new motor skills in healthy subjects across the age span as well as stroke patients, it was necessary to develop a laboratory-based motor task that promoted optimal learning. Employing principles from previous motor learning tasks (e.g. (Al-Sharman and Siengsukon, 2014; L. a Boyd and Winstein, 2004; Boyd and Winstein, 2006; Pew,

1974; Shea et al., 2001b; Siengsukon and Boyd, 2009; Wulf and Schmidt, 1997), a complex continuous tracking task was utilized, requiring subjects to perform smooth wrist movements in the wrist rig. The idea that “motor tasks represent different challenges for performers of different abilities” suggests that by adjusting task difficulty with regard to an individual’s skill level, motor learning can be optimized (challenge point framework, (Guadagnoli and Lee, 2004)). Therefore, factors such as task difficulty appropriate for an individual’s level of motor system and cognitive function, and the respective implemented task characteristics are outlined in the following sections.

3.2.2.1 Task design

The task involved tracking a circular target (in yellow) that moved back and forth along a fixed arc through a predefined sequence of 12 positions (**Figure 3.4**). The target always started and finished at the individual AROM mid-point position. In **Chapter 5**, the maximum range of the target motion was defined as ±45° around the AROM mid-point position of each subject (90° in total). In **Chapter 6** the maximum range of the target motion was reduced slightly, ranging from -30° to +30° around the AROM mid-point position (60° in total), to allow the inclusion of patients with more severe motor impairment and thus, smaller AROM.

Each block of the task consisted of two types of sequences, one *random* and one *repeated* sequence presented in random order, with a 3 s stationary target between both. Thus, within each block, subjects were given variable practice on the two types of sequences. The repeated sequence was identical throughout each block of the training and retest sessions, and randomly selected from a pool of 57 predefined, difficulty-matched sequences. Each random sequence was encountered only once; however, the same set of difficulty-matched sequences was used across subjects to ensure comparable learning processes between individuals. This design allowed differentiating between *sequence-specific* (repeated sequence) and *general* (random sequence) skill learning (Wulf and Schmidt, 1997) as discussed in **Chapter 1** section 1.1.1, while accounting for ordering effects such as fatigue or boredom (Adams, 1961). Please refer to section 3.2.2.2 and section 3.2.2.3 for details about the training and the sequences.

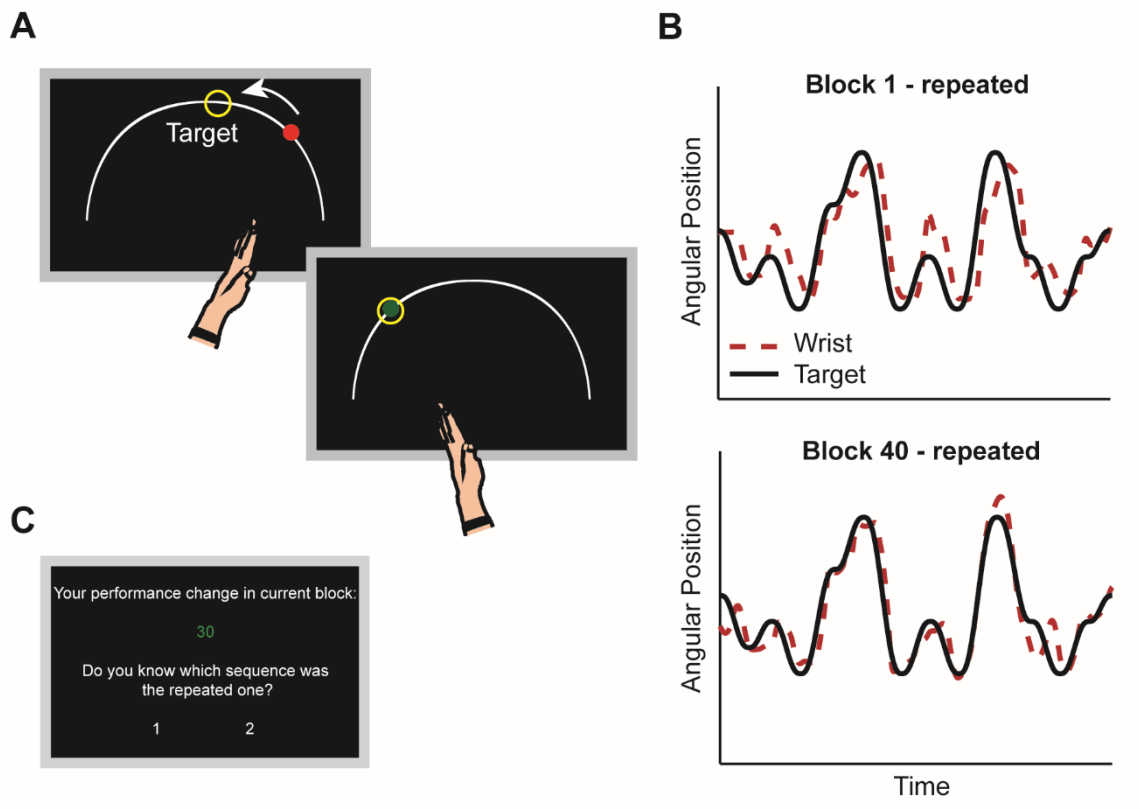

Figure 3.4 | Design of continuous tracking task.
***A**, Subjects were trained to track a target (yellow circle) moving back and forth along a fixed arc as accurately and smoothly as possible. Online visual feedback in terms of a colour change of the wrist cursor (red to green) was provided at times when the wrist cursor was located inside the circular target. **B**, Original recordings during the continuous tracking task at the beginning and end of the initial training are shown for the repeated sequence of an example subject. The solid black line represents the motion of the target, while the dashed red line represents the motion of the wrist. **C**, Between-block display of feedback score (-100 to 100; positive value in green reflects improvement, while decrements were displayed as negative values in red), reflecting the performance in the current block relative to the performance in the previous block, and forced-choice question about awareness of repeated sequence.*

3.2.2.2 Training

Each healthy subject (**Chapter 5**) and stroke patient (**Chapter 6**) was trained on the continuous tracking task for 40 blocks (20–40 min), with each block presenting both types of sequences (*random* and *repeated*). The number of blocks, and thus time spent on the task, was chosen to ensure that subjects' tracking performance improved beyond pre-training levels, considering the power law of practice (see **Chapter 1** section 1.1.1.3, (Newell and Rosenbloom, 1980)),

while minimising performance-dampening factors associated with practicing too long, thus aiming for optimal training benefits. Subjects' tracking performance was retested at two different time points: 45–60 min (retest1 on day 1; 5 blocks) and 24 hours (retest2 on day 2; 10 blocks) after initial training (**Figure 3.2**). These retest sessions allowed (i) temporary effects such as fatigue or boredom that build up over the course of training (Brawn et al., 2010; Rickard et al., 2008) to dissipate, thus only leaving the fairly permanent learning effects, and (ii) consolidation of motor memories to occur, resulting in stabilization, decrement or enhancement of acquired motor skills after a night's sleep (Robertson et al., 2004a; Walker, 2005). Importantly, subjects were retested on the *identical* repeated sequence that they encountered during the training phase.

Instructions to move the wrist so as to shift the red wrist cursor to match the movement of the target as 'accurately and smoothly as possible' were given at each session. Tracking performance was defined as the accuracy (in Root Mean Square Error; RMSE) with which the subject tracked the target movement. Please refer to section 3.7.1.1 for details about kinematic analysis.

As discussed in **Chapter 1** section 1.1.1.3, extrinsic feedback has been shown to generally enhance a person's ability to learn (for review see (Magill, 1994; Schmidt, 1991; Sigrist et al., 2013; Swinnen, 1996)). As such, online visual feedback in terms of a colour change of the wrist cursor (from red to green) was provided at times when the subject positioned the wrist cursor inside the circular target (**Figure 3.4**A). In addition, at the end of each block, subjects were made aware of their change in tracking performance by presenting a score on the screen, which reflected the performance in the current block relative to the performance in the previous block. Therefore, each training block was inter-leaved with at least 30 s of rest, reducing the accumulation of fatigue or attentional factors.

Prior to the start of training, subjects received explicit verbal information regarding the presence of a repeated sequence along with a random sequence in every block. However, they were not shown the repeated sequence. To determine the time point at which participants gained explicit knowledge of the repeated sequence, after each block they had to decide (forced-choice) which of the two sequences within each block the repeated sequence was – i.e. tell the

experimenter whether it was the first or second sequence they tracked within the block (**Figure 3.4**C). The trajectories of the target and subject's wrist cursor did not leave a residual trace on the screen and hence, subjects could not visualize the entire target sequence.

3.2.2.3 Difficulty-matched sequences

A set of different sequences of approximately equivalent difficulty were selected based on a pilot study of N = 4 independent subjects to ensure that changes in tracking performance were associated with learning and not with general variability due to differences in sequence difficulty or saliency. Each sequence was composed of six evenly spaced positions, three in flexion and extension range, respectively (i.e. **0**: position 1/6: AROM midpoint ±45°, position 2/5: AROM midpoint ±30° and position 3/4: AROM midpoint ±15°), repeated twice, and started and ended at the individual AROM mid-point (**Figure 3.5**A). Sequences only differed in the order of these positions (i.e. AROM midpoint–4–3–1–4–6–5–2–4–2–6–2–1–AROM midpoint) and were matched for the number of flexion and extension movements (median = 6) as well as absolute path length (median = 36). In total, 57 pre-designed, difficulty-matched sequences were used throughout the experiments in **Chapter 5** and **Chapter 6** from which the repeated sequence was randomly selected for each participant. Even though sequences were difficulty-matched, the random assignment of a different repeated sequence for each subject additionally guarded against the possibility of selecting a repeated sequence that was easier to track or more identifiable. This was a methodological issue identified in the tracking task originally used by Wulf and Schmidt (Chambaron et al., 2006; Wulf and Schmidt, 1997).

3.2.2.4 Smooth target trajectories

In order to ensure smooth target motion through the sequence positions, the minimum jerk trajectories (Flash and Hogan, 1985; Hogan, 1984) were generated – i.e. movement paths that have the smallest possible rate of change in acceleration (jerk). In general, if the target moved from its location $x = x_i$ to $x = x_n$

in *t* = *d* seconds, the minimum jerk trajectory was calculated using the following function:

$$x(t) = x_i + (x_n - x_i) * 10t/d^3 - 15t/d^4 + 6t/d^5$$

Equation 3.1

This fifth-order polynomial was piece-wise computed between the current position x_i and the next position x_n given a desired time for the point-to-point movement. The resulting trajectories have smooth position curves (**Figure 3.5**B) and resemble a bell-shaped velocity profile with the target accelerating and decelerating between successive positions. This is important, as previous studies have demonstrated that tracking performance improves with the target following biologically plausible trajectories compared to non-biological motion (Carlini and French, 2014; Pozzo et al., 2006).

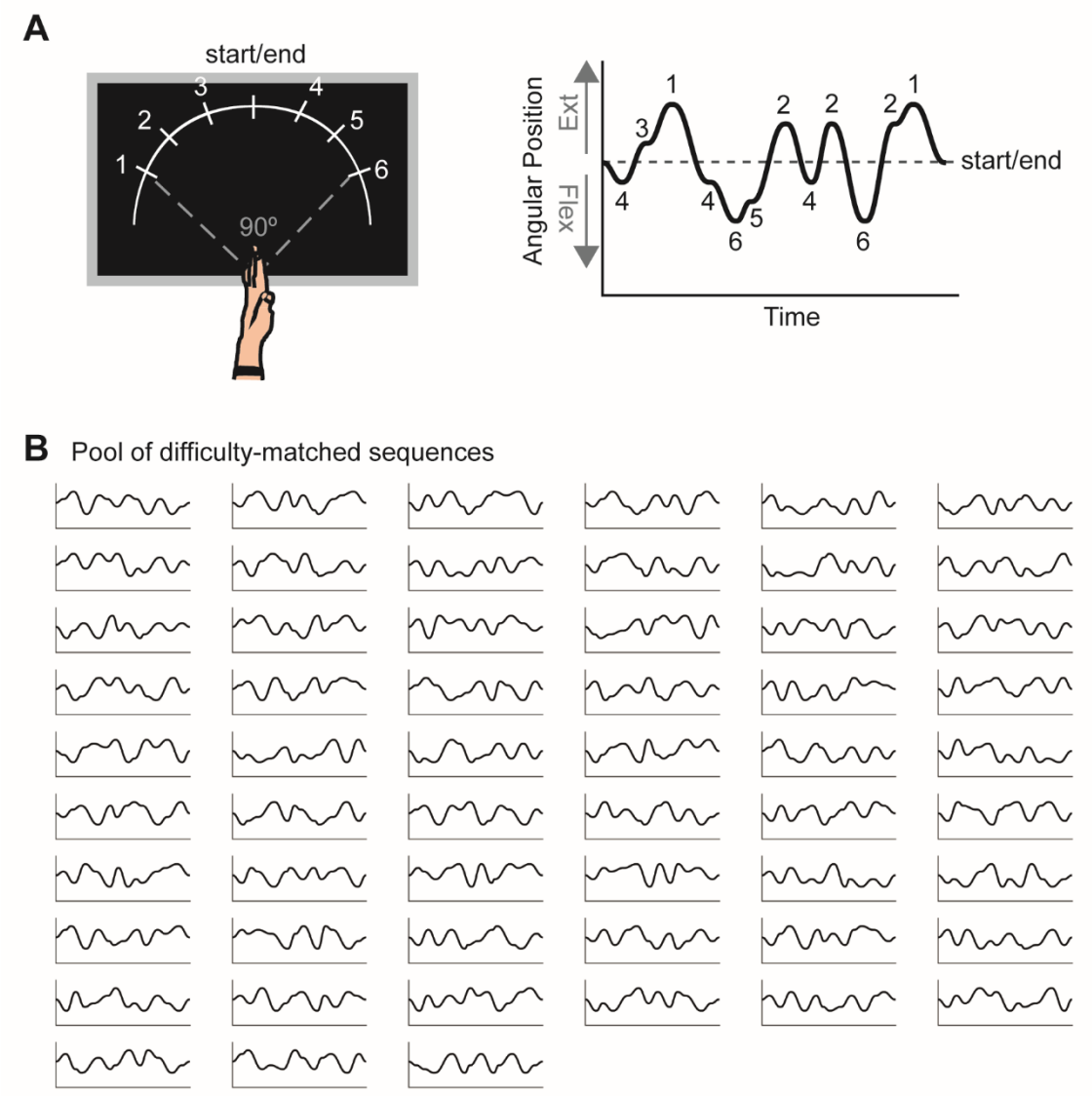

Figure 3.5 | Difficulty-matched sequences.
***A**, The six positions that reflect individual angular positions and which made up the exemplary trajectory (sequence: AROM mid-point–4-3-1-4-6-5-2-4-2-6-2-1–AROM mid-point) along which the target moved. **B**, Throughout the experiments, sequences were selected from the pool of predefined, difficulty-matched sequences generated from the six positions. For each subject, a repeated sequence was randomly selected from these 57 sequences while the remaining sequences served as random sequences.*

In order to calculate the minimum jerk trajectories, the time points t_i … t_n at which the target should reach the positions needed to be defined. Discrete point-to-point movements are characterised by a linear relationship between movement accuracy and movement speed, as quantified by Fitts' law (Fitts, 1954). Using the

logarithmic model proposed by Fitts, movement time (*MT*) is a function of the target width (*W*) relative to the distance (*A*) as described by the following function:

$$\mathrm{MT} = \mathrm{a} + \mathrm{b} * log_2\left(\frac{2A}{W}\right),$$

Equation 3.2

where *a* and *b* are empirical constants. Fitts' law thus demonstrates that there is a speed-accuracy trade-off when performing aimed rapid movements. The constants *a* and *b* were experimentally determined based on regression analysis of pilot movement time data acquired from the wrist rig (N = 1; only *A* was randomly changed). Please refer to **Figure 3.6** for values of *a* and *b*.

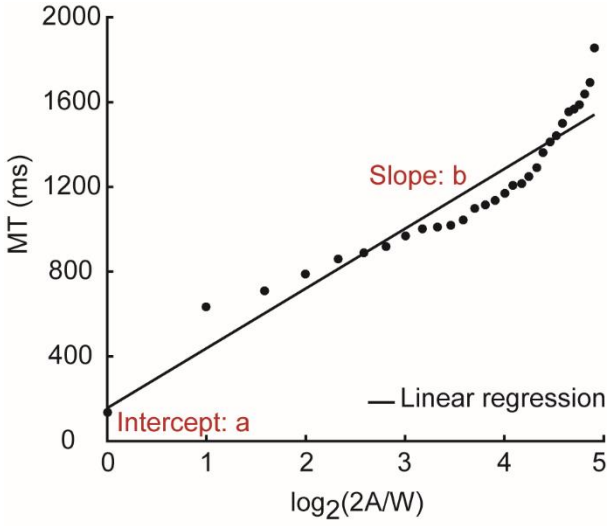

Figure 3.6 | Linear regression model of actual wrist movement time data. *The relationship between movement time (MT) and the index of difficulty, defined as $log_2(2A/W)$, was fitted as $MT=155.8 + 282.3 * log_2(2A/W)$, with $R^2=0.91$. The constant a was defined as 155.8 ms, a time specific to the apparatus, while the slope coefficient, b, was 282.3 ms.*

3.2.2.5 Individualisation of target velocity

Previous motor learning studies employed tracking tasks that either used a fixed target velocity (Al-Sharman and Siengsukon, 2014; Ao et al., 2015; Siengsukon and Al-sharman, 2011; Siengsukon and Boyd, 2009; Wadden et al., 2015) or a percentage of an individual's maximum movement speed (Wu et al., 2014). However, to avoid any between-subject differences in baseline tracking performance at the beginning of the training, and to ensure sufficient room for

learning-related improvement in healthy subjects and stroke patients, I chose to implement an adaptive up-down staircase procedure that individually determined the average velocity with which the target moved along the arc.

On any given trial of this procedure, the target velocity was adjusted (e.g. increased or decreased) dependent on the subject's preceding tracking performance, using five different step sizes. Initially, the target velocity was slow and thus, easy to track (initial target velocity = 34.8 deg/s). Then, the target velocity was modified until a pre-specified performance criterion range (15±0.9 RMSE) was reached, using varying step sizes dependent on the current tracking performance relative to the criterion range (95–100 % criterion: 0.0025 ms; 90–95 criterion: 0.005 ms; 75–90 % criterion: 0.010ms; 50–75 % criterion: 0.025 ms; and ≤ 50 % criterion: 0.050 ms). The staircase was interrupted when the tracking performance in three consecutive trials achieved the criterion, and the final target velocity was defined as the mean velocity of these last three trials (**Figure 3.7**). On average, this procedure took ~2±0.50 min. The individually determined target velocity with which subjects were subsequently trained on the continuous tracking task was applied to all sessions. Additionally, this procedure allowed for habituation to the task on day 1, thus reducing large warm-up decrements at the beginning of the training phase (Adams, 1961).

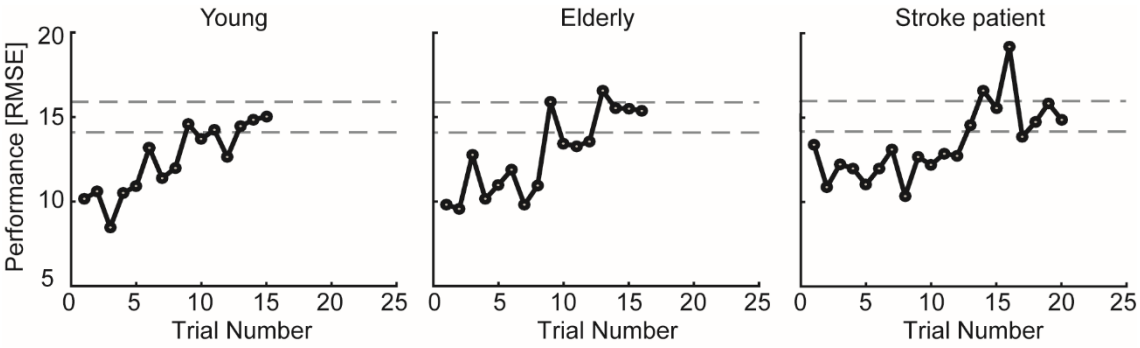

Figure 3.7 | Adaptive procedure for individual target velocity adjustment. *Example performance of three subjects (left: young subject; middle: elderly subject; right: stroke patient) on the adaptive up-down staircase procedure. The target velocity started off slow and was then adjusted using five different step sizes until a pre-specified criterion range was achieved (grey dashed lines) for at least three consecutive trials.*

3.2.3 Simple motor task to engender reliable beta oscillatory dynamics

By implementing a separate simple motor task with controlled wrist movements, it was possible to engender stereotypical movement-related modulations in beta oscillations in order to link them to individual differences in motor learning. The task required subjects to respond to the trial-wise presentation of one of two visual targets by performing wrist movements in the wrist rig while EEG was recorded. During each trial, wrist movements were always initiated from the same start position located at the centre of the screen, which represented the subject's individual AROM mid-point (see section 3.2.1 for details about AROM measurement). The cue to perform wrist flexion or extension movements was the random appearance of one of two squared targets (in blue) located on the left or right and equidistant from the central start position (**Figure 3.8**). Each of the targets represented the subject's maximum wrist flexion or extension position. This design controlled for the end position of the movement and ensured that the movement distance in each condition was the same; however, the actual movement distance between subjects was different based on their AROM.

Subjects were instructed to move the wrist upon presentation of the target so as to shift the red wrist cursor from the central start position to match the position of the target in a 'quick and discrete movement'. They were also asked to move as soon as possible and to avoid anticipation or guessing of target appearance. The target position was displayed for 3 s and subjects had to maintain the wrist cursor inside the blue target until being cued to return to the initial start position. Once subjects returned to the start position, the next cue to move was delivered following a delay of 7±1 s. This time interval between task epochs was chosen to account for the longevity of movement-related beta activities (Jurkiewicz et al., 2006), thus avoiding temporal overlap of neuronal activity. The task comprised 120 trials (60 trials for flexion and extension, respectively), and subjects were instructed to minimize eye movements by focusing on a centrally located fixation cross. Movement execution was analysed with regard to reaction time (RT, interval between visual cue and movement onset), movement time (MT, interval between movement onset and movement termination) and peak velocity (PV). Please refer to section 3.7.1.2 for details about kinematic analysis.

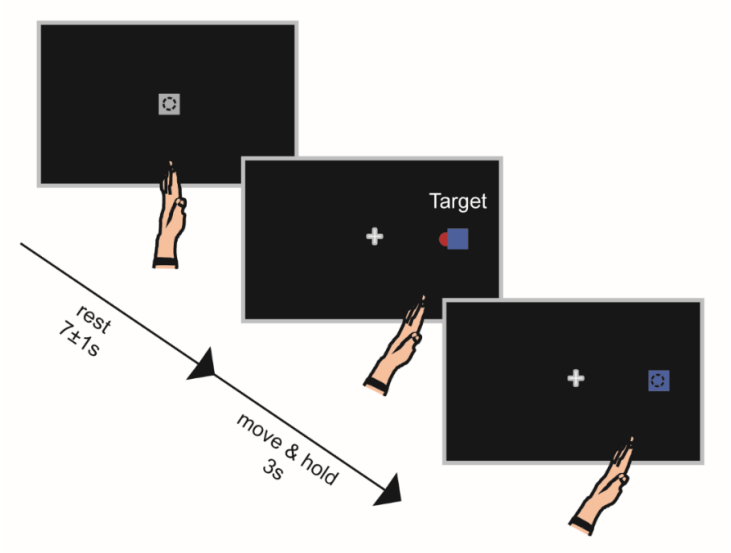

Figure 3.8 | Design of simple motor task.
Subjects were instructed to perform wrist movements upon presentation of a blue target so as to shift the red wrist cursor from the central start position to match the position of the target. Each target was presented for 3 s with an inter-trial interval of 7±1 s.

3.3 Controlling for confounding factors

Since several factors, such as upper limb (UL) function, attention or sleep, could influence motor learning behaviour, subjects were assessed on a range of tests, details of which are outlined below. In **Chapter 5**, the Nine Hole Peg Test (NHPT), grip strength test, Sustained Attention to Response Test (SART) and St Mary's sleep questionnaire were administered before testing. To characterise the severity of a patient's motor impairment in **Chapter 6,** and its potential effect on the patient's ability for motor skill learning (Vidoni and Boyd, 2009), the Action Research Arm Test (ARAT), Fugl-Meyer (FM) sensation assessment, and self-reported fatigue measures were additionally administered. The tests were selected based on published data regarding reliability and validity. All UL functional tests were performed on both sides.

3.3.1.1 Upper limb functional tests

Nine Hole Peg Test (NHPT) (Kellor et al., 1971; Mathiowetz et al., 1985) is a common measure of finger dexterity. Subjects were instructed to place nine pegs into the same number of holes as quickly as possible, using only one hand.

Subjects performed three timed repetitions, and the average score, expressed as the number of pegs/sec, was taken for each individual.

Grip strength is a dynamometer measurement of the maximum force produced during a five-finger grip. With verbal encouragement from the experimenter, subjects squeezed the dynamometer with maximum isometric effort. The average score of three attempts, in pounds, was taken for each individual.

Action Research Arm Test (ARAT) (Yozbatiran et al., 2008) is an assessment of a patient's ability to handle objects of varying sizes, weights and shapes with their contralesional (affected) and ipsilesional (unaffected) limb. It consists of 19 items and each of the four subscales - grasp, grip, pinch, and gross movement - are ordered according to ascending difficulty. Patients are scored on a four-level ordinal scale (0-3) and the maximum score is 57 for each arm, with a higher score indicating better arm motor function.

3.3.1.2 Sensation assessment

Fugl-Meyer sensation and proprioception is an assessment of upper limb sensation in patients. Sensation was assessed as absent, impaired, or normal for light touch (with a cotton ball) and proprioception (small alterations in the position) of the contralesional (affected) UL without visual input. The maximum score is 12, with a lower score indicating loss of sensation in the affected UL.

3.3.1.3 Cognitive test

Sustained Attention to Response Test (SART) (Robertson et al., 1997) is a computerised task that assesses an individual's ability to sustain their attention during a ~4 min long task. Subjects were asked to respond to the appearance of a number from 1–9 by pressing a button, except when the number 3 appeared. In total 225 trials are presented, of which 25 demand withholding a button press in response to the number 3. Subjects were instructed to give equal importance to accuracy and speed. The total error score (max score 225) and average reaction time [ms] were measured.

3.3.1.4 Self-reported measures

In order to record self-reported measures of fatigue and sleep, computerised versions of the following tests were implemented using visual analogue scales (VAS) (see **Appendix**).

Fatigue Severity Scale (FSS) (Johansson et al., 2014; Krupp et al., 1989) and the *Neurological Fatigue Index* (NFI) (Mills et al., 2012) are validated scales that assess the impact of fatigue on stroke patients. The FSS consists of 7 statements, such as “Fatigue interferes with my physical functioning”. Patients respond using a 7-point scale where low values indicate disagreement and high values indicate agreement. The NFI consists of 12 statements and patients respond using a 4-point scale: “strongly disagree”, “disagree”, “agree”, and “strongly disagree”. The average score was taken for each patient, with higher scores indicating higher fatigue.

St Mary’s sleep questionnaire (adapted from (Ellis et al., 1981)) is a self-reported assessment of the quality of sleep. Subjects respond to questions such as “At what time did you fall asleep last night?” and their sleep quantity [hours] and quality (from 1–8) was evaluated for both nights before testing.

3.4 Subject recruitment

Subjects were independently recruited for each study. Healthy subjects (**Chapter 4** and **Chapter 5**) were recruited from a volunteer database at the Institute of Cognitive Neuroscience and the Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology. Patients with chronic stroke (**Chapter 6**) were recruited from a database of stroke patients at the Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, which contains details from ~150 stroke patients. All studies were approved by the National Hospital for Neurology and Neurosurgery, UCL Hospitals NHS Foundation Trust and the local research ethics committee at University College London where the study was conducted. All subjects gave written informed consent in accordance with the Declaration of Helsinki. Please refer to individual chapters for details about subject characteristics and inclusion and exclusion criteria.

3.4.1 Sample size

In order to explore and detect a significant relationship between beta oscillatory activity and individual differences in motor learning behaviour, I performed a sample size calculation based on linear regression testing for association, with four key explanatory variables (i) beta oscillatory signals, (ii) age, (iii) level of impairment, and (iv) time since stroke (early and late). Estimates for a link between beta oscillations and motor learning were taken from a study showing an inverse correlation between the amount of beta power suppression and improvements in a serial reaction time task (Pollok et al., 2014) (Pearson r=-0.67, p<0.01, N = 15). The sample size calculation was based on the formula by Sokal and Rohlf (Sokal and Rohlf, 2009) with a $\rho^2 = 0.25$ (practical values suggested by (Linnet, 1987) range from 0.1 to 0.3):

$$n_1 = \frac{(\mathrm{Z}_{1-\alpha} + Z_{1-\beta})^2 \,/\, \mathrm{C(r)}^2 + 3}{(1-\rho^2)}$$

Equation 3.3

Where the Fisher's transformation is:

$$C(r) = \frac{1}{2} * \log(\frac{1+\mathrm{r}}{1-\mathrm{r}})$$

Equation 3.4

In order to allow for comparison between healthy subjects and stroke patients, a Bonferroni correction was applied, which set the type I error rate (α) equal to α/ number of comparisons. With these assumptions, an α value of 0.025 (α = 0.05 / 2) and a power (1–β, where β = type II error rate) of 0.8, a total of 36 healthy subjects and 36 stroke patients were required. To account for the possibility of drop-out and non-compliance, it was planned to recruit 40 healthy subjects in Chapter 5 (20 young and 20 elderly adults), and 20 chronic stroke patients in **Chapter 6**.

3.5 Electroencephalography (EEG)

As discussed in the **Chapter 1** section 1.5, neuronal oscillations may be a marker of GABAergic inhibitory and glutamatergic excitatory processes (Jensen et al., 2005; Murakami and Okada, 2006; Yamawaki et al., 2008), which are one major mechanism through which the potential for plasticity is regulated (Bavelier et al.,

2010; Benali et al., 2008; Traub et al., 2004). Thus, I used EEG to non-invasively measure neuronal oscillations and reveal appropriate biomarkers to assess net inhibitory and excitatory mechanisms in human cortex. EEG has several advantages, making it a powerful method for scientific and clinical research as discussed in more detail in **Chapter 2** section 2.1.1. In particular, EEG does not rely on intact neurovascular coupling (Blicher et al., 2012) which might be altered after stroke, nor the presence of MEPs in affected muscles, both of which hinder the use of fMRI and TMS in stroke patients. Furthermore, the high temporal resolution of the spectral data allow the examination of state-dependent dynamics during task-related movements (Lopes da Silva, 2013), which might play an important role in the mechanisms of motor impairment after stroke.

While subjects performed the simple motor task (**Chapter 4**, **Chapter 5** and **Chapter 6**), scalp EEG (ANT Neuro, Asalab, The Netherlands) was continuously recorded at 2084Hz using 64 electrodes mounted on an elastic cap (waveguard EEG cap, ANT Neuro). Two EEG caps with different size ranges were used to account for varying head sizes of subjects. The 64 electrodes were evenly distributed over the scalp according to the international 10-20 EEG system. To ensure comparable positioning of the EEG electrodes on separate days, the distance between nasion and inion, and left and right preauricular points was recorded for each subject. In order to lower the electrical impedance and allow for the recording of a clearer electrical signal, an abrasive electrolyte gel (Abralyt 2000, Easycap GmbH, Germany) was used. In addition, subjects were asked to wash their hair and to avoid hair spray or gels on the day of testing. The impedance was kept below ≤5 kΩ and the EEG signal was referenced to Cz during recordings. In order to align the oscillatory activity time-course with experimental events occurring in the simple motor task (e.g. the precise timing of the visual cues), separate triggers for each condition (flexion, extension) were sent via the testing computer's parallel port to the EEG system. For all EEG recordings, subjects were asked to remain relaxed and minimize eye movements by focusing on a centrally located fixation cross presented on the computer screen.

3.6 Electromyography (EMG)

Throughout both motor tasks, movements of the non-dominant hand (**Chapter 4** and **Chapter 5**) or contralesional (affected) hand (**Chapter 6**) were monitored by surface EMG using bipolar electrodes (Kendall ECG neonatal electrodes, Henleys Medical Supplies Ltd., UK) in a belly-tendon montage placed on the wrist extensor (extensor carpi radialis, ECR) and flexor (flexor carpi radialis, FCR) muscles. The ground electrode was positioned on the elbow. The raw EMG signal was amplified and band-pass filtered (10 Hz to 500 Hz; D360 amplifier, Digitimer, Hertfordshire, UK) and digitized at an A/D rate of 1 kHz per channel (CED Micro 1401, Cambridge Electronic Design, Cambridgeshire, UK). Please note that EMG was purely recorded for monitoring purposes and not analysed in this thesis.

3.7 Data analysis

In order to link an individual's cortical activity to his/her ability to learn and retain new motor skills, the raw kinematic and EEG data needed to be reduced to interpretable concepts or definitions. In the following, I describe the analysis pipeline for (I) the measurement of different aspects of motor learning behaviour and (II) the measurement of spectral dynamics of beta oscillations at EEG sensor level. Analysis pipelines were identical between chapters unless stated otherwise. All analyses were conducted using my own custom-written routines in Matlab (version R2016a; The MathWorks Inc., Natick, MA, USA) and the SPM12 toolbox (Wellcome Trust Centre for Neuroimaging, www.fil.ion.ucl.ac.uk/spm). For visualization of specific EEG data aspects, the fieldtrip toolbox ((Oostenveld et al., 2011), www.ru.nl/fcdonders/fieldtrip/) was additionally employed.

3.7.1 Kinematic data

3.7.1.1 Continuous tracking task

The behavioural measure "tracking performance" on the continuous tracking task (e.g. how accurately subjects tracked the target movement) in **Chapter 5** and **Chapter 6** was parameterized by *Root Mean Square Error* (RMSE), a measure that has been implemented by other motor learning studies (Al-Sharman and Siengsukon, 2014; Boyd and Winstein, 2006; Roig et al., 2014; Siengsukon and

Boyd, 2009). RMSE captures the deviation of the wrist position (w_i) from the target position (t_i), and serves as a composite measure of temporal and spatial measurements of time lag and distance as calculated using the following equation:

$$RMSE = \sqrt{\sum_{i=1}^{N}(t_i - w_i)^2/N}\,,$$

Equation 3.5

where *N* is the total number of time samples of the sequence in each block. RMSE was calculated for repeated and random sequences separately and averaged across each block for the training and retest sessions. Thereby, smaller RMSE values reflect better tracking performance. To quantify not only skill acquisition over the course of training but also the ability to retain acquired motor skills after training ended, performance during the first and last block of training and retest sessions were probed.

However, performance on individual blocks are poor and noisy measures of individual performance, and may be additionally biased by the warm-up decrement at the beginning or fatigue at the end (Adams, 1961). As a solution, and instead of simple averaging, I adopted a similar approach to a previous learning study (Waters-Metenier et al., 2014), fitting a linear regression model across 5 blocks at the beginning and end of individual training and retest sessions. Using this fit, a corrected performance estimate of the first and last blocks was derived and used for further analyses (see **Figure 3.9**).

The analysis then concentrated on six time points in order to assess tracking performance across time: first block of training (T0), last block of training (T1), first block of retest1 (T2), last block of retest1 (T3), first block of retest2 (T4), and last block of retest2 (T5). As discussed in **Chapter 1** section 1.1.1.1, various processes can occur during time periods during which the task is not practised, such as dissipitation of temporary effects (e.g. fatigue or boredom) (Brawn et al., 2010; Rickard et al., 2008) and motor memory consolidation, which may result in skill stabilization, enhancement or decrements (Hotermans et al., 2006; Robertson et al., 2004a; Walker, 2005). As such, tracking performance at T2 is most likely to reflect permanent learning effects unaffected by training-induced

temporary effects such as fatigue or boredom due to prolonged training, while performance at T4 likely indexes retention of the acquired motor skill overnight, due to motor memory consolidation. In the work presented, absolute levels of performance rather than normalized changes (i.e. difference between baseline and post-training performance) were used to assess the effect of training to avoid the conceptual pitfall associated with additive or multiplicative normalization approaches (Kitago and Krakauer, 2010). By implementing this analysis approach, it was possible to interrogate the effects of age (**Chapter 5**) and stroke (**Chapter 6**) on motor learning behaviour (referring to the performance on the continuous tracking task), and assess changes in tracking performance at various time points.

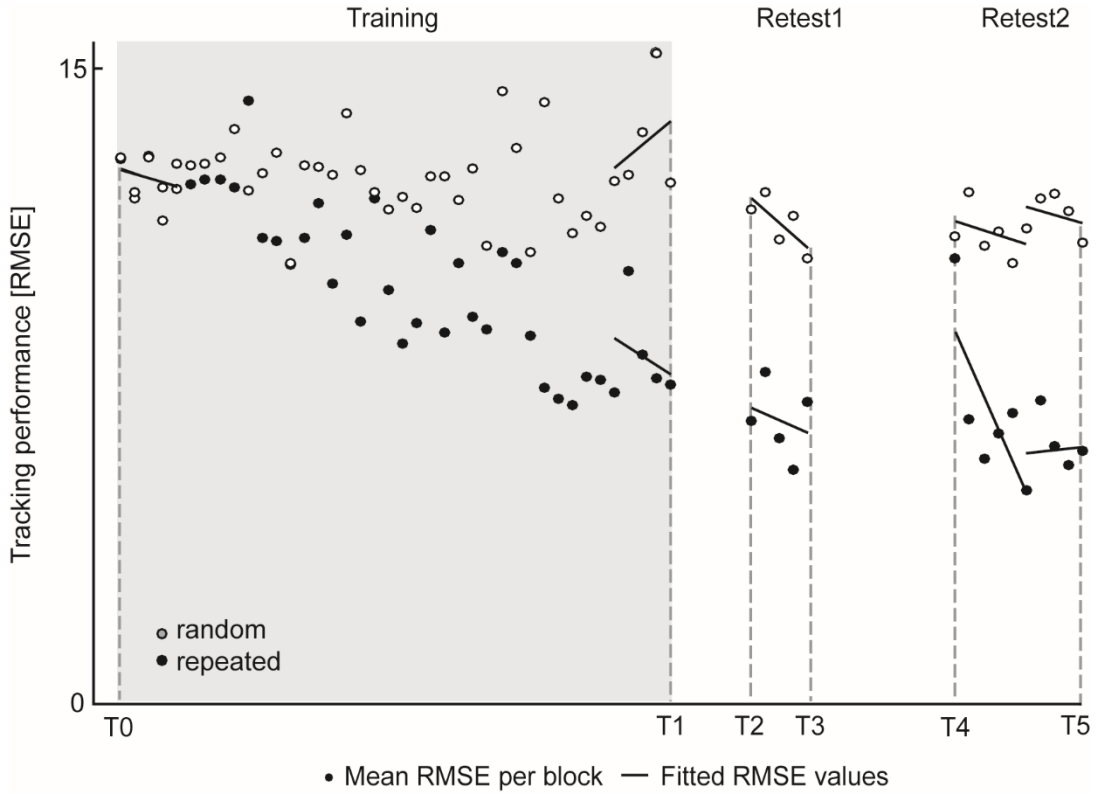

Figure 3.9 | Illustration of linear regression approach.
Dots represent performance in individual blocks on both types of sequences, random and repeated, respectively, for an example subject from Chapter 5 during training and retest sessions. Black lines represent linear regression models across 5 blocks at the beginning and end of individual sessions. Corrected performance estimates were derived from these linear regression models at six different time points (T0 = first block of training, T1 = last block of training, T2 = first block of retest1, T3 = last block of retest1, T4 = first block of retest2, and T5

= last block of retest2) and used for subsequent assessment of changes in tracking performance with training.

3.7.1.2 Simple motor task

Movement execution during the simple motor task was analysed with regard to reaction time (RT, interval between visual cue and movement onset), movement time (MT, interval between movement onset and movement termination) and peak velocity (PV). To this end, the angular position of the wrist, sampled at 100 Hz, was first filtered with a second-order zero-phase shift, low-pass Butterworth filter (cut-off frequency of 10 Hz) and then, differentiated to calculate velocity. Movement onset was defined as the time when the velocity of the wrist exceeded a threshold of 5 % of the maximum velocity and sustained this speed for at least 100 ms. Movement termination was defined as the time when the velocity fell below the threshold for that trial for at least 500 ms (see **Figure 4.1**C for exemplary wrist angular displacement and velocity profile). For each subject, trials in which the movement was initiated before the cue signal (e.g. anticipatory response), reaction time was excessively long (e.g. omitted response; >mean ± 2.5 SD), or movement time was excessively long (e.g. response not compliant with task demand of 'quick and discrete' movement; >mean ± 2.5 SD) were discarded. As I will demonstrate in **Chapter 4**, movement kinematics of the simple motor task were stable across sessions, a crucial prerequisite to engender reliable EEG-derived beta oscillatory dynamics.

3.7.2 EEG data

In order to verify whether neuronal oscillations at beta frequency, associated with motor system function, relate to an individual's ability to acquire a new motor skill, the raw EEG signal was pre-processed and time-frequency decomposed. The following analysis pipeline was applied to EEG signals recorded during the performance of the simple motor task in **Chapter 4, Chapter 5**, and **Chapter 6**. The EEG signal was first offline re-referenced to the average signal across all electrodes (Common Average Reference, CAR; (Mcfarland et al., 1997)) following removal of flat or very noisy electrodes. This technique removes common activity unrelated to specific cortical processes, thereby leading to

spatially more localized activity patterns. Then, the signal was bandpass filtered between 5–100 Hz, additionally filtered with a 50 Hz notch filter to reduce line noise contamination, and downsampled to 300 Hz. Data were epoched from -1 to 9 s relative to visual cue onset (0 s) in order to probe cortical activity during different movement phases (i.e. rest, movement, post-movement) of the simple motor task. Although, the use of the wrist rig minimized undesired hand and arm movement, poorly performed trials due to e.g. anticipatory or omitted responses (see section 3.7.1.2) were excluded and the remaining EEG trials were visually scrutinized. Trials containing artefacts, such as muscle activation or large eye blinks, were additionally removed. Since the recorded EEG signal reflects a mixture of cortical activity of different frequencies, artefact-free EEG time-series from each single trial were decomposed into their time-frequency representations in the 5–45 Hz range with frequency steps of 0.1 Hz in order to characterise changes in the beta frequency band with task performance. A Morlet wavelet with 7 cycles for each frequency was used for the continuous wavelet transformation. Then, *power* was averaged across all trials and rescaled in order to show changes in power (*P*) relative to the corresponding pre-movement baseline period (-1–0 s prior to cue onset), expressed as percentages of this baseline power (P_{ref}):

$$\%\ \text{power} = \frac{P - P_{ref}}{P_{ref}} * 100$$

Equation 3.6

Thus, a positive value indicates higher frequency band-specific power compared to pre-movement baseline power and vice versa.

Spectral power time-series were then derived from a pre-selection of electrodes overlying the sensorimotor cortices, both contralateral and ipsilateral to the moving hand (MRBD: ‘C4’ ‘CP4’ ‘CP2’ and ‘C3’ ‘CP3’ ‘CP1’ for contra- and ipsilateral hemispheres, respectively; PMBR: ‘C2’ ‘C4’ ‘CP4’ and ‘C1’ ‘C3’ ‘CP3’ for contra- and ipsilateral hemispheres, respectively). These electrodes were selected based on the independent dataset presented in **Chapter 4**, which showed that the most prominent task-related changes in beta activity were observed in these electrodes when performing the simple motor task. These bilateral electrodes were pooled as contralateral and ipsilateral regions of

interest, respectively. Please refer to **Chapter 4** for details about electrode selection from an orthogonal contrast (Kilner, 2013; Kriegeskorte et al., 2009).

Next, time-frequency windows were chosen based on peak changes in beta activity in time-frequency maps of these bilateral sensorimotor regions, which revealed clear movement-related beta-band (15–30Hz, (Jurkiewicz et al., 2006; Van Wijk et al., 2012; Yamawaki et al., 2008)) activity in two distinct time windows of interest in all experiments. This information was used to optimize the alignment of constant duration (1 s) and width (15 Hz) time-frequency windows to capture maximum *Movement-Related Beta Desynchronization* (MRBD), occurring between cue onset and movement termination, and *Post-Movement Beta Rebound* (PMBR), which emerges after movement cessation. Selected time-frequency windows and electrodes applied to all subjects and sessions in **Chapter 4**, **Chapter 5** and **Chapter 6**, and were not adjusted individually. Please refer to individual chapters for specifics about time-frequency window alignment, which, in the case of PMBR, was shown to differ between younger and elder adults in **Chapter 5**.

For each individual subject in each experiment, percentage decrease (MRBD) and increase (PMBR) in beta power were extracted from the respective 1 s time windows and averaged separately for each EEG session for the chosen electrodes over each hemisphere. The absolute pre-movement (resting) baseline beta (BB) power from -1 to 0 s relative to cue onset was also obtained. In **Chapter 4**, I additionally determined individual beta peak frequency for corresponding time windows (BB, MRBD, and PMBR) and show that these measures are less reliable compared to spectral power. Please refer to **Chapter 4** for details about peak frequency detection.

3.8 Statistical analysis

Unless stated otherwise, all data were assessed using parametric statistical tests following confirmation of normal distribution of data using Kolmogorov-Smirnov test. Specifically, a continuum of conventional statistical methods, including ANOVAs, t-tests, Pearson's correlations and stepwise multiple linear regressions, were used to analyse the information present in the kinematic and

neurophysiological data acquired during the two motor tasks. In **Chapter 4**, Intraclass Correlation Coefficient (ICC) were additionally employed to assess the intra-subject reliability of the various estimates of beta activity under investigation in this thesis. Significance for all procedures was set at a *p*-value below 0.05 and effect sizes were measured using partial eta squared (η^2). Details of the various ANOVAs, t-tests, correlational analyses, and ICCs are described in the relevant chapters. All statistical procedures were performed using the statistical package SPSS (IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY: IBM Corp) and custom-written Matlab routines.

Since the main objective of this work was to explore the oscillatory correlates of individual differences in motor learning, and their predictive value (**Chapter 5** and **Chapter 6**)**,** while accounting for possible influences of behavioural performance on the motor learning task, as well as functional/clinical and demographic characteristics, stepwise multiple linear regressions within leave-one-out cross-validation (LOOCV) were performed. In the next section, I will briefly outline the implemented statistical approach in more detail.

3.8.1 Stepwise multiple linear regression

Stepwise multiple linear regression is a multivariate method, which is used for predicting the relationship between a single dependent variable (DV) and various independent variables (IV), whilst removing or retaining variables based on their statistical contribution. By removing candidate variables that do not significantly contribute to the ability of the model to predict the dependent variable, this type of regression analysis finds the “linear combination of predictors that correlate maximally with the outcome variable” (Field, 2013).

The stepwise linear regression procedure with forward and backward algorithm and inclusion/exclusion probability levels of $\alpha_{Enter}<0.05$/ $\alpha_{Exclude}>0.1$ was implemented using the ‘stepwiselm’ function contained in Matlab’s Statistics and Machine Learning Toolbox. The stepwise method creates an initial model where the most statistically significant independent variable is added to the model for predicting the dependent variable ($p<\alpha_{Enter}$). Then, at every new iteration, a new variable is added until there are no more variables that satisfy the $p<\alpha_{Enter}$ condition. Each time a predictor is added to the model, a backward elimination

method is applied to remove the least statistically significant variable ($p>\alpha_{Exclude}$), thus constantly reassessing the model. Hence, the stepwise procedure selects the best predicting variables that maximally account for variance in the dependent variable on a purely data-driven basis. However, since this type of linear regression might be prone to overfitting, which is associated with models that perform well on one data set but do not generalize to new data sets, a cross-validation procedure was implemented.

3.8.2 Validation of model consistency

Cross-validation assesses the accuracy of a model across different samples, thus evaluating whether the same set of predictors generalize to a different population (Arlot and Celisse, 2010; Field, 2013). The approach consists in randomly splitting the acquired data into a training and a test set. By fitting a regression model to the training set, its accuracy on the test set can be evaluated, providing an indication of the predictive strength of the regression model. In this thesis, model performance was assessed employing the leave-one-out cross-validation (LOOCV) approach. In this case, on any given fold of this K-fold procedure, only one fold is spared as the test set, while the remaining data samples are used to build the regression model (**Figure 3.10**). This cross-validation method is an established procedure for assessing generalization of results to an independent data set, particularly with smaller sample sizes (Huang et al., 2011; Kang et al., 2014).

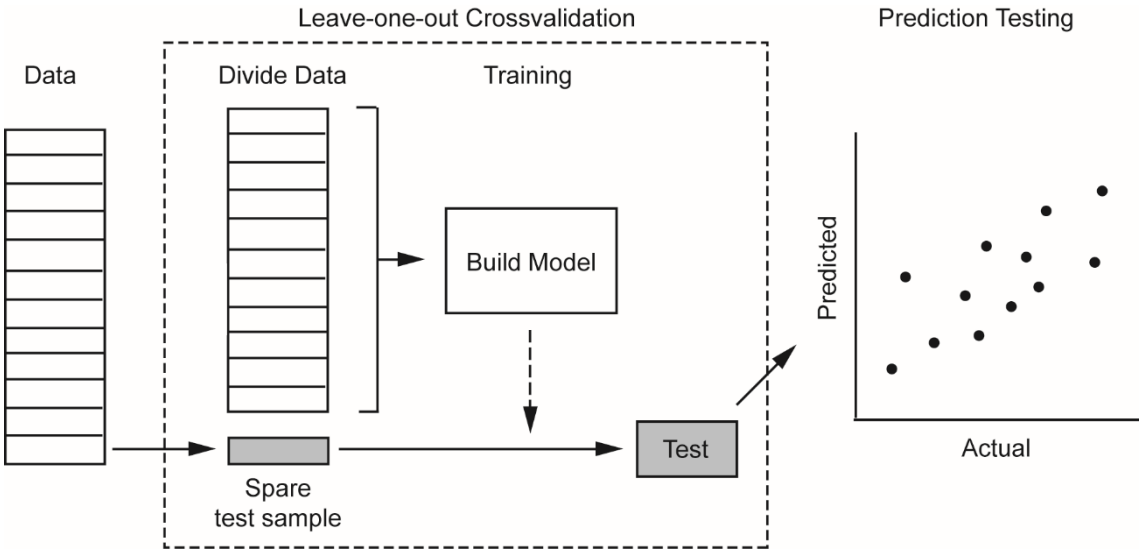

Figure 3.10 | Schematic of crossvalidation approach for model assessment.

A leave-one-out cross-validation (LOOCV) approach was employed in order to assess the accuracy of the regression model to predict the dependent variable in a different sample. This approach uses N-1 data samples to train the model and then the model predicts the remaining test sample. The process is repeated N times and the accuracy of the model is quantified by the correlation between actual and predicted data. N is the total number of samples.

Chapter 4 Intra-individual reliability of movement-related beta oscillations

This chapter is based on work previously published as:

> ***Espenhahn, S.**, de Berker, A. O., van Wijk, B. C. M., Rossiter, H. E., Ward, N. S. (2016) Movement-related beta oscillations show high intra-individual reliability. NeuroImage 147, 175–185*

4.1 Abstract

Despite increasing use of beta oscillatory activity in basic and clinical research, surprisingly little is known about their test-retest reliability. Identification of the oscillatory correlates underlying individual differences in the ability to learn and retain new motor skills requires establishing that beta measures are stable over time in healthy populations. In this chapter, I evaluate the intra-individual reliability of beta-band oscillations over six sessions, focusing on changes in beta activity during movement (Movement-Related Beta Desynchronization, MRBD) and after movement termination (Post-Movement Beta Rebound, PMBR). Subjects' EEG was recorded while they performed the simple motor task introduced in **Chapter 3**. I assessed Intraclass Correlation Coefficients (ICC) and between-session correlations for spectral power and peak frequency measures of movement-related and resting beta activity.

Movement-related and resting beta power from both sensorimotor cortices was highly reliable across sessions. Resting beta power yielded highest reliability (average ICC=0.903), followed by MRBD (average ICC=0.886) and PMBR (average ICC=0.663). Notably, peak frequency measures yielded lower ICC values compared to the assessment of spectral power, particularly for movement-related beta activity (ICC=0.386–0.402). The results highlight that power measures of movement-related beta oscillations are highly reliable, while corresponding peak frequency measures show greater intra-individual variability across sessions. Importantly, the finding that beta power estimates show high intra-individual reliability over time serves to validate the notion that these measures reflect meaningful individual differences that can be utilized in basic research and clinical studies.

4.2 Introduction

Oscillatory activity is ubiquitous in the brain and considered essential for the encoding and processing of information (Buzsáki and Draguhn, 2004). Neuronal oscillations in the beta frequency band (15–30 Hz), prevalent in sensorimotor cortex, are related to motor activity, as supported by a range of electroencephalography (EEG) and magnetoencephalography (MEG) studies showing a modulation of beta oscillations with active and passive movement (Alegre et al., 2002), motor imagery (McFarland et al., 2000; Nakagawa et al., 2011) and movement observation (Babiloni et al., 2002) (for review see (Kilavik et al., 2013)). Beta power decreases just prior to and during movement (Movement-Related Beta Desynchronization, MRBD), followed by a transient post-movement increase above pre-movement levels (Post-Movement Beta Rebound, PMBR) (Pfurtscheller and Lopes Da Silva, 1999; Pfurtscheller et al., 1998b; Salmelin and Hari, 1994; Stancak and Pfurtscheller, 1995), with each of these dynamics differentially modulated by experimental factors (for review see (Kilavik et al., 2013; Van Wijk et al., 2012)). MRBD is typically observed in both contralateral and ipsilateral sensorimotor cortices during unimanual movements, while PMBR typically shows a contralateral preponderance (Salmelin and Hari, 1994; Stancak and Pfurtscheller, 1995).

In addition to changes in power within the beta frequency band, individual peak frequency has been shown to be a behaviourally meaningful parameter of oscillatory activity (Kilavik et al., 2012) that differs across regions within the sensorimotor cortex (Salmelin and Hari, 1994), and which is of increasing interest considering recent attention on extrinsic neurostimulation approaches for modulating motor outputs (Guerra et al., 2016; Joundi et al., 2012; Pogosyan et al., 2009). However, despite extensive research, the functional relevance of beta oscillatory activity is still debated (Engel and Fries, 2010; Jenkinson and Brown, 2011; Pfurtscheller et al., 1996).

Direct manipulation of beta oscillations through the application of transcranial alternating current stimulation (tACS) at beta frequency can produce a slowing of movements (Joundi et al., 2012; Pogosyan et al., 2009) suggesting a causal role of sensorimotor beta oscillatory activity in motor control. As outlined in **Chapter**

1, alterations in beta activity are also observed in disease states such as stroke (Rossiter et al. 2014) and Parkinson's disease (Brown, 2007; Heida et al., 2014; Heinrichs-Graham et al., 2013; Little and Brown, 2014). Both patient populations show a reduction in the amplitude of MRBD together with deficits in some aspects of motor control, suggesting that MRBD may be a general assay of the state of the motor system, irrespective of the underlying pathophysiology. In addition, changes in beta oscillations have been observed with ageing, with resting beta power increasing as a function of age (Rossiter et al. 2014; Heinrichs-Graham & Wilson 2016), and the amplitude of MRBD and PMBR increasing during development (Gaetz et al., 2010).

Given its potential role as neurophysiological marker of motor system function and dysfunction, rhythmic activity at beta frequencies has received considerable interest in both basic and clinical research (Nicolo et al., 2015; Takemi et al., 2015; Ward, 2015; Wu et al., 2015). Measurements of beta activity may provide insight into the dynamics of disease, potentially providing a clinically relevant biomarker. However, despite prevalent use of EEG/MEG to explore beta oscillatory dynamics in normal brain functioning and pathology, to the best of my knowledge, no studies have systematically assessed their test-retest reliability across multiple recordings. If measures of beta oscillations in healthy individuals are highly variable between separate sessions (high intra-individual variability), EEG assays of beta oscillatory activity are unlikely to be useful as biomarkers (Mayeux, 2004). Reliable spectral estimates of oscillatory activity are therefore a prerequisite for studies designed to test longitudinal changes in clinical and non-clinical populations or therapeutic interventions.

Based on these considerations, at the beginning of my PhD, I assessed the test-retest reliability of spectral power and peak frequency measures of movement-related beta activity in a group of healthy subjects across several weeks. Since MRBD and PMBR estimates quantify movement-related changes in beta power *relative* to a pre-movement (resting) baseline, and recent work by Heinrichs-Graham and colleagues (Heinrichs-Graham and Wilson, 2016) suggests a direct relationship between MRBD and pre-movement baseline beta activity, the reliability of beta oscillations during the pre-movement (resting) baseline period

of the motor task was additionally evaluated. For measures of beta oscillations to be reliable and therefore useful biomarkers in basic and clinical research it is essential that these measures (I) display small within-subject variability and (II) do not change as a function of between-session time interval.

4.3 Methods

4.3.1 Subjects

Six healthy subjects (3 females, mean age ±SD = 27±4.7 years) took part in the study to assess the test-retest reliability of movement-related beta oscillations over six EEG sessions (S1–S6 in **Figure 4.3**, **Figure 4.4**, **Figure 4.7**). The time interval between sessions varied from one week for the first five sessions (range = 5–9 days, mean between-session time interval ±SD = 7±1 days) to six weeks between the fifth and sixth EEG session (range = 39–50 days, mean between-session time interval ±SD = 43±4 days; **Figure 4.1**A). This interval design was chosen to test for a systematic influence of interval length on test-retest reliability. All subjects were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971), had normal or corrected-to-normal vision, and fulfilled the following inclusion criteria: (a) no history of neurological or psychiatric disease; (b) no physical disability of the arms or wrists; and (c) no use of drugs affecting the central nervous system or self-reported abuse of any drugs. To minimize circadian fluctuations in beta oscillatory levels (Toth et al., 2007; Wilson et al., 2014), all subjects were tested in the time between 9am and 1pm after giving written informed consent.

4.3.2 Experimental design

Subjects performed visually cued wrist flexion and extension with their non-dominant (left) hand rested in the instrumented wrist rig (see **Chapter 3**) during EEG recording. For a detailed description of the simple motor task, please refer to **Chapter 3** section 3.2.3. Briefly, during each trial, wrist movements were always initiated from the same start position located at the centre of the screen that represented the mid-point of a subject's individual AROM (see **Chapter 3** section 3.2.1 for details about AROM measurement). The cue to perform wrist

flexion or extension movements was the random appearance of one of two targets (in blue) located equidistant from the central start position (**Figure 4.1**B, upper panel). Each of the targets represented the subject's maximum wrist flexion or extension position. Subjects were instructed to move the wrist upon presentation of the target so as to shift the red wrist cursor from the central start position to match the position of the target in a 'quick and discrete' movement. They were also asked to move as soon as possible and to avoid anticipation or guessing of target appearance. The target position was displayed for 3 s and subjects had to maintain the wrist cursor inside the blue target until being cued to return to the initial start position. Once subjects returned to the start position, the next cue to move was delivered following a delay of 7±1 s. The task comprised 120 trials (60 trials for flexion and extension, respectively), and subjects were instructed to minimize eye movements by focusing on a centrally located fixation cross.

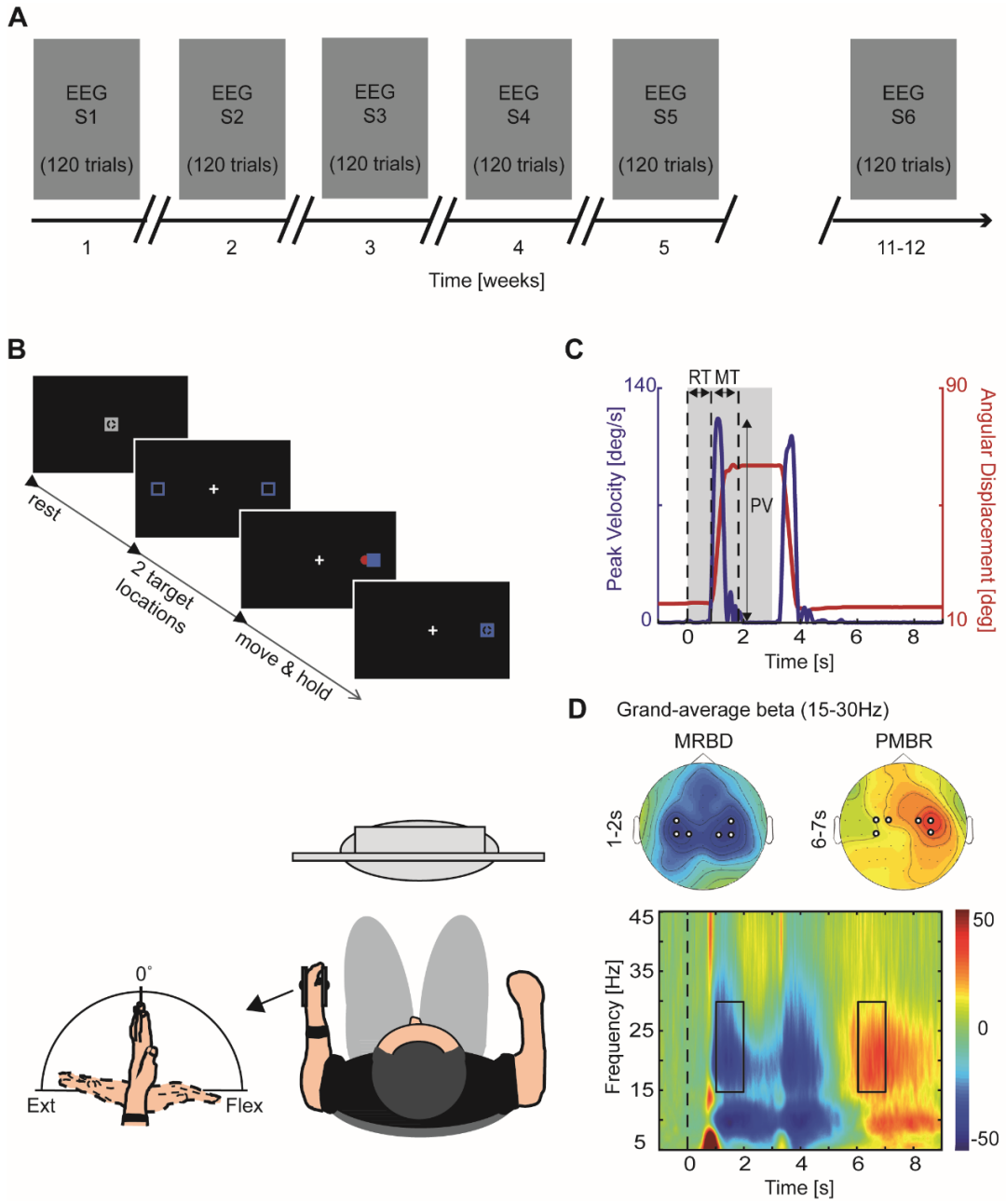

Figure 4.1 | Experimental setup and measurements.

***A**, Timeline of experiment. Subjects' EEG was repeatedly recorded over six sessions (S1–S6) during the performance of the simple motor task. **B**, Experimental paradigm. Subjects sat in front of a computer monitor and were instructed to perform wrist movements to move the wrist cursor (red circle) from the initial start position (grey square) to one of two target positions (blue squares) upon target presentation. **C,** Calculation of reaction time (RT), movement time (MT) and peak velocity (PV) where the grey patch represents target presentation. Velocity profile (blue line) and wrist angular displacement (red line) are shown for one trial of an example participant. **D,** Topographical distribution (top panel) and time-frequency map (bottom panel) of movement-related beta activity. Topographical plots of grand-average beta power revealed electrodes of peak change (highlighted as black-and-white disks) overlying contra- and ipsilateral*

sensorimotor cortices. Time-frequency map for pooled electrodes contralateral to moving hand showing two distinct time windows of peak changes in beta activity (MRBD: 1–2 s; PMBR: 6–7 s).

4.3.3 EEG recording

Scalp EEG was continuously recorded at 2084 Hz by 64 electrodes mounted on an elastic cap according to the international 10-20 EEG system. The impedance was kept below ≤5 kΩ and the EEG signal was referenced to Cz during recording. The timing of the visual cue (blue target) in the motor task was marked in the simultaneous EEG recording, with separate triggers for each condition (flexion, extension). Muscle activity was monitored by surface electromyography (EMG) on the wrist extensor (extensor carpi radialis, ECR) and flexor (flexor carpi radialis, FCR) muscles of the non-dominant arm.

4.3.4 Data analysis

Analyses were conducted using custom-written routines in Matlab and the SPM12 toolbox (Wellcome Trust Centre for Neuroimaging, www.fil.ion.ucl.ac.uk/spm). The fieldtrip toolbox ((Oostenveld et al., 2011), www.ru.nl/fcdonders/fieldtrip/) was additionally employed for EEG data visualization. Statistical analyses were performed using SPSS and custom-written Matlab routines.

4.3.4.1 Behavioural data

A detailed description of the kinematic data analysis has been provided in **Chapter 3** section 3.7.1.2. In brief, the angular position of the wrist was filtered and differentiated to calculate velocity. Movement onset was defined as the time when the velocity of the wrist exceeded a threshold of 5 % of the maximum velocity and sustained this speed for at least 100 ms. Movement termination was defined as the time when the velocity fell below the threshold for that trial for at least 500 ms. For each subject, trials in which the movement was initiated before the cue signal, reaction time was excessively long (>mean ±2.5 SD), or movement time was excessively long (>mean ± 2.5 SD) were discarded (average ~7 % of trials). Reaction time (RT), movement time (MT), and peak velocity (PV)

were calculated on the remaining trials (average 111±2) for each individual trial (**Figure 4.1**C) and then averaged within each subject for each experimental condition.

4.3.4.2 Spectral power and peak frequency measures

Pre-processing and time-frequency analysis of EEG data recorded during the performance of the simple motor task has been detailed in **Chapter 3** section 3.7.2. In brief, the raw EEG signal was first offline re-referenced to the average signal across all electrodes, bandpass filtered between 5–100 Hz, additionally filtered with a 50Hz notch filter, and downsampled to 300 Hz. Data were epoched from -1 to 9 s relative to visual cue onset (0 s). Poorly performed trials (see section 4.3.4.1) were excluded and the remaining EEG trials were visually scrutinized. Trials containing artefacts (e.g. muscle activation or large eye blinks) were additionally removed. For each session, on average 92±10 artefact-free EEG trials remained for further analyses, and number of trials did not differ between conditions (p>0.4) or sessions (p>0.1, repeated-measures ANOVA). Artefact-free EEG time-series from each single trial were decomposed into their time-frequency representations in the 5–45 Hz range with frequency steps of 0.1 Hz. A 7-cycle Morlet wavelet was used for the continuous wavelet transformation. Power was averaged across trials and rescaled in order to show changes in power relative to the corresponding pre-movement baseline period (-1–0 s prior to cue onset) (**Equation 3.6**).

To select electrodes and time-frequency windows of interest that were orthogonal to potential differences between sessions and conditions, firstly activity in the a priori chosen beta frequency band (15–30Hz, (Jurkiewicz et al., 2006; Van Wijk et al., 2012; Yamawaki et al., 2008)), grand-averaged over subjects, sessions and conditions was examined. Then, electrodes of peak change in beta oscillations were selected from topographical distributions of normalized power (% power), plotted for several time points after cue onset. The topographical maps revealed clear movement-related beta activity (MRBD, PMBR) overlying the sensorimotor cortices, both contralateral and ipsilateral to the moving hand (**Figure 4.1**C; MRBD: ‘C4’ ‘CP4’ ‘CP2’ and ‘C3’ ‘CP3’ ‘CP1’ for contra- and ipsilateral hemispheres, respectively; PMBR: ‘C2’ ‘C4’ ‘CP4’ and ‘C1’ ‘C3’ ‘CP3’

for contra- and ipsilateral hemispheres, respectively). These bilateral electrodes were pooled as contra- and ipsilateral regions of interest, respectively. Note that PMBR was located slightly more anterior to the central midline than the MRBD, consistent with previous EEG (Pfurtscheller et al., 1996) and MEG (Salmelin and Hari, 1994) studies.

Next, time-frequency windows were chosen based on peak changes in beta activity in time-frequency maps of these bilateral sensorimotor regions, which revealed clear movement-related beta-band activity in two distinct time windows of interest (**Figure 4.1**D). This information was used to optimize the alignment of constant duration (1 s) and width (15 Hz) time-frequency windows to capture maximum MRBD (1–2 s relative to cue onset), occurring between cue onset and movement termination, and PMBR (6–7 s relative to cue onset), which emerges after movement termination. Selected time-frequency windows and electrodes applied to all subjects and sessions, and were not adjusted individually.
Subsequently, for each individual subject, session and condition, mean percentage decrease (MRBD) and increase (PMBR) in beta power were extracted from the respective 1s time windows and averaged over the pre-selected electrodes for each hemisphere. The absolute pre-movement (resting) baseline beta (BB) power from -1 to 0 s relative to cue onset was also obtained and assessed for reliability.

In addition, individual beta peak frequency was determined semi-automatically for each corresponding time window (BB: -1–0 s; MRBD: 1–2 s, PMBR: 6–7 s). The peak frequency for the MRBD and PMBR were determined as the frequencies having the largest change in spectral power compared to baseline beta power. For the absolute power of baseline beta (BB), first the 1/f shape of the power spectrum was eliminated by fitting and subsequent subtraction of a straight line after log-log transformation (see e.g. (Nikulin and Brismar, 2006), **Figure 4.2**). All peaks were selected from the 15–30 Hz frequency range with 0.1 Hz resolution. Cases where no clear peak was present (e.g. Subject 5 Session 1 contra- and ipsilateral hemisphere, and Session 2 contralateral hemisphere), were left out of the analyses.
In total, 12 different beta parameter estimates were used for subsequent analysis: pre-movement beta baseline (absolute power and peak frequency), MRBD

(relative power and peak frequency) and PMBR (relative power and peak frequency) from contra- and ipsilateral sensorimotor cortices, respectively.

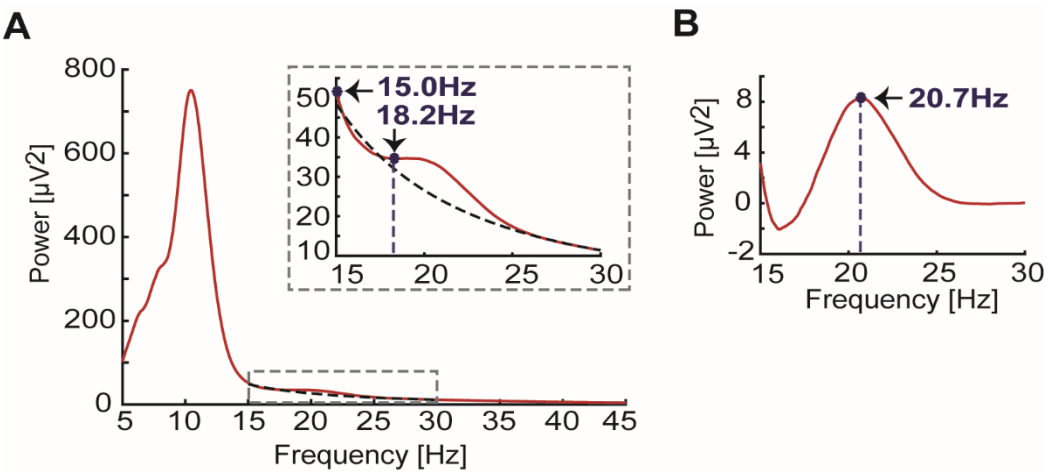

Figure 4.2 | Beta peak frequency detection.
Beta peak frequency was detected using least square fit procedure to remove 1/f component from spectrum. ***A****, Power spectrum of one example subject (subject 1) who did not show a clear peak in the beta frequency range (grey dashed rectangle). Black dashed line indicates 1/f component obtained from least square fit of log-log transformed data. Inset shows enlarged view of the spectrum for the beta frequency range.* ***B****, Corrected spectrum (after subtraction of 1/f component). Note that in the uncorrected spectrum (****A****) local maxima were found at 15 Hz or 18.2 Hz, whereas the peak is at 20.7 Hz in* ***B****.*

4.3.5 Statistical Analysis

Separate repeated-measures ANOVAs were used to test for differences between sessions, hemispheres and conditions for each of the beta parameter estimates, with 'time' (6 levels: sessions 1-6), 'hemisphere' (2 levels: contralateral vs ipsilateral), and 'condition' (2 levels: flexion vs extension) as within-subject factors. A Greenhouse-Geiger correction was applied whenever Mauchly's test indicated a lack of sphericity. *Post hoc* Bonferroni-adjusted paired-samples t-tests were performed whenever a main effect was detected. Prior to ANOVA and paired-samples t-tests, Kolmogorov-Smirnov test was used to assess normality. All beta parameter estimates and kinematic measures were normally distributed.

The main focus of the statistical analysis was to determine the reproducibility of absolute and relative beta power parameter estimates as well as their

corresponding peak frequencies. For this, Pearson correlations were used to assess reliability between two EEG sessions, while Intraclass Correlation Coefficients (ICC) (McGraw and Wong, 1996; Shrout and Fleiss, 1979), based on two-way random effects analysis of variance, were computed to assess the degree of consistency between all six sessions. The ICC method has been widely used (Muthukumaraswamy et al., 2010; Plichta et al., 2012; Tan et al., 2016a, 2015) and assesses the reliability of repeated measures of an individual's beta parameters by comparing the proportion of within-subject variability to all sources of variance; thus, a high ICC value means that within-subject variability is low and that most of the variance is caused by differences between subjects. Following Landis and Koch (1977) suggestions, ICC was rated on the following agreement level: 0.2–0.4 fair, 0.4–0.6 moderate, 0.6–0.8 substantial and >0.8 almost perfect (Landis and Koch, 1977). ICCs were assessed for both movement-related and absolute pre-movement baseline beta activity derived from both sensorimotor cortices. To account for multiple comparisons in the ICC analysis, the significance level was Bonferroni-corrected (corrected *p* values: 0.05/12 for beta parameter estimates and 0.05/6 for kinematic measures). In addition, exploratory Monte-Carlo simulations (50 iterations) were performed to investigate the minimum number of trials (5–50 trials; max trial number was limited by the smallest number of remaining trials across subjects and sessions) required to obtain highly reliable (ICC>0.8) beta power measures.

4.4 Results

Behavioural and EEG data during the performance of the simple motor task across six separate sessions for six healthy subjects are reported.

4.4.1 Behavioural results

All subjects were able to perform the motor task. The kinematic measures are summarised in **Table 4.1** for each of the six EEG sessions. As expected, reaction time (RT), movement time (MT) and peak velocity (PV) in the motor task were stable across separate sessions, as confirmed by a lack of main effect of 'time' for all kinematic measures [RT: $F_{(5,20)}$=2.242, p=0.156; MT: $F_{(5,20)}$=3.661, p=0.087; PV: $F_{(5,20)}$=0.414, p=0.709, all Greenhouse-Geisser corrected].

Subjects performed flexion and extension with similar kinematics [RT: $F_{(1,4)}$=0.714, p=0.446; MT: $F_{(1,4)}$=5.243, p=0.084; PV: $F_{(1,4)}$=0.771, p=0.430] and no significant interactions between 'time' and 'condition' were found [RT: $F_{(5,20)}$=1.29, p=0.328; MT: $F_{(5,20)}$=2.37, p=0.159; PV: $F_{(5,20)}$=3.12, p=0.090, all Greenhouse-Geisser corrected]. Since there was no significant difference between conditions (flexion, extension), the subsequent results are based on kinematic data collapsed across conditions. Reliability analysis across sessions revealed ICCs of fair to substantial agreement [ICC_{RT}=0.750, p<0.0001, ICC_{MT}=0.370, p=0.002], with peak velocity demonstrating highest intra-individual reliability [ICC_{PV}=0.774, p<0.0001]. This suggests that movement execution remained similar across sessions and that significant neurophysiological differences between sessions cannot be explained by changes in movement kinematics.

Table 4.1 | Summary of kinematic measures acquired during the performance of the simple motor task for each EEG session.

		Session					
		S1	S2	S3	S4	S5	S6
RT [ms]	Flex	529±41	543±48	550±38	536±80	492±53	501±49
	Ext	583±140	583±99	592±134	577±172	518±101	531±124
MT [ms]	Flex	905±166	822±162	793±120	767±79	768±92	753±75
	Ext	780±109	664±96	788±158	650±114	660±153	650±139
PV [deg/s]	Flex	238±93	238±85	238±57	235±74	257±97	246±76
	Ext	270±107	247±78	226±48	235±87	264±111	268±117

Kinematic measures are presented for each EEG session (S1–S6) and condition (flexion, extension). RT: Reaction Time; MT: Movement Time; PV: Peak. Values given are mean ±SD

4.4.2 Spectral power and peak frequency measures

Average spectral changes in contralateral and ipsilateral sensorimotor cortices in response to cue presentation are shown in **Figure 4.3** for each EEG session. After cue onset and during movement, a reduction in beta power, MRBD, was observed in both sensorimotor cortices with two distinguishable troughs: the first

during the movement towards the target and the second during the return to the initial start position. During the static contraction/holding phase of the motor task the strength of beta power increased. This is in agreement with studies demonstrating an increase in beta power as soon as the contraction becomes stable (Baker et al., 1999) or the movement is sustained (Cassim et al., 2000) in line with the hypothesis that beta oscillations play a role in stabilizing the current motor state whilst compromising initiation of new movements (Engel and Fries, 2010; Gilbertson et al., 2005b; Van Wijk et al., 2009). After return movement cessation, a strong but transient increase in beta power, PMBR, was observed predominantly in contralateral sensorimotor cortex. The gross morphology of the pattern of movement-related beta oscillations in both sensorimotor cortices shows good resemblance between shorter and longer between-session time intervals.

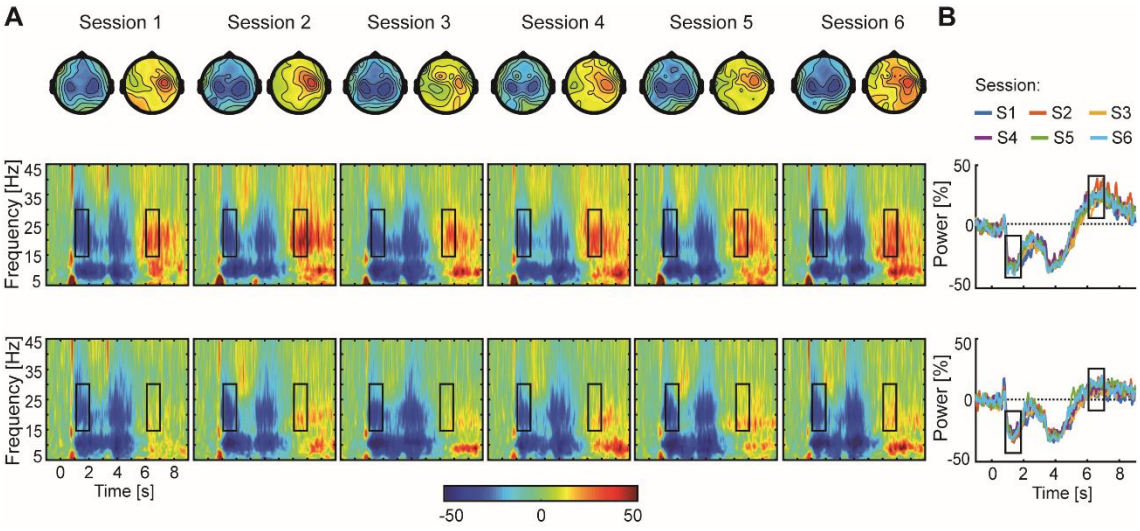

Figure 4.3 | Average movement-related changes in spectral power.
A*, Topographies of relative power change in beta frequency (15–30 Hz) during and after movement are averaged over the time window of interest 1–2 s and 6–7 s for MRBD and PMBR, respectively, as indicated by the black rectangles. Time-frequency spectrograms are averaged across subjects separately for contralateral (upper panel) and ipsilateral (lower panel) sensorimotor cortex for all EEG sessions and highlight good resemblance of gross morphology.* ***B****, Overlaid averaged beta power traces for the six sessions (S1 = blue, S2 = orange, S3 = yellow, S4 = purple, S5 = green, S6 = light blue). The grey patches indicate the time windows of interest (MRBD and PMBR) that were tested for significant differences between sessions and hemispheres.*

Estimates of power change during movement (MRBD) and after movement cessation (PMBR) were both unaffected by 'time' or 'condition' (F-statistics and p-values of all ANOVAS are summarized in **Table 4.2**). In addition, while no main effect of 'hemisphere' on the magnitude of MRBD was found, PMBR was significantly stronger in contralateral than ipsilateral sensorimotor cortex [$F_{(1,5)}$=7.03, p=0.045, effect size η_p^2=0.584], indicating contralateral predominance of the beta power rebound. Throughout the pre-movement baseline period, absolute power estimates were similar across all sessions, conditions and both sensorimotor cortices. Likewise, no significant 'time x condition', 'time x hemisphere', 'hemisphere x condition' or 'time x hemisphere x condition' interaction effects were found for any of the spectral power measures.

Peak frequency of beta activity in the pre-movement baseline period as well as in the time window in which MRBD occurred did not differ significantly within subjects between sessions, conditions or hemispheres. In contrast, PMBR peak frequency varied as a function of 'time' ($F_{(5,25)}$=2.70, p=0.044, effect size η_p^2=0.351), but not 'condition' or 'hemisphere'. Finally, there were no significant interactions for any of the peak frequency measures (**Table 4.2**).

***Table 4.2* | ANOVA results for spectral power and peak frequency estimates.**

	Time	*Condition*	*Hemisphere*	*Interactions*
Power				
BB	$F_{(5,25)}=1.45$, $p=0.240$	$F_{(1,5)}=0.01$, $p=0.958$	$F_{(1,5)}=1.44$, $p=0.284$	*n.s.*
MRBD	$F_{(5,25)}=0.77$, $p=0.583$	$F_{(1,5)}=0.46$, $p=0.528$	$F_{(1,5)}=2.68$, $p=0.163$	*n.s*
PMBR	$F_{(5,25)}=1.88$, $p=0.134$	$F_{(1,5)}=1.02$, $p=0.359$	**$F_{(1,5)}=7.03$, $p=0.045$**	*n.s*
Peak Frequency				
BB	$F_{(5,25)}=1.21$, $p=0.341$	$F_{(1,5)}=0.69$, $p=0.454$	$F_{(1,5)}=2.45$, $p=0.192$	*n.s*
MRBD	$F_{(5,25)}=0.35$, $p=0.876$	$F_{(1,5)}=0.99$, $p=0.375$	$F_{(1,5)}=0.63$, $p=0.471$	*n.s.*
PMBR	**$F_{(5,25)}=2.70$, $p=0.044$**	$F_{(1,5)}=0.00$, $p=0.959$	$F_{(1,5)}=0.09$, $p=0.777$	*n.s.*

Significant effects are indicated in bold. BB: pre-movement baseline beta; MRBD: Movement-related Beta Desynchronization; PMBR: Post-movement Beta Rebound; n.s.: not significant.

4.4.2.1 Reliability of spectral power and peak frequency measures

Figure 4.4 shows the pre-movement baseline and movement-related beta parameter estimates derived from contralateral and ipsilateral sensorimotor cortices. The degree of clustering in these plots provides a visual impression of the within- and between-subject variability. Individual baseline beta power ranged approximately 13.87–49.76 μV^2 in both sensorimotor cortices with an average of 27.6±9.79 μV^2 (mean ±SD), while within-subject variability was small with a range of 1.19–4.90 μV^2 (**Figure 4.4**A, left column). The magnitude of MRBD ranged between -52.1 to +20.2 % with an average of -30.4 ±14.1 % and -25.8±17.5 % for contralateral and ipsilateral sensorimotor cortex, respectively (**Figure 4.4**A, middle column). PMBR in contralateral sensorimotor cortex ranged between -10.1 and +70.6 % (25.4±19.7 %) whereas it only ranged between -12.6 and +28.1 % (10.2±7.4 %) in ipsilateral sensorimotor cortex (**Figure 4.4**A, right

column). By contrast, within-subject variability for MRBD and PMBR power measures was small and fell within a range of ~2–7 % per subject.

Individual peak frequencies during the pre-movement baseline period fell within a frequency range of 17.4 to 23.9 Hz (19.8±1.5 Hz) and displayed small within-subject variability of 0.2–1.6 Hz (**Figure 4.4**B, left column). In comparison, peak frequencies of movement-related beta oscillations spanned frequencies from 16.2–29.1 Hz with an average of 20.8±2.2 Hz for MRBD (**Figure 4.4**B, middle column) and 22.7±3.7 Hz for PMBR (**Figure 4.4**B, right column). Notably, within-subject variability was relatively large and ranged from approximately 0.4–4.8 Hz per subject.

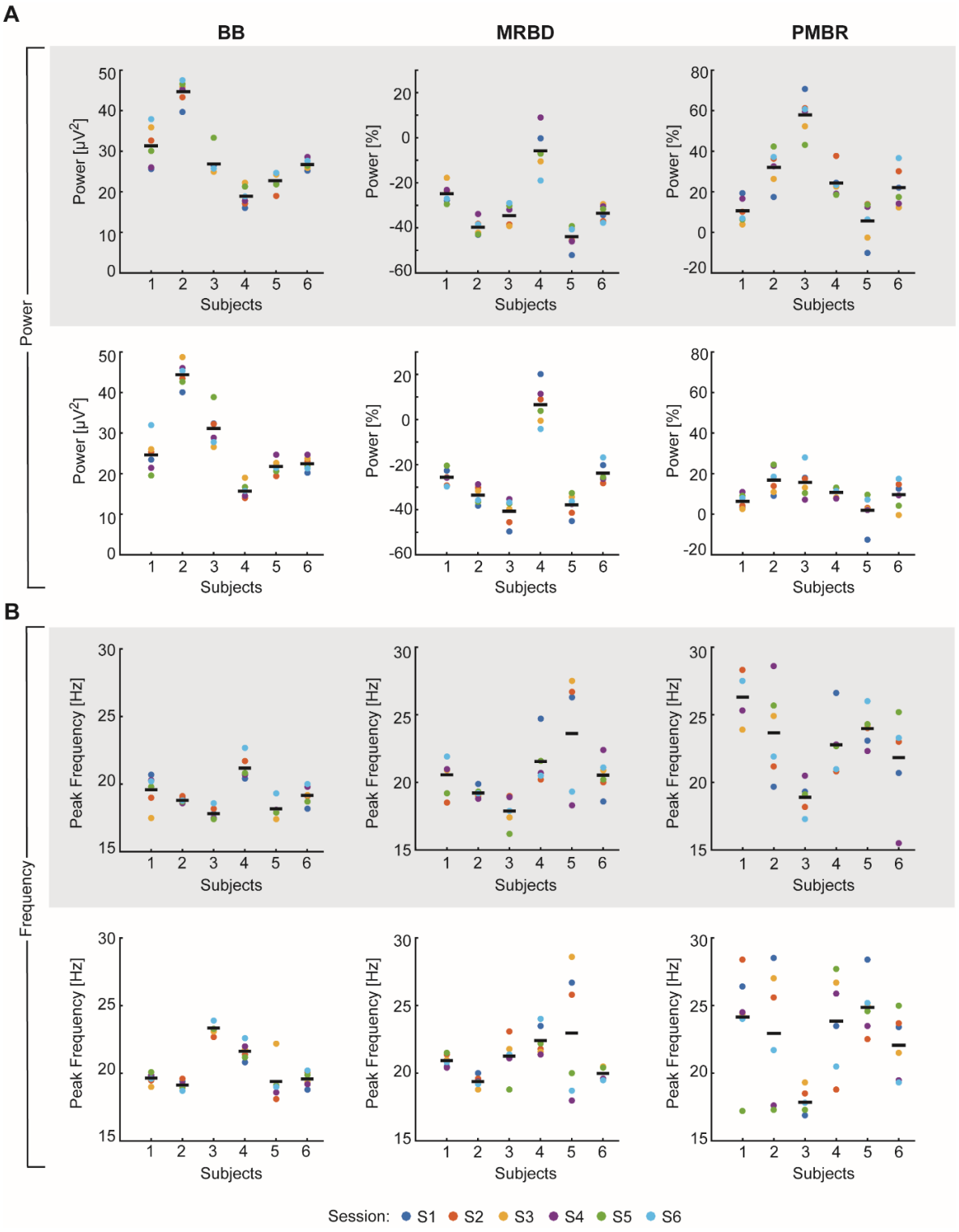

Figure 4.4 | Test-retest reliability of beta-band activity.
*Test-retest reliability of spectral power (**A**) and peak frequency (**B**) measures across separate sessions (S1–S6). Individual values were extracted for each EEG session from pre-selected electrodes overlying contralateral (grey shading) and ipsilateral sensorimotor cortex and distinct time windows (BB: -1–0 s; MRBD: 1–2 s; PMBR: 6–7 s). The degree of clustering gives a visual impression of the*

within-subject and between-subject variation. Black horizontal bars represent grand-mean (across sessions) for each subject.

For a quantitative measure of repeatability of beta oscillations, Intraclass Correlation Coefficients (ICC) were calculated for spectral power of the selected time windows (pre-movement baseline, MRBD and PMBR) and the corresponding peak frequency. Overall, ICC values indicated almost perfect reliability for power measures [mean ICC=0.832, ICC range=0.490–0.912, p<0.001; refer to **Figure 4.5**A], but only moderate reliability for peak frequency estimates [mean ICC=0.537, ICC range=0.231–0.929, p<0.033; refer to **Figure 4.5**B]. ICC values were consistently highest for pre-movement baseline beta power [contralateral sensorimotor cortex: ICC=0.894, p<0.0001; ipsilateral sensorimotor cortex: ICC=0.907, p<0.0001], followed by MRBD [contralateral sensorimotor cortex: ICC=0.859, p<0.0001; ipsilateral sensorimotor cortex: ICC=0.907, p<0.0001] and PMBR power measures [contralateral sensorimotor cortex: ICC=0.818, p<0.0001; ipsilateral sensorimotor cortex: ICC=0.420, p<0.001]. Interestingly, ICC values derived for pre-movement baseline beta and MRBD power estimates yielded slightly higher reliability for ipsilateral than contralateral sensorimotor cortex, while reliability of PMBR power estimates was higher for contralateral sensorimotor cortex. The lower ICC value for PMBR power from ipsilateral sensorimotor cortex was likely due to low between-subject variability, with most values ranging between 0 % and 20 %, thereby primarily reflecting random fluctuations around the baseline level (**Figure 4.4**A).

Assessment of peak frequency yielded a similar reliability trend, with pre-movement baseline beta peak frequency showing highest ICC values [contralateral sensorimotor cortex: ICC=0.717, p<0.0001; ipsilateral sensorimotor cortex: ICC=0.929, p<0.001], followed by MRBD [contralateral sensorimotor cortex: ICC=0.540, p<0.0001; ipsilateral sensorimotor cortex: ICC=0.231, p<0.05] and PMBR peak frequency [contralateral sensorimotor cortex: ICC=0.483, p<0.01; ipsilateral sensorimotor cortex: ICC=0.321, p<0.01]. Beyond the lower reliability of peak frequency measures compared to spectral power measures of beta activity, movement-related beta peak frequency estimates

showed substantially lower reliability, and this appeared to be driven by greater within-subject variability across sessions (**Figure 4.4**B).

In summary, the ICC values indicate that spectral power measures of beta activity were more consistent across EEG sessions than the corresponding peak frequency measures. Additionally, peak frequency during the pre-movement (resting) baseline period was more reliable compared to peak frequency estimates of MRBD and PMBR.

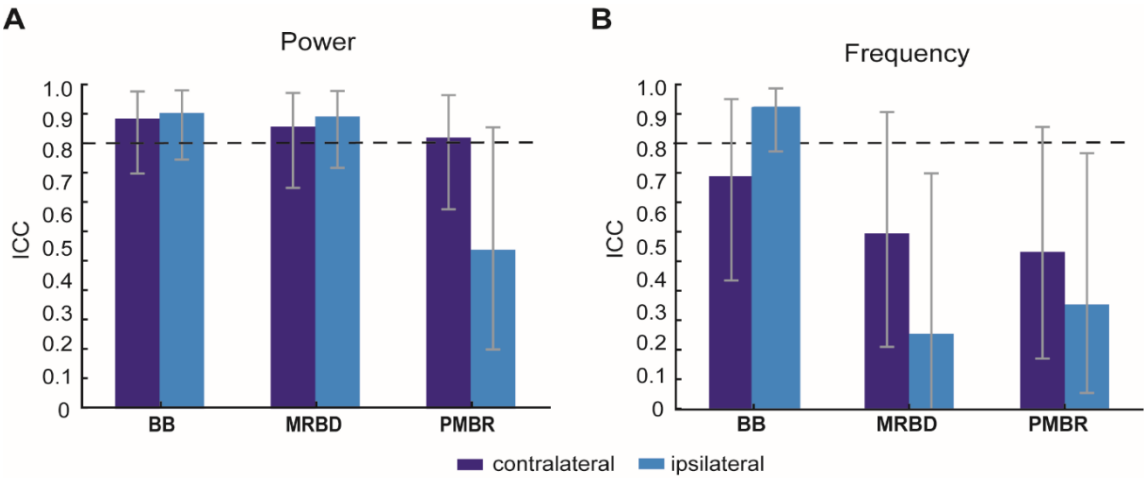

Figure 4.5 | Intraclass correlation coefficient (ICC) analysis.
*Test-retest reliability of spectral power (**A**) and peak frequency (**B**) measures of beta oscillatory activity derived from contralateral and ipsilateral sensorimotor cortices, respectively. Values given are intraclass correlations (ICCs). Grey error bars represent lower and upper boundaries of the ICC. ICCs > 0.8 indicate almost perfect levels of agreement across sessions. Spectral power measures demonstrate high reliability across sessions while frequency measures were more variable.*

To assess reliability of beta power estimates as a function of the number of trials required (i.e. 5, 10, 50), exploratory Monte-Carlo simulations were performed. **Figure 4.6** shows the minimum number of trials required in order to obtain estimates of beta power that show satisfying within-subject reliability across sessions. Based on these findings, the minimum number of trials required to achieve high ICC values varies for the three different beta power measures, but on average at least 40 trials are advisable to reliably detect these beta dynamics.

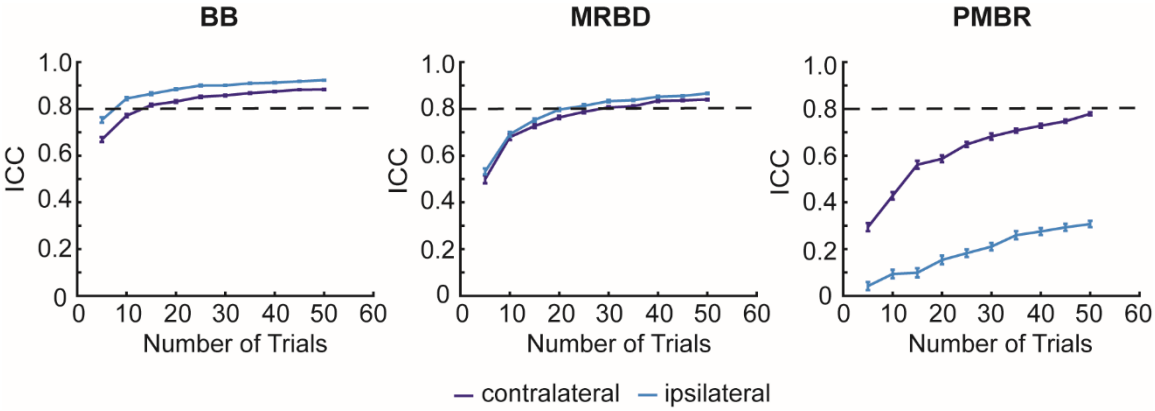

Figure 4.6 | Intraclass correlation coefficients as a function of trial number. *Monte-Carlo simulations in which ICC was repeatedly calculated (50 iterations), using varied numbers of trials (5–50 trials), were used to assess the relationship between trial number and reliability of pre-movement (resting) and movement-related beta power measures derived from both sensorimotor cortices. ICCs > 0.8 indicate almost perfect levels of agreement across sessions. Error bars represent SEM. On average, 40 trials were sufficient to reliably detect beta-band dynamics.*

4.4.2.2 Reliability as a function of time

To explore whether test-retest reliability varies as a function of time interval between sessions (i.e. one week apart: session 1–2; two weeks apart: session 1–3; six weeks apart: session 5-6), we calculated Pearson correlation coefficients between each session. **Figure 4.7** illustrates the correlation coefficients between EEG sessions, separately for spectral power (**Figure 4.7**A) and peak frequency (**Figure 4.7**B) measures in the pre-movement baseline (**Figure 4.7**, left column), MRBD (**Figure 4.7**, middle column) and PMBR (**Figure 4.7**, right column) time window. The correlations fluctuated across beta parameter estimates and hemispheres, but no systematic influence of the length of the time interval was observed. Whereas the correlations for pre-movement baseline beta and MRBD power estimates were consistently high across the different test-retest intervals for both contralateral [BBP: *r* range=0.880–0.988, *p* range=0.0002–0.021; MRBD: *r* range=0.880–0.988, *p* range=0.0002–0.021] and ipsilateral sensorimotor cortices [BBP: *r* range=0.750–0.980, *p* range=0.0006–0.060; MRBD: *r* range=0.750–0.980, *p* range=0.0006–0.060], the coefficients for PMBR power showed larger variability, specifically in the ipsilateral [*r* range=0.075–

0.900, *p* range=0.014–0.888] compared to the contralateral [*r* range=0.602–0.971, *p* range=0.006–0.207] hemisphere. The notable hemispheric variation in test-retest reliability of PMBR potentially resulted from the absence of an ipsilateral peak in PMBR. While spectral power measures of beta activity demonstrated consistently high between-session correlations, correlation coefficients for peak frequency estimates varied widely. Particularly low coefficients were obtained for movement-related beta activity from contralateral [MRBD: *r* range=-0.427–0.920, *p* range=0.009–0.743; PMBR: *r* range=0.161–0.957, *p* range=0.003–0.760] and ipsilateral [MRBD: *r* range=-0.559–0.954, *p* range=0.003–0.958; PMBR: *r* range=-0.438–0.796, *p* range=0.035–0.916] sensorimotor cortex, while peak frequency of pre-movement baseline beta activity was somewhat more consistent between sessions [contralateral sensorimotor cortex: *r* range=0.285–0.935, *p* range=0.006–0.642; ipsilateral sensorimotor cortex: range=0.439–0.975, *p* range=0.0009–0.384].

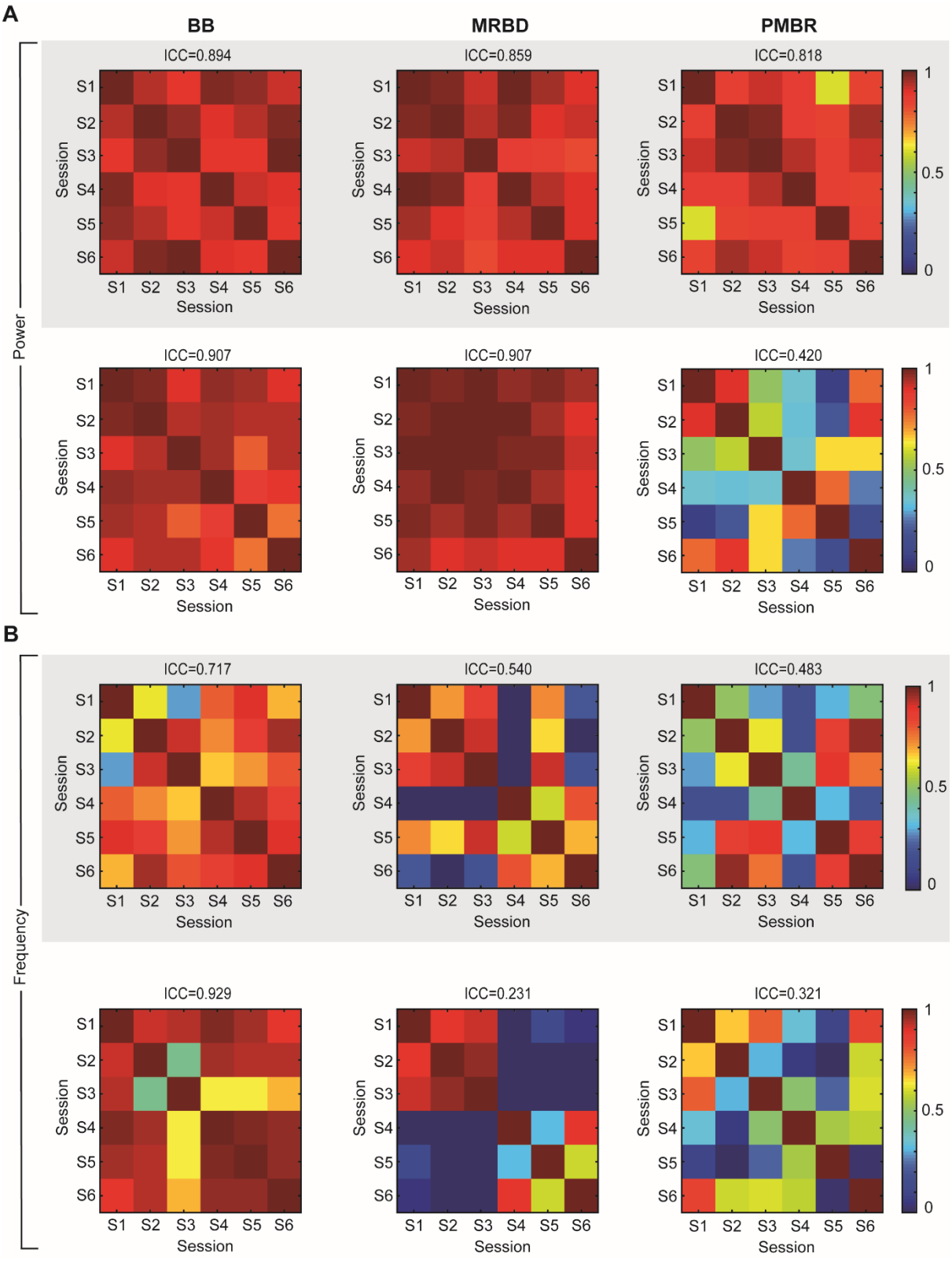

Figure 4.7 | Between-sessions correlation coefficients.
Between-session (S1–S6) correlation coefficients and corresponding intraclass correlation coefficients (ICCs) for spectral power and peak frequency estimates for contralateral (grey shading) and ipsilateral sensorimotor cortices. The colour bar indicates the correlation coefficients (r) presented in the matrices.

4.5 Discussion

By implementing a longitudinal design, it was possible to characterise the intra-individual reliability of sensor-derived EEG-based oscillatory measures in the power and frequency domain, and assess their reliability as a function of time interval between sessions.

4.5.1 Movement-related beta oscillations show high test-retest reliability

The present study assessed the test-retest reliability of movement-related and pre-movement (resting) beta oscillatory activity in a group of healthy subjects across several weeks. The aim was to determine whether EEG-derived spectral power and peak frequency measures of beta oscillations (I) show small within-subject variability and (II) are stable as a function of between-session time interval, two prerequisites for their use as clinically relevant biomarkers. The present results demonstrate that spectral power estimates of resting (BB: average ICC=0.901) and movement-related beta activity (MRBD: average ICC=0.883; PMBR: average ICC=0.619) are remarkably consistent across sessions. In addition, corresponding peak frequency measures yielded lower ICC values compared to the assessment of spectral power. While pre-movement baseline beta peak frequency was highly reliable across sessions, peak frequency measures of movement-related beta activity displayed greater within-subject variability (MRBD: average ICC=0.386; PMBR: average ICC=0.402). The respective between-session correlation coefficients further corroborate these findings. This suggests that measures of spectral power as well as resting peak frequency reflect stable individual activation patterns that could be used to evaluate functional dynamic changes in the brain, such as the impact of disease or treatment administration.

Abundant evidence exists for the reliability of spontaneous resting-state beta activity within the same recording session and between sessions with time intervals of days, weeks and up to years (e.g. Pollock et al. 1991; Burgess & Gruzelier 1993; Kondacs & Szabo 1999; McEvoy et al. 2000; Nikulin & Brismar 2004; Corsi-Cabrera et al. 2007; Napflin et al. 2007; Martin-Buro et al. 2016)). However, there is no such literature on movement-related beta oscillations, even though these beta-band dynamics appear to be especially interesting in the study

of individual differences related to tracking performance. Studies investigating event-related oscillatory activity using cognitive and imagery tasks highlight that their reliability varies as a function of frequency band, brain region and type of task (Friedrich et al., 2013; Krause et al., 2001; Neuper et al., 2005).

Whilst beta oscillations have shown acceptable between-session reliability (Cronbach's alpha > 0.7) during motor imagery (Friedrich et al., 2013), little is known regarding reliability during active movements. An indirectly related study from Wilson and colleagues (Wilson et al. 2014) found a linear increase from morning (9:00) to afternoon (16:00) in the amplitude of MRBD and PMBR during a finger tapping task, but small variability over three consecutive days, indicating the reliability of movement-related beta-band signatures. The current study augments the work by Wilson and colleagues by systematically assessing the reliability of spectral power and peak frequency estimates of movement-related beta activity across several weeks.

Compared to previous studies, the motor task utilized in this study involved wrist flexion and extension, which are known to elicit stronger PMBR compared to finger and thumb movement (Pfurtscheller et al., 1998a). As a result, consistent with prior findings, bilateral suppression of beta oscillatory activity during movement (Gross et al., 2005; Pfurtscheller et al., 1996; Salmelin and Hari, 1994) and clear beta rebound after movement termination, which was significantly larger for contralateral compared to ipsilateral motor cortex (Salmelin and Hari, 1994; Stancak and Pfurtscheller, 1995) was found. Rau et al. (2003) demonstrated that ipsilateral MRBD corresponds to increased cortical excitability of ipsilateral M1, in line with the argument that MRBD indicates activation of the sensorimotor cortex (Pfurtscheller and Berghold, 1989; Pfurtscheller and Lopes, 1999; Rau et al., 2003). However, ipsilateral MRBD has also been proposed to reflect neural processes inhibiting mirror movements through interhemispheric inhibition (Jurkiewicz et al., 2006; Van Wijk et al., 2012). In contrast, PMBR has been associated with inhibition of movement initiation (Gilbertson et al., 2005b) in conjunction with decreased corticospinal excitability (Chen et al., 1998). Although the functional role of ipsilateral activity in unimanual motor tasks is not fully understood, the different contra- and ipsilateral modulation patterns for

MRBD and PMBR imply that these beta-band dynamics are, at least to a certain degree, independent processes with distinct functional significance.

The high test-retest reliability of movement-related beta power measures suggest that they might be useful in repeated-measures studies, for example, investigating longitudinal changes in clinical and non-clinical populations or assessing the impact of pharmacological interventions. ICC values for MRBD and PMBR estimates were comparably high in both contralateral and ipsilateral sensorimotor cortices, except for PMBR from the ipsilateral hemisphere, which was markedly lower. A reliable measure (high ICC) requires small within-subject variance relative to between-subject variance. Closer inspection suggests that the reduced reliability observed for the ipsilateral PMBR was related to the low between-subject variability of this power estimate (see **Figure 4.4**A). In line with previous studies demonstrating a contralateral preponderance of PMBR (Salmelin and Hari, 1994; Stancak and Pfurtscheller, 1995), the ipsilateral PMBR estimates likely reflect random fluctuation around the baseline level, which explains the low between-subject variability and therefore, the lower ICC value.

Individual variability in EEG-derived estimates of beta-band oscillations can be accounted for not only by neural signals of the brain but also by the conductivity of the electrical tissue between the current source and the recording electrode (Buzsáki et al., 2012; Lopes da Silva, 2011). While factors such as pyramidal cell density, cortical microarchitecture, skull thickness and skin conductance affect sensor-derived measures of neuronal oscillations and thus are likely to account for subject-specific differences, they are also expected to be stable over time and therefore also contribute to low intra-individual variability. Accordingly, the present findings that test-retest reliability of beta oscillatory activity was independent of between-session time intervals may be attributed to these stable individual differences and a consistent behaviour during the performance of the motor task. However, it should be noted that some of the spectral power measures were less reliable than others (i.e. ipsilateral PMBR), demonstrating that reliability of sensor-derived measures is not solely due to these morphological differences but reflects the variable stability of different neural signals.

Compared to spectral power, peak frequency displayed greater within-subject variability (see **Figure 4.4**B). Although peak frequency during the pre-movement baseline period yielded the highest measures of reliability, test-retest reliability was lower compared to spectral power measures, in particular for contralateral sensorimotor cortex. Peak frequency estimates of MRBD and PMBR displayed fair-to-moderate reliability. Importantly, the reduced test-retest reliability of movement-related beta peak frequency compared to resting peak frequency seems to be related to the active engagement of the motor system. It should be noted that peak detection for pre-movement baseline beta in some cases was ambiguous when the power spectra showed no clear peak in the beta range even after compensation for the 1/f effect. Furthermore, some subjects displayed double frequency peaks during movement-related beta modulation in line with previous studies suggesting a functional subdivision into low and high frequencies within the beta band (Litvak et al., 2011; Oswal et al., 2016; Van Wijk et al., 2016). These factors might be reasons why ICC values were lower.

While measures of beta activity may be affected by a variety of factors, the present study provides evidence that these signatures are highly reliable and consistent over several weeks in a small sample of healthy subjects. The almost perfect intra-individual reliability and high number of sessions provide support to the finding of stable beta power measures. This is important as EEG is an excellent tool for the identification of widely-available and cost-effective biomarkers that might have the potential to bridge the gap between cellular and behavioural accounts of cortical function and plasticity in both healthy and diseased states (Ward, 2015). Establishing the reproducibility of neuronal oscillations is crucial for the identification of EEG-derived biomarkers, with substantial clinical utility for patient stratification and prediction of treatment response.

A potential limitation of this study is the sample of healthy young subjects, which limits the generalizability of the reliability results. In particular, resting and movement-related beta-band estimates have been shown to be modulated by healthy ageing (Gaetz et al. 2010; Rossiter et al. 2014; Heinrichs-Graham & Wilson 2016) and pathology (Brown 2007; Heinrichs-Graham et al. 2013; Heida et al. 2014; Rossiter et al. 2014) possibly resulting in different reliability patterns.

Future studies should thus determine the reliability of movement-related beta-band activity across the lifespan and in the context of movement disorders.

4.5.2 Conclusion

In conclusion, this study is the first to comprehensively evaluate the reliability of spectral power and peak frequency measures of movement-related beta oscillations across several weeks. The present study highlights that spectral power measures of EEG-derived oscillatory signatures associated with the performance of a motor task are highly reproducible. This finding is important as it suggests that measurements of beta-band power reflect meaningful and reliable individual differences in the motor system that may be utilized as biomarkers in clinical and/or longitudinal research. In addition, the assessments indicate that beta peak frequencies are more variable across sessions which should be taken into account when using extrinsic neurostimulation at beta frequency (Guerra et al., 2016; Joundi et al., 2012; Pogosyan et al., 2009). Overall, the highly reproducible nature of beta oscillations suggests that they may be an appropriate assay for longitudinal studies and/or clinical studies employing sensor-derived EEG-based oscillatory read-outs.

Chapter 5 Predicting individual differences in motor skill learning

5.1 Abstract

People vary in their capacity to learn and retain new motor skills, but the electrophysiological mechanisms underlying individual differences in motor learning are incompletely understood. The findings reported in **Chapter 4** served to validate the notion that EEG-derived measures of beta-band activity reflect meaningful individual differences, a prerequisite for exploring their relationship with motor learning behaviour in humans. Employing a multivariate approach, I here investigate whether these standard measures of resting and movement-related beta power from bilateral sensorimotor cortex could explain inter-individual differences in motor learning behaviour. Twenty young (18–30 years) and twenty elderly (62–77 years) healthy adults were trained on the continuous tracking task introduced in **Chapter 3** and subsequently retested at two different time points after initial training (45–60 min and 24 hours later). Scalp EEG was recorded during the performance of the simple motor task before each training and retest session.

Although short-term motor learning was comparable between young and elderly individuals, elderly subjects exhibited higher resting beta power and movement-related beta desynchronization (MRBD). Multivariate modelling within leave-one-out cross-validation (LOOCV) revealed that a combination of subjects' behaviour on the continuous tracking task together with movement-related beta activity significantly predicted performance levels 45–60 min, but not 24 hours after initial training. Crucially, pre-training levels of movement-related beta activity helped to explain individual differences in performance in a way that behaviour alone could not. In the context of disease, these findings suggest that measurements of beta-band activity may offer novel targets for therapeutic interventions designed to promote rehabilitative outcomes after brain injury.

5.2 Introduction

The ability to learn and retain new motor skills is pivotal for everyday motor activities and sustained independence in senior adults (Seidler et al., 2010). As outlined in **Chapter 1**, the process of learning a motor skill does not only involve the improvement in performance during initial training (online) but also performance changes after training ended (offline). Following training, motor memory consolidation takes place, resulting in retention of the acquired motor skill or even further improvements (Brashers-Krug et al., 1996a; Halsband and Lange, 2006; Magill, 2011; Robertson et al., 2004a; Walker, 2005). However, people show considerable inter-individual heterogeneity in their capacity to learn and retain new skills. Understanding the neurophysiological processes underlying individual differences, and their predictive value in the context of motor learning, is of significant scientific and clinical importance for improving response to treatment and long-term outcomes of rehabilitation in the elderly and patients with brain injury (Stinear, 2010; Ward, 2017).

Neuroimaging studies have revealed substantial motor learning-related plasticity within the sensorimotor cortex network, involving functional and structural reorganization that occurs early during motor skill acquisition (Halsband and Lange, 2006; Karni et al., 1995; Muellbacher et al., 2002; Nudo et al., 1996a; Robertson et al., 2005; Sanes and Donoghue, 2000). Crucially, this includes the modulation of GABAergic inhibitory activity as discussed in detail in **Chapter 1** (Buetefisch et al., 2000; Floyer-Lea et al., 2006; Pleger et al., 2003; Stagg et al., 2011a). Changes in the balance between GABAergic inhibitory and glutamatergic excitatory processes are one major mechanism through which the potential for plasticity is regulated (Bavelier et al., 2010; Benali et al., 2008), and are thought to be reflected in the amplitude of oscillations as picked up with electroencephalography (EEG) (Jensen et al., 2005; Murakami and Okada, 2006; Traub et al., 2004; Yamawaki et al., 2008).

Oscillations in the beta (15–30 Hz) frequency range, prevalent in sensorimotor cortex, are fundamental for motor control (Engel and Fries, 2010; van Wijk et al. 2012). It is well established that beta-band oscillations are dominant at rest and show distinctive movement-related power modulations, including the suppression of beta oscillations during movement (Movement-Related Beta

Desynchronization, MRBD) and a rebound after movement cessation (Post-Movement Beta Rebound, PMBR) (Pfurtscheller and Lopes Da Silva, 1999; Pfurtscheller et al., 1998a; Salmelin and R. Hari, 1994; Stancak and Pfurtscheller, 1995). While their relationship with motor behaviour is well established, the functional role of resting and dynamic movement-related beta activity for the capacity to both learn and retain new motor skills remains unclear.

The main objective of this study was to (I) explore the neurophysiological mechanisms associated with individual differences in short-term motor learning behaviour in healthy ageing subjects. By including both young and elderly subjects, inter-subject variability was maximised, because alterations in beta oscillations have been seen with ageing (Gaetz et al., 2010; Heinrichs-Graham and Wilson, 2016; Rossiter et al., 2014b), and previous studies have suggested an age-related reduction in the potential for plasticity (Chollet, 2013; Fathi et al., 2010; Tecchio et al., 2008; Todd et al., 2010). Given the link between beta oscillations and both inhibitory GABAergic activity (Hall et al., 2011, 2010a; Jensen et al., 2005; Muthukumaraswamy et al., 2013) and learning (Boonstra et al., 2007; Houweling et al., 2008; Pollok et al., 2014), I hypothesized that beta oscillatory activity can account for differences in the capacity to learn and retain new motor skills. Importantly, my chosen EEG measures of resting and movement-related beta-band power have previously been shown to have high intra-subject reliability (Espenhahn et al., 2016), a prerequisite for exploring the longitudinal relationship between individual neurophysiological variations and differences in the capacity to learn a new motor skill.

Since ageing is thought to affect both the potential for plasticity (Chollet, 2013; Fathi et al., 2010; Tecchio et al., 2008; Todd et al., 2010) and the ability for motor learning (for review see (Ren et al., 2013; Seidler, 2006; Voelcker-Rehage, 2008)), although this seems to be dependent on the nature of the task, secondary objectives were to assess (II) whether the ability to learn and retain new motor skills deteriorates with age, and (III) whether age-related changes in properties of beta oscillations are in line with, and/or augment previous findings (Gaetz et al., 2010; Heinrichs-Graham and Wilson, 2016; Rossiter et al., 2014b).

5.3 Methods

5.3.1 Subjects

Forty subjects took part in the present study over two consecutive days. Two subjects had to be excluded because they either did not comply with the task requirements (n = 1 young; subject 17) or later disclosed a neurological disease (n = 1 elderly; subject 24). Thus, nineteen young (mean age = 25±4 years, range 18–30 years, 1 left-handed; for more details see **Table 5.1**) and nineteen elderly (mean age = 69±4 years, range 62–77 years, 1 left-handed) subjects were included for analyses (N = 38). All subjects had normal or corrected-to-normal vision, and fulfilled the following inclusion criteria: (a) no history of neurological or psychiatric disease; (b) no physical disability of the arms or wrists; (c) no use of drugs affecting the central nervous system or self-reported abuse of any drugs (e.g. analgesics, anticonvulsants, muscle relaxants, sedatives, hypnotics); and (d) age within specified range (18–30 years or 60–80 years). To minimize circadian fluctuations in beta oscillatory levels (Toth et al., 2007; Wilson et al., 2014), all subjects were tested in the time between 9am and 2pm after giving written informed consent. In addition, subjects were instructed to abstain from alcohol and caffeine the evening and morning before the testing.

At the beginning of the experiment, subjects underwent functional assessments to quantify upper limb (UL) motor ability, including NHPT (Kellor et al., 1971; Mathiowetz et al., 1985b) and grip strength task. Performance on the SART (Robertson et al., 1997) was used as a proxy of cognitive functioning (see **Table 5.1**). Since sleep has been shown to affect motor memory consolidation (Korman et al., 2007; Walker et al., 2002; Wilson et al., 2012), on both days, subjects additionally provided information about their sleep (computerised version of St. Mary's Hospital sleep questionnaire (Ellis et al., 1981)) for the nights preceding testing. Please refer to **Chapter 3** section 3.3 for details about the various tests.

5.3.2 Experimental design

The experimental design is illustrated in **Figure 5.1**. Since the primary objective of this study was to explore whether cortical beta-band activity is associated with individual differences in motor learning capacity, I here combined neuroimaging and motor learning on the continuous tracking task introduced in **Chapter 3** section 3.2.2. All subjects trained with their non-dominant hand on the continuous tracking task over a single training session (40 blocks; 20–40 min) with the aim of improving tracking performance beyond pre-training levels. The tracking task involved two types of sequences within each block, a *random* and a *repeated* sequence. Improvement on the random sequence is a measure of general skill learning, whilst any additional improvement on the repeated sequence reflects sequence-specific motor learning of the precise sequence pattern (Wulf and Schmidt, 1997). Tracking performance was defined as the accuracy (measured in RMSE) with which subject's wrist movement tracked the target movement (**Figure 5.2**A). Participants' tracking performance was retested at two different time points: 45–60 min (retest1 on day 1; 5 blocks) and 24 hours (retest2 on day 2; 10 blocks) after initial training. These retest sessions allowed (i) temporary effects (e.g. fatigue or boredom) that build up over the course of training (Brawn et al., 2010; Rickard et al., 2008) to dissipate, thus only leaving the fairly permanent learning effects and (ii) consolidation of motor memories to occur, which may result in retention, decrement or even enhancement of the previously acquired motor skill after a night's sleep (Robertson et al., 2004a; Walker, 2005).

EEG recorded during the performance of the simple motor task was used to assess pre-movement (resting) and movement-related beta activity before (Pre), immediately after (Post1) and 24-hours after (Post2) the initial training phase. On day 1, prior to the motor tasks, the mid-point and maxima of an individual's maximum AROM (see **Chapter 3** section 3.2.1 for details) around the wrist joint was measured and subsequently used as start and/or target positions in the continuous tracking task and simple motor task, respectively.

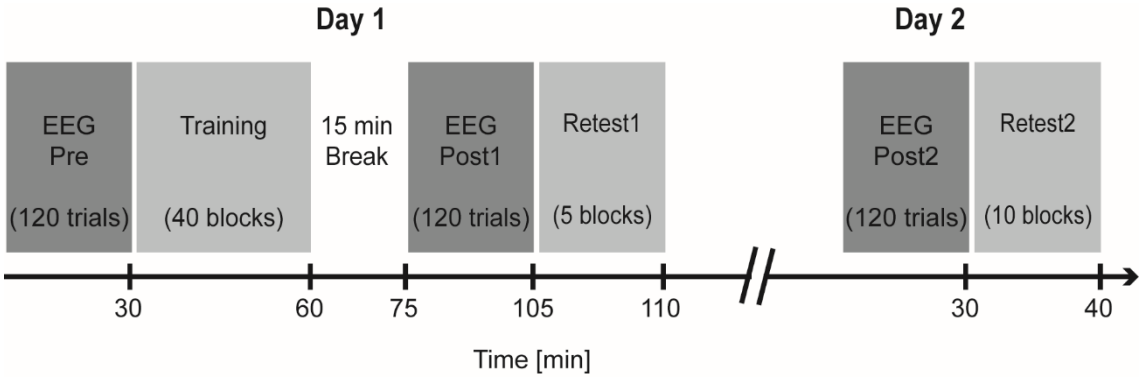

Figure 5.1 | Timeline of experiment employing EEG and motor learning. *EEG was recorded during the performance of a simple motor task before (Pre) and at two time points after the training phase (Post1 and Post2). Performance on the motor learning task was retested after a time delay on the same day (retest1 on day 1, 45–60 min after initial training) and the following day (retest2 on day 2, 24-hours after initial training).*

5.3.2.1 Apparatus and stimuli

All tasks were performed with the non-dominant hand resting in the instrumented wrist rig introduced in **Chapter 3** section 3.2.1. The wrist rig restricted movement to flexion and extension around the wrist joint in the horizontal plane and ensured minimal hand and arm movement during the experiment and EEG recording. Wrist angular displacement was sensed by a built-in potentiometer, with a displacement of 0° indicating a neutral position of the wrist, with the hand being in the same plane as the forearm. The angular position of the wrist was continuously displayed on a computer monitor as a cursor in the form of a red circle – referred to as "wrist cursor". The target was displayed either as an open yellow circle (continuous tracking task) or as a blue square (simple motor task).

5.3.2.2 Continuous tracking task

Subjects were required to continuously track a circular target (in yellow) that moved back and forth along a fixed arc through a predefined sequence of 12 positions (**Figure 5.2**A). For a detailed description of the continuous tracking task, please refer to **Chapter 3** section 3.2.2. In brief, the minimum jerk approach (Flash and Hogan, 1985; Hogan, 1984) was employed to ensure smooth target motion through the sequence positions. The maximum range of the target trajectory was defined as ±45° of wrist flexion and extension and the target always

started and finished at the individual mid-point position of each subject's AROM. Each block consisted of two sequences, one *random* and one *repeated* sequence presented in randomised order, with a 3 s stationary target between both. The repeated sequence was identical throughout initial training (40 blocks), and retest sessions (retest1 on day 1: 5 blocks; retest2 on day 2: 10 blocks) and randomly selected from a pool of 57 difficulty-matched sequences. Please refer to **Chapter 3** section 3.2.2.3 for details about the sequences. Each random sequence was encountered only once; however, the same set of difficulty-matched sequences was used across subjects. Subjects were instructed to move their wrist so as to shift the red wrist cursor to match the movement of the target as 'accurately and smoothly as possible'.

Prior to the training session, the average velocity with which the target moved along the arc was individually determined in order to ensure that the task was of equal difficulty for everyone at the beginning of the training and left enough room for improvement in performance. For this purpose, an adaptive up-down staircase procedure, which on any given trial, adjusted (increased/decreased) the target velocity dependent on the subject's preceding tracking performance until a pre-specified criterion range was reached was implemented. On average, subjects reached the criterion in 14.4±4.5 trials and there was no difference in the number of trials required between groups ($t_{(1,36)}$=0.94, p=0.072). The individually determined target velocity with which subjects were subsequently trained on the continuous tracking task was applied to all sessions and did not significantly differ between young (mean velocity ±SD = 55.38±6.92 deg/s) and elderly (mean velocity ±SD = 50.78±9.41 deg/s) subjects [$t_{(1,36)}$=1.71, p=0.095]. Please refer to **Chapter 3** section 3.2.2.5 for details about the adaptive staircase procedure used for individual determination of target velocity.

During initial training and retest sessions, online visual feedback in terms of a colour change of the wrist cursor (from red to green) was provided at times when the subject positioned the wrist cursor inside the circular target. In addition, at the end of each block, subjects were made aware of their change in tracking performance by presenting a score on the screen. Prior to the start of training, subjects received explicit verbal information regarding the presence of a repeated

sequence along with a random sequence in every block. However, they were not shown the repeated sequence. To determine the time point at which participants gained explicit knowledge of the repeated sequence, after each block they had to decide (forced-choice) which of the two sequences within each block the repeated sequence was – i.e. tell the experimenter whether it was the first or second sequence they tracked within the block (**Figure 3.4**C). The trajectories of the target and subject's wrist cursor did not leave a residual trail on the screen and hence, subjects could not visualize the entire target sequence.

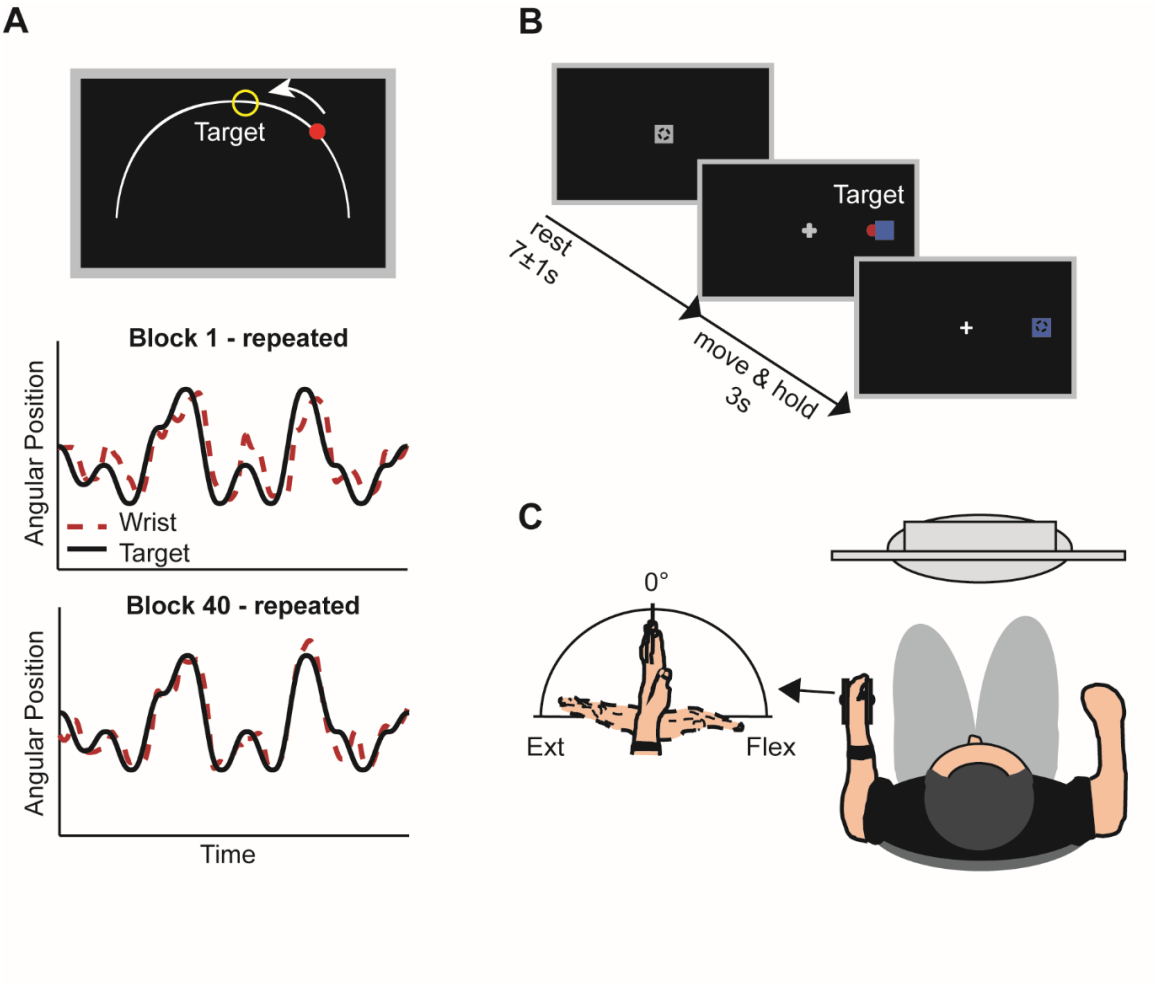

Figure 5.2 | Experimental setup and paradigms.
***A**, Subjects were trained to track a target (yellow circle) moving back and forth along a fixed arc as accurately and smoothly as possible. Online visual feedback in terms of a colour change of the wrist cursor (red to green) was provided at times when the wrist cursor was located inside the circular target. Original recordings during the continuous tracking task at the beginning and end of the initial training are shown for the repeated sequence of an example participant (A, lower panel). The solid black line represents the motion of the target, while the dashed red line represents the motion of the wrist. **B,** For the simple motor task,*

subjects were instructed to perform wrist flexion and extension to move the wrist cursor (red circle) from the initial start position (grey square) to one of two target positions (blue square) upon target presentation. ***C****, During both tasks, subjects sat in front of a computer monitor with their non-dominant hand rested in the wrist rig that restricted movement to flexion and extension around the wrist joint.*

5.3.2.3 Simple motor task

The simple motor task served to link individual differences in motor learning of the continuous tracking task with inter-subject differences in standard measures of EEG-derived beta power. For a detailed description of the simple motor task, please refer to **Chapter 3** section 3.2.3. Briefly, subjects performed visually cued wrist flexion and extension with their non-dominant hand during EEG recording. During each trial, wrist movements were always initiated from the same start position displayed at the centre of the screen that represented the mid-point of a subject's individual AROM (see **Chapter 3** section 3.2.1 for details about AROM measurement). The cue to perform wrist flexion or extension movements was the random appearance of one of two targets (in blue), on the left or right, equidistant from the central start position (**Figure 5.2**B). Each of the targets represented the subject's maximum wrist flexion or extension position. Subjects were instructed to move their wrist upon presentation of the target so as to shift the red wrist cursor from the central start position to match the position of the target in a 'quick and discrete' movement. They were also asked to move as soon as possible and to avoid anticipation or guessing of target appearance. The target position was displayed for 3 s and subjects had to maintain the wrist cursor inside the blue target until being cued to return to the initial start position. Once subjects returned to the start position, the next cue to move was delivered following a delay of 7±1 s. The task comprised 120 trials, and subjects were instructed to minimize eye movements by focusing on a centrally located fixation cross. As described in detail in **Chapter 3** section 3.7.1.2, kinematic data of individual wrist movements were analysed with regard to reaction time (RT), movement time (MT), and peak velocity (PV) and averaged per experimental condition on an average of 110±4 remaining trials. Since movement time and peak velocity were highly correlated (r>0.8), only reaction time and movement time were reported.

5.3.3 EEG recording

Scalp EEG was continuously recorded at 2084 Hz using 64 electrodes mounted on an elastic cap according to the international 10-20 EEG system. The impedance was kept below ≤5 kΩ and the EEG signal was referenced to Cz during recording. The timing of the visual cue (blue target) in the motor task was marked in the simultaneous EEG recording, with separate markers for each condition (flexion, extension). Surface EMG using bipolar electrodes in a belly-tendon montage placed on the wrist extensor (extensor carpi radialis, ECR) and flexor (flexor carpi radialis, FCR) muscles monitored movements of the non-dominant hand.

5.3.4 Data analysis

Analyses were conducted using custom-written routines in Matlab and the SPM12 toolbox (Wellcome Trust Centre for Neuroimaging). The fieldtrip toolbox (Oostenveld et al., 2011) was additionally employed for EEG data visualization. Statistical analyses were performed using SPSS and custom-written Matlab routines.

5.3.4.1 Motor learning data

For a detailed description of the kinematic data analysis, please refer to **Chapter 3** section 3.7.1.1. In brief, the behavioural measure “tracking performance” on the continuous tracking task was parametrized by RMSE (see **Equation 3.5**), an established composite measure of temporal and spatial measurements of time lag and distance (Al-Sharman and Siengsukon, 2014; Boyd and Winstein, 2006; Roig et al., 2014; Siengsukon and Boyd, 2009). Thereby, smaller RMSE values reflect better tracking performance. RMSE was calculated for *repeated* and *random* sequences separately and averaged across each block of the training and retest sessions.

As the beginning and end of individual training and retest sessions might not be representative of actual tracking performance (e.g. due to warm-up decrement at the beginning or fatigue at the end), a linear regression model was fitted across the first and last 5 blocks of individual training and retest sessions (approach adopted from (Waters-Metenier et al., 2014)). This fit provided a corrected

performance estimate of the first and last blocks of each session (**Figure 5.3**). Please note that performance refers to this corrected performance estimate unless stated otherwise.

The analysis then concentrated on six time points in order to assess changes in tracking performance across time: first block of training (T0), last block of training (T1), first block of retest1 (T2), last block of retest1 (T3), first block of retest2 (T4), and last block of retest2 (T5). As outlined above, various processes can occur during time periods during which the task is not practised (i.e. between T1 and T2 or T3 and T4), such as dissipitation of temporary effects (e.g. fatigue or boredom) (Brawn et al., 2010; Rickard et al., 2008) and motor memory consolidation, resulting in skill retention, enhancement or decrements (Hotermans et al., 2006; Robertson et al., 2004a; Walker, 2005). As such, tracking performance at T2 is most likely to reflect fairly permanent learning effects unaffected by training-induced temporary effects such as fatigue or boredom, while performance at T4 likely indexes retention of the acquired motor skill overnight, due to motor memory consolidation.

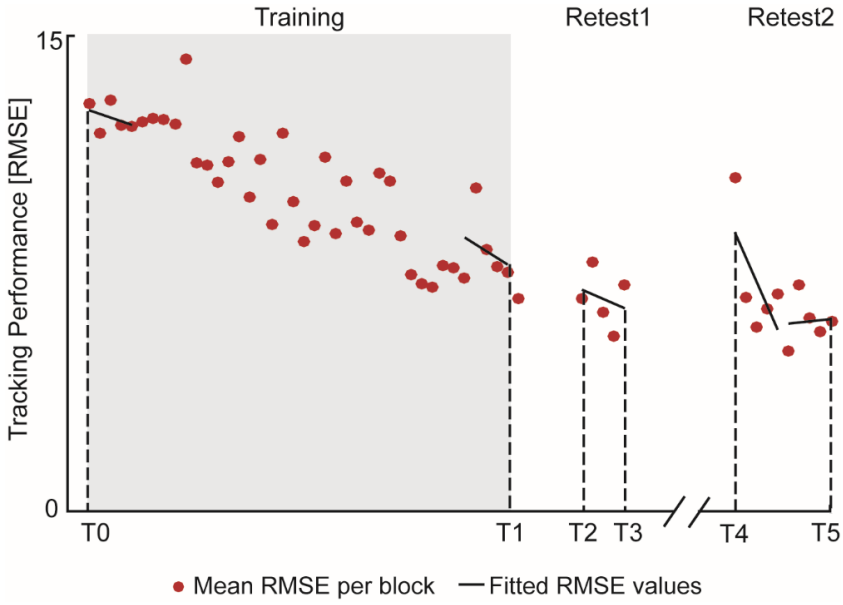

Figure 5.3 | Linear regression approach for exemplary healthy subject. *Dots represent individual blocks of an example subject during training and retest sessions of repeated sequence only. Black lines represent linear regression models across 5 blocks at beginning and end of individual sessions. Corrected performance estimates were derived from these linear regression models at six different time points (T0 = first block of training, T1 = last block of training, T2 = first block of retest1, T3 = last block of retest1, T4 = first block of retest2, and T5*

= last block of retest2) and used to subsequently assess changes in performance with training.

5.3.4.2 Spectral power measures

Pre-processing and time-frequency analysis of EEG data recorded during the performance of the simple motor task has been detailed in **Chapter 3** section 3.7.2. Briefly, the raw EEG signal was first offline re-referenced to the average signal across all electrodes, bandpass filtered between 5–100 Hz, additionally filtered with a 50 Hz notch filter, and downsampled to 300 Hz. Data were epoched from -1 to 9 s relative to visual cue onset (0 s). Poorly performed trials (see section 5.3.2.3) were excluded and the remaining EEG trials were visually scrutinized. Trials containing artefacts (e.g. muscle activation or large eye blinks) were additionally removed. For each session, on average 91±12 and 87±15 artefact-free EEG trials remained for younger and older subjects, respectively, and the number of trials did not significantly differ between conditions (p>0.1) or groups (p>0.3, repeated-measures ANOVA). Artefact-free EEG time-series from each single trial were decomposed into their time-frequency representations in the 5–45 Hz range with frequency steps of 0.1 Hz. A 7-cycle Morlet wavelet was used for the continuous wavelet transformation. Power was averaged across trials and rescaled in order to show changes relative to the corresponding pre-movement baseline period (-1–0 s prior to cue onset) (**Equation 3.6**).

Spectral power time-series were then derived from a pre-selection of electrodes overlying the sensorimotor cortices, both contralateral and ipsilateral to the moving hand. These electrodes were selected based on the independent dataset presented in **Chapter 4** which showed that the most prominent task-related changes in beta activity were observed in these electrodes when performing the simple motor task (MRBD: ‘C4’ ‘CP4’ ‘CP2’ and ‘C3’ ‘CP3’ ‘CP1’ for contra- and ipsilateral hemispheres, respectively; PMBR: ‘C2’ ‘C4’ ‘CP4’ and ‘C1’ ‘C3’ ‘CP3’ for contra- and ipsilateral hemispheres, respectively). These bilateral electrodes were pooled as contralateral and ipsilateral regions of interest, respectively.

To select time-frequency windows of interest that were orthogonal to potential differences between conditions (flexion and extension) when the simple motor

task was performed (Pre, Post1, and Post2), I averaged over conditions, sessions, and subjects for each group separately. Then, specific time-frequency windows were chosen based on peak changes in beta activity in time-frequency maps of the bilateral sensorimotor regions, which, consistent with **Chapter 4**, revealed clear movement-related beta-band activity in two distinct time windows of interest. This information was used to optimize the alignment of constant duration and width time-frequency windows to capture maximum MRBD (1–2 s relative to cue onset; mean peak latency: young group: 1.31±0.23 s, elderly group: 1.64±0.03 s), occurring between cue onset and movement termination, and PMBR (young group: 5.5–6.5 s relative to cue onset; elderly group: 6–7 s relative to cue onset; mean peak latency: young group: 5.85±0.16s, elderly group: 6.63±0.39 s), which emerges after movement cessation. This was done for young and elderly subjects separately because of known age-related reduction of beta peak frequency (Rossiter et al., 2014b). Indeed, in elderly subjects peak changes in beta activity after movement cessation (PMBR) appeared at lower beta frequencies (10–25 Hz) and ~500 ms later compared to younger subjects, however this could not be explained by age-related differences in return movement kinematics (**Figure 5.4**A). Selected time-frequency windows and electrodes applied to all subjects and sessions, and were not adjusted individually.

Subsequently, for each individual subject, percentage decrease (MRBD) and increase (PMBR) in beta power were extracted from the respective 1 s time windows and averaged separately for each EEG session (Pre, Post1 and Post2) for the pre-selected electrodes over each hemisphere. The absolute pre-movement (resting) baseline beta (BB) power from -1 to 0 s relative to cue onset was also obtained and assessed for age-related differences and training-related changes.

In total, 6 different beta power estimates were used for subsequent analyses: pre-movement baseline beta (absolute power), MRBD (relative power) and PMBR (relative power) from contra- and ipsilateral sensorimotor cortices, respectively. As demonstrated in **Chapter 4**, these spectral power measures have high intra-subject reliability (Espenhahn et al., 2016), a prerequisite for exploring the

relationship between these beta oscillatory estimates and individual differences in motor learning.

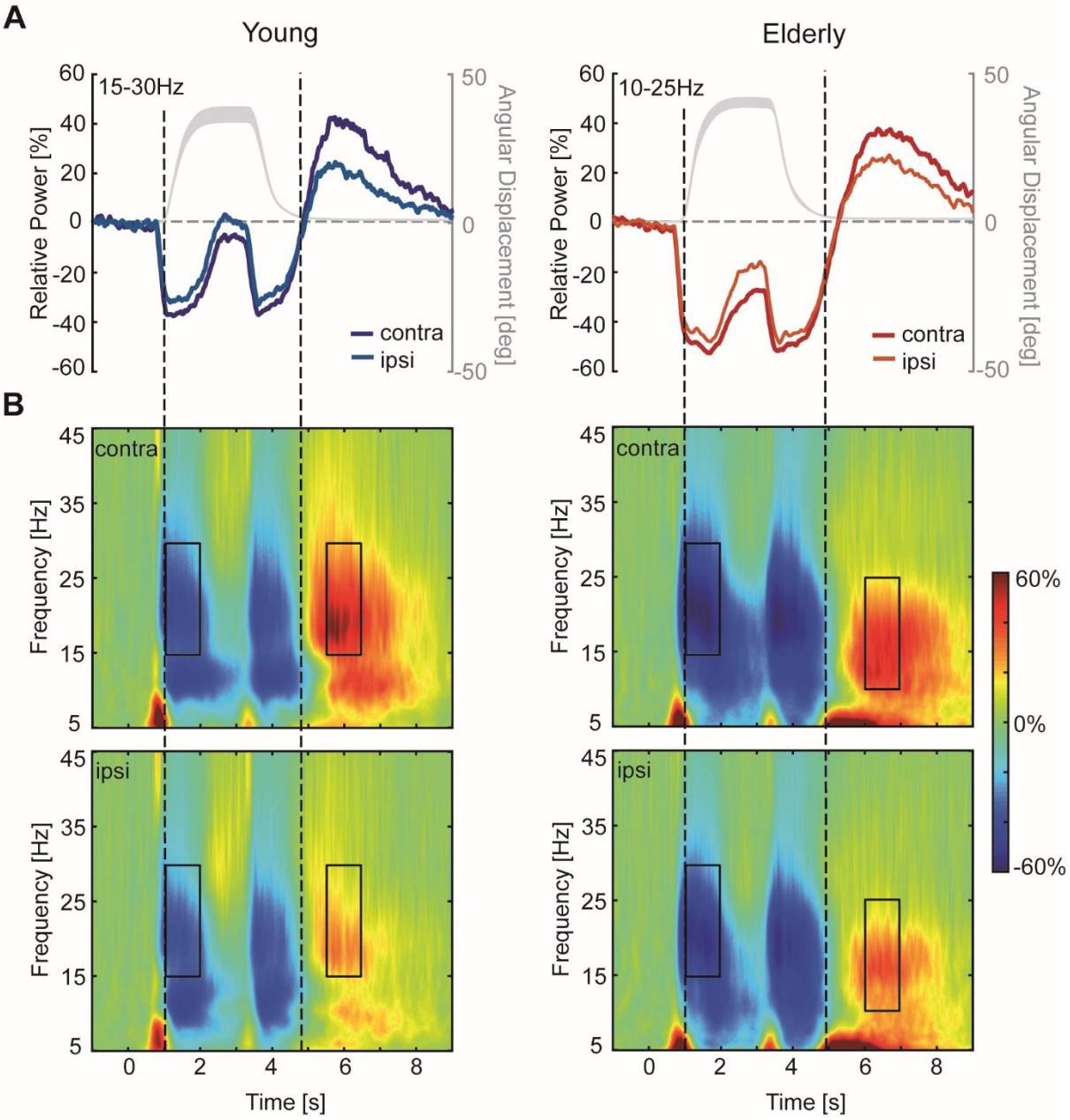

Figure 5.4* | *Angular displacement and respective changes in beta activity. ***A****, Group-averaged angular position trajectory (grey curve) and beta power time courses for contra- and ipsilateral sensorimotor cortex for young (left panel) and elderly (right panel) subjects, respectively. Movement kinematics were similar between both groups and illustrate the movement towards the target, the static contraction/holding phase, and the return movement to the initial start position.* ***B****, Time-frequency maps from contralateral and ipsilateral sensorimotor cortex show two distinct time windows of peak changes in beta activity (MRBD and PMBR) indicated by black rectangles. Please note that the PMBR in elderly subjects occurred at lower beta frequencies (10–25 Hz) and ~500 ms later*

compared to younger subjects. These time-frequency windows were tested for significant differences between groups and EEG sessions.

5.3.5 Statistical analysis

Before (I) investigating the relationship between beta-band activity and individual differences in motor learning, a series of conventional analyses were first conducted to assess (II) whether young and elderly subjects learned to a similar extent on the continuous tracking task (their behaviour), and (III) whether beta-band activity was altered with training or ageing (neurophysiology).

To assess whether tracking performance improved across training and was maintained, enhanced or decreased at retest sessions, a repeated-measures ANOVA on tracking performance score (RMSE) was performed, with 'group' (2 levels: young vs elderly) as between-subject factor and 'sequence type' (2 levels: repeated vs random) and 'time' (5 levels: T0 vs T1 vs T2 vs T3 vs T4) as within-subject factors. Additionally, to ensure comparable baseline performance and thus, allow for direct comparison between age groups, a repeated-measures ANOVA of tracking performance at T0 (baseline) was used.

Since beta oscillations have been shown to be altered with ageing (Gaetz et al., 2010; Rossiter et al., 2014b) and motor learning (Boonstra et al., 2007; Houweling et al., 2008; Mary et al., 2015; Pollok et al., 2014), measures of resting and movement-related beta activity were evaluated applying separate repeated-measures ANOVAs with 'group' (2 levels: young vs elderly) as between-subject factor and 'hemisphere' (2 levels: contralateral vs ipsilateral) and EEG 'session' (3 levels: Pre vs Post1 vs Post2) as within-subject factors.

A Greenhouse-Geiger correction was applied whenever Mauchly's test indicated a lack of sphericity. *Post hoc* Bonferroni-adjusted t-tests were performed whenever main effects and interaction effects were detected in the ANOVAs. Prior to ANOVAs and *post hoc* t-tests, Kolmogorov-Smirnov test was used to affirm normal distribution of the data. Results were considered significant if *p*-values were below 0.05. All data presented in the text and tables are represented as mean ±SD unless stated otherwise.

5.3.5.1 Regression analysis combining neurophysiological and behavioural measures

Finally, a multiple linear regression approach was employed in order to investigate whether spectral power measures of beta-band activity relate to individual differences in the capacity for motor learning, accounting for multicollinearity between neurophysiological (Heinrichs-Graham and Wilson, 2016) and behavioural performance measures. Specifically, separate stepwise multiple linear regression models (with forward and backward algorithm; inclusion/exclusion probability levels: $\alpha_{Enter}<0.05$/ $\alpha_{Exclude}>0.1$) were used to select those variables that provided a unique contribution to explaining tracking performance at T2 and T4 for the repeated and random sequence, respectively. Tracking performance at T2 reflects fairly permanent learning effects unaffected by training-induced temporary effects such as fatigue or boredom, while performance at T4 indexes retention of the acquired motor skill overnight, reflecting motor memory consolidation. Specifically, a combination of neurophysiological measures, including (a) baseline beta power, (b) MRBD, and (c) PMBR from both sensorimotor cortices, as well as behavioural performance measures during the training session, i.e. (d) tracking performance at T0 and (e) at T1, were used to explain performance at T2, while behavioural performance measures during retest1, i.e. (f) at T2 and (g) T3, were further included to explain performance at T4. In addition, functional and demographic information such as age, motor function, cognitive function and sleep characteristics were equally included. All predictors were z-scored before analysis to produce regression coefficients (β) of comparable magnitude.

To avoid overfitting and evaluate the predictive strength of each regression model, a leave-one-out cross-validation (LOOCV) approach was employed (Arlot and Celisse, 2010; Picard and Cook, 1984). For this purpose, at each iteration the regression model was fitted on data from N-1 subjects (training set), with the removed subject being used as a test set for assessing model performance. This cross-validation method is an established procedure for assessing generalization of results to an independent data set, particularly with smaller sample sizes (Huang et al., 2011; Kang et al., 2014). The strength of the prediction model was quantified in terms of the correlation coefficient between actual and predicted

tracking performance. A permutation-test (100 iterations) was used to assess whether the difference between the actual and predicted performance was greater than would be expected by chance. For this, the entire LOOCV approach was repeated 100 times and in each iteration, the ordering of the performance values to the subjects was randomly permuted beforehand. This has the desired effect of the test set being selected randomly in each iteration and also guarantees the independence of the training and test sets in every fold. Inferences about the relevance of predictor variables (i.e. whether a predictor variable affects tracking performance in a consistent way) were based upon the distribution of regression coefficients (β) across subjects, using single-sample t-tests to test for differences from zero. To compare models fitted with neurophysiological or behavioural performance measures only, or a combination of both (i.e. whether a model's prediction more accurately resembles the data than another model), independent t-tests were used to test for differences in RMSE across subjects between models.

5.4 Results

Behavioural and EEG data recorded during the performance of the continuous tracking task and the simple motor task for 38 healthy ageing subjects are reported.

As expected, young and elderly subjects differed in aspects of UL motor ability and cognitive function (**Table 5.1**). In line with studies demonstrating a decrease in total sleep time with age (for review see (Ohayon et al., 2004)), elderly subjects reported sleeping fewer hours compared to their younger counterparts.

Table 5.1 | Characteristics of young and elderly subject groups.

	Young	Elderly	Between-group difference
N	19	19	-
Age	25±4	69±4	***t(36)=-34.8, p<0.001***
Male:Female ratio	8:11	7:12	*X^2=0.11, p=0.740*
Handedness (Edinburgh)	94±8	84±21	*t(23.01)=1.86, p=0.076*
Grip Strength [lb]	75±25.11	60±18.51	***t(36)=2.05, p=0.048***
NHPT [pegs/s]	0.67±0.08	0.60±0.08	***t(36)=2.73, p=0.010***
SART (Error score, 0-225)	8±3.79	13±10.70	***t(22.44)=-2.14, p=0.043***
SART (RT in ms)	363±70.11	446±144.64	***t(26.02)=-2.25, p=0.033***
Sleep Quantity [hours]$^{\#}$	7±0.70	6±0.96	***U=70.0, p=0.001***
Sleep Quality (1-8)$^{\#}$	5.6±1.12	5.2±0.87	*U=130.5, p=0.138*

Between-group comparisons revealed a significant difference in NHPT, grip strength, SART, and sleep quantity the previous night. For continuous data, independent-samples t-tests were used to test for between-group differences. For discrete data ($^{\#}$), Mann-Whitney U-tests were applied. Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). Upper limb functional measures are non-dominant hand only and sleep measures are averaged across both days (both sleep measures were not significantly different between day 1 and day 2, p>0.05). Significant effects are indicated in bold. Values given are mean ±SD. NHPT: Nine Hole Peg Test; SART: Sustained Attention to Response Test.

5.4.1 Presence of motor skill learning with healthy ageing

Tracking performance for both young and elderly subjects at training and retest sessions is shown in **Figure 5.5**A. Firstly, no systematic differences in baseline (block 1) tracking performance between young and elderly groups [$F_{(1,36)}$=0.047, p=0.830] or repeated and random sequences [$F_{(1,36)}$=0.12, p=0.730] nor an interaction effect [$F_{(1,36)}$=0.482, p=0.492] were found (**Figure 5.5**B), thus allowing for direct comparison of tracking performance between age groups.

A repeated-measures ANOVA on tracking performance revealed a significant main effect of 'time' [$F_{(4,144)}$=63.14, p<0.001, η^2=0.637] and 'sequence type' [$F_{(1,36)}$=92.56, p<0.001, η^2=0.720], but no effect of age [$F_{(4,36)}$=0.31, p=0.584] on tracking performance. In addition, a significant 'time x sequence type' interaction

was found [$F_{(4,144)}$=19.74, p<0.001, η^2=0.354]. *Post hoc* analyses were thus performed to separately assess changes in tracking performance with initial training (online) and following a shorter (retest1) or longer (retest2) time delay during which subjects did not practice the task (offline).

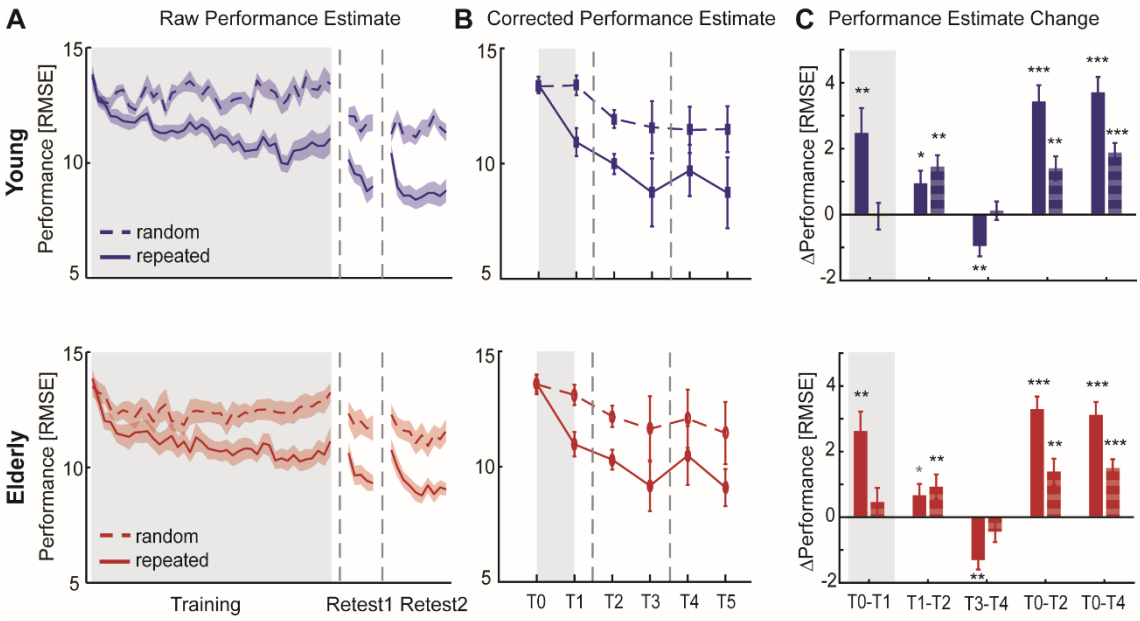

Figure 5.5 | Motor skill learning of young and elderly subjects.
***A**, Average tracking performance (RMSE) for repeated and random sequences (solid and dashed lines respectively) across training (day 1), retest1 (day 1) and retest2 (day 2) sessions suggest comparable performance improvements of young (blue) and elderly (red) subjects. Vertical dashed lines represent time away from the motor learning task. **B**, Corrected performance estimates at the beginning and end of training (T0, T1) and retest (retest1: T2, T3; retest2: T4, T5) sessions. **C**, Performance differences (Δ) between time points, focusing on online learning (T0-T1) and offline learning across a shorter (retest1, T1-T2) or longer (retest2, T3-T4) time delay as well as overall performance changes from baseline (T0-T2; T0-T4). Solid bars represent Δ performance on the repeated sequence and striped bars on the random sequence. Positive and negative values, respectively, signify performance improvement and decrement. Shaded area (**A**) and error bars (**B, C**) indicate between-subject SEM. *p<0.05, **p<0.01, ***p<0.001, grey * p<0.1 (trend).*

5.4.1.1 Performance changes over the course of training

During the training phase, tracking performance improved over time (T0 vs T1) irrespective of age, but these improvements were different between repeated and random sequences [*F*-statistics and *p*-values of ANOVAs are summarized in

Table 5.2]. *Post hoc* analyses revealed a significant improvement in tracking performance of ~19 % for the repeated sequence [$t_{(37)}$=5.43, p<0.001, η^2=0.443] (**Figure 5.5**C). This was not seen for the random sequence [$t_{(37)}$=0.69, p=0.489], indicating that improvements primarily occurred via a sequence-specific learning effect which appeared to be unaffected by ageing.

5.4.1.2 Performance changes after training on the same day – retest1

After establishing that young and elderly subjects showed a comparable ability to learn the sequence-specific motor skill, next tracking performance at retest1 was examined. During the short time delay between the end of the initial training and the retest1 session (T1 vs T2), tracking performance significantly improved without further training for both the repeated and random sequence. Across groups, tracking performance on the repeated sequence improved by 7 % [$t_{(37)}$=3.17, p=0.003, η^2=0.215], while a 9 % improvement was observed for the random sequence [$t_{(37)}$=4.71, p<0.001, η^2=0.382], indicating a boost in performance early after initial training (45-60 min) (**Figure 5.5**C). Please note that the performance improvement on the repeated sequence did not reach significance in the elderly subject group [$t_{(18)}$=1.93, p=0.070]. Overall, performance significantly improved from T0 to T2 not only for the repeated sequence (25 % improvement) [$t_{(37)}$=10.91, p<0.001], but also the random sequence (10 % improvement) [$t_{(37)}$=5.31, p<0.001], despite the non-significant general learning across training.

5.4.1.3 Performance changes after training 24 hours later – retest2

Finally, changes in tracking performance, without practice, at 24 hours (retest2) after initial training were assessed. Performance significantly deteriorated from T3 to T4 irrespective of age, but dependent on the type of sequence. *Post hoc* analyses revealed that while tracking performance on the random sequence was retained overnight [$t_{(37)}$=-1.21, p=0.236], significant performance decrements (i.e. overnight forgetting) of ~13 % were observed for the repeated sequence [$t_{(37)}$=-5.79, p<0.001, η^2=0.478] (**Figure 5.5**C). Thus, while training-related improvements in general tracking performance were retained for at least 24 hours, overnight forgetting that was specific to the repeated sequence

occurred for both young and elderly subjects. Despite these sequence-specific offline decrements, overall performance at T4 was significantly better compared to T0 for the repeated sequence (24 % improvement) [$t_{(37)}$=10.87, p<0.001]. Similarly, overall performance on the random sequence was significantly better at T4 compared to T0 (12 % improvement) [$t_{(37)}$=7.87, p<0.001].

Table 5.2 | ***ANOVA results of subjects' tracking performance at different time points during the motor learning process.***

	Group	Time	Sequence Type	Interactions
Performance changes across initial training				
T0 vs T1				**time x sequence:**
	$F_{(1,36)}$=0.01, p=0.933	***$F_{(1,36)}$=17.57, p<0.001, η^2=0.328***	***$F_{(1,36)}$=30.93, p<0.001, η^2=0462***	***$F_{(1,36)}$=28.33, p<0.001, η^2=0.440***
Performance changes after time delay (retest1, retest2)				
T1 vs T2				
	$F_{(1,36)}$=0.02, p=0.895	***$F_{(1,36)}$=25.97, p<0.001, η^2=0.419***	***$F_{(1,36)}$=65.49, p<0.001, η^2=0.645***	n.s.
T3 vs T4				**time x sequence:**
	$F_{(1,36)}$=0.86, p=0.361	***$F_{(1,36)}$=20.81, p<0.001, η^2=0.366***	***$F_{(1,36)}$=106.43, p<0.001, η^2=0.747***	***$F_{(1,36)}$=13.12, p=0.001, η^2=0.268***
Overall performance changes from baseline				
T0 vs T2				**time x sequence:**
	$F_{(1,36)}$=0.32, p=0.575	***$F_{(1,36)}$=93.08, p<0.001, η^2=0.721***	***$F_{(1,36)}$=19.99, p<0.001, η^2=0.357***	***$F_{(1,36)}$=40.99, p<0.001, η^2=0.532***
T0 vs T4				**time x sequence:**
	$F_{(1,36)}$=1.11, p=0.299	***$F_{(1,36)}$=129.77, p<0.001, η^2=0.783***	***$F_{(1,36)}$=18.70, p<0.001, η^2=0.645***	***$F_{(1,36)}$=34.87, p<0.001, η^2=0.492***

Significant effects are indicated in bold. T0: beginning of training session; T1: end of training session; T2: beginning of retest1; T3: end of retest1; T4: beginning of retest2. n.s.: not significant.

5.4.1.4 Factors potentially influencing tracking performance

Many factors can influence motor learning behaviour in healthy subjects. For example, lower levels of attention or sleep might be detrimental to performance on the here employed continuous tracking task. Thus, next some factors that potentially impacted on the observed tracking performance were explored.

The initial ability to perform the motor skill might influence subsequent performance levels, whereby e.g. subjects who perform worse at the beginning of the training might have more room for improvement with training. To determine the relationship between motor skill performance at different time points, Pearson correlation coefficients were performed. In general, tracking performance was positively correlated across various time points (**Figure 5.6**). Notably, the initial ability to perform the motor learning task (T0) had the least influence on subsequent performances, in particular for the repeated sequence (repeated sequence: average r=0.24, p=0.319; random sequence: average r=0.55, p=0.002).

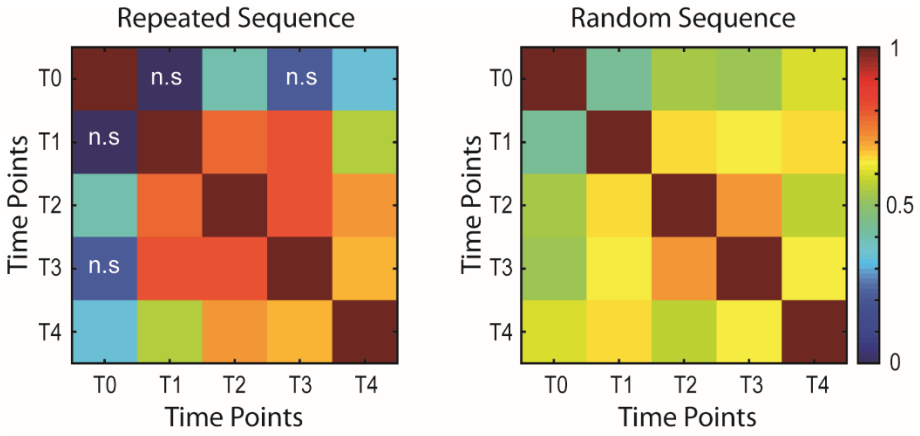

Figure 5.6 | Correlations of subjects' performance between time points. *Between-time points (T0–T4) correlation coefficients for performance on the repeated (left panel) and random (right panel) sequence. The colour bar indicates the correlation coefficients (r) presented in the matrices. Specifically, performance on the repeated sequence at the beginning of training did not relate to performance at the end of training (T1) or retest1 session on the same day (T3). n.s.: not significant.*

In addition, functional characteristics such as grip strength, hand dexterity, attention or sleep were significantly different between age groups (see **Table 5.1**), with elderly subjects being weaker, less dexterous, less attentive, and sleeping

fewer hours compared to their younger counterparts. However, these functional characteristics were not associated with subjects' performance at any time point (all $p>0.05$).

Lastly, the acquisition of knowledge regarding the repeated sequence might interact with how well subjects learn and maintain the sequence-specific performance level. Young subjects were better in gaining awareness of the repeated sequence during the initial training (95±8.8 % correct) compared to elderly subjects (84±16.5 % correct) [Mann-Whitney $U=100.5$, $p=0.018$]. The younger group also performed better at correctly recognizing the repeated sequence at retest2, 24 hours after the initial training (young: 96±10.0 % correct; elderly: 83±22.2 % correct) [$U=98$, $p=0.015$], indicating less forgetting in younger subjects. However, these age-related differences in the level of awareness of the repeated sequence did not relate to subjects' tracking performance at any time point (all $p>0.4$).

5.4.2 Changes in spectral power measures with age and training

All subjects were able to perform the simple motor task used during EEG recording and there were no significant differences in movement kinematics between age groups neither for the movement towards the target [RT: $F_{(1,36)}=0.02$, $p=0.896$; MT: $F_{(1,36)}=1.14$, $p=0.293$] nor the return movement towards the initial start position [RT: $F_{(1,36)}=0.61$, $p=0.441$; MT: $F_{(1,36)}=0.58$, $p=0.450$] (**Table 5.3**). Average spectral changes in contralateral and ipsilateral sensorimotor cortices in response to wrist movement are shown in **Figure 5.4**B before (Pre) and at two time points (Post1 and Post2) after the initial training. General features of the spectral changes in beta activity induced by the simple motor task have been detailed in **Chapter 4** (Espenhahn et al., 2016). Briefly, a reduction in beta power, MRBD, was observed in both sensorimotor cortices during movement towards the target and during return movement to the initial start position. Following return movement cessation, a strong but transient increase in beta power, PMBR, with a contralateral preponderance was observed.

Table 5.3 | Summary of kinematic measures acquired during the performance of the simple motor task for each age group.

	Young	*Elderly*
RT [ms]	989±55	975±44
MT [ms]	1166±250	1056±332
PV [deg/s]	124±55	185±93

Kinematic measures are presented for each EEG session (S1–S6) and condition (flexion, extension). RT: Reaction Time; MT: Movement Time; PV: Peak. Values given are mean ±SD

5.4.2.1 Resting beta power

Analysis of absolute beta power during the pre-movement (resting) baseline period demonstrated a significant effect of age, with elderly subjects exhibiting higher absolute beta power in both contralateral and ipsilateral sensorimotor cortices (**Figure 5.7**A, *F*-statistics and *p*-values of all ANOVAs are summarized in **Table 5.4**), consistent with previous observations (Heinrichs-Graham and Wilson, 2016; Rossiter et al., 2014b). While there was no hemispheric difference, absolute beta power was significantly different between EEG sessions. *Post-hoc* analyses revealed a significant but transient increase in beta power immediately after training (Post1) in both contralateral [Pre vs Post1: $t_{(37)}$=-2.98, p=0.011; Post1 vs Post2: $t_{(37)}$=2.59, p=0.032] and ipsilateral [Pre vs Post1: $t_{(37)}$=-4.60, p<0.001; Post1 vs Post2: $t_{(37)}$=2.48, p=0.05] sensorimotor cortex which returned back to pre-training levels on day 2 [Pre vs Post2: $t_{(37)}$=0.28, p=1.00]. In addition, there was a trend for a 'group x session' interaction effect [$F_{(2,72)}$=2.66, p=0.077, η_p^2=0.075] indicating that the increase immediately after the training phase predominantly occurred in elderly subjects.

Table 5.4* | *ANOVA results for spectral power measures of healthy ageing subjects.

	Group	Hemisphere	Session	Interactions
BB	***$F_{(1,36)}$=7.01, p=0.012, n_p^2=0.163***	*$F_{(1,36)}$=1.80, p=0.188*	***$F_{(2,72)}$=7.06, p=0.002, n_p^2=0.164***	n.s.
MRBD	***$F_{(1,36)}$=10.78, p=0.002, η_p^2=0.230***	***$F_{(1,36)}$=31.81, p<0.001, η_p^2=0.469***	***$F_{(2,72)}$=3.29, p=0.043, η_p^2=0.084***	***3-way: $F_{(2,72)}$=4.10, p=0.021, η_p^2=0.102***
PMBR	*$F_{(1,36)}$=0.01, p=0.939*	***$F_{(1,36)}$=21.99, p<0.001, η_p^2=0.379***	***$F_{(2,72)}$=4.17, p=0.019, η_p^2=0.104***	n.s.

Significant effects are indicated in bold. BB: Pre-movement baseline beta; MRBD: Movement-Related Beta Desynchronization; PMBR: Post-Movement Beta Rebound; n.s.: not significant.

5.4.2.2 Movement-related beta power changes

Averaged beta power changes during movement (MRBD) and after movement cessation (PMBR) in both sensorimotor cortices and topographic maps are shown in **Figure 5.7**C-D. Interestingly, the magnitude of MRBD and PMBR were differentially affected by age. Elderly subjects showed a greater beta power decrease in both sensorimotor cortices during the movement towards the target than their younger counterparts (**Figure 5.7**C) consistent with previous findings (Heinrichs-Graham and Wilson, 2016; Rossiter et al., 2014b). In contrast, the magnitude of the power increase after movement termination was not significantly different between young and elderly subjects (**Figure 5.7**D). As expected, a significant hemispheric difference in the magnitude of MRBD and PMBR indicated that both beta-band dynamics were overall more pronounced in the hemisphere contralateral to the moving hand. Also, a marginally significant effect of ‘session’ and a significant ‘group x hemisphere x session’ interaction was

found for MRBD. *Post hoc* analyses indicated that the age-related difference in the magnitude of MRBD was significant in both sensorimotor cortices [contralateral sensorimotor cortex $F_{(1,36)}$=12.93, p=0.001, η_p^2=0.264; ipsilateral sensorimotor cortex: $F_{(1,36)}$=8.12, p=0.007, η_p^2=0.184], but a significant linear reduction in the magnitude of MRBD across sessions was only found in the ipsilateral hemisphere [$F_{(2,72)}$=4.26, p=0.018, η_p^2=0.106].

In addition, a decrease in the magnitude of PMBR across sessions was found, but no interactions. *Post hoc* analyses showed that this decrease in PMBR across sessions was restricted to the ipsilateral sensorimotor cortex and elderly subjects only [$F_{(2,36)}$=7.47, p=0.002, η_p^2=0.293]. Inspection of the topographical distribution of PMBR (**Figure 5.7**D, right panel) confirmed a training-related change in PMBR, with elderly subjects exhibiting a more bilateral distribution of PMBR prior to training which shifted towards a contralateral preponderance following training.

Lastly, neither pre-movement beta power nor movement-related beta dynamics from either contralateral or ipsilateral sensorimotor cortex were related to any functional characteristics (i.e. grip strength, NHPT, SART), after controlling for age (all p>0.05).

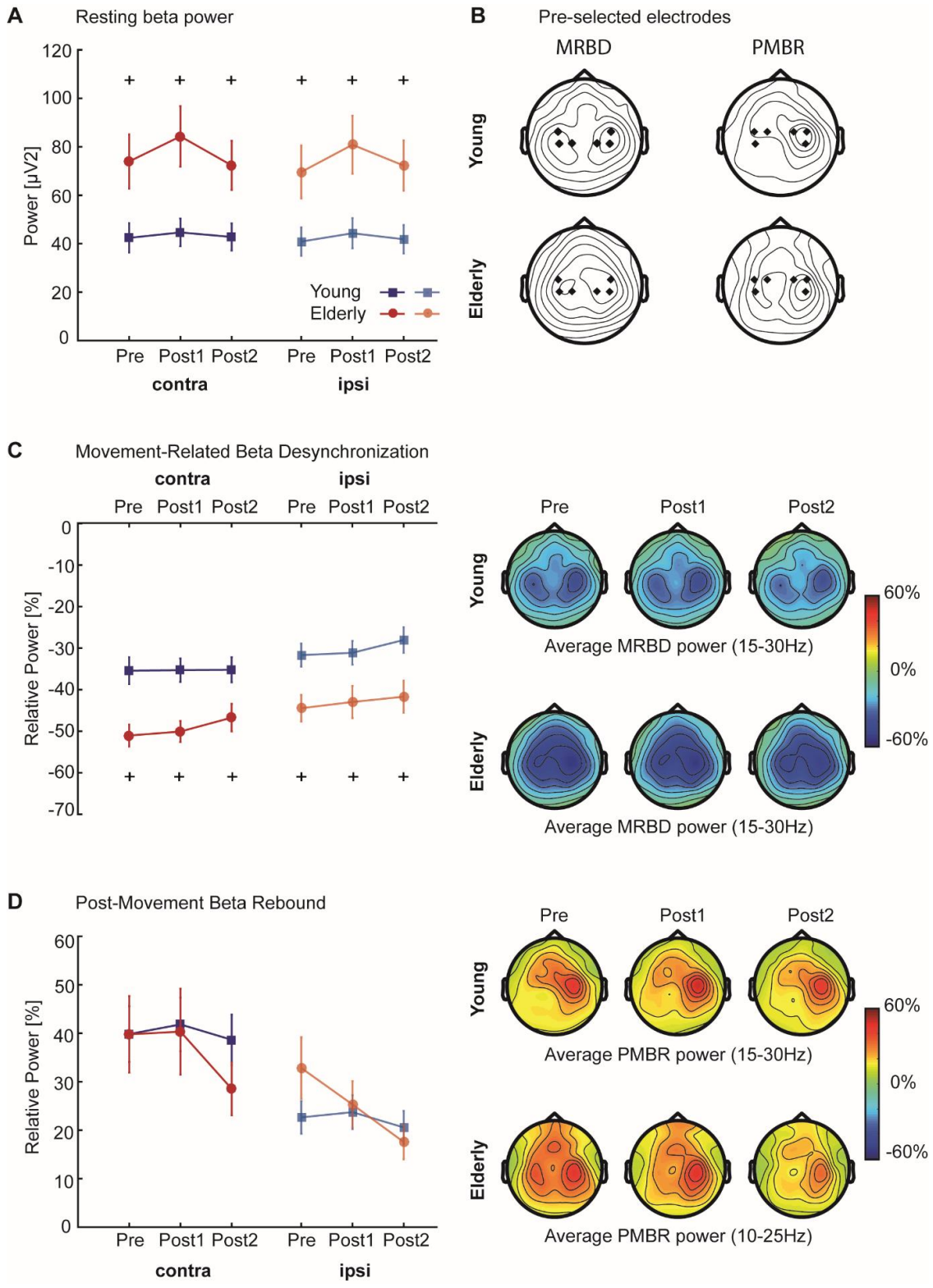

Figure 5.7 | Alterations in beta power and corresponding topographic maps. ***A****, Average pre-movement (resting; -1–0 s) beta power was significantly higher in the elderly group (red and light red) compared to the younger subjects (dark and light blue) for both sensorimotor cortices before (Pre), immediately after (Post1), and 24-hours after (Post2) training.* ***B****, Topographical plots of grand-averaged beta power showing the pre-selected electrodes (black diamonds)*

which were pooled as contralateral and ipsilateral regions of interest. ***C-D****, Power in the movement (1–2s; MRBD) and post-movement time window (5.5–6.5 s/ 6-7 s; PMBR) before (Pre), immediately after (Post1), and 24-hours after (Post2) training derived from contralateral and ipsilateral sensorimotor cortices of young (dark and light blue) and elderly (red and light red) subjects indicated a differential effect of age upon these beta dynamics. Error bars indicate between-subject SEM. Significant between-group differences are indicated with a '+'. Topographical distributions (right panels) of movement-related beta activity show differential contralateral and ipsilateral modulation patterns for MRBD and PMBR. Note, that PMBR in elderly subjects showed a bilateral distribution before training compared to the contralateral preponderance in younger subjects (****D****, right panel), but this topographical distribution shifted towards a more contralateral PMBR after the initial training.*

5.4.3 Prediction of post-training tracking performance from a combination of neurophysiological and behavioural measures

In order to gain insight into the role of beta activity in explaining motor learning behaviour, a stepwise multiple linear regression approach within a leave-one-out cross-validation (LOOCV) was utilized. As a first step, I assessed whether a combination of neurophysiological (beta power measures), behavioural (performance on the motor learning task) and functional characteristics, accounting for multicollinearity between measures, explains individual tracking performance at two different time points, shortly after the training (T2) and 24 hours after (T4), respectively. Performance at T2 was used as an index of fairly permanent learning effects, while T4 provides a reflection of the maintenance of the acquired motor skill overnight. Consequently, I next evaluated the contribution of neurophysiological and behavioural measures alone in predicting tracking performance.

5.4.3.1 Prediction of tracking performance at T2

Pre- and post-training beta activity (Pre, Post1), and behavioural performance at T0 and T1, as well as functional characteristics (age, attention, motor ability, sleep) were explored as potential predictors of tracking performance at T2 (total number of predictors = 22) using stepwise linear regression.

This analysis approach revealed that 74 % of the variance in performance on the repeated sequence was predicted by a combination of these variables [r=0.86, p<0.001] (**Figure 5.8**A). By assessing which predictor variables consistently affected tracking performance, neurophysiological and behavioural performance measures, but none of the functional characteristics, were shown to consistently affect performance. Specifically, initial and final performance during the training phase (T0, T1) exerted a large effect upon performance at T2, as captured by large positive regression coefficients [T0: $t_{(37)}$=156.85, p<0.001; T1: $t_{(37)}$=284.36, p<0.001]. Despite controlling for tracking performance during the initial learning, pre-training MRBD in ipsilateral sensorimotor cortex significantly influenced performance at T2 [$t_{(37)}$=-24.72, p<0.001] (**Figure 5.8**B). Since the beta power decrease is expressed as a negative percentage value (relative to baseline), the negative coefficient value implies that smaller magnitude of MRBD in ipsilateral sensorimotor cortex prior to training predicts better tracking performance. Similarly, a partial correlation analysis including performance during training as confounding covariates, showed a significant negative correlation between MRBD and performance at T2 [r=-0.38, p=0.021].

Further, performance on the random sequence was significantly predicted by a combination of neurophysiological and behavioural performance measures, however only 36 % of the variance in tracking performance could be explained [r=0.60, p<0.001] (**Figure 5.8**C). Beyond behavioural performance during the training phase [T0: $t_{(37)}$=2.06, p=0.046; T1: $t_{(37)}$=76.01, p<0.001], pre-training MRBD [$t_{(37)}$=-4.64, p<0.001] and post-training PMBR [$t_{(37)}$=-46.94, p<0.001] from contralateral sensorimotor cortex, respectively, consistently affected tracking performance (**Figure 5.8**D). The negative coefficient values for the neurophysiological measures imply better tracking performance with smaller magnitude of MRBD prior to training and greater magnitude of PMBR after training. However, partial correlation analysis with performance during training as confounding covariates remained significant only for post-training PMBR [r=-0.38, p=0.023].

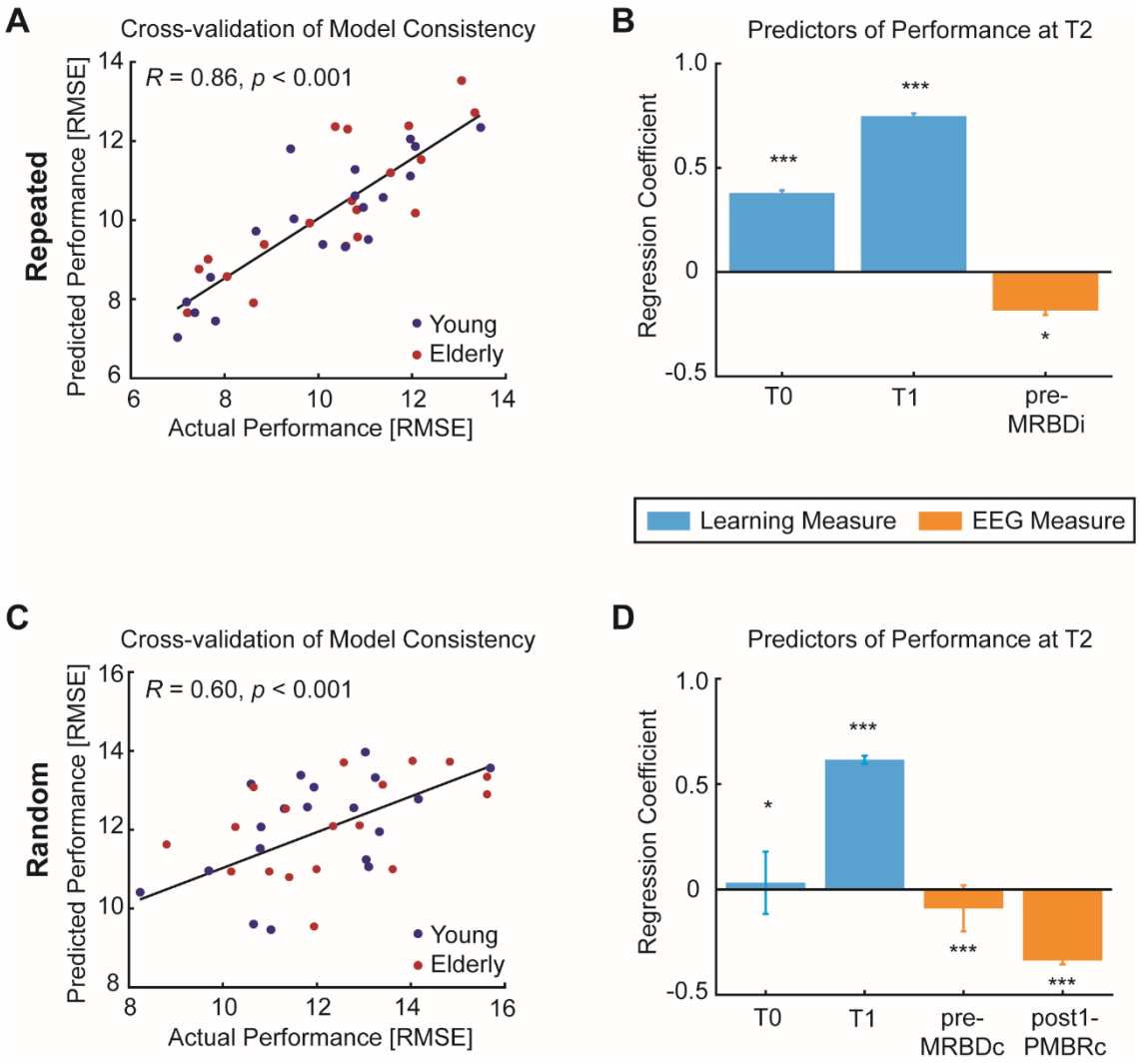

Figure 5.8 | Prediction of tracking performance at T2.
*Stepwise multiple linear regression with a combination of neurophysiological and behavioural performance measures provided statistically significant performance prediction (**A, C**) as quantified by the correlation coefficient between the actual and predicted tracking performance across healthy subjects. Together, these measures accounted for 74 % and 36 % of variance in performance on the repeated and random sequence, respectively. Significance of these correlations was determined by permutation-testing. **B**, Subjects' behavioural performance during training exerted the strongest effect on performance of the repeated sequence. An additional model parameter relating to movement-related beta activity prior to training was negative, indicating that smaller magnitude of MRBD is associated with better performance. **D**, Performance on the random sequence was affected by model parameters relating to behavioural performance and once again movement-related beta activity. The negative coefficients for the beta power parameters indicate that smaller magnitude of MRBD prior to training and greater magnitude of post-training PMBR is associated with better performance at T2. Averaged z-scored regression coefficients (β) quantify the influence of each significant predictor upon performance level at T2. Error bars represent*

*SEM. Single-sample t-tests to test for differences from zero were employed. *p<0.05, **p<0.01, ***p<0.001.*

To examine more precisely this relationship between neurophysiological and behavioural performance measures for predicting tracking performance at T2, regression analyses with neurophysiological or behavioural performance measures alone, or a combination of both were performed and compared with regard to their predictive strength (summary of comparison is provided in **Table 5.5**).

Neurophysiological measures alone did not explain performance on the repeated sequence whereas behavioural performance measures alone did significantly explain individual variation in tracking performance, echoing a strong effect of behaviour. However, when neurophysiological measures were combined with behavioural performance measures, the prediction accuracy significantly improved, exceeding the information provided by behavioural performance parameters alone [$t_{(1,37)}$=37.84, p<0.001]. Similarly, while behavioural performance measures alone also significantly explained performance on the random sequence, neurophysiological measures alone were not of significant predictive value. However, when combined with behavioural performance measures, they again significantly improved the prediction accuracy compared to a model containing behavioural performance parameters alone [$t_{(1,37)}$=12.10, p<0.001]. These results suggest that beta oscillatory measures explain some of the individual differences in performance and improve predictions, but only when accounting for the strong effect of behaviour.

Table 5.5 | Comparison of prediction accuracy for performance at T2.

Predictor variables	R	R^2	Mean RMSE	Sum RMSE
Performance on repeated sequence				
Neurophysiology	-0.59	-0.35	0.98	37
Behaviour	0.85***	0.72	0.52	20
Neurophysiology + Behaviour	*0.86****	*0.74*	*0.48*	*18*
Performance on random sequence				
Neurophysiology	0.22	0.05	0.93	35
Behaviour	0.60***	0.36	0.73	28
Neurophysiology + Behaviour	*0.60****	*0.36*	*0.69*	*26*

*Regression models were fitted with neurophysiological (pre- and post-training (Pre, Post1) BB, MRBD, and PMBR from both sensorimotor cortices) and behavioural performance measures (tracking performance at T0 and T1) alone, and a combination of both. The predictive strength is quantified by the correlation (R) between the actual and predicted performance, based on LOOCV. Beta oscillatory measures in combination with behavioural performance estimates best predicted performance at T2 (blue ink). RMSE are averaged and summed across the 38 subjects. RMSE: Root Mean Square Error. *p<0.05, **p<0.01, ***p<0.001.*

5.4.3.2 Prediction of tracking performance at T4

Pre- and post-training beta activity (Pre, Post1, Post2), and behavioural performance at training (T0, T1) and retest1 (T2, T3) sessions as well as functional characteristics (age, attention, motor ability, sleep) were explored as potential predictors of tracking performance at T4 (total number of predictors = 29).

Separate regression models, using these potential predictor variables, significantly predicted performance 24 hours after the initial training for both the repeated and random sequence, with models accounting for 36 % and 64 % of variance, respectively [repeated sequence: r=60, p<0.001, **Figure 5.9**A; random sequence: r=0.80, p<0.001, **Figure 5.9**C]. Assessing the relevance of individual variables for tracking performance revealed that behavioural performance, but not neurophysiological measures exerted an effect upon performance at T4. Specifically, tracking performance during the retest1 session related to

performance on both repeated [T2: $t_{(37)}$=2.24, p=0.031; T3: $t_{(37)}$=22.60, p<0.001] and random [T2: $t_{(37)}$=78.17, p<0.001] sequence, while initial performance was a significant parameter only for the performance of the random sequence [T0: $t_{(37)}$=81.09, p<0.001] (**Figure 5.9**B, D). Interestingly, sleep quantity the night prior to the retest2 session was of relevance in explaining tracking performance 24 hours after training, with more sleep relating to better performance [repeated sequence: $t_{(37)}$=-3.36, p=0.002; random sequence: $t_{(37)}$=-34.46, p<0.001].

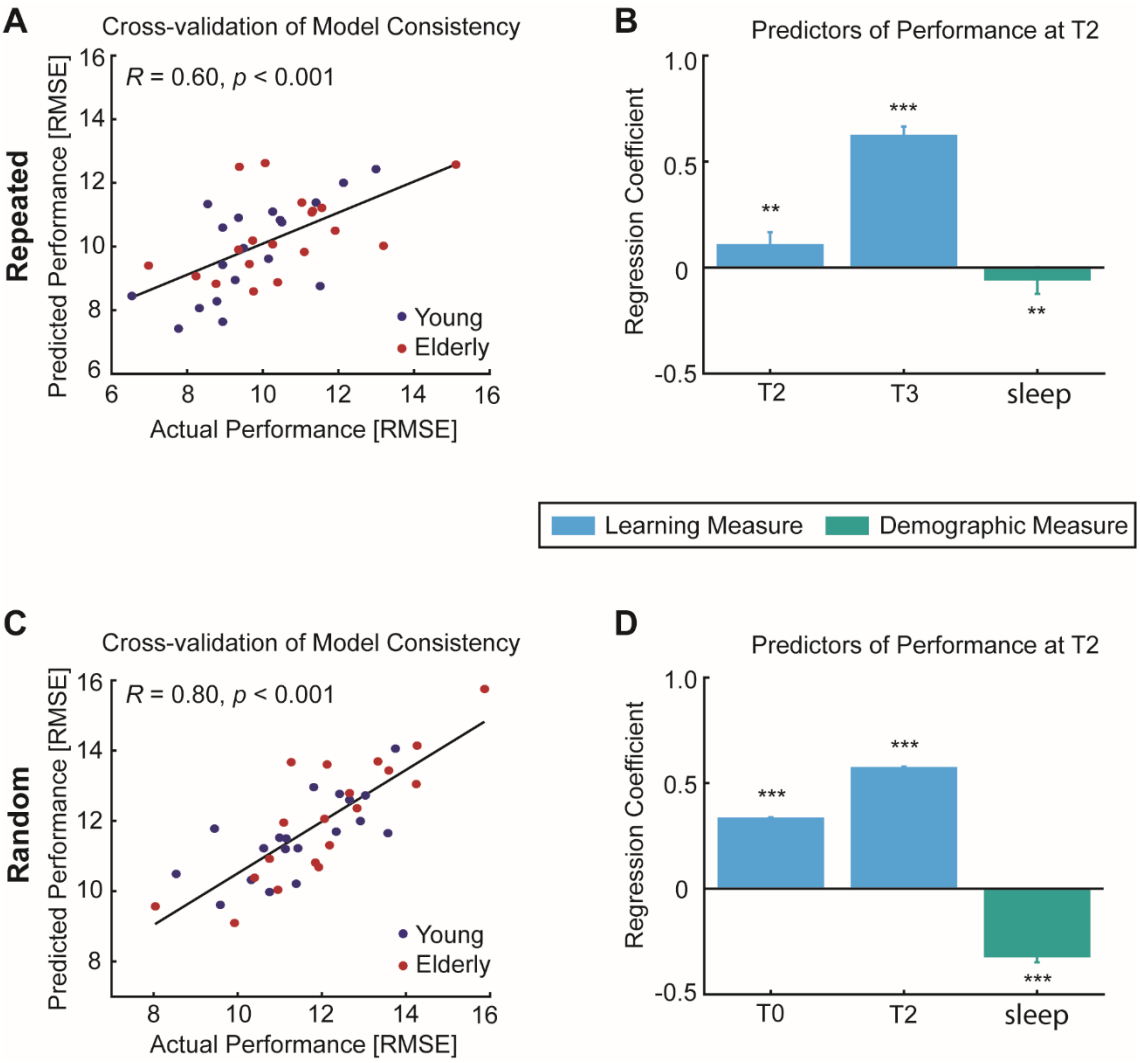

Figure 5.9 | Prediction of tracking performance at T4.
*Stepwise multiple linear regression with a combination of behavioural performance and functional characteristics provided statistically significant performance prediction (**A, C**) as quantified by the correlation coefficient between the actual and predicted tracking performance across healthy subjects. Together these measures accounted for 36 % and 64 % of variance in performance on the repeated and random sequence, respectively. Significance of these correlations was determined by permutation-testing. **B**, Subjects' behavioural performance*

during retest1 exerted the strongest effect on performance of the repeated sequence. An additional model parameter relating to sleep quantity the night before was negative, indicating that longer sleep duration is associated with better performance. ***D****, Performance on the random sequence was affected by model parameters relating to behavioural performance at the beginning of training and retest1 session, respectively. Again, sleep duration was a predictive variable. Averaged z-scored regression coefficients (β) quantify the influence of each significant predictor upon performance level at T4. Error bars represent SEM. Single-sample t-tests to test for differences from zero were employed. *p<0.05, **p<0.01, ***p<0.001.*

In line, comparison of the contribution of neurophysiological and behavioural performance measures echoed the result that beta oscillatory measures did not have any independent explanatory value (summary of comparison is provided in **Table 5.6**). However, while sleep quantity alone did not significantly explain tracking performance, it significantly improved the predictive strength compared to models with behavioural performance measures only [repeated sequence: $t_{(1,37)}$=3.18, p=0.003; random sequence: $t_{(1,37)}$=25.78, p<0.001].

Table 5.6 | Comparison of prediction accuracy for performance at T4.

Predictor variables	R	R^2	Mean RMSE	Sum RMSE
Performance on repeated sequence				
Neurophysiology	-0.30	-0.09	0.97	37
Behaviour	0.62***	0.38	0.69	26
Neurophysiology + Behaviour	0.62***	0.36	0.69	26
Behaviour + Functional characteristics (Sleep)	*0.60****	*0.36*	*0.68*	*25*
Performance on random sequence				
Neurophysiology	-0.07	-0.01	1.0	108
Behaviour	0.76***	0.58	0.58	73
Neurophysiology+Behaviour	0.71***	0.50	0.58	73
Behaviour + Functional characteristics (Sleep)	*0.80****	*0.66*	*0.51*	*67*

*Regression models were fitted with neurophysiological (pre- and post-training (Pre, Post1, Post2) BB, MRBD, and PMBR from both sensorimotor cortices) and behavioural performance measures (tracking performance at T0, T1, T2 and T3) alone, and a combination of both. The predictive strength is quantified by the correlation (R) between the actual and predicted performance, based on LOOCV. A combination of behavioural performance measures and sleep quantity best predicted performance at T4 (blue ink). RMSE values are averaged and summed across the 38 subjects. RMSE: Root Mean Square Error. *p<0.05, **p<0.01, ***p<0.001.*

5.5 Discussion

By employing a continuous tracking task assaying individuals' motor learning capacity and acquiring standard measures of EEG-derived beta power, the present work reported several key findings:

1. Firstly, young and elderly subjects showed comparable ability to learn and retain a motor skill with short-term training.
2. Secondly, resting beta power and MRBD were altered with ageing, but no age-related modulations in the magnitude of PMBR were observed.
3. Finally, by implementing a multivariate approach that accounted for multicollinearity of the various measures, it was possible to explore the complex relationship between cortical beta activity and the degree to which healthy ageing individuals learn and retain new motor skills. Specifically, prior behaviour played a strong role in predicting future tracking performance, but here I have been able to show a significant contribution of beta oscillatory activity to the prediction of motor learning.

5.5.1 Training induces performance improvements independent of age

Preserved ability to develop new motor skills with practice over time is crucial for functional independence and quality of life with advancing age. Ageing is associated with changes in the central and peripheral nervous system that can limit its sensorimotor functioning (for review see (Ketcham and Stelmach, 2001; Lustig et al., 2009; Seidler et al., 2010)), potentially causing motor learning deficits. Although advanced age has been argued to reduce the ability to acquire a new motor skill (Boyd et al., 2008; Ehsani et al., 2015; Harrington and Haaland, 1992; Howard and Howard, 1997; McNay and Willingham, 1998; Shea et al.,

2006) dependent on the nature of the task (Seidler, 2006; Voelcker-Rehage, 2008), or alternatively exert a detrimental effect on motor memory consolidation (Brown et al., 2009; Howard and Howard, 1989; Spencer et al., 2007; Wilson et al., 2012) , there is no consensus over the capability of the ageing brain for motor learning.

The present study employed a laboratory-based motor task to conduct a finely controlled assessment of the ability to learn in healthy ageing adults. By matching baseline performance, it was possible to directly compare the amount learned by young versus elderly subjects. Although young and elderly individuals in the current study demonstrated differences in motor function, cognition and sleep, short-term motor learning for both sequence-specific (repeated sequence) and general (random sequence) motor skills as well as their changes after training ended (offline) were comparable between both age groups. This lack of age-related deficits in motor learning may be attributed to the task requirements of wrist movements as opposed to fine finger movements (Voelcker-Rehage, 2008). Alternatively, older adults might exhibit compensatory strategies in order to support comparable task performance (e.g. (Boudrias et al., 2012; Mattay et al., 2002; Reuter-Lorenz et al., 2000, 1999; Stern, 2009; Ward et al., 2008; Wu and Hallett, 2005)). As such, recruitment of additional brain regions, beyond those used in younger adults might explain similar performance levels between age groups found in this study. Although, brain activity was not measured during the performance of the motor learning task, more widespread activation as well as bilateral activation of sensorimotor areas in elderly adults was noticeable during the performance of the simple motor task, echoing compensatory mechanisms in the ageing brain.

After training ended, tracking performance improved without further training (offline) on the same day for both the sequence-specific and general motor skill. This “early boost” in performance (Albouy et al., 2006; Hotermans et al., 2008, 2006) may simply be attributable to the dissipation of temporary effects such as boredom and fatigue that build up over the course of initial training (Brawn et al., 2010; Rickard et al., 2008) and which were the reasons for focusing on T2 as a measure of fairly permanent early learning (as opposed to T1). Although, the experimental design attempted to minimize the accumulation of fatigue during

training by providing subjects with ample rest between blocks, closer inspection of tracking performance in **Figure 5.5**A still suggests a small decline in performance towards the end of the training phase. Alternatively, previous studies suggested that the “early boost” of performance represents an active/labile state of motor memory with functional relevance for long-term motor memory consolidation (Albouy et al., 2006; Hotermans et al., 2008, 2006; Muellbacher et al., 2002; Nettersheim et al., 2015; Schmitz et al., 2009).

Differential changes in tracking performance on the two types of sequences were observed 24 hours after initial training. Specifically, while training-related improvements in general motor skill were retained, overnight forgetting occured for the sequence-specific motor skill, related to the explicit memory of the sequence structure. As discussed in detail in **Chapter 1** section 1.1.1.3, sleep plays a fundamental role in learning and memory consolidation. Although, the process of sleep-dependent consolidation appears to be reduced with ageing (Brown et al., 2009; Spencer et al., 2007; Wilson et al., 2012), most likely due to age-related changes in sleep patterns (Ohayon et al., 2004), no significant difference in performance levels following a night’s sleep was evident between young and elderly subjects in the current study, despite older adults reporting reduced sleep quantity. In addition, changes in performance overnight did not correlate with sleep measures alone. Nevertheless, a potential influence of sleep cannot entirely be ruled out as perhaps sleep parameters others than the here used self-reported measures might drive sleep-dependent processes mediating motor sequence consolidation (e.g. EEG-measured sleep spindles, (Barakat et al., 2013; Fogel et al., 2017).

5.5.2 Beta oscillations are altered with ageing and motor learning

Although short-term motor learning was comparable between young and elderly individuals on the continuous tracking task, pre-movement (resting) beta power and levels of MRBD were significantly increased in the elderly, consistent with prior literature (Gaetz et al., 2010; Heinrichs-Graham and Wilson, 2016; Rossiter et al., 2014b). At a mechanistic level, a wealth of animal and human literature suggests that oscillatory activity in the beta-band reflects underlying inhibitory GABAergic activity (Hall et al., 2011, 2010a; Jensen et al., 2005;

Muthukumaraswamy et al., 2013; Roopun et al., 2006; Yamawaki et al., 2008). For example, increased baseline beta power (Hall et al., 2010a; Jensen et al., 2005; Muthukumaraswamy et al., 2013), enhanced MRBD (Hall et al., 2011; Muthukumaraswamy et al., 2013), enhanced PMBR (Gaetz et al., 2011), and reduced beta frequency (Jensen et al., 2005) have been demonstrated with pharmacologically increased levels of GABAergic inhibition. In this respect, the age-related changes in beta power at rest and during movement observed in the current study might reflect increased GABAergic inhibition in both contralateral and ipsilateral sensorimotor cortex in older subjects.

Age-related changes in cortical excitation and inhibition have been evidenced in a number of TMS studies, however no consensus with regard to the direction of alterations in GABAergic inhibition exists (Heise et al., 2013; Kossev et al., 2002; Marneweck et al., 2011; McGinley et al., 2010; Peinemann et al., 2001; Smith et al., 2009), most likely due to methodological differences with regard to stimulus parameters, target muscle and age group selection. Notwithstanding, altered inhibitory activity might underlie the age-dependent reduction in cortical plasticity observed in studies assessing TMS-induced (Fathi et al., 2010; Muller-Dahlhaus et al., 2008; Tecchio et al., 2008; Todd et al., 2010) and practice-dependent plasticity (Rogasch et al., 2009; Sawaki et al., 2003). These findings together with the age-related increase in beta power suggest that both performance on the simple motor task and the continuous tracking task should be disrupted, but this does not seem to be the case. It might be that decreased plasticity does not necessarily equate to poor tracking performance or learning (i.e. floor and ceiling effects) and that beta oscillations, as candidate biomarkers of the potential for plasticity, are not necessarily linearly related to learning.

Another possible explanation for the observed increase in beta power with age might be neuroanatomical changes associated with typical ageing. While factors such as skull thickness, conductivity of the electrical tissues, grey matter volume and pyramidal cell density can be altered with ageing and affect sensor-derived measures of neuronal oscillations (Fjell et al., 2014; Hamalainen et al., 1993; McGinnis et al., 2011; Terribilli et al., 2011; Wendel et al., 2010), they are also expected to influence EEG estimates in equal measures and therefore, do not explain the differential effect of age on movement-related beta dynamics

observed in the current study (i.e. age-related modulation was observed only for MRBD, but not PMBR). As such, changes in spectral power measures most likely reflect underlying changes in the functional properties of neuronal circuits generating beta oscillations.

Despite previous findings pointing to an increase in the magnitude of PMBR as a function of age in healthy developing individuals (Gaetz et al., 2010) and an absence in elderly subjects in a go/no-go tasks (Schmiedt-Fehr et al., 2016), no significant differences in the magnitude of PMBR between young and elderly adults were found in the present work. In line with findings of lower beta peak frequency with ageing (Rossiter et al., 2014b), peak changes in PMBR were observed at lower frequencies and ~500 ms later compared to the younger subjects, a finding independent of behavioural differences between age groups (i.e. movement time or peak velocity). It is therefore unlikely that the lack of age-related changes in the magnitude of PMBR and the later occurrence of PMBR in older individuals are artefacts of movement variability or temporal overlap of neuronal activity (see **Chapter 3** section 3.2.3 for details about inter-trial interval selection) or suboptimal time-frequency window selection (see section 5.3.4.2), but rather might reflect maturational differences in the cortical networks generating these distinct beta dynamics and their link to different types of GABAergic inhibition (phasic vs tonic) (Hall et al., 2011; Muthukumaraswamy et al., 2013). The differential effect of age on MRBD and PMBR together with their well described differential modulation in contra- and ipsilateral hemispheres (Van Wijk et al., 2012) support the notion that these beta-band dynamics are, at least to a certain degree, independent processes with distinct functional significance.
Interestingly, elderly subjects demonstrated a more bilateral topographic distribution of PMBR, echoing the idea of greater involvement of the ipsilateral hemisphere in motor control with advanced age (e.g. (Boudrias et al., 2012; Mattay et al., 2002; Reuter-Lorenz et al., 2000, 1999; Stern, 2009; Ward et al., 2008)). However, this observation was not statistically significant and additional analysis of PMBR ratio (contralateral PMBR divided by ipsilateral PMBR) did also not reveal a significant temporal evolution of PMBR with training in elderly subjects [$F_{(2,36)}$=2.18, p=0.128].

Few studies have reported changes in beta oscillations in the context of motor learning. These studies demonstrated changes in movement-related beta dynamics such as increased MRBD and PMBR with training and argued that these changes in movement-related beta dynamics reflect early plastic changes in sensorimotor cortex associated with motor learning (Boonstra et al., 2007; Houweling et al., 2008; Mary et al., 2015; Moisello et al., 2015; Nelson et al., 2017; Pollok et al., 2014) as discussed in **Chapter 1** section 1.2. Unexpectedly, and possibly due to methodological differences such as type of motor learning task, task complexity and study design, movement-related beta activity in the current study was not enhanced following motor training. Corroborating previous findings of training-related changes in beta power at rest (Moisello et al., 2015; Nelson et al., 2017), pre-movement (resting) beta power was significantly enhanced after training. This training-related modulation of beta power might be related to a reduction in cortical excitability due to the saturation of LTP-like plasticity (temporary occlusion) with motor learning (Cantarero et al., 2013; Rioult-Pedotti et al., 2007, 2000, 1998; Rosenkranz et al., 2007; Stefan et al., 2006; Ziemann et al., 2004). Consistent with the concept of temporary suppression of cortical plasticity by neuronal mechanisms involved in motor learning, the observed increase in beta power was transient as it returned to original pre-training levels after a night's sleep. Further supporting evidence for this interpretation comes from studies demonstrating an association between increased beta power and GABAergic inhibitory processes (Hall et al., 2011, 2010a; Jensen et al., 2005; Muthukumaraswamy et al., 2013; Roopun et al., 2006; Yamawaki et al., 2008) as well as decreased cortical excitability (McAllister et al., 2013; Noh et al., 2012)

Alternatively, since alterations in beta power have also been observed with motor fatigue (Fry et al., 2017; Shigihara et al., 2013; Tecchio et al., 2006), the transient increase in beta power might be related to training-induced fatigue effects. A potential influence of fatigue cannot be ruled out and it would be interesting in the future to explore the relationship between beta oscillations and fatigue, and their respective influences on motor learning.

5.5.3 Beta oscillations are predictive of motor learning effects

As discussed above, changes in the properties of beta oscillations, predominantly in contralateral sensorimotor areas, have been observed with motor learning. For instance, the change in the magnitude of MRBD has been linked to superior motor learning and is thought to reflect reorganization of neural activity during motor skill acquisition (Boonstra et al., 2007; Houweling et al., 2008; Pollok et al., 2014). This is further supported by studies reporting altered training-related changes with ageing (Mary et al., 2015) and in pathology (Moisello et al., 2015; Nelson et al., 2017), suggesting abnormal plasticity processes. However, the functional role of these training-related changes in beta activity has yet to be elucidated. Given that, in my data, motor learning appears to occur without training-related changes in beta activity, cortical beta activity may be only one of several mechanisms important for motor learning.

In the current study, a multivariate approach combining neurophysiological and behavioural measures was employed in order to explore the complex relationship between beta oscillatory activity and motor skill learning, providing greater insight into the predictive role of beta oscillations. Implementing a regression approach with leave-one-out cross-validation (LOOCV) accounted for co-varying neurophysiological (Heinrichs-Graham and Wilson, 2016) and performance measures (see section 5.4.1.4), while reducing model overfitting and assessing the generalizability of results to predict new data. My findings highlight that estimates of movement-related beta activity provide a significant contribution to predicting individual differences in tracking performance, but only after accounting for the predictive effect of prior behaviour. Specifically, while measures of beta dynamics alone did not explain tracking performance, the linear combination of these measures together with measures of behavioural performance accounted for 74 % and 36 % of the total variance in early post-training sequence-specific and general tracking performance, respectively, and significantly exceeded the information provided by performance measures alone. This emphasizes that even though behavioural measures were the strongest predictors of motor learning, including EEG-derived beta oscillations, which provide greater insight into cortical processes underlying the potential for

plasticity, helps to explain individual differences in a way that behaviour alone cannot.

Within models, pre-training level of movement-related beta activity was a significant predictor, such that subjects who exhibited smaller MRBD prior to training performed better on the task. Consistent with insight gleaned from animal and pharmacological studies linking properties of beta oscillations to GABAergic inhibition (Hall et al., 2011, 2010a; Jensen et al., 2005; Muthukumaraswamy et al., 2013; Roopun et al., 2006; Yamawaki et al., 2008), smaller pre-training MRBD, reflecting lower GABAergic inhibition, may facilitate motor learning induced LTP-like plasticity and result in better post-training tracking performance. However, rather unexpectedly, in the model predicting sequence-specific tracking performance, MRBD in the ipsilateral rather than contralateral sensorimotor cortex was related to early motor learning. Ipsilateral suppression of beta oscillatory activity during unimanual movement is a well established phenomenon (Gross et al., 2005; Pfurtscheller et al., 1996; Salmelin and Hari, 1994), but its functional role is not fully understood. It has been proposed that ipsilateral MRBD does not merely reflect interhemispheric ‘cross-talk’ between motor cortices that facilitates movements, but may be a consequence of neural processes inhibiting mirror movements through interhemispheric inhibition (Jurkiewicz et al., 2006; Van Wijk et al., 2012). Since EMG was not recorded from both hands, it cannot be verified whether reduced ipsilateral MRBD is associated with mirror movements, even though subjects were instructed to relax their non-moving UL and were monitored by the experimenter throughout EEG recordings.

Interestingly, post-training level of PMBR was identified as a significant predictor of general motor learning only, implying that the two types of learning might, at least to a certain degree, relate to independent neural networks with distinct functional significance for motor learning. In line with previous motor learning studies (Boonstra et al., 2007; Houweling et al., 2008; Mary et al., 2015; Pollok et al., 2014), greater post-training PMBR might reflect neural processes that facilitate practice-dependent sensorimotor reorganization after training. While beta activity, and by inference PMBR, has been suggested to promote the status quo of motor states (Engel and Fries, 2010; Gilbertson et al., 2005b) and has been associated with the processing of sensory afference (Alegre et al., 2002;

Cassim et al., 2001), Tan and colleagues have recently proposed a unifying theory in which PMBR is modulated by the history of task-relevant errors and is related to the uncertainty associated with feedforward predictions (Tan et al., 2016b, 2014). An alternative explanation might thus be that greater post-training PMBR, reflecting better accuracy (or less error) during the previous training, might then preserve motor commands or forward models that require little updating. However, the current work was not designed to study the role of beta-band dynamics for error monitoring, and thus, this interpretation is purely speculative.

Despite beta activity being linked to post-training tracking performance on the same day, tracking performance 24 hours after training was not predicted by beta oscillatory measures, but rather behavioural performance. Interestingly, longer sleep duration appeared beneficial for retention of tracking performance on both the repeated and random sequence, most likely due sleep-dependent motor memory consolidation (Al-Sharman and Siengsukon, 2014; Diekelmann and Born, 2010; Fischer et al., 2002; Nettersheim et al., 2015; Walker, 2005; Walker et al., 2002). The unique contribution of sleep for tracking performance retention should be taken into account in order to maximise motor learning in healthy adults and, in the context of stroke-related brain damage, may have consequences for movement rehabilitation, which depends on motor learning and consolidation.

Together, these findings highlight the importance of multivariate approaches for identifying key factors that contribute to the prediction of motor learning. Specifically, the link between movement-related beta dynamics and early phase motor learning suggests that these neurophysiological measures might, at least partly, explain individual performance differences in a way that behaviour alone cannot. It is important to note that the effect of beta oscillations was only revealed after accounting for behavioural effects, and that measures of beta-band activity were not predictive by themselves. However, given a complex and dynamic system, it might not be surprising that cortical oscillations may be only one of several factors important for motor learning. Clearly, multivariate approaches provide the best opportunity to detect these influences and interactions, in the same model. While motor sequence learning has been shown to elicit widespread activity changes in the cortical-striatal network (Dayan and Cohen, 2011; Doyon

et al., 2003), the current study focused on beta oscillatory activity as candidate biomarkers of the potential for plasticity in sensorimotor cortex. This was not meant to imply that practice-dependent plasticity was confined to sensorimotor cortex, but rather was based on previous work demonstrating the crucial role of sensorimotor cortex for motor learning and early consolidation (Muellbacher et al., 2002; Nudo et al., 1996a; Plautz et al., 2000; Robertson et al., 2005). Clearly, further work is required to understand the complex relationship between neuronal activity and motor learning, but my results demonstrate a unique contribution of the pre-training state of cortical beta oscillations for post-training tracking performance, and an important role of sleep for long-term retention of acquired motor skills. Both findings have important implications for therapeutic interventions in patient populations.

5.5.4 Conclusion

In conclusion, the current results show that the state of the brain's sensorimotor cortex as captured by beta oscillatory activity prior to training provides a unique contribution to the prediction of individual differences in early post-training tracking performance. It demonstrates the potential of neurophysiological measures to enhance prediction accuracy and implies that accessible measurements of beta activity, as markers of net inhibitory and excitatory mechanisms in humans, reflect meaningful individual differences in the motor system that can be utilized in basic research and clinical studies.

Chapter 6 Predicting individual differences in motor learning after stroke

6.1 Abstract

Stroke is the leading neurological cause of physical disability in the world today. Recovery of skilled movement after stroke is reliant on physical training to 'relearn' lost motor skills, but stroke patients show considerable heterogeneity in recovery potential. The factors that lead to inter-individual differences in the recovery process itself are not clear, but their identification would allow accurate prediction of motor recovery and provide novel and important targets for promoting post-stroke rehabilitative outcomes. Since the experiment in **Chapter 4** revealed that estimates of movement-related beta activity explain some of the individual differences observed in the ability to learn in healthy adults, I here extend this line of research to investigate the relationship between cortical beta oscillations and motor learning after stroke.

Eighteen stroke survivors (50–74 years; 90±50 months post-stroke) were trained on the continuous tracking task introduced in **Chapter 3** and subsequently retested after initial training (45–60 min and 24 hours later). Scalp EEG was recorded during the performance of the simple motor task before each training and retention session. To compare patients' capacity for motor learning and assess stroke-related changes in beta activity, age-matched healthy controls were selected from the study in **Chapter 5**.

Despite preserved motor learning capacity, the level of performance change achieved by stroke patients was significantly smaller compared to healthy controls. However, patients did not show altered resting nor movement-related beta activity. Multivariate modelling within leave-one-out cross-validation (LOOCV) revealed that stroke patients' behaviour combined with movement-related beta dynamics on the day of training best predicted their performance levels 24 hours after training, independent of motor impairment, age and lesion side. Thus, while cortical beta oscillations may offer novel targets for therapeutic interventions, combining behavioural measures with neuroimaging has the potential to increase prediction accuracy and might provide the basis for stratification in restorative trials.

6.2 Introduction

Globally, the impact of stroke-related impairment remains high, with persistent upper limb deficits being a common post-stroke outcome reducing quality of life (Feigin et al., 2014; Raghavan, 2015). Post-stroke rehabilitation is fundamentally a process of learning new or relearning lost motor skills through repetitive training. However, stroke survivors show considerable inter-individual differences in recovery potential, making predictions about treatment response challenging (Di Pino et al., 2014; Stinear, 2010). The reasons for this clinical phenomenon are unclear, but understanding the underlying neurophysiological processes would provide novel and important targets for improving post-stroke upper limb recovery.

As discussed in **Chapter 1** section 1.3.3, evidence from animal models and humans suggest that training during the time-limited window of spontaneous biological recovery that occurs early after stroke may have a synergistic effect (Biernaskie et al., 2004; Krakauer et al., 2012; Zeiler and Krakauer, 2013), with heightened effects of training on recovery compared to training in the chronic phase (Hardwick et al., 2017). Crucially, these time-dependent modulations in the potential for plasticity are, at least partly, due to alterations in cortical inhibitory and excitatory mechanisms (Carmichael, 2012; Cramer, 2008; Murphy and Corbett, 2009; Zeiler et al., 2013). Early stroke-induced hyperexcitability triggered by reduced GABAergic inhibition and increased glutamatergic excitation (Que et al., 1999) facilitates long-term potentiation (LTP) (Hagemann et al., 1998), downstream changes in neuronal structure (Chen et al., 2011), and remapping of sensorimotor functions to intact cortical areas (Takatsuru et al., 2009). Further, the idea that GABAergic inhibitory mechanisms are involved in stroke recovery is supported by studies in humans using pharmacological manipulation (Chollet et al., 2011; Hall et al., 2010b) or neuroimaging techniques such as transcranial magnetic stimulation (Swayne et al., 2008), magnetic resonance spectroscopy (Blicher et al., 2015) and positron emission tomography (Kim et al., 2014). Consequently, understanding how to take advantage of post-stroke alterations in cortical inhibition and excitation to promote recovery is an important clinical and scientific goal.

Bridging the gap between cellular and behavioural accounts of post-stroke recovery, requires an appropriate biomarker reflecting underlying biological processes that predict recovery and treatment response in a way that behaviour alone cannot (Aronson and Ferner, 2017; Ward, 2017). Since neuronal oscillations at beta frequency, measured non-invasively with EEG and MEG, are fundamental for motor control control (Engel and Fries, 2010; van Wijk et al. 2012) and have recently been linked to GABAergic activity (Hall et al., 2011, 2010a; Jensen et al., 2005; Muthukumaraswamy et al., 2013), properties of beta activity may provide insight into the dynamics of disease, potentially providing a clinically relevant biomarker of net inhibitory and excitatory mechanisms in human cortex. Recent evidence suggests that sensorimotor cortex beta power is altered after stroke, with beta activity closely tied to the degree of motor impairment (Hall et al., 2010b; Laaksonen et al., 2012; Rossiter et al., 2014a; Shiner et al., 2015; Thibaut et al., 2017). Although relevant for motor control and sensorimotor pathology, and allegedly instrumental to motor learning (Boonstra et al., 2007; Houweling et al., 2008; Pollok et al., 2014), little is known about the relationship between beta oscillations and motor learning after stroke.

Thus, the current study aimed to (I) explore the neurophysiological mechanisms associated with individual differences in motor learning after stroke. In order to ensure that patients could perform the continuous tracking task and that the performance of the wrist movement was not prevented by their motor impairments, here well-recovered patients who were at least 6 months post-stroke, commonly referred to as the chronic phase, were tested. Since behavioural and functional/clinical measures only incompletely characterize inter-individual differences in response to treatment and motor recovery (see **Chapter 1** section 1.3.2), and following on from the findings in **Chapter 5**, I hypothesized that post-stroke measurements of beta oscillatory activity, reflecting alterations in cortical excitatory and inhibitory signalling, might provide additional insight into individual differences in the response to motor learning after stroke.

Despite abnormal patterns of brain activity that occur after stroke (Chollet et al., 1991; Johansen-Berg, 2002; Marshall et al., 2000; Ward et al., 2003a; Weiller et al., 1993), the few studies that examined stroke patients' capacity for motor learning suggest that they retain the ability to learn ((Krakauer, 2006), also see

Chapter 1 section 1.3.5 for more details), even at the chronic stage. Given evidence that the contralesional hemisphere is not “unaffected” after stroke, and its functional role for motor recovery is yet to be fully elucidated (Graziadio et al., 2012; Johansen-Berg et al., 2002; Murase et al., 2004; Riecker et al., 2010; Ward and Cohen, 2004; Werhahn et al., 2003), measures of beta oscillatory activity from both contralesional (unaffected) and ipsilesional (affected) sensorimotor cortex were explored. Since only few studies have explored motor learning after stroke, secondary objectives were to investigate (II) whether stroke patients demonstrate comparable learning as age-matched healthy adults, and (III) explore whether abnormal movement-related beta oscillations as reported in previous studies (Rossiter et al., 2014a; Shiner et al., 2015) persist in patients with low level of impairment (well-recovered).

6.3 Methods

6.3.1 Subjects

Eighteen stroke patients with a first-time ischaemic lesion took part in the present study over two consecutive days. Two patients had to be excluded because of technical problems during data acquisition (patient 13, patient 18). Thus, sixteen stroke patients (mean age = 64±8 years, range 50–74 years, 1 ambidextrous, for more details see **Table 6.1**) were included for analyses (N=16).

All patients were in the chronic stage, having suffered a stroke more than 6 months ago (time since stroke 90±50 months, range 42–220 months). Specifically, the time since stroke was distributed as follows: one patient greater than 180 months (15 years), four patients between 120–180 months (10–15 years), five patients between 60–120 months (5–10 years), and six patients between 36–60 months (3–5 years).

All patients had normal or corrected-to-normal vision, and fulfilled the following inclusion criteria: (a) no reported history of other neurological or psychiatric disease; (b) no language or cognitive deficits sufficient to impair cooperation in the experiment; (c) no use of drugs affecting the central nervous system or self-reported abuse of any drugs (e.g. analgesics, anticonvulsants, muscle relaxants, sedatives, hypnotics); and (d) active range of motion around the affected wrist

greater than 60° in total. To minimize circadian fluctuations in beta oscillatory levels (Toth et al., 2007; Wilson et al., 2014), all patients were tested in the time between 9am and 2pm after giving written informed consent. In addition, patients were instructed to abstain from alcohol and caffeine the evening and morning before the testing.

At the beginning of the experiment, stroke patients underwent a battery of functional assessments to quantify upper limb (UL) motor ability, including ARAT (Yozbatiran et al., 2008), NHPT (Kellor et al., 1971; Mathiowetz et al., 1985b), and grip strength test. Since sensory loss is common after stroke (Tyson et al., 2008), patients' sensation was tested using the FM sensation and proprioception assessment. Performance on the SART (Sustained Attention To Response Test) (Robertson et al., 1997) was used as a proxy of cognitive functioning. In addition, patients provided information about their level of fatigue (computerised version of FSS-7 and NFI (Johansson et al., 2014; Krupp et al., 1989; Mills et al., 2012)) and their sleep (computerised version of St. Mary's Hospital sleep questionnaire (Ellis et al., 1981)) on the nights preceding testing. Please refer to **Chapter 3** section 3.3 for details about various tests.

In order to evaluate how motor learning, beta oscillatory activity and their relationship are altered after stroke, twenty age-matched healthy controls (mean age = 68±5 years, range 53–77 years) were selected from the elderly subject group in the study presented in **Chapter 5**. Please note that in order to select an age-matched healthy control group, one subject that previously did not match the inclusion and exclusion criteria due to the age specification of that study (age range 60–80 years), was now included.

Table 6.1 | Characteristics of chronic stroke patients.

SN	Sex	Age	Time since stroke	Affected hand	Lesion location/ type
1	F	74	136	Nondominant (L)	Right | LACI
2	M	71	41	Nondominant (L)	Right | LACI
3	M	57	80	Nondominant (L)	Right | anterior thalamus
4	M	50	43	Dominant (R)	Left | posterior MCA
5	M	63	122	Dominant (R)	Left | striatocapsular
6	M	63	70	Dominant (R)	Left | LACI
7	F	63	44	Nondominant (L)	Right | frontal lobe
8	M	71	220	Nondominant (L)	Right | LACI
9	M	56	49	Nondominant (L)	Right | thalamus
10	F	63	71	Ambidexterous (L)	Right | LACI
11	M	60	42	Dominant (R)	Left | anterior MCA
12	M	73	128	Dominant (R)	Left | LACI
14	F	71	57	Nondominant (L)	Right | LACI
15	F	75	136	Dominant (R)	Left | PCA
16	M	56	83	Nondominant L)	Right | hypothalamus
17	F	58	105	Dominant (R)	Left | anterior MCA
		64±7	**89±49**	**R=7; L=9**	

Age (years); Time since stroke (months); M: Male; F: Female; L: Left; R: Right; D: Dominant; ND: Non-dominant; MCA: Middle cerebral artery; PCA: Posterior cerebral artery; LACI: Lacunar infarct

6.3.2 Experimental design

The experimental design was identical to the study presented in **Chapter 5** and is illustrated in **Figure 6.1**. The primary objective of this study was to explore whether cortical beta-band activity from stroke patients is predictive of individual differences in motor learning capacity. Chronic stroke patients trained with their affected (contralesional) hand on the continuous tracking task, introduced in **Chapter 3** section 3.2.2, over a single training session (40 blocks; 20–40 min) with the aim of improving tracking performance beyond pre-training levels. The tracking task involved two types of sequences within each block, a *random* and a *repeated* sequence. Improvement on the random sequence was again taken as a measure of general skill learning, whilst any additional improvement on the repeated sequence index sequence-specific motor learning of the precise sequence pattern (Wulf and Schmidt, 1997). Tracking performance was defined as the accuracy (measured in RMSE) with which subject's wrist movement

tracked the target movement (**Figure 6.2**). Patient's tracking performance was retested at two different time points: 45–60 min (retest1 on day 1; 5 blocks) and 24 hours (retest2 on day 2; 10 blocks) after the initial training session. These retest sessions allowed (i) temporary effects (e.g. fatigue or boredom) that build up over the course of training (Brawn et al., 2010; Rickard et al., 2008) to dissipate, thus only leaving the fairly permanent learning effects and (ii) consolidation of motor memories to occur, which either results in stabilization or even enhancement of acquired motor skill performance after a night's sleep (Robertson et al., 2004a; Walker, 2005).

EEG recorded during the performance of the simple motor task was used to assess pre-movement (resting) and movement-related beta activity before (Pre), immediately after (Post1) and 24-hours after (Post2) the initial training phase. On day 1, prior to the motor tasks, the mid-point and maxima of a patient's maximum AROM (see **Chapter 3** section 3.2.1 for details) around the wrist joint was measured (mean AROM = 113.3±20.5 deg) and subsequently used as start and/or target positions in the continuous tracking task and simple motor task, respectively.

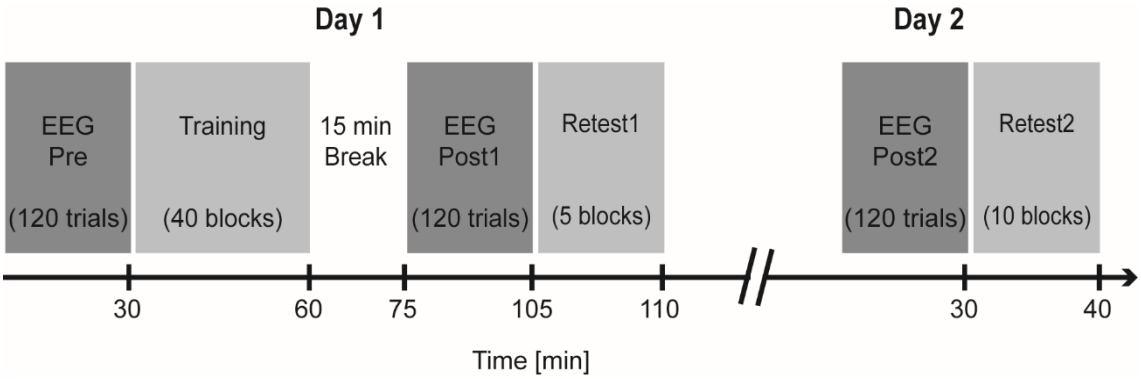

Figure 6.1 | Timeline of experiment employing EEG and motor learning.
EEG was recorded during the performance of a simple motor task before (Pre) and at two time points after the training phase (Post1 and Post2). Retention of motor skill acquisition was assessed on the same day (45–60 min, retest1 on day 1) and the following day (24-hours, retest2 on day 2).

6.3.2.1 Apparatus and stimuli

In accordance with the previous studies presented in this thesis, patients were comfortably seated with their contralesional (affected) hand resting in the instrumented wrist rig (see **Chapter 3** section 3.2.1). The wrist rig restricted movement to flexion and extension around the wrist joint and ensured minimal hand and arm movement during the experiment. The angular position of the wrist, sensed by the build-in potentiometer of the wrist rig, was continuously displayed on a computer monitor as a cursor in the form of a red circle – referred to as "wrist cursor". The target in both motor tasks was displayed as either an open yellow circle (continuous tracking task) or as a blue square (simple motor task).

6.3.2.2 Continuous tracking task

Stroke patients were required to continuously track a circular target (in yellow) that moved back and forth along a fixed arc through a predefined sequence of 12 positions (**Figure 6.2**A). For a detailed description of the continuous tracking task please refer to **Chapter 3** section 3.2.2. In brief, the minimum jerk approach (Flash and Hogan, 1985; Hogan, 1984) was employed to ensure smooth target motion through the sequence positions. The maximum range of the target trajectory was defined as ±30° of wrist flexion and extension and the target always started and finished at the individual mid-point position of each patient's AROM. Each block consisted of two sequences, one *random* and one *repeated* sequence presented in randomised order, with a 3 s stationary target between both. The repeated sequence was identical throughout initial training (40 blocks), and retest sessions (retest1 on day 1: 5 blocks; retest2 on day 2: 10 blocks) and randomly selected from the same pool of 57 difficulty-matched sequences used **Chapter 5**. Please refer to **Chapter 3** section 3.2.2.3 for details about the sequences. Each random sequence was encountered only once; however, the same set of difficulty-matched sequences was used across subjects. Patients were instructed to move their wrist so as to shift the red wrist cursor to match the movement of the target as 'accurately and smoothly as possible'.

Prior to the training, the average velocity with which the target moved along the arc was determined on an individual basis in order to ensure that the task was of

equal difficulty for all patients at the beginning of the training and left enough room for improvement in performance. For this purpose, the adaptive up-down staircase procedure introduced in **Chapter 3** section 3.2.2.5 was used for individual determination of target velocity. On average, patients reached the criterion in 15.5±5.1 trials and the number of trials required was not significantly different from the healthy adults in **Chapter 5** (one-way ANOVA with 'group' (3 levels: young adults vs elderly adults vs stroke patients) as between-subject factor $F_{(2,53)}$=0.33, p=0.721). The individually determined target velocity with which patients were subsequently trained on the continuous tracking task was applied to all sessions and was significantly slower for patients (mean velocity ±SD = 45.39±5.22 deg/s) compared to the healthy controls (mean velocity ±SD = 51.29±9.43 deg/s) [$t_{(34)}$=-2.38, p=0.032].

During initial training and retest sessions, online visual feedback in terms of a colour change of the wrist cursor (from red to green) was provided at times when the patient positioned the wrist cursor inside the circular target. In addition, at the end of each block, patients were made aware of their change in tracking performance by presenting a score on the screen. Prior to the start of training, patients received explicit verbal information regarding the presence of a repeated sequence along with a random sequence in every block. However, they were not shown the repeated sequence. To determine the time point at which patients gained explicit knowledge of the repeated sequence, after each block they had to decide (forced-choice) which of the two sequences within each block the repeated sequence was – i.e. tell the experimenter whether it was the first or second sequence they tracked within the block (**Figure 3.4**C). The trajectories of the target and patient's wrist cursor did not leave a residual trace on the screen and hence, patients could not visualize the entire target sequence.

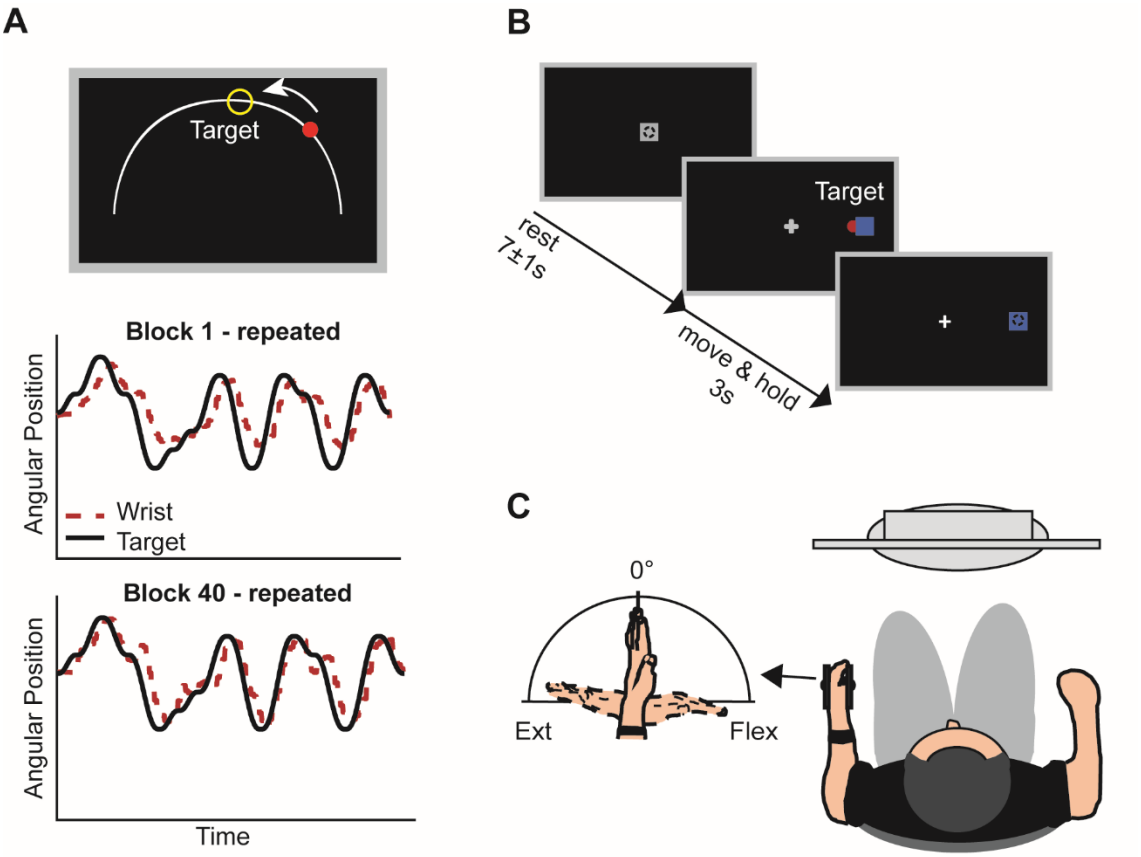

Figure 6.2 | Experimental setup and paradigms.
A*, Patients were trained to track a target (yellow circle) moving back and forth along a fixed arc as accurately and smoothly as possible. Online visual feedback in terms of a colour change of the wrist cursor (red to green) was provided at times when the wrist cursor was located inside the circular target. Original recordings during the continuous tracking task at the beginning and end of the initial training are shown for the repeated sequence of an example patient (A, lower panel). The solid black line represents the motion of the target, while the dashed red line represents the motion of the wrist.* ***B,*** *For the simple motor task, subjects were instructed to perform wrist flexion and extension to move the wrist cursor (red circle) from the initial start position (grey square) to one of two target positions (blue square) upon target presentation.* ***C****, During both tasks, patients sat in front of a computer monitor with their affected hand rested in the wrist rig that restricted movement to flexion and extension around the wrist joint.*

6.3.2.3 Simple motor task

For a detailed description of the simple motor task, please refer to **Chapter 3** section 3.2.3. Briefly, patients performed visually cued wrist flexion and extension

movements with their contralesional (affected) hand during EEG recording. During each trial, wrist movements were always initiated from the same start position displayed at the centre of the screen that represented the mid-point of a patient's individual AROM. The cue to perform wrist flexion or extension movements was the random appearance of one of two targets (in blue), on the left or right, equidistant from the central start position (**Figure 6.2**B). Each of the targets represented the patient's maximum wrist flexion or extension position. Stroke patients were instructed to move their wrist upon presentation of the target so as to shift the red wrist cursor from the central start position to match the position of the target in a 'quick and discrete' movement. They were also asked to move as soon as possible and to avoid anticipation or guessing of target appearance. The target position was displayed for 3 s and patients had to maintain the wrist cursor inside the blue target until being cued to return to the initial start position. Once patients returned to the start position, the next cue to move was delivered following a delay of 7±1 s. The task comprised 120 trials, and patients were instructed to minimize eye movements by focusing on a centrally located fixation cross. As described in detail in **Chapter 3** section 3.7.1.2, kinematic data of individual wrist movements were analysed with regard to reaction time (RT), movement time (MT), and peak velocity (PV) and averaged per experimental condition on an average of 109±4 remaining trials. Since movement time and peak velocity were highly correlated (r>0.7), only reaction time and movement time were reported.

6.3.3 EEG recording

Scalp EEG was continuously recorded at 2084 Hz using 64 electrodes mounted on an elastic cap according to the international 10-20 EEG system. The impedance was kept below ≤5 kΩ and the EEG signal was referenced to Cz during recording. The timing of the visual cue (blue target) in the motor task was marked in the simultaneous EEG recording, with separate markers for each condition (flexion, extension). Surface EMG using bipolar electrodes in a belly-tendon montage placed on the wrist extensor (extensor carpi radialis longus) and flexor (flexor carpi radialis) muscles monitored movements of the affected hand.

6.3.4 Data analysis

Analyses were conducted using custom-written routines in Matlab and the SPM12 toolbox (Wellcome Trust Centre for Neuroimaging, www.fil.ion.ucl.ac.uk/spm). The fieldtrip toolbox ((Oostenveld et al., 2011), www.ru.nl/fcdonders/fieldtrip/) was additionally employed for EEG data visualization. Statistical analyses were performed using SPSS and custom-written Matlab routines.

6.3.4.1 Functional assessment measures

ARAT, grip strength, and NHPT test scores were normalized by expressing the affected UL score relative to the unaffected UL. Adopting a similar approach as previous studies (Rossiter et al., 2014a; Ward et al., 2003a), a principle component analysis (PCA) was performed on ARAT, NHPT, grip strength and sensation assessment in order to create a single sensorimotor impairment score unaffected by floor and ceiling effects in individual scores. The first principle component was extracted to generate a PCA sensorimotor impairment score, whereby a lower PCA score corresponds to greater impairment. The same procedure was used to generate an overall score of the level of fatigue experienced by patients, based on FSS and NFI ratings, with lower PCA scores reflecting lower levels of fatigue.

6.3.4.2 Motor learning measures

Analysis of kinematic data was identical to **Chapter 5** and a detailed description can be found in **Chapter 3** section 3.7.1.1. In brief, the behavioural measure “tracking performance” on the continuous tracking task was parametrized by RMSE (see **Equation 3.5**), an established composite measure of temporal and spatial measurements of time lag and distance (Al-Sharman and Siengsukon, 2014; Boyd and Winstein, 2006; Roig et al., 2014; Siengsukon and Boyd, 2009), with smaller RMSE values reflecting better tracking performance. RMSE was calculated for *repeated* and *random* sequences separately and averaged across each block of the training and retest sessions.

As the beginning and end of individual training and retest sessions might not be representative of actual tracking performance (e.g. due to warm-up decrement at the beginning or fatigue at the end), a linear regression model was fitted across the first and last 5 blocks of individual training and retest sessions (approach adopted from (Waters-Metenier et al., 2014)). This fit provided a corrected performance estimate of the first and last blocks of each session (please refer to **Chapter 3** section 3.7.1.1 for illustration of this approach). Please note that performance refers to this corrected performance estimate unless stated otherwise.

The analysis then concentrated on six time points in order to assess changes in tracking performance across time: first block of training (T0), last block of training (T1), first block of retest1 (T2), last block of retest1 (T3), first block of retest2 (T4), and last block of retest2 (T5). As outlined in **Chapter 1** section 1.1.1.1, various processes can occur during time periods during which the task is not practised (i.e. between T1 and T2 or T3 and T4), such as dissipitation of temporary effects (e.g. fatigue or boredom) (Brawn et al., 2010; Rickard et al., 2008) and motor memory consolidation, resulting in skill retention, enhancement or decrements (Hotermans et al., 2006; Robertson et al., 2004a; Walker, 2005). As such, tracking performance at T2 is most likely to reflect fairly permanent learning effects unaffected by training-induced temporary effects such as fatigue or boredom, while performance at T4 likely indexes retention of the acquired motor skill overnight, due to motor memory consolidation.

6.3.4.3 Neurophysiological measures

Pre-processing and time-frequency analysis of EEG data recorded during the performance of the simple motor task has been detailed in **Chapter 3** section 3.7.2 and followed the same procedure as in **Chapter 5**. Briefly, the raw EEG signal was first offline re-referenced to the average signal across all electrodes, bandpass filtered between 5–100 Hz, additionally filtered with a 50 Hz notch filter, and downsampled to 300 Hz. Data were epoched from -1 to 9 s relative to visual cue onset (0 s) and poorly performed trials (see 6.3.2.3 Simple motor task) were excluded. The remaining EEG trials were visually scrutinized and trials containing

artefacts (e.g. muscle activation or large eye blinks) were additionally removed. For each session, on average 82±17 artefact-free EEG trials remained, and the number of trials did not differ between conditions (p>0.9, repeated-measures ANOVA). Artefact-free EEG time-series from each single trial were then decomposed into their time-frequency representations in the 5–45 Hz range with frequency steps of 0.1 Hz. A 7-cycle Morlet wavelet was used for the continuous wavelet transformation. Power was averaged across trials and rescaled in order to show changes relative to the corresponding pre-movement baseline period (-1–0 s prior to cue onset) (**Equation 3.6**).

Spectral power time-series were then derived from electrodes pre-selected from the independent data presented in **Chapter 4** overlying both sensorimotor cortices (MRBD: ‘C4’ ‘CP4’ ‘CP2’ and ‘C3’ ‘CP3’ ‘CP1’ for contra- and ipsilateral hemispheres, respectively; PMBR: ‘C2’ ‘C4’ ‘CP4’ and ‘C1’ ‘C3’ ‘CP3’ for contra- and ipsilateral hemispheres, respectively). These bilateral electrodes were pooled as contralateral and ipsilateral regions of interest, respectively.

To select time-frequency windows of interest that were orthogonal to potential differences between conditions (flexion and extension) when the simple motor task was performed (Pre, Post1, and Post2), I averaged over conditions, sessions, and all patients. Then, specific time-frequency windows were chosen based on peak changes in beta activity in time-frequency maps of the bilateral sensorimotor regions, which revealed clear movement-related beta-band activity in two distinct time windows of interest. This information was used to optimize the alignment of constant duration and width time-frequency windows to capture maximum MRBD (1–2 s relative to cue onset; mean peak latency: 1.66±0.08 s), occurring between cue onset and movement termination, and PMBR (6–7 s relative to cue onset; mean peak latency: 6.47±0.14 s), which emerges after movement cessation (**Figure 6.3**). In line with the elderly subject group in **Chapter 5** and known age-related reduction of beta peak frequency (Rossiter et al., 2014b), patients’ peak changes in beta activity after movement cessation appeared at lower beta frequencies compared to young healthy subjects (10–25 Hz). Selected time-frequency windows and electrodes applied to all stroke patients and sessions, and were not adjusted individually.

Subsequently, for each individual patient, percentage decrease (MRBD) and increase (PMBR) in beta power were extracted from the respective 1 s time windows and averaged separately for each EEG session (Pre, Post1 and Post2) for the pre-selected electrodes over each hemisphere. The absolute pre-movement (resting) baseline beta (BB) power from -1 to 0 s relative to cue onset was also obtained.

In total, the same 6 highly reliable beta parameter estimates as in **Chapter 5** were used for subsequent analyses: pre-movement baseline beta (absolute power), MRBD (relative power) and PMBR (relative power) from contra- and ipsilateral sensorimotor cortices, respectively.

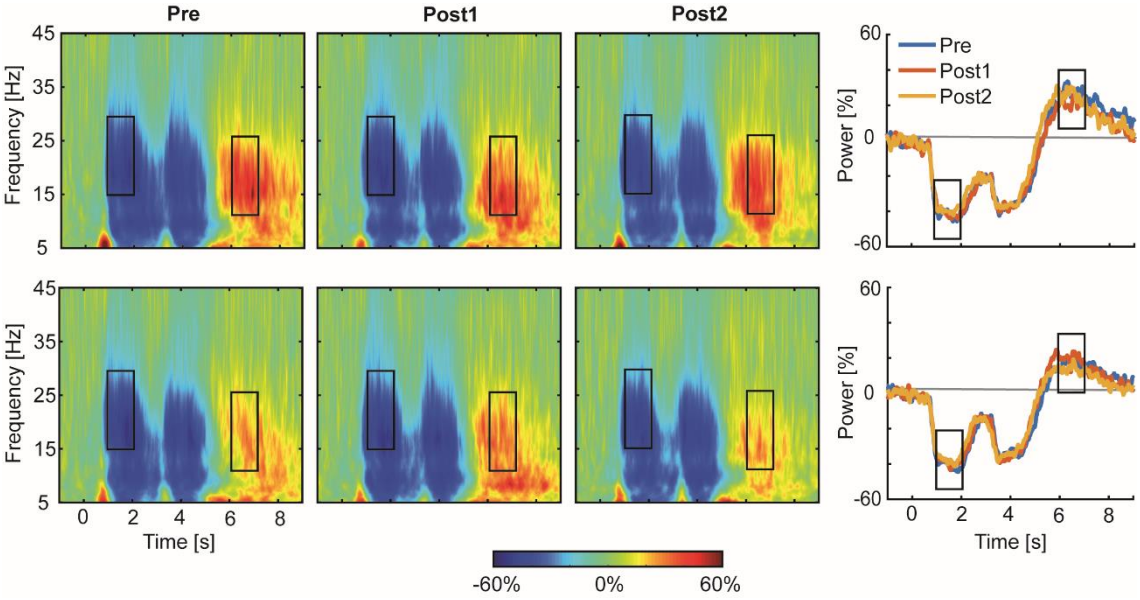

Figure 6.3 | Movement-related changes in spectral power after stroke. *Time-frequency spectrograms are averaged across patients separately for contralateral (upper panel) and ipsilateral (lower panel) sensorimotor cortex for each EEG session (Pre, Post1, and Post2). The right hand panel displays overlaid beta power traces for the three sessions. The black rectangles indicate the time windows of interest of peak changes in beta activity (MRBD and PMBR). Please note that PMBR occurred at lower beta frequencies (10–25 Hz) compared to MRBD. These time-frequency windows were tested for significant differences between groups and EEG sessions.*

6.3.5 Statistical analysis

Before (I) investigating the relationship between beta-band activity and individual differences in motor learning, a series of conventional analyses were first

conducted to assess (II) whether stroke patients ability to learn on the continuous tracking task (their behaviour) was comparable to the age-matched healthy control subjects, and (III) whether stroke-related alterations in beta-band activity (neurophysiology) were present in the here examined well-recovered patient group.

To assess whether tracking performance improved across training and was maintained, enhanced or decreased at retest sessions, a repeated-measures ANOVA on tracking performance score (RMSE) was performed, with 'group' (2 levels: patients vs controls) as between-subject factor and 'sequence type' (2 levels: repeated vs random) and 'time' (5 levels: T0 vs T1 vs T2 vs T3 vs T4) as within-subject factors. Additionally, to ensure comparable baseline performance and thus, allow for direct comparison between stroke patients and healthy controls, a repeated-measures ANOVA of tracking performance at the beginning of training (T0) was used.

Standard measures of resting and movement-related beta activity were evaluated applying separate repeated-measures ANOVAs with 'group' (2 levels: patients vs controls) as between-subject factor and 'hemisphere' (2 levels: contralateral vs ipsilateral) and EEG 'session' (3 levels: Pre vs Post1 vs Post2) as within-subject factors.

A Greenhouse-Geiger correction was applied whenever Mauchly's test indicated a lack of sphericity. *Post hoc* Bonferroni-adjusted t-tests were performed whenever main effects and interaction effects were detected in the ANOVAs. Prior to ANOVAs and *post hoc* t-tests, Kolmogorov-Smirnov test was used to affirm normal distribution of the data. Results were considered significant if *p*-values were below 0.05. All data presented in the text and tables are represented as mean ±SD unless stated otherwise.

6.3.5.1 Regression analysis combining neurophysiological, behavioural and clinical measures

Finally, a multiple linear regression approach was employed in order to investigate whether post-stroke spectral power measures of beta-band activity relate to individual differences in the capacity for motor learning, accounting for

multicollinearity between neurophysiological (Heinrichs-Graham and Wilson, 2016) and behavioural performance measures. Specifically, separate stepwise multiple linear regression models (with forward and backward algorithm; inclusion/exclusion probability levels: $\alpha_{Enter}<0.05$/ $\alpha_{Exclude}>0.1$) were used to select variables that provided a significant contribution to explaining tracking performance at T2 and T4 for the repeated and random sequence, respectively. Tracking performance at T2 reflects fairly permanent learning effects unaffected by training-induced temporary effects such as fatigue or boredom, while performance at T4 indexes retention of the acquired motor skill overnight, reflecting motor memory consolidation. Specifically, a combination of neurophysiological measures, including (a) baseline beta power, (b) MRBD, and (c) PMBR from both sensorimotor cortices, as well as behavioural performance measures during the training session, i.e. (d) at T0 and (e) at T1, were used to explain performance at T2, while behavioural performance measures during retest1, i.e. (f) at T2 and (g) T3, were further included to explain performance at T4. In addition, the following functional/clinical variables were equally included: age, time since stroke, affected side, level of sensorimotor impairment, fatigue severity, cognitive function, and sleep characteristics. All predictors were z-scored before analysis to produce regression coefficients (β) of comparable magnitude.

To avoid overfitting and evaluate the predictive strength of each regression model, a leave-one-out cross-validation (LOOCV) approach, as previously implemented in **Chapter 5**, was employed (Arlot and Celisse, 2010; Picard and Cook, 1984). For this purpose, at each iteration the regression model was fitted on data from N-1 subjects (training set), with the removed subject being used as a test set for assessing model performance. This cross-validation method is an established procedure for assessing generalization of results to an independent data set, particularly with smaller sample sizes (Huang et al., 2011; Kang et al., 2014). The strength of the prediction model was quantified in terms of the correlation coefficient between actual and predicted tracking performance. A permutation-test (100 iterations) was used to assess whether the difference between the actual and predicted performance was greater than would be expected by chance. For this, the entire LOOCV approach was repeated 100

times and in each iteration, the ordering of the performance values to the subjects was randomly permuted beforehand. This has the desired effect of the test set being selected randomly in each iteration and also guarantees the independence of the training and test sets in every fold. Inferences about the relevance of predictor variables (i.e. whether a predictor variable affects tracking performance in a consistent manner) were based upon the distribution of regression coefficients (β) across subjects, using single-sample t-tests to test for differences from zero. To compare models fitted with neurophysiological or behavioural performance measures only, or a combination of both, independent t-tests were used to test for differences in distributions of RMSE across subjects between models.

6.4 Results

Behavioural and EEG data recorded during the performance of the continuous tracking task and the simple motor task for 16 chronic stroke patients and 20 age-matched healthy control subjects are reported. Please note that the healthy control data was identical to the elderly data presented in **Chapter 5** apart from the inclusion of one additional subject.

6.4.1 Functional assessment

Functional assessment of stroke patients based on a variety of tests is summarized in **Figure 6.4**. The patient group studied here had an overall low level of sensorimotor impairment as reflected by similar values for the affected and unaffected side. Only performance on the NHPT was impaired on the affected compared to the unaffected side [$t_{(15)}$=1.22, p=0.028], suggesting reduced dexterity in the contralesional (affected) hand. Comparison of stroke patients and age-matched healthy controls, as summarized in **Table 6.2**, demonstrated that patients performed similar to controls on the various tests, further implying that the here studied patients were well-recovered.

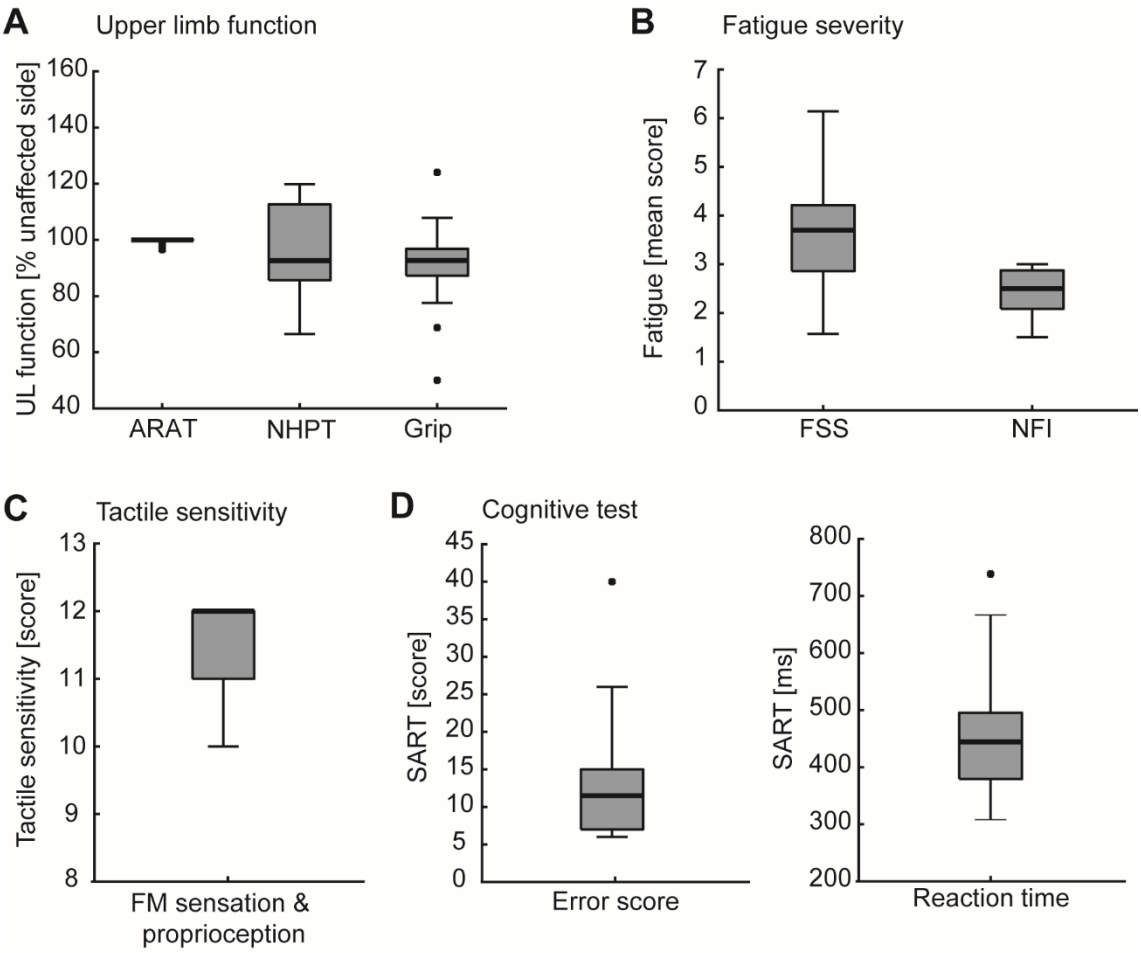

Figure 6.4 | Patients' functional/clinical test scores.

A, *Upper limb motor function of the contralsional (affected) UL assessed by ARAT, NHPT and grip strength test was expressed as a percentage of the unaffected side in 16 stroke patients. (**B**) Self-reported fatigue was quantified using two computerised questionnaires, FSS-7 and NFI. Fatigue severity reported by the stroke patients ranged across a broad spectrum of fatigue levels. (**C**) UL sensation as measured by the FM sensation and proprioception assessment showed normal sense of touch or sensation, except for four patients who showed reduced sense of touch (hypoesthesia). (**D**) Patients showed good cognitive abilities as shown by relatively low error scores (max 225) and fast reaction times. The boxplots show the distribution of the data points, with the horizontal line representing the median and the black dots representing outliers.*

Table 6.2 | Group characteristics of stroke patients and healthy controls.

	Patients	Controls	Between-group difference
N	16	20	-
Age	64±8	68±5	*t(25.2)=-1.84, p=0.078*
Male:Female ratio	11:5	8:12	*X^2=2.94, p=0.086*
Handedness (Edinburgh)	87±24	85±21	*t(34)=-0.21, p=0.833*
Grip Strength [lb]	66±26.04	63±21.03	*t(34)=0.41, p=0.682*
NHPT [pegs/s]	0.57±0.13	0.60±0.07	*t(34)=-0.93, p=0.362*
SART (Error score, 0-225)	13±8.97	13±10.73	*t(34)=0.13, p=0.897*
SART (RT in ms)	456±114.3	451±142.9	*t(34)=0.108, p=0.915*
Sleep Quantity [hours]$^{\#}$	7±1.02	6±0.94	***U=93.5, p=0.033***
Sleep Quality (1-8)$^{\#}$	4.7±1.57	5.2±0.87	*U=141.0, p=0.560*

Between-group comparisons only revealed a significant difference in sleep quantity the previous night. For continuous data, independent-samples t-tests were used to test for between-group differences. For discrete data ($^{\#}$), Mann-Whitney U-tests were applied. Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). Upper limb functional measures are affected hand/non-dominant hand only and sleep measures are averaged across both days (both sleep measures were not significantly different between day 1 and day 2, p>0.1). Significant effects are indicated in bold. Values given are mean ±SD. NHPT: Nine Hole Peg Test; SART: Sustained Attention to Response Test.

6.4.2 Reduction of motor skill learning after stroke

Tracking performance of chronic stroke patients and healthy age-matched controls at training and retest sessions is shown in **Figure 6.5**A. Testing for systematic differences in tracking performance at baseline (block 1) did not reveal a significant difference between patients and healthy controls [$F_{(1,34)}$=0.42, p=0.523] or repeated and random sequences [$F_{(1,34)}$=0.002, p=0.969] nor an interaction effect [$F_{(1,34)}$=0.051, p=0.823], thus allowing direct comparison of t performance between both groups.

A repeated-measures ANOVA on tracking performance revealed a significant main effect of ‘time’ [$F_{(4,136)}$=32.33, p<0.001, η^2=0.487], ‘sequence type’ [$F_{(1,34)}$=55.216, p<0.001, η^2=0.619] and ‘group’ [$F_{(1,34)}$=4.80, p=0.035, η^2=0.124].

In addition, significant interactions between 'time x group' [$F_{(4,136)}$=4.25, p=0.006, η^2=0.111], 'time x sequence type' [$F_{(4,136)}$=10.98, p<0.001, η^2=0.244], and 'sequence type x group' [$F_{(1,34)}$=5.58, p=0.024, η^2=0.141] were found. *Post hoc* analyses were thus performed to separately assess changes in motor performance with initial training (online) and following a shorter (retest1) or longer (retest2) time delay during which subjects did not practice the task (offline), focusing on how stroke patients' motor learning differs from healthy controls.

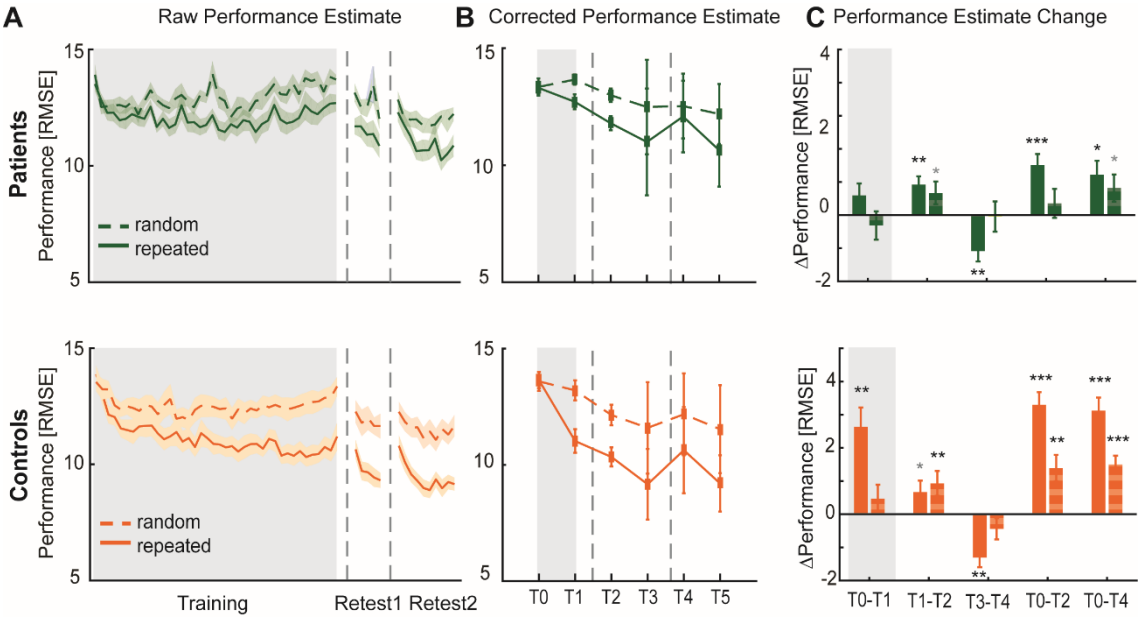

Figure 6.5 | Motor learning performance of patients and healthy controls. ***A****, Average tracking performance (RMSE) for repeated and random sequences (solid and dashed lines respectively) across training (day 1), retest1 (day 1) and retest2 (day 2) sessions for chronic stroke patients (green) and healthy controls (orange). Vertical dashed lines represent time away from the motor learning task.* ***B****, Corrected performance estimates at the beginning and end of training (T0, T1) and retest (retest1: T2, T3; retest2: T4, T5) sessions.* ***C****, Performance differences (Δ) between time points, focusing on online learning (T0-T1) and offline learning over a shorter (retest1, T1-T2) or longer (retest2, T3-T4) time delay delay as well as overall performance changes from baseline (T0-T2; T0-T4). Solid bars represent Δ performance on the repeated sequence and striped bars on the random sequence. Positive and negative values, respectively, signify performance improvement and decrement. Shaded area (****A****) and error bars (****B, C****) indicate between-subject SEM. *p<0.05, **p<0.01, ***p<0.001, grey *p<0.1 (trend).*

6.4.2.1 Performance over the course of training

During the training phase, stroke patients did not significantly improve their tracking performance [T0 vs T1; *F*-statistics and *p*-values of ANOVAs are summarized in **Table 6.3**] for neither the repeated [$t_{(15)}$=1.62, p=0.127] nor random sequence [$t_{(15)}$=-0.73, p=0.476], but a significant difference between sequences at T1 was observed [$t_{(15)}$=-3.37, p=0.004, η^2=0.431]. In comparison, the healthy control group demonstrated significant sequence-specific learning [$t_{(19)}$=4.72, p<0.0001, η^2=0.539] (**Figure 6.5**C). Closer inspection of the tracking performance in **Figure 6.5**A shows a decline in performance towards the end of the training phase, suggesting that temporary effects such as fatigue or boredom might have depressed performance towards the end of training.

6.4.2.2 Performance at retest1

Because stroke patients did not significantly improve their performance over the course of training, their performance levels on the repeated sequence at T1 and T2 were significantly different from the healthy control group [T1: $t_{(30.8)}$=2.82, p=0.008; T2: $t_{(34)}$=2.73, p=0.010]. However, patients and healthy controls had similar performance levels on the random sequence [T1: $t_{(27.56)}$=0.94, p=0.354; T2: $t_{(31.09)}$=1.62, p=0.115]. Across the short time period between T1 and T2, patients' tracking performance significantly improved by 7 % without further training for the repeated sequence only [$t_{(15)}$=3.72, p=0.002, η^2=0.480], while there was a trend for the random sequence [$t_{(15)}$=1.95, p=0.070]. This indicates a boost in performance early after the initial training (45-60 min) comparable to the healthy controls [$t_{(34)}$=0.56, p=0.582], which might be due to the dissipation of training-induced temporary effects (**Figure 6.5**C).

In line, patients' overall performance significantly improved from T0 to T2 for the repeated sequence (11 % improvement) [$t_{(15)}$=4.53, p<0.001], but not random sequence. This indicates that patients actually learned, but that the learning effects were masked at the end of training, most likely due to temporary effects. However, these learning-related improvements were significantly smaller compared to the healthy control group [repeated sequence: $t_{(34)}$=-3.55, p=0.001; random sequence: $t_{(34)}$=-1.90, p=0.066].

6.4.2.3 Performance at retest2

Lastly, overnight changes in tracking performance were assessed. Again, performance levels on the repeated sequence at T3 and T4 were significantly different between stroke patients and healthy controls [T3: $t_{(34)}$=2.88, p=0.007; T4: $t_{(34)}$=3.36, p=0.002], with patients overall being less accurate in tracking the target (mean performance = 11.54 RMSE) than controls (mean performance = 9.71 RMSE). No significant difference between groups was evident for the random sequence [T3: $t_{(34)}$=1.34, p=0.188; T4: $t_{(34)}$=1.13, p=0.266]. Overnight, stroke patients suffered a significant 10 % performance decrease (i.e. forgetting) of the repeated sequence only [$t_{(15)}$=-3.51, p=0.003], which was similar to the 12 % performance decrement observed in healthy controls [$t_{(34)}$=0.01, p=0.992]. This phenomenon of overnight forgetting was specific for the repeated sequence and was not evident for the random sequence in either patients [$t_{(15)}$=-0.09, p=0.927] nor healthy controls [$t_{(19)}$=-0.72, p=0.483] (**Figure 6.5**C).

Overall, stroke patients demonstrated significantly improved performance on the repeated sequence at T4 compared to T0 (9 % improvement) [$t_{(15)}$=2.91, p=0.011] and a trend for the random sequence (6 % improvement) [$t_{(15)}$=1.99, p=0.066]. However, stroke patients' overall sequence-specific performance improvements were significantly smaller compared to healthy controls [$t_{(34)}$=-3.67, p=0.001].

Table 6.3 | ANOVA results of patients' and healthy controls' tracking performance at different time points.

	Group	Time	Sequence Type	Interactions
Performance changes across initial training				
T0 vs T1	*$F_{(1,33)}$=0.01, p=0.330*	***$F_{(1,34)}$=9.69, p=0.004, η^2=0.222***	***$F_{(1,34)}$=15.73, p<0.001, η^2=0.316***	**time x group:** ***$F_{(1,34)}$=6.70, P=0.014, η^2=0.165*** **time x sequence:** ***$F_{(1,34)}$=16.74, p<0.001, η^2=0.330***
Performance changes after time delay (retest1, retest2)				
T1 vs T2	***$F_{(1,34)}$=5.84, p=0.021, η^2=0.147***	***$F_{(1,34)}$=20.96, p<0.001, η^2=0.381***	***$F_{(1,34)}$=48.79, p<0.001, η^2=0.589***	**sequence x group:** ***$F_{(1,34)}$=4.39, P=0.044, η^2=0.114***
T3 vs T4	***$F_{(1,34)}$=6.84, p=0.013, η^2=0.167***	***$F_{(1,34)}$=8.41, p=0.006, η^2=0.198***	***$F_{(1,34)}$=44.83, p<0.001, η^2=0.569***	**sequence x group:** ***$F_{(1,34)}$=5.56, p=0.024, η^2=0.140*** **time x sequence:** ***$F_{(1,34)}$=9.07, p=0.005, η^2=0.211***
Overal performance changes				
T0 vs T2	*$F_{(1,34)}$=1.03, p=0.317*	***$F_{(1,34)}$=50.39, p<0.001, η^2=0.597***	***$F_{(1,34)}$=20.49, p<0.001, η^2=0.376***	**time x group:** ***$F_{(1,34)}$=9.61, p=0.004, η^2=0.220*** ***time x sequence:*** ***$F_{(1,34)}$=29.53, P<0.001, η^2=0.465***
T0 vs T4	*$F_{(1,34)}$=1.30, p=0.262*	***$F_{(1,34)}$=56.25, p<0.001, η^2=0.623***	***$F_{(1,34)}$=6.99, p=0.012, η^2=0.171***	**time x group:** ***$F_{(1,34)}$=10.33, p=0.003, η^2=0.233*** ***time x sequence:*** ***$F_{(1,34)}$=12.74, P=0.001, η^2=0.273***

Significant effects are indicated in bold. T0: beginning of training session; T1: end of training session; T2: beginning of retest1; T3: end of retest1; T4: beginning of retest2. n.s.: not significant.

6.4.2.4 Factors potentially influencing tracking performance

Functional characteristics and awareness about the repeated sequence did not relate to individuals' tracking performance, but performance level at various time points were related to one another. Therefore, I next evaluated whether these inter-dependences also exist in chronic stroke patients. Again, the initial ability to perform the motor skill appeared to have the least influence on subsequent performances, for both the repeated sequence (average r=0.21, p=0.432) and random sequence (average r=0.06, p=0.599) (**Figure 6.6**).

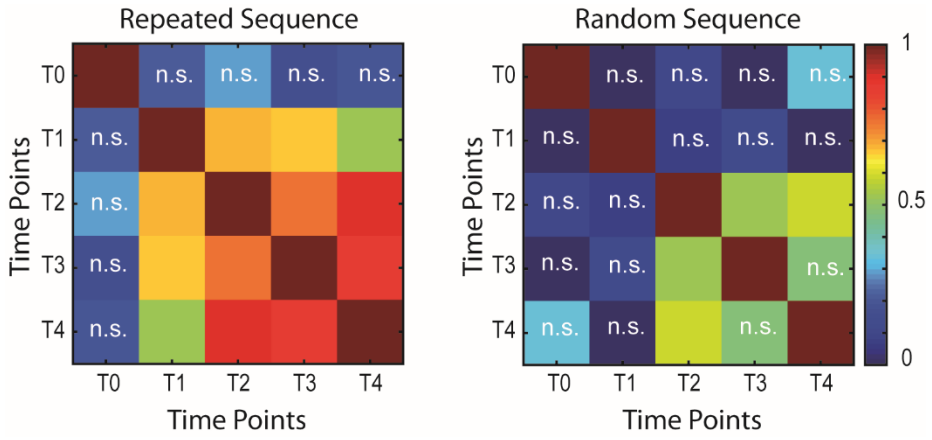

Figure 6.6 | Correlations of patients' performance between time.
Between-time points (T0–T4) correlation coefficients for performance on the repeated (left panel) and random (right panel) sequence. The colour bar indicates the correlation coefficients (r) presented in the matrices.

There were no significant correlations between functional/clinical characteristics such as motor impairment (indexed by PCA score), fatigue (FSS, NFI) or sleep and patients' tracking performance level (p>0.06). Compared to healthy controls, patients similarly well gained awareness of the repeated sequence during initial training (patients: 75±19.0 % correct; healthy controls: 80±15 % correct) [Mann-Whitney U=136.0, p=0.459] and recognized the repeated sequence 24 hours later, at retest2 (patients: 71±24 % correct; healthy controls: 84±22 correct) [Mann-Whitney U=114.5, p=0.149]. The level of patients' awareness/recognition of the repeated sequence was unrelated to their performance on the motor learning task.

6.4.3 Changes in spectral power measures with training

All patients were able to perform the simple motor task and there were no significant differences in movement kinematics between patients and healthy controls for the movement towards the target [RT: $F_{(1,34)}$=0.01, p=0.971; MT: $F_{(1,34)}$=0.13, p=0.719], however stroke patients were slower in returning to the initial start position [MT: $F_{(1,34)}$=27.37, p<0.001].

Averaged spectral changes in contralateral and ipsilateral sensorimotor cortices in response to wrist movement are shown in **Figure 6.3** before (Pre) and at two time points (Post1 and Post2) after the initial training. The general features of the spectral changes in beta activity induced by the simple motor task in stroke patients were comparable to those observed in healthy adults (**Chapter 5**). As previously described, a reduction in beta power, MRBD, was observed in both sensorimotor cortices during movement towards the target and during return movement to the initial start position. Following return movement cessation, a strong but transient PMBR, with a stronger expression in contralateral sensorimotor cortex was observed.

Table 6.4 | Summary of kinematic measures acquired during the performance of the simple motor task for patients and healthy controls.

	Patients	*Controls*
RT [ms]	982±16	983±14
MT [ms]	949±59	977±52
PV [deg/s]	133±19	200±17

Kinematic measures are presented for each EEG session (S1–S6) and condition (flexion, extension). RT: Reaction Time; MT: Movement Time; PV: Peak. Values given are mean ±SD.

6.4.3.1 Resting beta power

Analysis of absolute beta power during the pre-movement (resting) baseline period revealed no significant difference between stroke patients and age-matched healthy controls in either contralateral or ipsilateral sensorimotor cortices (**Figure 6.7***A*, *F*-statistics and *p*-values of all ANOVAs are summarized in **Table 6.5**), consistent with previous observations (Rossiter et al., 2014a). In

line with findings in **Chapter 5**, no hemispheric difference in beta power was identified, but again a significant change in absolute beta power across EEG sessions was identified. This change in absolute beta power was reflected by a significantly increased beta power immediately after training (Post1) in both contralateral [Pre vs Post1: $t_{(35)}$=-4.06, p<0.001; Post1 vs Post2: $t_{(35)}$=2.86, p=0.007] and ipsilateral sensorimotor cortices [Pre vs Post1: $t_{(35)}$=-3.27, p=0.002; Post1 vs Post2: $t_{(35)}$=2.22, p=0.033], which was transient in nature. However, this effect was driven by the healthy control group and was not evident when assessing the stroke patients alone [$F_{(2,30)}$=1.45, p=0.250]. Lastly, no significant interactions were found.

Table 6.5** | **ANOVA results for spectral power of stroke patients and controls

	Group	Hemisphere	Session	Interactions
BB				
	$F_{(1,34)}$=0.21, p=0.653	*$F_{(1,34)}$=1.80, p=0.188*	***$F_{(2,68)}$=5.90, p=0.004, η_p^2=0.148***	n.s.
MRBD				
	$F_{(1,34)}$=2.22, p=0.146	***$F_{(1,34)}$=21.06, p<0.001, η_p^2=0.383***	***$F_{(2,68)}$=.94, p=0.004, η_p^2=0.149***	*n.s.*
PMBR				
	$F_{(1,34)}$=0.31, p=0.576	***$F_{(1,34)}$=7.25, p=0.011, η_p^2=0.176***	***$F_{(2,68)}$=3.29, p=0.043, η_p^2=0.088***	n.s.

Significant effects are indicated in bold. BB: Pre-movement baseline beta; MRBD: Movement-Related Beta Desynchronization; PMBR: Post-Movement Beta Rebound; n.s.: not significant.

6.4.3.2 Movement-related beta power changes

Averaged beta power changes during movement (MRBD) and after movement cessation (PMBR) for both stroke patients and healthy controls and topographic maps are shown in **Figure 6.7**C-D. Interestingly, although MRBD was on average ~10 % smaller in patients compared to healthy controls, estimates of MRBD in both contralateral and ipsilateral sensorimotor cortex were not significantly different between groups (**Figure 6.7**C). Similarly, estimates of PMBR were

comparable between stroke patients and age-matched healthy controls (**Figure 6.7**D). As expected and observable in the topographical distributions, in particular for the PMBR, a significant hemispheric difference in the magnitude of both MRBD and PMBR was observed for patients and healthy controls, indicating that both beta-band dynamics were overall more pronounced in the hemisphere contralateral to the moving hand. Finally, a significant effect of 'session' was found for both movement-related beta dynamics. *Post hoc* analyses revealed a significant reduction across sessions in both contralateral [$F_{(2,68)}$=6.33, p=0.003, η_p^2=0.157] and ipsilateral sensorimotor cortex [$F_{(2,68)}$=3.31, p=0.043, η_p^2=0.089] for the magnitude of MRBD, but only in ipsilateral sensorimotor cortex for PMBR [$F_{(2,68)}$=4.66, p=0.013, η_p^2=0.120].

Since previous studies reported that movement-related beta measures correlate with motor impairment (Rossiter et al., 2014a; Shiner et al., 2015), I next examined whether resting and movement-related beta power was associated with clinical or behavioural parameters acquired on day 1. However, no correlations between beta power measures and motor impairment were identified. Interestingly, absolute baseline beta power from both sensorimotor cortices and across all sessions was positively correlated with the level of fatigue (average across sessions; contralateral sensorimotor cortex: r=0.67, p=0.004; ipsilateral sensorimotor cortex: r=0.71, p=0.002). In other words, beta power was enhanced in stroke patients with more severe fatigue. However, closer inspection revealed that this effect was driven by one stroke patient with severe fatigue.

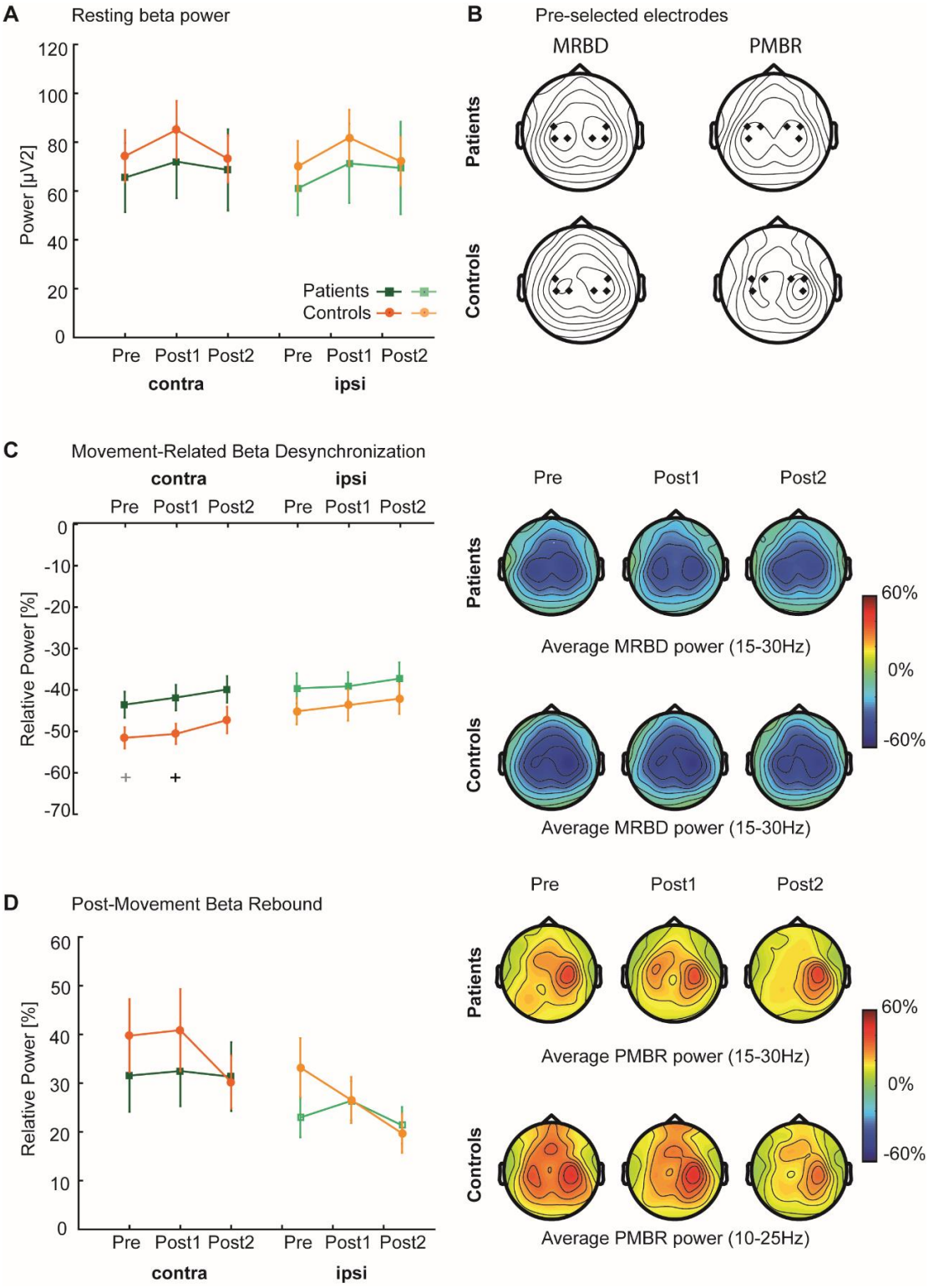

Figure 6.7 | Changes in beta power and corresponding topographic maps. ***A****, Average pre-movement (resting) beta power of young and elderly groups from both sensorimotor cortices. Power in the pre-movement time window (-1–0 s) before (Pre), immediately after (Post1), and 24-hours after (Post2) training was derived from contralateral and ipsilateral sensorimotor cortices of young (dark and light blue) and elderly (red and light red) subjects.* ***B****, Topographical plots of grand-averaged beta power showing the pre-selected electrodes (black*

diamonds) which were pooled as contralateral and ipsilateral regions of interest. ***C-D****, Power in the movement (1–2 s; MRBD) and post-movement time window (6–7 s; PMBR) before (Pre), immediately after (Post1), and 24-hours after (Post2) training derived from contralateral and ipsilateral sensorimotor cortices of stroke patients (green and light green) and age-matched healthy controls (orange and light orange). Error bars indicate between-subject SEM. Significant between-group differences are indicated with a '+' (grey '+' indicates trend). Topographical distributions (right panels) of movement-related beta activity show contralateral and ipsilateral modulation patterns for MRBD and PMBR.*

6.4.4 Prediction of patients' post-training tracking performance from a combination of neurophysiological, behavioural and functional/clinical measures

In order to gain insight into the role of beta activity in explaining motor learning behaviour after stroke, a stepwise multiple linear regression approach within a LOOCV was utilized. In the next sections, I firstly assessed whether a combination of neurophysiological (beta power measures), behavioural (performance on the motor learning task) and functional/clinical characteristics can explain stroke patients' tracking performance at two different time points, shortly after training (T2) and 24 hours later (T4). To reiterate, performance at T2 was used as an index of fairly permanent learning effects, while T4 provides a reflection of the maintenance of the acquired motor skill overnight. Next, the contribution of neurophysiological and behavioural measures alone in predicting motor performance was explored.

6.4.4.1 Prediction of patients' tracking performance at T2

Pre- and post-training beta activity (Pre, Post1), and behavioural performance at T0 and T1, as well as functional/clinical characteristics (age, time since stroke, lesion side, motor impairment, fatigue severity, attention, sleep) were explored as potential predictors of tracking performance at T2 (total number of predictors = 23), using stepwise linear regression.

None of these variables significantly explained performance on the repeated sequence [r=0.32, *n.s.*]. Similarly, performance on the random sequence could not be significantly predicted based on a combination of neurophysiological, behavioural and clinical measures [r=-0.34, *n.s*.].

6.4.4.2 Prediction of patients' tracking performance at T4

Pre- and post-training beta activity (Pre, Post1, Post2), and behavioural performance at training (T0, T1) and retest1 (T2, T3) sessions as well as functional/clinical characteristics (age, time since stroke, lesion side, motor impairment, fatigue severity, attention, sleep) were explored as potential predictors of tracking performance at T4 (total number of predictors = 31).

While performance on the random sequence could not be predicted from these variables [r=0.03, *n.s.*], performance on the repeated sequence was significantly predicted, accounting for 81 % of variance [r=0.91, p<0.001] (**Figure 6.8**A). Beyond the behavioural performance at the end of training [T1: $t_{(15)}$=-4.26, p<0.001] and during retest1 [T2: $t_{(15)}$=14.14, p<0.001; T3: $t_{(15)}$=7.81, p<0.001], the magnitude of contralateral (ipsilesional) PMBR immediately after training (Post1) consistently affected the level of performance on the next day, at T4 [$t_{(15)}$=4.79, p<0.001] (**Figure 6.8**B). The positive coefficient for the beta power measure suggests that lower PMBR following training is associated with better performance 24 hours later. An additional parameter relating to the time post-stroke demonstrated that greater time since stroke was beneficial for tracking performance [$t_{(15)}$=-2.58, p=0.021]. Similarly, a partial correlation analysis with performance measures and time since stroke as confounding covariates showed a significant positive correlation between post-training PMBR in contralateral (ipsilesional) sensorimotor cortex and performance at T4 [r=0.78, p=0.005]. In other words smaller rebound is related to better performance at T4 (note that higher RMSE denotes worse performance).

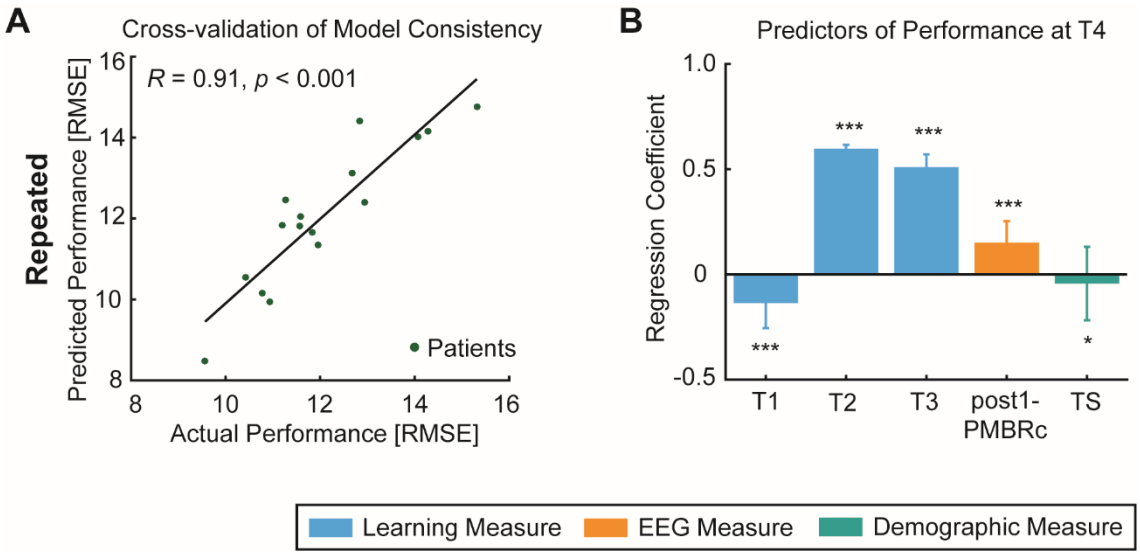

Figure 6.8 | Prediction of stroke patients' tracking performance at T4. *Stepwise multiple linear regression with a combination of neurophysiological, behavioural and functional/clinical measures provided statistically significant performance prediction (**A**) as quantified by the correlation coefficient between the actual and predicted tracking performance of stroke patients. Together, these measures accounted for 81 % of variance in performance on the repeated sequence. Significance of this correlation was determined by permutation-testing. **B**, Patients' behavioural performance at the end of training and during retest1 exerted the strongest effect on performance of the repeated sequence. In addition, post-training movement-related beta activity related to performance, such that smaller magnitude of PMBR in contralateral (ipsilesional) sensorimotor cortex explained better performance 24 hours after training. Time since stroke also consistently affected performance. Averaged z-scored regression coefficients (β) quantify the influence of each significant predictor upon performance level at T4. Error bars represent SEM. Single-sample t-tests to test for differences from zero were employed. TS: Time since Stroke. *p<0.05, **p<0.01, ***p<0.001.*

Next, the predictive strength of neurophysiological or behavioural performance measures alone, or a combination of both was assessed to better understand their explanatory value (summary of comparison is provided in **Table 6.6**). While neurophysiological measures alone did not predict performance on the repeated sequence, in combination with behavioural performance measures, they significantly improved the prediction accuracy compared to the simple behavioural model [$t_{(15)}$=6.77, p<0.001]. Although time since stroke exerted a significant effect upon tracking performance at T4, it did not add further predictive

strength to the combination of neurophysiological and behavioural measures [$t_{(15)}$=2.02, *n.s.*].

Table 6.6 | Comparison of prediction accuracy for stroke patients' performance at T4.

Predictor variables	R	R^2	Mean RMSE	Sum RMSE
Performance on repeated sequence				
Neurophysiology	0.20	0.04	0.66	11
Behaviour	0.90***	0.81	0.32	5
Neurophysiology + Behaviour	*0.92****	*0.85*	*0.21*	*3*
Neurophsyiology + Behaviour + Functional characetristics (Time since stoke)	0.91***	0.81	0.18	3
Performance on random sequence				
Neurophysiology	-0.43	-0.18	0.94	15
Behaviour	0.10	0.01	0.83	13
Neurophysiology + Behaviour	0.03	0.00	0.82	13

*Regression models were fitted with neurophysiological (pre- and post-training (Pre, Post1, Post2) BB, MRBD, and PMBR from both sensorimotor cortices) and behavioural performance measures (tracking performance at T0, T1, T2 and T3) alone, and a combination of both, and additionally demographic information. The predictive strength is quantified by the correlation (R) between the actual and predicted performance, based on LOOCV. A combination of oscillatory beta measures and behavioural performance estimates best predicted performance on the repeated sequence (blue ink). RMSE values are averaged and summed across the 16 subjects. RMSE: Root Mean Square Error. *p<0.05, **p<0.01, ***p<0.001.*

6.5 Discussion

By examining the motor learning capacity of well-recovered, chronic stroke patients and acquiring standard measures of EEG-derived beta power, the current study reported several key findings:

1. Firstly, stroke patients' ability to learn the continuous tracking task was preserved, but the overall level of performance achieved with short-term training was significantly reduced compared to healthy controls.
2. Secondly, no stroke-related alterations were evident in the properties of beta oscillations, although an effect for MRBD in the direction reported by previous studies was observed (Rossiter et al., 2014a; Shiner et al., 2015).
3. Following on from **Chapter 5**, by implementing a multivariate approach, the relationship between cortical beta activity and the degree to which patients in the chronic phase post-stroke learn and retain new motor skills was explored. Crucially, although behaviour played a strong role, beta oscillatory activity significantly contributed to the prediction of 81 % of the variance in tracking performance 24 hours after initial training.

6.5.2 Reduced training-related performance improvements in stroke patients compared to healthy controls

Reacquisition of motor skills through rehabilitation is paramount to recovery from motor impairment after stroke and has been proposed to be a form of learning (Kitago and Krakauer, 2013; Krakauer, 2006). By assessing stroke patients' capacity to learn a motor skill with their affected hand, and compare their performance to healthy controls, my results indicate that stroke patients are able to improve their performance on a trained task. However, despite a preserved ability to learn, the overall level of performance achieved by patients was significantly lower compared to the healthy control group, indicating stroke-related motor learning deficits that result in overall smaller performance gains.

Analysis of stroke patients' performance did not reveal significant improvements with initial training. This was most likely due to temporary effects such as fatigue and boredom depressing performance temporarily at the end of training (see **Figure 6.5**A) (Adams, 1961; Brawn et al., 2010; Rickard et al., 2008; Schmidt and Wrisberg, 2008b), thus resulting in an underestimation of the actual post-training performance level in patients. Allowing the temporary effects from the training to dissipate (i.e. rest between training and retest1 session), revealed that stroke patients actually were able to improve their performance, indicating

preserved motor learning capacity after stroke. This pitfall also highlights the importance of identifying appropriate target behaviour and selecting valid measures to assess (fairly permanent) gains in performance related to training, and further justifies my motivation to predict performance at T2 (as opposed to T1). Crucially, by matching baseline performance, it was possible to directly compare the training-related changes in performance of stroke patients to healthy age-matched controls. Hence, my results demonstrate that even though stroke patients were able to learn on the task, their post-training level of performance was significantly lower compared to healthy adults, even though offline learning was similar. As such, stroke patients demonstrated overall smaller performance gains with short-term motor learning. This suggests that matched performance does not necessarily imply that both groups have the same ability to improve and that even though the ability to learn is preserved, it is impaired compared to healthy controls.

Taken together with the existing studies discussed in **Chapter 1** section 1.3.5, my results support the notion that motor learning is preserved in stroke patients, most likely due to the distributed nature of the neural network supporting learning (Doyon and Ungerleider, 2002a; Karni et al., 1995; Sanes and Donoghue, 2000). However, it is difficult to draw unifying conclusions due to differences in tasks, duration of practice, effectors, patient characteristics, and outcome measures. In particular, most studies have used the difference between baseline and post-training performance as a measure of motor learning, however, this type of analysis might be conceptually mistaken since normalization, either additive or multiplicative, can lead to contradictory results (Kitago and Krakauer, 2010). Thus, as opposed to normalized changes, here the absolute level of performance was assessed, which allowed to reveal that despite both groups demonstrating improvements in task performance and similar patterns of change in performance with rest (e.g. early boost and overnight forgetting), final levels of performance were significantly different between stroke patients and healthy controls.

It could be argued that inclusion of well-recovered patients with mostly no overt impairment might compromise the study, however I view this as a strength as it allowed the investigation of motor learning independent of potentially obscuring influences of motor impairments. Furthermore, it clearly shows that well-

recovered patients with ‘normal’ motor control remain different to healthy adults in terms of their ability to learn, most likely due to lesion-induced structural and functional changes in the neural networks supporting motor learning. Since the present study examined motor learning in chronic stroke patients over a short, single training session, it is possible that prolonged training (i.e. weeks) could lead to greater performance improvements. For example, patients might have a slower rate of improvement (Wadden et al., 2017), but are actually able to achieve the same level of performance as healthy adults with prolonged training. The amount or “dose” of practice required for stroke patients to learn is an important topic in rehabilitation, and it has been shown that the dose required for training-related neuroplasticity to occur and thus, exert a positive influence on outcome is fairly high (Lohse et al., 2014). Therefore, it would be interesting in the future to investigate whether stroke patients can further improve on the motor learning task given an adequate dose of training or whether they reach a performance plateau that remains categorically different to healthy adults (Hardwick et al., 2017).

6.5.3 Beta oscillations are unaffected by stroke but altered with motor learning

In contrast to normal beta oscillations, aberrant beta activity is a signature of sensorimotor pathology (Brown, 2007; Doyle et al., 2005; Heida et al., 2014; Heinrichs-Graham et al., 2014; Kühn et al., 2004; Little and Brown, 2014; Rossiter et al., 2014a; Shiner et al., 2015). Impairment in beta rebound after stroke has previously been demonstrated with tactile stimulation (Laaksonen et al., 2012). More recently, MEG studies have also demonstrated stroke-related alterations in the properties of beta oscillations in the motor system. Specifically, the magnitude of movement-related beta dynamics was significantly reduced, with these dynamics also exhibiting a more bilateral pattern in patients compared to healthy controls (Rossiter et al., 2014a; Shiner et al., 2015). In addition, these studies revealed that greater motor impairment was associated with lower magnitude MRBD and PMBR in ipsilesional sensorimotor cortex, suggesting that the dynamic modulation of beta oscillations may be important for motor control.

Given these findings, rather unexpectedly, the current results did not reveal significant differences in the magnitude of MRBD and PMBR from both

sensorimotor cortices between stroke patients and age-matched healthy controls. A possible explanation for the lack of stroke-related alterations in beta activity might be the narrow spectrum of post-stroke impairment in the current patient group, representing well-recovered patients with mostly no overt functional motor impairments compared to previous studies of moderate-to-severely impaired patients. For example, stroke patients in the study by Rossiter and colleagues presented with an average ARAT score of 45±19 for the contralesional (affected) hand (maximum score 57) (Rossiter et al., 2014a), while patients in the current study had a homogeneous score of 56±0.5, and similar motor abilities of the affected and unaffected upper limb. Given that effective recovery of motor function is associated with a normalization of brain activity back towards a pattern seen in healthy controls (Johansen-Berg, 2002; Ward et al., 2003a), it appears likely that the lack of post-stoke alteration in beta dynamics is due to restitution of nearly 'normal' beta activity in my well-recovered patient cohort.

An alternative explanation might be the rather small sample of well-recovered patients. Although the study by Shiner and colleagues detected aberrant movement-related beta activity with as little as 10 chronic stroke patients (Shiner et al., 2015), this is most likely due to the heterogeneous sample of patients with a broad spectrum of motor functions. Indeed, closer inspection and post hoc analyses of beta power revealed that the magnitude of MRBD from contralateral sensorimotor cortex was significantly reduced in patients compared to healthy controls, or showed a trend, for two of the three EEG sessions. This suggests that a larger cohort would have likely yielded a significant effect for MRBD in the direction reported by previous studies.

Interestingly, my results indicated that stroke patients who reported higher fatigue severity, exhibited higher beta power across both sensorimotor cortices. Whilst this effect was mainly driven by one stroke patient, it is an interesting and novel finding possibly linking beta oscillations and subjective levels of post-stroke fatigue. In particular, higher beta power in chronic stroke patients might reflect greater GABAergic inhibition consistent with recent findings of low excitability of cortical and subcortical inputs that drive motor cortex output with high fatigue (Kuppuswamy et al., 2015). Given the sparse literature on fatigue and cortical oscillations, with most studies investigating the effect of mental and physical

fatigue, but not chronic, post-stroke fatigue on resting and movement-related beta activity (Fry et al., 2017; Shigihara et al., 2013; Tecchio et al., 2006), future studies with a greater number of stroke patients and a broader spectrum of post-stroke fatigue severity might be worthwhile to provide new perspectives on the neural mechanisms underlying fatigue and its implications for motor learning after brain damage. In the context of the current study, post-stroke fatigue besides lesion location, level of motor impairment, and time since stroke was thus considered as another source of variability in response to motor learning.

In accordance with previous studies (Rossiter et al., 2014a), no difference in the overall power of pre-movement (resting) beta activity was observed between patients and controls or hemispheres. However, while healthy controls demonstrated a transient post-training increase in beta activity that returned to pre-training levels on day 2, stroke patients did not show a comparable pattern. Since the training-related modulation of beta power might be a marker of temporary suppression of LTP-like plasticity after motor learning, the lack of modulation observed in stroke patients might represent altered plasticity processes, potentially explaining the overall reduced ability to learn compared to the healthy cohort. However, whether this physiological response to training, i.e. a temporary increase in beta power, is necessary for practice-dependent plasticity processes to occur, and if absent or reduced, results in reduced motor learning ability, needs to be further investigated.

6.5.4 Beta oscillations are predictive of tracking performance retention

As discussed in **Chapter 1** section 1.4, behavioural, clinical and demographic measures contribute to predictive models of response to treatment and long-term outcome after stroke (Hope et al., 2013; Kwakkel et al., 2003; Prabhakaran et al., 2015; Shelton and Reding, 2001). Incorporating neuroimaging data that reveal the mechanisms underlying post-stroke plasticity and heterogeneity of motor recovery and response to rehabilitative training is likely to provide greater insight into the capacity for reorganization (Burke and Cramer, 2014; Ward, 2017). Thus, here, the predictive role of EEG-derived beta oscillations for post-stroke motor learning was explored, using a multivariate approach combining behavioural, clinical and neurophysiological measures.

My findings provide evidence that retention of sequence-specific tracking performance 24 hours after initial training can be successfully predicted by a combination of behavioural and beta oscillatory measures. In particular, even though performance scores had the strongest effect upon post-training performance levels, incorporating beta oscillatory measures enhanced the ability to predict stroke patients' capacity to retain a newly acquired motor skill, such that a total of 81 % of variance was explained. Even though the type of beta measure and the direction of the association was different to the healthy subjects in **Chapter 5**, this generally supports the idea that estimates of movement-related beta activity provide a significant contribution to predicting individual differences in tracking performance not only in healthy, but also clinical population. The ability to accurately predict patients' capacity for motor learning is important for individualised treatment planning and patient stratification of novel treatment approaches (Stinear, 2010; Ward, 2017).

To date, most studies have investigated the relationship between properties of cortical beta oscillations and post-stroke motor impairment (Hall et al., 2010b; Laaksonen et al., 2012; Rossiter et al., 2014a; Shiner et al., 2015; Thibaut et al., 2017), but to the best of my knowledge, no study has explored the relationship between beta oscillatory power and post-stroke motor learning capacity. When controlling for behavioural performance, post-training contralateral (ipsilesional) PMBR related to performance levels retained 24 hours after training, with patients who exhibited lower PMBR after training, performing better after a night's sleep. Given the link between beta oscillations and GABAergic inhibition (Hall et al., 2011, 2010a; Jensen et al., 2005; Muthukumaraswamy et al., 2013; Roopun et al., 2006; Yamawaki et al., 2008), smaller post-training PMBR, reflecting lower GABAergic inhibition might facilitate cortical plasticity associated with motor learning and early consolidation, thus resulting in better motor skill retention. This general interpretation is in line with MRS and PET studies reporting decreases in GABA levels being associated with better motor recovery after stroke (Blicher et al., 2015; Kim et al., 2014). Since plasticity is activity dependent, it should be noted that variability in post-training performance was explained not by resting beta activity but specifically by event-related (dynamic) changes in beta power, which are more closely related to motor function. This also demonstrates the

importance of using EEG/MEG in order to follow these dynamic changes in cortical excitatory and inhibitory processes. Thus, EEG-derived measures of beta oscillations, as markers of net inhibitory and excitatory mechanisms in humans, might improve our understanding of how motor skills are acquired on an individual level, beyond information provided by behavioural scores, which are unlikely to adequately reflect an individual's potential for cortical reorganisation in response to motor learning.

Although evidence suggest heightened responsiveness to motor training during the early post-stroke phase, likely due to increased potential for cortical plasticity (Cramer, 2008; Krakauer et al., 2012; Murphy and Corbett, 2009; Ward, 2017; Zeiler and Krakauer, 2013), the current study only included stroke patients in the chronic phase. This was motivated by practical considerations in their recruitment. In addition, as the sample size was relatively small with variable lesion location and time post-stroke, a deeper understanding of the relationship between cortical beta oscillations and motor learning should be achieved in a larger patient population including acute stroke patients in order to determine whether beta oscillatory measures early after stroke can similarly explain differences in motor learning capacity. Clearly, further work is required to understand the complex relationship between neuronal activity and motor learning after stroke, but the present results open new interesting lines of investigation, in particular for future rehabilitation research that employs predictive models of motor learning. Specifically, the predictive methodological approach may not only specify if the individual may respond to training but also provide an indication of when to best provide rehabilitation.

6.5.5 Conclusion

In conclusion, the current results extend my previous findings on the unique contribution of beta oscillatory dynamics in explaining individual differences in motor learning. Specifically, it demonstrates the potential of neurophysiological measures to enhance prediction of retained tracking performance of a previously learned motor skill and suggest that beta oscillations may have value as biomarkers of cortical function and plasticity after stoke.

Chapter 7 General discussion

The brain's intrinsic potential to react as a highly dynamic system that changes in response to motor learning and injury is paramount for everyday life activities and functional recovery after stroke. In this thesis, I have attempted to bridge the gap between cellular and behavioural accounts of cortical plasticity by investigating the relationship between cortical beta oscillations, as candidate biomarkers of net excitatory and inhibitory processes in humans, and individual differences in the ability to learn and retain new motor skills in both healthy (**Chapter 5**) and diseased states (**Chapter 6**). I have demonstrated that properties of beta-band activity help to explain individual differences in performance in both healthy individuals and stroke patients in a way that behaviour alone could not. These findings built upon the demonstration that the here employed beta power estimates show high intra-individual reliability over time, validating the notion that these measures reflect meaningful individual differences that can be utilized in basic and clinical research (**Chapter 4**). Together, the work presented here suggests that measures of beta oscillations provide useful predictive information about an individual's motor learning capacity, beyond information provided by behavioural characteristics.

Since each experimental chapter contains a relatively extensive discussion of the issues pertinent to that study, in this summary I draw together the main findings of the experiments, outline the implications of this body of work, and discuss some limitations and future extensions to the field.

7.1 Key findings

The work presented here is founded upon a large body of physiological, pharmacological, behavioural and neuroimaging studies proposing a role for cortical plasticity in motor skill learning and recovery after stroke. Having ventured into several research fields such as motor learning, neuronal oscillations and stroke, the experiments presented provide novel findings that advance these respective fields. The key findings are summarised below.

Given the massive upsurge in the interest in neuronal oscillations, and in particular rhythmic activity at beta frequencies, due to their potential role as

neurophysiological marker of motor system function and dysfunction (Nicolo et al., 2015; Takemi et al., 2015; Ward, 2015; Wu et al., 2015), in **Chapter 4**, I established for the first time that, given careful execution of experimental conditions, movement-related beta dynamics show high intra-individual reliability. The highly reproducible nature validated the notion that these measures are an appropriate assay for longitudinal and clinical studies, and was a prerequisite for the subsequent enquiry.

Based on daily life experience that people show considerable inter-individual differences in their ability to learn, I then started to explore the neurophysiological processes underlying these differences, which is of significant clinical importance for improving long-term rehabilitative outcomes after brain injury (Stinear and Byblow, 2014; Stinear, 2010; Ward, 2017). In **Chapter 5**, I firstly demonstrated that elderly adults show comparable motor learning as their younger counterparts, supporting the view of preserved motor learning with advancing age (for review on the debate see (Seidler, 2006; Voelcker-Rehage, 2008)). Corroborating previous findings (Gaetz et al., 2010; Heinrichs-Graham and Wilson, 2016; Rossiter et al., 2014b), I further show that elderly subjects exhibited higher resting beta power and MRBD in both contralateral and ipsilateral sensorimotor cortex, implying increased GABAergic inhibition, and potentially reduced cortical plasticity in the elderly. By implementing a multivariate approach with LOOCV, accounting for multicollinearity between measures and allowing generalization of results, I then revealed that pre-training movement-related beta activity explains some of the individual differences in motor learning, but only after accounting for behaviour. As such, the state of the brain's sensorimotor cortex prior to learning, as captured by beta oscillatory activity, might provide useful predictive information that can be utilized in basic research and clinical studies.

Finally, in **Chapter 6**, I explored the neurophysiological processes underlying individual differences in motor learning after stroke. I showed that chronic stroke patients have a preserved ability for motor learning, although reduced when compared to healthy controls. Unexpectedly, and contradicting previous findings (Rossiter et al., 2014a; Shiner et al., 2015), possibly due to various factors such as sample size and level of impairment, no significant stroke-related alterations in resting or movement-related beta activity were observed. Multivariate

modelling, taking into account behavioural, clinical and demographic characteristics, then revealed that post-training movement-related beta activity explains some of the variation observed in 24-hour retention of the previously acquired motor skill in stroke patients.

Together, the findings in **Chapter 5** and **Chapter 6** indicate that beta oscillations may have value as biomarkers of cortical function and plasticity in the healthy as well as lesioned brain. Although further studies with larger cohorts are needed to establish a robust link between individual differences in motor learning and beta oscillatory dynamics, the novel findings illustrate the potential value of incorporating cortical oscillatory measures, reflecting neurophysiological mechanisms, together with behavioural information to enhance prediction accuracy.

7.2 Clinical implications for rehabilitation

The reason for wanting to understand the relationship between cortical beta oscillations and individual differences in motor learning is the desperate clinical need for improved restorative treatments to maximize outcomes after stroke. As discussed in **Chapter 1**, accumulating evidence suggests that NIBS and pharmacological approaches represent promising treatment strategies to dramatically improving patients' outcome (Chollet et al., 2011; Kim et al., 2006; Zimerman et al., 2012). However, current implementation of plasticity-modifying interventions in phase III trials lack a clear mechanistic approach and are thus unlikely to succeed (Ward, 2008). To achieve progress, the biological mechanisms underlying the observed behaviour need to be understood in humans. Appropriate biomarkers that bridge the gap between cellular and behavioural accounts of cortical function and plasticity in both healthy and diseased states, would help to demonstrate efficacy of therapeutic therapies in the elderly and stroke patients, improve decision-making about who and when to treat, and allow individualised treatment planning rather than a 'one size fits all' approach. For example, given the discussed post-stroke structural and functional changes, with evidence for an early critical window of heightened plasticity, the timing of rehabilitative treatment will clearly have a major effect on patients' outcome.

The growing interest in biomarkers that predict patients' motor recovery and outcomes has led to the identification of several anatomical and functional measures that carry predictive potential beyond the early clinical assessment of motor impairment (Kwakkel et al., 2003; Prabhakaran et al., 2015). For example, patients with intact TMS-induced MEPs in their affected UL typically experience better motor recovery. In addition, more extensive lesion-induced corticospinal tract (CST) damage accounts for worse UL motor recovery (for review see (Bembenek and Kurczych, 2011; Burke and Cramer, 2014; Stinear, 2010)), while incorporating information about damage to cortical and subcortical areas involved in sensorimotor function together with information about CST damage is better able to predict motor outcome (Rondina et al., 2016). Recent attempts with EEG demonstrated that greater post-stroke resting functional connectivity in the beta frequency was associated with better subsequent clinical improvement (Nicolo et al., 2015; Wu et al., 2015). However, since no single clinical nor neurophysiological/neuroimaging measure has been able to accurately explain individual recovery potential, combining these measures might provide greater insight into the capacity for reorganization and might provide the optimal approach for prediction of long-term outcomes after stroke.

Approaches incorporating a combination of clinical and/or neurophysiological and/or neuroimaging measures into predictive models of long-term outcome have been undertaken (Quinlan et al., 2015; Stinear et al., 2017, 2012), but the predictive role of neuroimaging measures needs to be further explored. Notwithstanding, neuroimaging/neurophysiological measures might have an ascending role in individualised treatment planning and clinical decision making. In that regard, EEG that can be rapidly performed at the bedside is a promising tool for the identification of widely available and cost-effective biomarkers that advance our understanding of cortical function in health and disease.

7.3 Methodological considerations and future directions

As I demonstrated in **Chapter 5** and **Chapter 6**, EEG-derived oscillatory measures hold the potential to extend the insights offered by animal and pharmacological studies of the mechanisms contributing to learning and post-stroke recovery. Importantly, by designing a motor learning task that optimally

promotes learning in healthy and clinical populations as outlined in **Chapter 3**, and ensuring that the employed EEG-derived beta oscillatory measures are highly reliable within individuals as shown in **Chapter 4**, it was possible to demonstrate a link between beta oscillatory dynamics and individual differences in motor learning. However, further studies are clearly needed to establish the robustness and generalizability of these findings, with the aim of translating them into the clinical setting.

In particular, the work presented here focused on stroke patients in the chronic phase post stroke with well-recovered motor functions. The emphasis on chronic stroke was motivated by practical considerations in their recruitment as well as their relatively stable levels of motor function, which allows attributing changes in performance to the experimental training. However, given heightened responsiveness to training during the critical period early after stroke (Biernaskie et al., 2004; Zeiler and Krakauer, 2013), future studies in acute stroke patients with a broad spectrum of motor impairments are needed to further shed light upon the mechanisms underlying early spontaneous biological recovery, and how to better take advantage of or augment this window of opportunity to maximise therapeutic effects. Along these lines, longitudinal studies should investigate the evolution of oscillatory measures, including event-related dynamics, associated with recovery from stroke with and without rehabilitative interventions. Further, some pharmacological agents are known to have an impact on both GABAergic inhibition and properties of beta oscillations (Baker and Baker, 2003b; Hall et al., 2011; Jensen et al., 2005; Muthukumaraswamy et al., 2010). Future studies should thus manipulate the balance between excitatory and inhibitory mechanisms in order evaluate the concurrent changes in beta oscillatory dynamics and motor learning behaviour, thus strengthening the here identified association between both.

Since rehabilitation interventions are based on motor learning principles, the choice and accuracy of metrics to examine different features of movement behaviour and learning is important. As highlighted in **Chapter 6**, rather than using normalized performance (e.g. relative to baseline) which might be conceptually fraught (Kitago and Krakauer, 2010), the current work assessed learning based on absolute performance levels at two different time points. While

inaccurate deduction of learning caused by inadequate metric selection, might for example suggest a failure of training, when in fact poor choice of outcome measures rather than a lack of efficacy of training is the problem, it highlights the pitfall associated with the diversity of analytical approaches employed in the field of motor learning. Currently there are no standard procedures regarding the choice of outcome measures (Huang and Krakauer, 2009), which makes comparisons between motor learning studies difficult. As such, in order to advance our understanding of motor learning in humans, and its underlying processes, a unified approach needs to be developed in the future.

7.4 Concluding remarks

The picture that this thesis paints is one of a complex relationship between the brain and behaviour, with a potential role of EEG-derived cortical oscillations for motor learning in the healthy and diseased brain. My research and that of others suggests promising routes to a better understanding of the biological mechanisms underlying motor learning and recovery from stroke, with important translational value. Although all the work reported here is based on a laboratory-based motor learning task, my hope is that future work incorporating various sources of information about the neurophysiological mechanisms by which the human brain supports learning of different motor aspects will lead to clinical advances in how rehabilitative treatments for stroke are delivered, helping stroke survivors in their daily struggle to regain lost motor functions.

Even though spontaneous brain activity emerges without an external force, for a brain to be useful it should adapt to the outside world.

György Buzsaki in Rhythms of the brain, 2006

Appendix

Edinburgh Handedness Inventory

Handedness

Which hand do you use for the following activities?

Do you ever use the other hand?

Which hand do you use when?		Left	No pref	Right	Do you ever use the other hand
1	Writing				
2	Drawing				
3	Throwing				
4	Using scissors				
5	Using toothbrush				
6	Using knife (without fork)				
7	Using spoon				
8	Using broom (upper hand)				
9	Striking match				
10	Opening box (holding lid)				
11	Holding a computer mouse				
12	Using a key to unlock a door				
13	Holding a hammer				
14	Holding a brush or comb				
15	Holding a cup while drinking				

Mark Cohen, 2008
adapted from Oldfield (1971).
Neuropsychologia.

Subject DOB:_____
Date:_____
Experimenter:_____

Fatigue Severity Scale (FSS)

Please read each statement below and rate your agreement or disagreement with the statements using numbers between 1 and 7 based on how you felt in the last one week. A low value (e.g. 1) indicates strong disagreement and a high value (e.g. 7) indicates strong agreement.

1. I am easily fatigues.
2. Fatigue causes frequent problems for me.
3. My fatigue prevents sustained physical functioning.
4. Fatigue interferes with carrying out certain duties and responsibilities.
5. Fatigue is among my three most disabling symptoms.
6. Fatigue interferes with my work, family or social life.

Neurological Fatigue Index (NFI)

For each statement please state if you 1. strongly disagree, 2. disagree, 3. agree, 4. strongly agree based on how you have been feeling in the past two weeks.

1. I can become tired easily.
2. Sometimes I lose my body strength.
3. My limbs can become very heavy.
4. My body can’t keep up with what I want to do.
5. The longer I do something the more difficult it becomes.
6. Sometimes I have no option but to simply stop what I have been doing.
7. I usually get tired on most days.
8. I can become weak even if I am not doing anything.
9. Sometimes I really have to concentrate on what are usually simple things.
10. I have problems with my speech when I am tired.
11. My coordination gets worse as the day goes on
12. Mental effort really takes it out on me

St Mary's sleep questionnaire

This questionnaire refers to your sleep over the past 24 hours.

1. At what time did you settle down for the night?
2. At what time did you fall asleep last night?
3. At what time did you finally wake this morning?
4. At what time did you get up this morning?
5. Was your sleep:

- Very light
- Light
- Fairly light
- Light average
- Deep average
- Fairly deep
- Deep
- Very deep

6. How many times did you wake up?
7. How much sleep did you have last night?
8. How much sleep did you have during the day, yesterday?
9. How well did you sleep last night?

- Very badly
- Badly
- Fairly badly
- Fairly well
- Well
- Very well

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