Towards cerebral and behavioral representations of motor learning and its interaction with interference and sleep

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To Heidi, Jona, and Lena

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Summary

Motor learning is a fundamental aspect of animals struggle for survival. Regarding humans, most of our complex motor behavior is developed ontogenetically by means of motor practice in our everyday life. The representation of these motor abilities in the brain and how different practice conditions affect the learning processes remain unknown. A thorough understanding of motor learning especially on the neural level would lead to improved training protocols in rehabilitation and sports and might even be able to help in the treatment of neuromuscular diseases.

There is a big consensus in the literature that interference in motor practice does have an impact on the subsequent memory consolidation and that this impact can either be positive or negative. That is why the integration of different forms of interference into training protocols reflects a prominent field of research. Positive affects are mostly observed in retention and transfer tests when interference occurs within the practice session, leading to variable or unstable practice conditions. However, if interference occurs due to a separate practice session by means of the same motor task but of opposing kinematic or dynamic conditions, recall of the previously learned motor task is hampered. The underlying neural mechanisms which either in- or decrease the memory consolidation are still not understood. The aim of this thesis was to investigate both types of interference on the behavioral and neural level. Therefore, three empirical studies were conducted which used the force field adaptation paradigm flanked by electroencephalographic (EEG) recordings. In total, these studies captured the whole memory process from the encoding over the consolidation to the retrieval.

The first study aimed to examine if highly unstable compared to more stable practice conditions have an impact on the motor memory consolidation in force field adaptation tasks. The behavioral findings support previous work showing that variable practice comes in line with positive consolidation affects. Neural recordings support this view. Behavioral and neural findings together led to the suggestion that motor benefits are facilitated by online feedback corrections during movement execution and that these mechanisms might be linked to the brains alpha frequencies over parietal areas.

These findings of motor benefits after variable practice were reproduced in the second study of this thesis. This study also aimed to investigate if motor adaptation to force field conditions depends on sleep and if such a potential role of sleep depends on different practice schedules. To do so, this study combined force field adaptation learning with wake EEG and night polysomnographic recordings. The results showed that consolidation of force field adaptation does not depend on sleep, regardless of the variability during practice. However, slow wave's sleep spindle activity correlated

with the behavioral performance which needs further investigation.

In the third study of this thesis, interference was implemented in a separate training session 24 h after the first session. Within this second session, the direction of the force field to be practiced was in the opposite direction compared to the first practice session. This so called 'ABA' paradigm led to a reduced retrieval performance in the experimental group compared to a control group which did not practice under interfering conditions. The comparably better motor performance of the control group came in line with an increased power in the EEG's higher gamma frequencies over frontal areas. However, this effect was short lasting and vanished during retesting.

Altogether, this thesis is able to show that EEG recordings are feasible in motor adaptation tasks using robotic devices. High interference during practice is able to increase the motor memory consolidation and these benefits are associated with the brains parietal alpha power. There are several indications for a potential role of online feedback corrections during movement execution with this facilitating the motor benefits, but future work is needed. The studies in this thesis also showed that alpha power was predictive for the subsequent consolidation performance but only when subjects practiced under more stable and not highly unstable conditions.

If interference was implemented in an opposing task in a different practice session, retest performance was hampered. However, if the practice session took place under variable conditions (e.g. interspersed with catch trials) the effects of interference were less intense. This indicates that motor memory consolidation must not purely represent a time dependent process, since there was a 24 h consolidation period between the two practice sessions. However, the findings here are not consistently reported by other studies. It seems that time but not sleep plays a role in the motor memory consolidation of force field adaptation tasks but other factors, like the variability of practice, contribute as well.

Zusammenfassung

Das Lernen neuer Bewegungen spielt eine fundamentale Rolle in der Natur. Menschliche Bewegungen sind in der Regel sehr komplex, auch wenn es auf den ersten Blick nicht so erscheint. Die meisten dieser komplexen Bewegungen werden im Laufe des Lebens erlernt und erfordern somit eine Lernfähigkeit des Individuums. Wie diese motorischen Lernprozesse funktionieren, ist im Detail bisher nicht bekannt. Dennoch ist ein tieferes Verständnis dieser Prozesse notwendig, um Trainingsprotokolle in der Rehabilitation oder im Sport zu verbessern.

In der wissenschaftlichen Literatur liegen zahlreiche Befunde vor, die darauf hindeuten. dass Interferenzen im Üben einen Einfluss auf die spätere Gedächtnisleistung und somit die Konsolidierung haben. Solche Einflüsse können sowohl positiv als auch negativ sein, in Abhängigkeit davon, ob Interferenzen während des Übens oder aber in unterschiedlichen Übungseinheiten mit entgegengesetzten kinematischen oder dynamischen Bedingungen stattfinden. Die neuronalen Mechanismen, die entweder zu einem Vorteil oder einen Nachteil führen, sind bisher unbekannt. Das Ziel dieser Dissertationsschrift war es deshalb, in drei empirischen Arbeiten die neuronalen Grundlagen zu untersuchen, die entweder positive oder negative Effekte nach einem interferenzhaltigen Üben hervorrufen. Dabei wurde neben der motorischen Adaptation an Kraftfeldbedingungen auch das Elektroenzephalogramm (EEG) aufgezeichnet.

Die erste Studie untersuchte, ob sehr instabile im Vergleich zu eher stabilen Übungsbedingungen zu einer besseren Konsolidierungsleistung führten. Dieses Phänomen, welches bereits als Kontextinterferenzeffekt bekannt ist, konnte hier mit einer motorischen Adaptationsaufgabe an veränderte dynamische Bedingungen bestätigt werden. Zusätzliche EEG-Analysen zeigten, dass diese positiven Effekte auf der Verhaltensebene mit Veränderungen in den Alpha-Frequenzen des parietalen Kortex in Verbindung zu stehen scheinen. Tiefgreifende Analysen deuten an, dass die positiven Befunde variablen Übens durch effektive Korrekturen auf Grund von Feedbackmechanismen hervorgerufen wurden. Jedoch sind zukünftige Studien notwendig, um diese Annahme zu bestätigen.

Die Befunde aus der ersten Studie konnten auch in der zweiten Studie dieser Dissertationsschrift reproduziert werden. Zusätzlich wurde in dieser zweiten Studie untersucht, ob Schlaf einen Einfluss auf die Konsolidierungsfähigkeit einer Kraftfeldadaptationsaufgabe hat und ob solch ein Einfluss durch instabile Übungsbedingungen beeinflusst wird. Dazu wurden drei unterschiedliche Methoden kombiniert, nämlich: das Kraftfeldparadigma, das EEG und das Polysomnogramm. Die Ergebnisse zeigten keinen Hinweis auf einen Schlafeffekt, unabhängig von den Übungsbedingungen. Dennoch konnte im Polysomnogramm eine erhöhte Spindelaktivität

in den niedrigen Frequenzbändern gefunden werden, welche mit der motorischen Leistung korrelierte.

Die dritte Studie untersuchte, ob eine separate Übungseinheit, 24 Stunden nach der ersten Übungseinheit, einen negativen Einfluss auf den Wiederabruf der motorischen Aufgabe hat. Dabei bestand die Interferenz darin, dass das zu adaptierende Kraftfeld in der separaten Übungseinheit dem Kraftfeld der ersten Übungseinheit räumlich entgegengesetzt war. Dieses so genannte 'ABA' Paradigma führte zu einer verringerten motorischen Leistung im Wiederabruf der Aufgabe aus der ersten Übungseinheit, verglichen mit einer Kontrollgruppe, die keine separate Übungseinheit hatte. Die vergleichsweise bessere Leistung der Kontrollgruppe beim Wiederabruf trat zusammen mit einer erhöhten Leistung der Gamma-Frequenzen im EEG über frontalen Gehirnarealen auf. Dieser Effekt war jedoch nur von kurzer Dauer und verringerte sich während der Nachtestung.

Insgesamt konnte diese Dissertationsschrift zeigen, dass EEG Aufnahmen während motorischer Adaptationsaufgaben an Robotermanipulanda möglich sind. Hohe Interferenzen während der Übungseinheit können einen positiven Einfluss auf die Konsolidierungsleistung haben, welche mit den Alpha-Frequenzen über parietalen Gehirnarealen in Verbindung steht. Es ist möglich, dass die positiven Befunde auf der Verhaltensebene durch Feedback-Korrekturmaßnahmen während der Bewegungsdurchführung hervorgerufen wurden. Außerdem konnte die zweite Studie zeigen, dass die Leistung im EEG Alpha Band die behaviorale Konsolidierungsleistung prädizieren kann, sofern das Üben unter eher stabilen Bedingungen stattfand.

Wenn Interferenzen jedoch durch unterschiedliche Übungseinheiten mit gegensätzlichen Kraftfeldrichtung hervorgerufen werden, verringert diese Interferenz die motorische Leistung beim Wiederabruf. Dieser verringerte Wiederabruf fällt jedoch weniger stark aus, wenn das Üben mittels eingestreuter 'catch trials' variabler gestaltet wird. Somit scheint die Konsolidierung motorischer Erinnerungen nicht nur auf den Faktor 'Zeit' zu beruhen. Unterschiedliche Resultate ähnlicher Studien lassen vermuten, dass 'Zeit', aber nicht 'Schlaf', ein wichtiger Faktor für die Konsolidierung von Adaptationsaufgabe darstellt, es jedoch noch weitere Faktoren wie zum Beispiel die Übungsvariabilität gibt, die den uneinheitlichen Forschungsstand hervorrufen.

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Chapter 1

Introduction

"It isn't all over; everything has not been invented; the human adventure is just beginning."
— Eugene Wesley Roddenberry

1.1 Motivation

Motor control is a key function in every actively moving creature (Llinás, 2001). Only through motor control an animal is able to swim, run, fly, or jump. The development of optimized motor control strategies gives advantages in the struggle for survival (Darwin, 1880). In humans, this importance of the motor system is usually not noticed in everyday life, as lots of our movements are automized and performed without explicit knowledge (Koch, 2005). However, the great value of motor control in humans can easily be depicted by the fact that it would be impossible to locomote or even to communicate in an active way (e.g. talk or gesture) after the complete loss of motor control (Rosenbaum, 2009). Furthermore, it is fascinating that most of these complex motor control strategies did not develop themselves phylogenetically but ontogenetically, for babies are born with a limited repertoire of movements. Especially this last aspect leads to the eligibility of motor learning as an important research topic in science.

There is a long history of motor learning research but still, the underlying mechanisms are not sufficiently understood. For instance, it is possible to build computers which can beat the best human players in the most strategic intellectual games like chess or go (Silver et al., 2016), but no robot can perform such skillful motor behavior like an average human. This view is even more astonishing if we keep in mind that most of our behavior was ontogenetically developed within a relatively short period of time. Therefore, it is remarkable that the human brain is capable of extremely fast learning and adaptation processes of complex control systems. However, scientists are still not able to understand these underlying mechanisms.

Up to now, there are different models verifying the mechanisms of motor learning, but there is no general theory which can integrate these different learning models and, thus, explain every aspect of motor learning (Wolpert et al., 2011). Besides the limitation to integrate these different models into a general motor learning theory, some of these models were developed on the behavioral level and, yet, cannot be explained on the neural level. But this is especially important as it is general consensus that neurons are the basic unit that drives our actions (Koch, 2012). This leads to a gap between motor learning models on the systemic and on the neural level.

In the future, neuroimaging methods might be able to fill this gap. These methods developed quickly within the last decades and were already able to confirm some of the most influential brain theories like the Hebbian learning theory (Hebb, 1949; Wittmann et al., 2005) or the neural plasticity (Zatorre et al., 2012). Further improvements in neuroimaging technology, and in computers in general, will allow to investigate neural processes with an increased time and spatial resolution with which it might even become possible to investigate the whole human connectome (Seung, 2012).

The purpose of this thesis, hence, was to combine current methodological approaches on the behavioral and neural level to enhance the current motor learning knowledge. In this interdisciplinary approach the procedure was to investigate possible effects on the behavioral and computational level first, before examining the deeper, neural level (Krakauer et al., 2017). The first step is important, as the methodological reduction to the neural level increases the dimensionality of the results, which makes it hard to interpret possible findings without distinct behavioral findings. The second step is important, as the neural level is the primary source of our actions and should be taken into consideration if a distinct behavioral effect is observed.

1.2 Theoretical background

A thorough understanding of motor control strategies is of importance for this thesis, for this knowledge serves as a key to understand the subsequent theoretical background on motor memory and learning. Furthermore, theories of motor control and motor learning are interconnected and not clearly distinguishable. After motor control, a general overview of memory processes is given with a focus on motor memory. Finally, this section ends with the theoretical background and current knowledge on the consolidation of motor memory. In general, this section provides both the behavioral and neural aspects of motor control and memory and forms the theoretical basis for the subsequent sections targeting motor learning phenomena.

1.2.1 Basics of motor control

Evolution and neuroanatomy of motor control
Motor control can be described as the control of actuators (muscles) by the nervous system. The evolutionary history of motor control goes back to the immediate ancestors of modern vertebrates more than 500 million years ago and to the first moving life forms which developed even more than 700 million years ago (Shadmehr and Wise, 2005). Before that time, life forms were only able to move passively or weren't able to move at all, like plants and trees. With the ability to move, animals were able to hunt, flee, or hide which served as big advantages in the struggle for survival (Darwin, 1880). Therefore, it is widely stated that the development of the motor control system through the nervous system was a game changer in evolution (Llinás, 2001).

Throughout evolution, movements of these active moving animals became more and more skillful and complex. That was facilitated by the evolved Central Nervous System (CNS) which increased in volume and differentiated into sub-networks. This development also led to more sophisticated non-motor abilities. However, despite the evolutionary changes and especially the development of non-motor abilities in humans, still, most of the areas of the CNS are involved in processes of motor control (Ungerleider, 2002). These areas include mainly the spinal cord, brainstem, thalamus, cerebral cortex, basal ganglia, and cerebellum, which will briefly be discussed now.

The spinal cord connects the peripheral muscles with the brain and is important for short lasting reflexes, but also for the forwarding of afferent and efferent action potentials. Although far less complex than the brain, the spinal cord also contains several neurons and interneurons and is able to facilitate central pattern generators (Rizzolatti and Strick, 2013; Schmidt and Lee, 2011).

The brainstem is the next region which is entered by upstreaming information coming from the spinal cord. Parts of the brainstem are directly involved in motor control, as the pons connects the cerebral cortex with the cerebellum and is thought to influence basic functions like chewing or breathing (Magill and Anderson, 2014). Other parts have an immediate influence on motor control, like it appears for the reticular formation, which has access to all sensory information and, thus, serves as a regulator for sensory signals. It is widely known that these mechanisms within the brainstem play a critical role for basic control movements like postural control

(Macpherson and Horak, 2013).

Between brainstem and cerebral cortex lies the thalamus. In mammals, every sensory information (except olfactory input) reaches the thalamus first before entering the cerebral cortex (Murakami et al., 2005). The thalamus is anatomically connected to different areas of the cortex. For a long time, the thalamus was 'only' seen as a gateway, but recent findings show that cortico-thalamo-cortico feedback loops are involved in many brain functions which are, by now, not fully understood (Roth et al., 2015; Sherman, 2016).

The cerebral cortex is the part of the human brain with the biggest volume. Parietal areas of the cerebral cortex are involved in voluntary control of movements. In detail, sensory information enters the cortex through the primary sensory areas (e.g. S1 for somatosensory or V1 for visual information) and this sensory input is then integrated in associational areas, which belong to the posterior parietal cortex (PPC) (Whitlock, 2017). In addition, due to fronto-parietal connections, also frontal input is processed within the PPC. Therefore, the parietal cortex with its long distance connections is seen as an important hub in the integration of information coming from different brain areas, including areas of motor control. The processing of voluntary motor control is suggested to take place in the frontal lobe (Magill and Anderson, 2014). In more detail, motor planning is related to the supplementary motor area (SMA) and the premotor area, whereas the prefrontal cortex (PFC) is more seen as a controller, which is related to decision making and executive functions (Domenech and Koechlin, 2015). Just anterior to the central sulcus lies the primary motor cortex (M1), which facilitates processes of movement execution and inhibition, as the motor neurons within M1 target to the peripheral muscles (Ebbesen and Brecht, 2017).

The basal ganglia are also a suggested key region for motor control, which was proofed in patient studies. For instance, a lack of dopamine production in the substantia nigra triggers Parkinson's disease. These patients suffer from bradykinesia, tremor, and muscular rigidity. However, despite the loss of motor control, Parkinson's patients are still able to learn by adapting their motor control strategies on a trial-by-trial basis (Macpherson and Horak, 2013). Besides the substantia nigra, other parts of the basal ganglia are important for motor control, as well. The striatum is the biggest part of the basal ganglia and is connected to the promotion and inhibition of movements (Calabresi et al., 2014). With its anatomical connections to premotor and thalamic areas, the striatum is suggested to be a main controller for sequential motor tasks (Doyon and Ungerleider, 2002).

The cerebellum is a comparably small part at the back of the brain, but it contains almost two thirds of all approximately 87 billion neurons in the human brain (Herculano-Houzel, 2009). Intriguingly, despite this huge amount of neurons in the cerebellum, it's role in non-motor processes is comparably low and still unclear (Koziol et al., 2014). However, the important role of the cerebellum in accurate and skillful motor control is widely accepted (Magill and Anderson, 2014; Shadmehr, 2017; Shmuelof and Krakauer, 2011). Especially mechanisms of motor adaptation are clearly related to the cerebellum (Taylor and Ivry, 2014; Wolpert et al., 1998).

Altogether, this brief overview shows that motor control must be seen as a process which is distributed among several brain regions and includes billions of neurons. Therefore, it is useful to first gain a deeper understanding of motor control processes on the behavioral level, before examining the even more complex, underlying processes on the neural level. The investigation of motor control on the behavioral level has a long history and produced various computational models of which only the most relevant for this thesis will be discussed.

Complexity of the motor control system

In the 19th century, motor control in all animals was widely seen as an concatenation of reflexes, which were triggered by afferent input (James, 1890; Llinás, 2001). However, in the early 20th century, Charles Sherrington (1906) and Graham Brown (1911) challanged this view by showing that deafferented animals and humans are able to perform movements without afferent input from the limbs to the spinal cord. This led to the modern view that motor control is not just a construct of concatenated reflexes. Although there are definitely movements, which are performed by a chain of reflexes and can be seen for instance as central pattern generators (Schmidt and Lee, 2011), voluntary movements in humans mostly contain higher order feedback loops.

This view was further influenced by the work of Nicolai Bernstein who developed theories about how the nervous system is capable of handling the "degrees of freedom problem" (Bernstein, 1967). Simplified, this problem describes the fact that coordinated movements, which involve different limbs, muscles, and joints, are from a computational perspective extremely complex and it is not known how a control system in the brain is capable of handling the degrees of freedom to produce a desired outcome (Scott, 2004). The brain with its approximately 87 billion neurons and at least the same amount of glial cells (Kandel et al., 2013) seems to handel these degrees of freedom quite easily. On the other side, the combination of the degrees of freedom problem and the vast amount of neurons, glial cells, and synapses in the CNS, make research in motor control strategies extremely difficult.

Although the degrees of freedom problem might be the most prominent way to illustrate the complexity of motor control from a computational perspective, there are other influences as well which increase the complexity: e.g. noise of the nervous system, different signal transmission delays of different sensory systems, or the nonlinear nature of the motor system (see Franklin and Wolpert, 2011, for a detailed

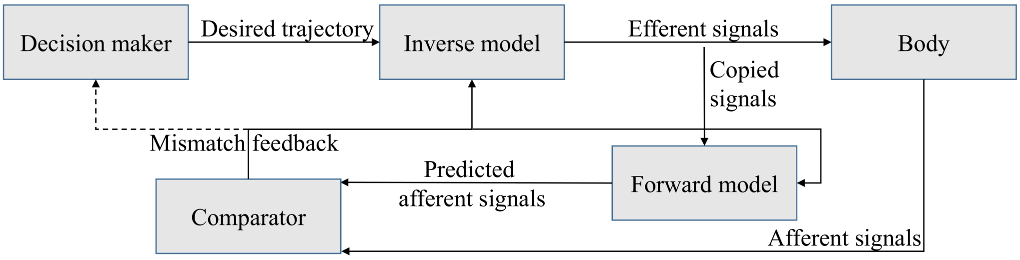

Figure 1.1: Simplified schema of internal model theory. An inverse model transforms the desired trajectory into the efferent signals which target the muscles (body). A copy of these efferent signals is processed in the forward model into the predicted incoming sensory information due to movement. Mismatch between predicted and actual sensory input will adapt the inverse and/or forward model. Although not mentioned in the literature, information about mismatch might also be fed back to the decision maker (indicated by dashed arrow).

review). All these influences together lead to the widely accepted phenomenon that movements reveal a high variability during execution although endpoint performance is quite accurate and reliable. These observations of the motor control system led to several models and theories of motor control - like schema (Schmidt, 1975) or dynamical systems theory (Kelso, 1984) - of which only two will be discussed here in detail, namely: internal model theory and optimal feedback control.

1.2.2 Computational models of motor control

Internal model theory
This theory is based on the assumption that internals (body) and externals (e.g. surroundings) are represented as images in the brain (Craik, 1967). Internal model theory (Wolpert et al., 1995) proposes that accurate motor control is achieved by the interplay of at least two internal models in the brain: inverse model and forward model (Kawato, 1999; Wolpert et al., 1995). These models facilitate the transformation of the relevant information either into the motor (inverse) or sensory (forward) domain and the comparison of these information will lead to recursive updates of these models in order to correct movements (Figure 1.1).

The inverse model describes the transformation from the desired goal to the motor commands, where the goal is defined as the desired future sensory input. Therefore, inverse models serve as controllers for the efferent neural signals (Ito, 2008; Krakauer and Shadmehr, 2006). However, a motor control system with only an inverse model would be limited in its learning abilities, because the inverse model is the only model which could be adapted and this adaptation could only be based on the comparison of old and new afferent sensory information. Thus, a learning process which depends only on an inverse model would be slow. Furthermore, evidence proofs that the ability to track a visible object is improved when the object is moved by the observer (Mathew et al., 2017). But this improvement can not be explained by an inverse model as this does not use the outgoing efferent information of hand control to plan eye movements.

The forward model brings another loop into this theory which solves the above describe discrepancies. The forward model represents the transformation of the efferent outgoing information of the inverse model into the predicted afferent sensory information. Therefore, this forward model predicts the actual consequences of the muscle activation patterns from the inverse model (Pekny et al., 2011; Wolpert et al., 2011). This leads to a comparison of new afferent sensory information with the predicted afferent sensory information.

According to the theory of internal models, motor control is corrected by actual mismatches between predicted and actual afferent sensory information. This way of motor control due to internal models is quite fast and accurate as predicted sensory information can be computed while the movement is executed and mismatch comparisons base on internal (inverse + forward models) and external (sensory input) processes. However, it is not easy to distinguish which internal model (inverse or forward) is updated. Therefore, this thesis will solely use the term internal model and, with this term, refer to both, inverse and forward model.

Optimal feedback control

A limitation of internal model theory is that it does not directly predict when a correction of motor control is necessary and if internal model updates take place during movement execution or on an inter-trial basis. Optimal feedback control (Todorov and Jordan, 2002), however, accounts for these limitations with a computational model which predicts when updates of motor control processes are necessary and which dimensions of the complex motor system should be corrected. This model puts ongoing movement corrections due to feedback loops as a prime mechanism for motor control.

It is important to note that optimal feedback control assumes that the achievement of the behavioral goal and not the desired movement trajectory is the control variable which will be corrected by the motor system. According to optimal feedback control, movements are generated and corrected by modular pattern generators - called motor synergies or primitives - which describe solid, coordinative neuromuscular structures with each synergy leading to a specific motor pattern (Bizzi and Cheung, 2013). Due to motor synergies, the degrees of freedom of the motor system are reduced. In addition, the general variability of movements is also not seen as a real problem and neglected by the motor planner, as long as variability does not hinder the achievement of the task goal. However, variability which does put task goal at risk will be reduced by movement corrections facilitated by motor synergies. In other words, movements are only corrected if the deviation is in a task relevant dimension. These corrections are postponed to the last possible moment, to take as much as possible unpredictable variability into account for an accurate correction (Todorov and Jordan, 2002).

The above described reduction of variability in the task relevant dimension is based on the uncontrolled manifold hypothesis. Derived from this hypothesis, variability is allowed in the redundant, task irrelevant dimension (according to the task goal). Accordingly, the motor control system uses a cost and reward comparator which takes costs, rewards, noise, feedback, and internal models into account (Shadmehr and Krakauer, 2008) and, thus, the motor control system will not waste energy to control the task goal's irrelevant dimensions (Figure 1.2 A).

Assumptions of optimal feedback control and the internal model theory can be integrated into one unified model (Shadmehr and Krakauer, 2008). Accordingly, the comparison of the predicted sensory feedback and the actual sensory feedback will give the current state of the body and the world. This information will be fed to a feedback controller which uses all available information (e.g. cost, reward, and state estimation) to adjust the motor control in order to optimize motor performance. This last step of motor corrections in task relevant dimensions to optimize performance is called the optimal control and can be integrated into the internal model schema as depicted in Figure 1.2 B.

Another benefit of optimal feedback control is its accordance with the neurophysiology (Scott, 2004). However, a more detailed look into optimal feedback control and its neural representations is not provided here, for the primary goal of this thesis is the investigation of motor learning. Figure 1.2 B shows, that in optimal feedback control the cerebellum, basal ganglia, parietal cortex, premotor cortex, and primary motor cortex also seem to represent important hubs (Shadmehr and Krakauer, 2008). In the following sections, this thesis will focus on how motor control processes are developed or adapted. But to investigate this question, some basics about memory and memory processes are needed.

1.2.3 Memory processes and memory consolidation

Memory processes

Memory is a fundamental ability and the foundation for the general capability of learning. The broad term 'memory' contents three different processes, which are: encoding, consolidation, and retrieval of memory. Memory encoding describes the

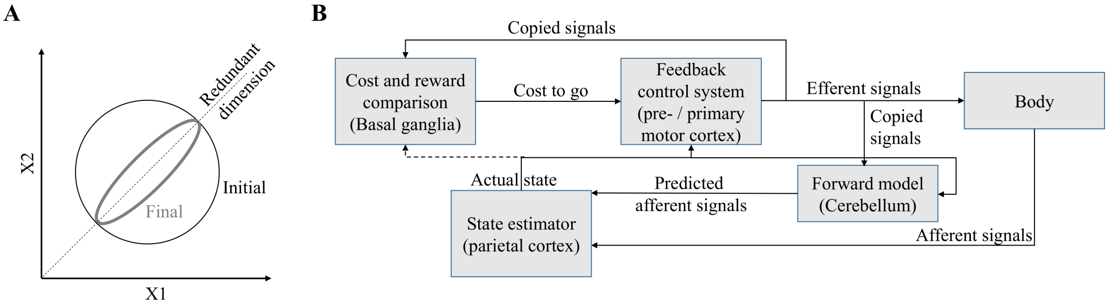

Figure 1.2: Simplified schema of optimal feedback control. **A** shows how variability in optimal feedback control is constrained to the redundant subspace (uncontrolled manifold) of state variables X1 and X2. **B** this schema basis on the internal model schema but with some important changes. Optimal control uses the costs and rewards of the task goal and not the desired trajectory. Planning and execution of the efferent signal is done in a feedback control system which receives input about the cost to go and the actual state of the body and world. Dashed arrow indicates that there might be a direct connection from the state estimator to the cost and reward comparison. This figure is based on the work of Todorov and Jordan (2002), Scott (2004), and Shadmehr and Krakauer (2008).

initial stage in which the memory engram is built. Consolidation describes the stabilization or sometimes even enhancement of the already encoded memory engram. The last process is the memory retrieval, which describes the recall of the memory engram.

Memory is divided into a declarative and non-declarative part. The declarative memory contains semantic and episodic information and is widely seen as the memory which requires awareness and conscious retrieval. The Encoding and retrieval of declarative memory elements is therefore usually seen as an explicit (i.e. with awareness) process. It is widely accepted that memory processes of these declarative memory systems rely on the involvement of the medial temporal lobe (Rasch and Born, 2013). On the contrary, non-declarative memory contains procedural memory for which encoding, consolidation, and retrieval of memory is seen as an implicit (i.e. without awareness) process. It is widely accepted that consolidation of procedural memory relies on the involvement of brain areas, which do not belong to the medial temporal lobe (Squire and Zola, 1996). Motor memory is seen as a part of procedural memory.

The fact that most of our procedural memory is recalled implicitly comes from the observation that humans are not permanently aware of their own movements and that humans are not able to voluntarily control all muscles (e.g. heart or other organs). This led Christof Koch and Francis Crick to describe some parts of human behavior as Zombie agents (Koch and Crick, 2001). Zombi agents describe actions humans do in their daily live but which are not consciously controlled or recognized by them. However, this should not lead to the view that humans are not able to control their movements consciously because, obviously, that is possible. Neal Miller (1969) was able to show this impressively in a set of experiments with which he found out that it is possible to explicitly control even the most autonomous and implicit control processes in the CNS such as heart rate or blood pressure. Accordingly, in more recent work motor control is suggested to be declarative and non-declarative dependent (Huberdeau et al., 2015; Rasch and Born, 2013).

Memory consolidation

The consolidation of encoded memory engrams is still a vast research field reaching from the synaptic to the behavioral level. The most accepted theory regarding motor memory consolidation is the theory of synaptic long-term potentiation (LTP) or depression (LTD), which is based on the idea of neural plasticity. This theory - developed by Donald Hebb (1949) - describes an increased synaptic connection between neurons in a network due to repeated firing. This network represents the specific memory engram of the brain. Although it was further investigated, the basis of this hebbian learning theory still serves as the main learning mechanism on the synaptic level (Song et al., 2000). For example, this theory can explain why specific sensorimotor areas increase their volume when frequently needed (Münte et al., 2002).

Another learning theory, which is based on the idea of neural plasticity, describes learning on a neural-systems level (Dudai, 2004). This theory describes a redistribution of the neural representation of the memory engram to other neural networks for long-term storage (Rasch and Born, 2013). In other words, consolidation describes the migration of the memory engram to different brain areas. Both views of neural plasticity form the theoretical basics for memory consolidation.

An important question of memory consolidation targets the limitation of the brain's capacity to store memory. Humans are not able to retrieve all experiences they have or all motor control strategies they have learned in their lifetime. The memory capacity of the human brain is limited. But if memory storage is limited, when does the learning of a new memory engram delete an old one? A widely accepted two-stage model accounts for this important question (Marr, 1971). This model differentiates memory consolidation into a short- and long-term storage. First, a memory engram is encoded into a fast but short-term storage. This ensures the ability to retrieve information quickly after encoding, but this storage is highly unstable and its content will be forgotten within a short period of time. However, gradually over time, the memory engram will transform into a long-term storage which is more stable and will not overwrite older long-term memory engrams. It is assumed that this migration from short- to long-term memory needs reverberation of the relevant neural networks (Rasch and Born, 2013). For declarative memory it is assumed that transformation is connected to the migration from one brain area to another. Animal studies were able to clearly show that declarative forms of short-term memory depend on hippocampal structures whereas long-term memory does not (Tse et al., 2007). However, it is unknown if a similar mechanism also takes place in procedural memory.

1.2.4 Consolidation of motor memory

Sleep dependency of motor memory consolidation
Although the two-stage model is widely accepted for declarative memory, it is not clear if this also is the case for procedural memory and, if so, which brain areas are involved in this process. Findings of studies which investigated the consolidation of motor memory show ambiguous results regarding this topic (Krakauer and Shadmehr, 2006; Rasch and Born, 2013). In this thesis it is assumed that there is also a consolidation process for motor memories and, thus, motor memory consolidation is defined as an improvement or stabilization of the motor memory from encoding to retest.

Furthermore, regarding declarative memory components, it is widely accepted that memory consolidation depends on sleep (Rasch and Born, 2013). However, previous sleep research showed ambiguous results regarding the sleep's benefit on motor memory (Pan and Rickard, 2015; Rieth et al., 2010). Several studies found consolidation of motor memory to be sleep dependent (Stickgold, 2005; Walker et al., 2002), whereas others did not (Tucker et al., 2006). These diverged results might reflect the contribution of different memory systems according to the different tasks which have been trained. Sleep dependent motor memory improvements might predominantly rely on explicit knowledge rather than on implicit components (e.g. Robertson et al., 2004), even though explicit knowledge was tested to be minimal prior to sleep (Fischer et al., 2006; Wilhelm et al., 2013). The preferential consolidation of explicit aspects of memory during sleep in memory systems has been hypothesized to rely on prefrontal-hippocampal involvement during encoding (Marshall and Born, 2007; Rasch and Born, 2013). The case for explicit, implicit or an interactive contribution throughout initial motor memory encoding and their influence on long-term persistence, remains unclear, but it was suggested to be mainly dependent on implicit representations in force field motor adaptation tasks (Shadmehr et al., 1998), which will be discussed in more detail in Section 1.3.1. The potential role of sleep in motor memory consolidation is an important aspect and will be further investigated in

Chapter 3.

Ways to improve motor memory consolidation

Investigations on the improvement of motor memory consolidation range from behavioral (Shea and Morgan, 1979) or mental (Debarnot et al., 2015) interventions up to non-invasive brain stimulation (Reis et al., 2008) and show promising results. Due to the vast amount of literature, this thesis will be restricted to improvements of motor memory consolidation on the behavioral level induced by inter-trial interference during practice.

Two frequently used practice schedules to improve memory consolidation are the distribution of practice and the variability of practice. The distribution of practice effect describes an enhanced retest performance when memory encoding during practice was interleaved by periods of rest. The literature reveals a quite robust effect for motor memory tasks, which show an enhanced performance during practice and retest with a distributed practice period (Schmidt and Lee, 2011).

Another well known effect, which improves motor memory consolidation, is the variability of practice effect. This describes the effect that practice performance decrease under unstable conditions but retest performance increases after a period of consolidation (Magill and Hall, 1990; Schmidt and Lee, 2011). Furthermore, this effect meets the predictions of the schema theory by Schmidt (1975), which predicts increased retest and transfer performance after variable practice. From the 1950's up to now, several studies were able to reproduce these findings and show that some sort of variability in practice leads to a better performance after a consolidation period compared to constant practice.

Derived from these findings, different studies showed that the amount of variability played an important role in the process of memory consolidation. This led to the hypothesis of the contextual interference effect, which describes that higher variability or instability during practice leads to higher memory interference and thus, improves memory consolidation better than lower interference (Brady, 1997; Shea and Morgan, 1979). Studies which investigated this hypothesis compared different practice schedules with the same amount of trials. One practice schedule was defined as a low-interference schedule, which is mostly a blocked trial design. In such a blocked schedule, a skill or task is practiced several times before switching to the next skill. The other schedule was defined as a high-interference schedule, which is usually a random trial design of the different skills (the skill switches from trial-to-trial). Similar to the general variability of practice effect, there are studies targeting the contextual interference effect that were able to reproduce the findings of increased retest and transfer performance after unstable practice (e.g. Magill and Hall, 1990; Wright et al., 2015), although there are also studies which were not able to reproduce these findings (e.g. Brady, 1997; Jarus et al., 1997).

The two most prominent hypotheses explaining positive effects after learning under high-interference conditions are the elaboration (Shea and Morgan, 1979) and reconstruction (Lee and Magill, 1983) hypotheses. The elaboration hypothesis describes the improved retest and transfer performance via the differences in the planning and evaluation of consecutive trials. This hypothesis proposes that task related processes are kept in parallel in the working memory and due to the high-interference schedule, the differences between the task requirements can be computed which lead to a stronger representation in memory. The reconstruction hypothesis, however, proposes that task related processes cannot be kept in working memory in parallel. Therefore, under high-interference conditions, the task-related memory must be reconstructed from memory for each single trial which, in turn, is suggested to improve consolidation.

1.3 Features of motor learning

This section differentiates motor adaptation from skill learning and discusses the actual knowledge of motor adaptation and consolidation on the behavioral and neural level. This is in so far important, because experiments in this thesis only investigated the subjects' motor adaptation and not their skill acquisition.

1.3.1 Motor adaptation as a part of motor learning

Skill learning and motor adaptation

The process in which motor control develops ontogenetically is called motor learning. The field of motor learning can be divided into skill acquisition and motor adaptation (Krakauer and Mazzoni, 2011). Skill acquisition describes the learning of an unknown movement skill (e.g. learning the discus throw in athletics) or the optimization of a skill to a new performance level (e.g. increase your discus throw performance over the years). Therefore, skill acquisition leads to an increase in motor performance compared to a previous baseline level. Motor adaptation, however, describes the regaining of the baseline level despite the occurrence of changes in the internal or external conditions of the movement (e.g. you are capable of the discus throw but the mass of the discus has changed). Those changes or disturbances will initially decrease motor performance and thus serve as a trigger for a subsequent learning process in which motor control strategies are adapted to the new conditions. This shows, that motor adaptation is a part of motor learning but should not be confused with skill acquisition (Shadmehr et al., 2010; Wolpert et al., 2011).

Studies frequently investigated motor adaptation under laboratory conditions in which the subjects' movements were perturbed in a systematic way. Within time, the subjects adapt to this perturbation and regain almost equal motor performances like at undisturbed conditions. These perturbations can be induced either on the kinematic or dynamic level. Kinematic perturbations of the subjects' movements, like in prism adaptation (Held and Freedman, 1963) or visuomotor rotation studies (Krakauer et al., 2000), lead to disturbances on the visual-spatial level. Dynamic perturbations, like attaching a load to the subjects' arm (Krakauer et al., 1999) or inducing Coriolis forces by rotating environments (Lackner and DiZio, 2005), lead to disturbances on the musculo-skeletal level. Another frequently used dynamic perturbation to induce motor adaptation is the application of force fields via robotic devices (Shadmehr and Mussa-Ivaldi, 1994), which is also applied in this thesis. The methodology of force field adaptation will be discussed in more detail in Section 1.5.1.

Motor adaptation research is of general interest since adaptation happens all the time in everyday life. For instance, running on a treadmill, driving a new car, or even eating with a bigger fork lead to small adaptations in the initial movements, which are barely recognized by people. Despite everyday life, motor adaptation learning plays an important role in the area of rehabilitation for many patients can already perform a skill, but their kinematics and/or dynamics need to be re-adapted to the new internal conditions.

Computational mechanisms facilitating motor adaptation

The findings of motor learning experiments cannot be explained by just one computational mechanism or strategy. Hence, different mechanisms are thought to be relevant and take place during learning (Haith and Krakauer, 2013). These mechanisms can be divided into model based or model free learning mechanisms.

A model based mechanism called error-based learning is widely accepted as the primary strategy explaining the experimental findings for motor adaptation learning (Wolpert et al., 2011). Commonly, error-based learning describes motor improvements on the basis of the internal model theory. By this means, sensory-prediction errors will lead to updates of internal models (mostly the forward model, Haith and Krakauer, 2013) which, in turn, will improve motor performance across trials. Empirical evidence shows that such a mechanism indeed depends on sensory-prediction errors and not on the target error itself. In his study, Mazzoni (2006) was able to show that even when movement goals are achieved and target error is at minimum, adaptation occurs. These findings could not be reproduced with patients suffering from cerebellar ataxia (Taylor et al., 2010), indicating the cerebellum's important role for error-based learning (Wolpert et al., 2011).

However, patients suffering from cerebellar ataxia are still able to adapt to perturbations as long as these perturbations increase gradually (Criscimagna-Hemminger et al., 2010). This indicates that beside error-based learning other mechanisms can facilitate motor adaptation as well. A prominent model free mechanism accounting for this phenomenon is reinforcement learning. Reinforcement learning depends on the dopaminergic reward system, meaning that a reduced dopamine production in the substantia nigra, due to low task reward, will lead to direct updates of the motor controller (Haith and Krakauer, 2013). It is suggested that reinforcement learning accounts for late learning mechanisms, when error-based learning is not able to improve motor performance any further, and might be a hallmark for skill acquisition (Haith and Krakauer, 2013; Wolpert et al., 2011). Furthermore, reinforcement learning facilitates motor improvements by reducing the variability of movement execution. Therefore, it is assumed that reinforcement learning accounts for the predictions of optimal feedback control (Wolpert et al., 2011).

Use-dependent learning - a model free mechanism - is another relevant mechanism for motor learning (Krakauer and Mazzoni, 2011). According to this mechanism, future movements are directly biased by former movements. It was shown that this also takes place in motor adaptation (Diedrichsen et al., 2010). Therefore, use-dependent learning is similar to priming in psychology, for the movement itself and not the reward or task goal biases future movements.

So far, these are the most prominent learning mechanisms in the research community of motor adaptation, however, the strategies which also affect the motor performance shouldn't be disregarded. For instance, every volitional movement starts with the intention to act, which reflects an explicit motor strategy. It was shown that such explicit strategies can account for some learning phenomena, but that their influence on the motor performance is short lasting (Huberdeau et al., 2015). As these explicit mechanisms reflect the usage of strategies and do not reflect a pure learning mechanism of the motor system, this aspect is not discussed any further here but will be referred to in Chapter 4.

1.3.2 Neural correlates of motor adaptation

Brain areas linked with motor adaptation

Motor adaptation is thoroughly investigated on the behavioral level and mostly explained by error-based learning. Although motor adaptation is also investigated on the neural level, the neural mechanisms behind this learning phenomenon are far less understood.

The brain areas described in Section 1.2.1 are potential candidates for areas linked to motor adaptation processes. Especially the cerebellum is seen as an area which is directly connected to motor adaptation (Debas et al., 2010; Nezafat et al., 2001; Shadmehr and Holcomb, 1997; Tseng et al., 2007) and assumed to be involved in computations of internal models (Herzfeld and Shadmehr, 2014). Studies were able to show an inverse association between the motor performance and cerebellar activity, indicating that an increased performance is accompanied by less cerebellar activation (Flament et al., 1996; Imamizu et al., 2000) and that such a transformation happens during adaptation. However, it is not clear if cerebellar processes are equally important for both, early and late phases of motor adaptation, since research suggests that cortico-cerebellar loops are critical only during late phases of motor adaptation (Doyon et al., 2003). In contrast to this, the early phase of motor adaptation is assumed to be connected with cortico-striatal loops and, thus, with the involvement of the basal ganglia (Krebs et al., 1998). For this reason, the cerebellum can not be seen as the core region of motor adaptation because different brain regions are also involved (Diedrichsen, 2005; Shadmehr and Holcomb, 1997).

Besides the cerebellum and basal ganglia, also neocortical areas seem to be involved in motor adaptation processes. A recent study by Inoue et al. (2016) was able to show that premotor and primary motor cortices are involved in motor adaptation. Furthermore, some studies indicated a frontal and prefrontal involvement in motor adaptation (Floyer-Lea, 2004; Gentili et al., 2015; Shadmehr and Holcomb, 1997), whereas others showed parietal processes involved in adaptation as well (Krebs et al., 1998).

Altogether, the current knowledge of potential neural correlates of motor adaptation mechanisms reveals a complex network mainly involving the cortex, the cerebellum, and the basal ganglia.

Motor adaptation and Electroencephalography

The identification of brain areas which are involved in specific actions is a typical goal of several neuroscientific studies. However, a different approach targets the way the brain functions and processes information. This latter approach is made possible by the usage of neuroscientific apparatuses like electroencephalography (EEG). Studies using EEG to investigate motor adaptation and its neural basis are limited and used either event-related potentials (e.g. Anguera et al., 2009), sensory-evoked potentials (e.g. Nasir et al., 2013), some form of connectivity measures (e.g. Perfetti et al., 2011), or time-frequency power (e.g. Tombini et al., 2009). Since this thesis only investigated parameters which are based on time-frequency power, the subsequent reviewing of former work will focus on these time-frequency parameters.

The literature pictures consistent findings across the motor adaptation studies which shows that theta, alpha and gamma frequency bands (Gentili et al., 2015, 2011; Kranczioch et al., 2008; Novakovic and Sanguineti, 2011; Perfetti et al., 2011; Pitto et al., 2011; Tombini et al., 2009) but not beta frequencies (Novakovic and

Sanguineti, 2011; Pitto et al., 2011; Tombini et al., 2009) are related to changes in planning processes due to adaptation. However, on a closer look inconsistencies can be detected regarding the direction of power changes due to the learning process. Where some studies showed an increase in theta power from early to late adaptation in electrodes over the frontal lobe (Gentili et al., 2011; Novakovic and Sanguineti, 2011), other studies showed a decrease over the same areas (Pitto et al., 2011; Tombini et al., 2009). Ambiguous results were also found for the alpha band power for which both, an increase over ipsilateral-frontal (Gentili et al., 2011; Tombini et al., 2009) and a broad decrease (Kranczioch et al., 2008) of power were observed. Due to its possible artifactual superposition, the gamma band power is rarely investigated even though research investigating gamma frequencies found promising results, indicating that motor adaptation correlates with an increase of the gamma band power over frontal areas (Perfetti et al., 2011).

EEG recordings during movement execution are more affected by a decreased signal-to-noise ratio compared to recordings during rest. For this reason, only some studies investigated EEG frequency bands during movement execution. These studies did not observe any changes in the theta and alpha band power with motor adaptation in the execution phase (Studer et al., 2010). None the less, increases in the beta band were observed over fronto-central and sensorimotor areas (Kranczioch et al., 2008; Studer et al., 2010). Furthermore, similar to the motor planning, gamma band power increases over frontal areas were observed with motor adaptation (Perfetti et al., 2011).

Altogether, the EEG literature on motor adaptation paints a limited and inconsistent picture. These inconsistencies led to different interpretations of the underlying brain functions pointing towards an explanation of an increased motor performance either by higher cognitive demands or active inhibition, dependent on an in- or decrease in the theta and alpha power with adaptation (Klimesch, 2012). This thesis tries to extent this current knowledge and sets EEG findings in context to the behavioral findings.

1.4 Aims and scope of this thesis

The aim of this thesis was the investigation of cerebral and behavioral mechanisms enabling human motor learning. This was investigated by three empirical studies, each operating with a different form and amount of practice interference, induced by either stable or unstable conditions. The studies in question are already published or submitted to international journals and underwent peer-reviewing:

- Chapter 2: This manuscript contains the influence of unstable practice conditions during memory encoding on the motor memory consolidation.

Thürer, B., Stockinger, C., Putze, F., Schultz, T., and Stein, T. (2017). Mechanisms within the parietal cortex correlate with the benefits of random practice in motor adaptation. *Frontiers in Human Neuroscience*, 11: 403.

- Chapter 3: This manuscript examines the influence of sleep and wake time on the motor memory consolidation.

  Thürer*, B., Weber*, F., Born, J. and Stein, T. (2018). Variable training but not sleep improves consolidation of motor adaptation. *In Review.* Preprint available at: https://doi.org/10.1101/259671
  * shared first-authorship

- Chapter 4: This manuscripts targets the general feasibility of EEG recordings in the experimental paradigm of force field adaptation and examines possible EEG correlates of motor memory retrieval.

  Thürer, B., Stockinger, C., Focke, A., Putze, F., Schultz, T., and Stein, T. (2016). Increased gamma band power during movement planning coincides with motor memory retrieval. *NeuroImage*, 125: 172-181.

The first two experiments of this thesis (Chapters 2 and 3) and the drafting of this thesis were supported by the "Graduate Funding from the German States". These two experiments investigated the influence of unstable practice during memory encoding and if motor memory consolidation is, at least in some degree, sleep dependent.

The experiment in Chapter 4 was done within the Young Investigator Group (YIG) "Computational Motor Control and Learning", which was funded by the "Concept for the Future" of the Karlsruhe Institute of Technology within the framework of the German Excellence Initiative. This experiment examined the neural correlates of motor memory retrieval by a force field adaptation task.

Besides these three studies, I contributed to other motor learning studies performed within the YIG, which are not part of this thesis:

- Stockinger, C., **Thürer, B.**, Focke, A., and Stein, T. (2015). Intermanual transfer characteristics of dynamic learning: direction, coordinate frame, and consolidation of interlimb generalization. *Journal of Neurophysiology*, 114: 3166-3176.

- Focke, A., Spancken, S., Stockinger, C., **Thürer, B.**, and Stein, T. (2016). Bilateral practice improves dominant leg performance in long jump. *European Journal of Sport Science*, 16: 787-793.

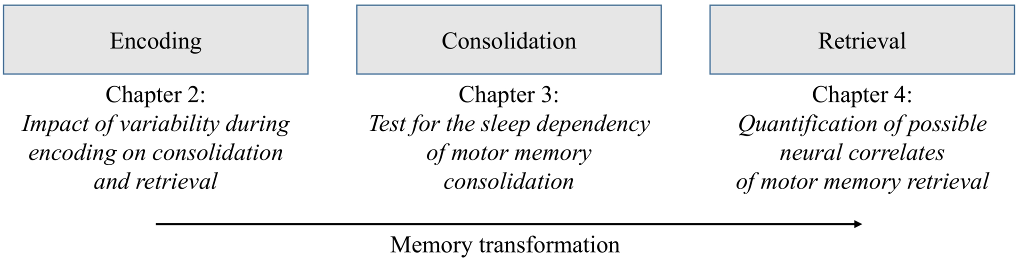

Figure 1.3: Schematic overview of the studies performed in this thesis. This shows how the main research questions of the three experiments can be allocated to different parts of the motor memory transformation.

- Stockinger, C., **Thürer, B.**, and Stein, T. (2017). Consecutive learning of opposing unimanual motor tasks using both arms causes intermanual interference. *PloS One*, 12: e0176594.

Altogether, the three experiments of this thesis cover the whole process of memory transformation (encoding, consolidation, and retrieval; Figure 1.3), although the allocation of each experiment to just one memory process is not distinctive.

1.4.1 Consequences of unstable memory encoding

The work in Chapter 2 hypothesized that interference due to unstable conditions during memory encoding have a positive influence on the process of motor memory consolidation. Furthermore, if unstable encoding enhances retest performance, EEG recordings might be able to find the neural correlates which enable this effect on the behavioral level. These hypotheses were investigated using the methodological approach of contextual interference studies.

1.4.2 Sleep and motor memory consolidation

It is still an ongoing mystery if motor memory consolidation depends on sleep or not. Therefore, the work in Chapter 3 investigated if sleep influences the performance in force field adaptation and, in addition, if such an influence varies with the practice conditions during encoding. Similar to the work in Chapter 2, two groups adapted under almost stable and two groups under highly unstable practice conditions. For each subgroup of each practice condition, one group spend the retention period awake, whereas the other group went to sleep with polysomnographic recordings.

1.4.3 Neural correlates of motor memory retrieval

The work in Chapter 4 investigated the neural correlates of motor memory retrieval. The aim of this work was to find out if EEG recordings could locate differences between two groups of which one did and the other did not consolidate the previously adapted force field. To do so, the ABA paradigm was used in which the memory retrieval of one intervention group was interfered by the adaptation to an opposing force field 'B'.

1.5 General methodology

This section introduces the general methodology for the investigation of electroencephalographic correlates of motor adaptation, which is used in this thesis. First, the experimental paradigm of force field adaptation is described in detail. In the second part of this section, the technical mechanism of EEG is broadly introduced and the basic steps in signal processing are described according to the literature.

1.5.1 Methodology of force field adaptation

Section 1.3.1 discussed the learning phenomenon of motor adaptation and showed that adaptation alters the kinematics or dynamics of movements. The experimental paradigm of force field adaptation is one prominent methodological approach to investigate the motor adaptation towards dynamic environmental changes. The force field adaptation paradigm was developed by Shadmehr and Mussa-Ivaldi (1994), who introduced dynamic changes of subjects' arm movements via force fields, which were induced by the motors of a robotic device. Such force fields can be programmed with different structures, directions, and parameters and lead to various kinds of perturbations. A commonly used force field in the scientific literature is a velocity-dependent curl force field (the magnitude of the perturbation depends on the velocity of the hand) which perturbs subjects' movements either in clockwise or counter-clockwise direction. Such velocity-dependent curl force fields were used in this thesis and Figure 1.4 depicts the two robotic devices which were used to induce these force fields.

In force field adaptation experiments, subjects sit at a robotic device and grab the handle of the manipulandum. In most experiments, subjects perform point-to-point reaching movements in the horizontal plane. To do so, subjects control a cursor on a screen via the robotic handle and perform hand-reaching movements to targets which are displayed on the screen. Under normal conditions (without force fields turned on), subjects are able to perform straight reaching movements with no big

Figure 1.4: Robotic Manipulanda of the BioMotion Center. **A** this picture shows the BioMotionBot (Bartenbach et al., 2013), a custom-made robotic device for motor adaptation research. **B** this picture shows the KinArm End-Point-Lab, a commercial robotic device by BKIN Technologies Ltd., Canada.

effort (Figure 1.5 A). However, when a velocity-dependent curl force field in clockwise direction is induced (Figure 1.5 B, left), subjects movements become perturbed (Figure 1.5 B, middle). Practicing several trials under the same force field condition leads to motor adaptation, which can be seen in almost straight trajectories (Figure 1.5 B, right). Please note that, although the trajectories are almost straight, the force field perturbation is still the same. Proof about this adaptation is given by so called aftereffects (Figure 1.5 C), which occur when subjects perform reaching movements under unperturbed, normal conditions after a former force field adaptation. These aftereffects are characterized by trajectories showing perturbations in the opposite direction compared to the trajectories of the initial force field movements. These aftereffects reveal that straight trajectories under force field conditions are facilitated by motor adaptation and not by a simple muscle co-contraction strategy in which subjects contract all arm muscles and, thus, reduce the degrees of freedom (Thoroughman and Shadmehr, 1999).

Motor adaptation to force field conditions represents a long-term memory. This is supported by several studies showing reduced deviations of trajectories when subjects experienced the same force field again, after a consolidation period of several hours (e.g. Brashers-Krug et al., 1996; Shadmehr and Holcomb, 1997). However, it is possible to inhibit the memory retention of the previous learned force field (A) by practicing an opposing force field (B) afterwards (Focke et al., 2013; Shadmehr and Brashers-Krug, 1997). This opposing force field 'B' is similar to 'A' in its magnitude and structure but different in its dircetions (clockwise vs. counter-clockwise). From a theoretical point of view, it is assumed that such an inhibition can only take

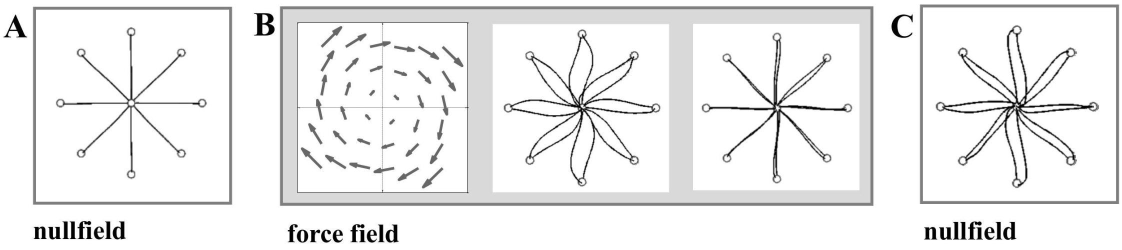

Figure 1.5: Adaptation progress in force field adaptation. **A** shows straight trajectories under normal conditions (no forces). **B** shows a curl force field in clockwise direction (left) and deviated reaching trajectories due to this force field perturbation (middle). With trials, subjects adapt to the perturbation and regain almost straight trajectories (right). **C** when subjects perform movements under normal conditions again, after force field adaptation, aftereffects can be observed.

place when the motor memory is not consolidated. Therefore, this so called ABA paradigm is used to test how much time it takes for the adapted motor memory to be consolidated and, thus, to be resistant against interference (Shadmehr and Holcomb, 1997). The results on this topic are inconsistent. On the one hand, it is shown that consolidation takes at least 5 h until it's completion (Shadmehr and Holcomb, 1997) but these finding were not reproduced by others, who showed that even 24 h after encoding, memory representations can be interfered (Caithness, 2004; Focke et al., 2013). This led to a more recent view that not time alone but practice influences motor memory consolidation (Overduin et al., 2006; Stockinger et al., 2014).

Altogether, force field adaptation reflects a powerful experimental paradigm to investigate motor adaptation. The literature goes back to 1994 and, since then, there is a growing research community pushing motor adaptation research forward. However, despite the vast literature on motor adaptation, some findings are inconsistent and the underlying mechanisms of motor adaptation are still not completely understood.

1.5.2 Methodology of EEG recordings

Functionality of EEG

EEG was invented by Hans Berger in the early 20th century (Berger, 1929) and records the electrical fields of neural activity on the surface of the head. This is possible because synchronized firings of populations of neurons accumulate their electric fields. For this accumulation it is important that the neurons are aligned in the same direction and perpendicular to the surface. These electrical fields can travel through the brain, cerebrospinal fluid, skull, and scalp to the surface due to volume conduction. With this travel, the electrical field is transformed and

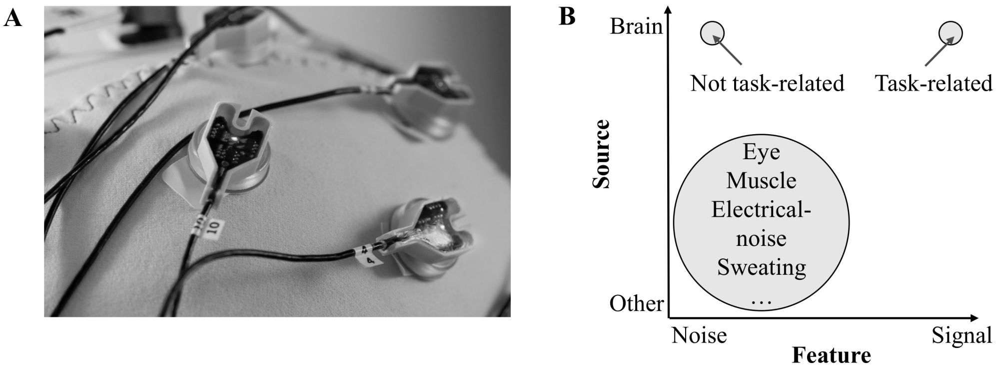

Figure 1.6: EEG electrodes and signal features. **A** shows active EEG electrodes (Brain Products GmbH, Gilching, Germany) mounted on a cap which is commonly used for recordings. **B** simplifies the signal-to-noise ratio in EEG. Sizes of the circles indicate signals' amplitude in EEG. Researchers are mostly interested in task-related EEG signals (at the top-right) but this signal is superimposed by other signals which are of bigger value.

attenuated. Therefore, EEG electrodes can only record summarized neural firings of neurons aligned in a specific direction and which are located quite close to the surface. That is why EEG is limited in the recordings of deeper, sub-cortical neural activity. Furthermore, the mechanisms described above show that EEG is limited in its spatial resolution which can be partially compensated by newer high-density EEG systems with up to 256 electrodes and source reconstruction. Figure 1.6 A shows the active EEG electrodes which were used in this thesis.

Arriving at the surface, electrical fields are of low amplitude, usually in the range of some microvolts (Nunez and Srinivasan, 2006). This leads to the signal-to-noise problem of EEG recordings. Artifacts like line noise, eye movements, or muscle artifacts are recorded with EEG and reach quite easily into the millivolt scale (Figure 1.6 B). Therefore, highly standardized recordings are necessary to avoid or reduce these artifacts and facilitate recordings of signals which are as clean as possible. The fact that EEG recordings will always be affected by artifacts and brain signals, which are not the primary interest of the specific experiment, leads to several steps in the preprocessing, in order to increase the signal-to-noise ratio. Traditionally, this includes filtering, detection of bad trials and channels, re-referencing, principal or independent component analysis, and averaging over several trials or time bins. Preprocessing is customized according to the specific parameters which should be computed and according to the specific conditions of the experiment and recording. Thus, an adequate implementation of these preprocessing steps can increase the data quality and is highly recommended.

It is widely assumed that the wave forms and oscillations, which can be seen in EEG recordings, have their origins in local field potentials (LFPs) in the brain. These LFPs, in turn, are generated by spiking activity of the neurons (Lopes da Silva, 2013). This serves as the basis to investigate frequency oscillations in the EEG, which are thought to be the prime mechanism of brain functions. The idea of specific frequency oscillations facilitating brain functions, is quite old and several scientists agreed with this view (e.g. Berger, 1929; Fries, 2009; Llinás, 2001; Singer, 2001). In EEG recordings, this led to the distinction of different frequency bands which are assumed to be involved in different brain functions: infraslow (<0.2 Hz), delta (0.2 - 3.5 Hz), theta (4-7 Hz), alpha (8-13 Hz), beta (14-30 Hz), gamma (30-90 Hz), and high-frequency oscillations (>90 Hz). The investigation of the power within these frequency bands led to several suggestions how frequency band power is connected to different brain functions (Klimesch, 1999, 2012; Pfurtscheller and Lopes, 1999). These interpretations of band powers will be discussed in more detail in the specific studies of Chapters 2, 3, and 4.

Advantages and disadvantages of EEG recordings

Possible neural correlates of motor adaptation have been investigated several times using positron emission tomography (PET; e.g. Krebs et al., 1998), functional magnetic resonance imaging (fMRI; e.g. Diedrichsen, 2005), magnetoencephalography (MEG; e.g. Bradberry et al., 2009), or non-invasive brain stimulation (e.g. Galea et al., 2011). Neural correlates of motor adaptation to dynamic perturbations are less investigated and, furthermore, studies using EEG in this context are extremely rare.

EEG brings advantages and disadvantages. Some typical limitations of EEG might explain the sparse use of this method in former motor adaptation studies. For instance, EEG only records brain signals of the cortex and is not able to detect signals of deeper brain sources. In addition, spatial resolution is further reduced by the limited source localization of the recorded signals. Although high density EEG and advanced source reconstruction can account at least to some extent for this inverse problem of EEG, spatial resolution is not comparable to fMRI.

None the less, EEG also brings clear benefits which are of advantage especially in the studies of motor adaptation. For instance, EEG facilitates the direct recording of neural activity with high temporal resolution (recent EEG systems are able to record with up to 4 kHz), which is a clear benefit for the examination of motor adaptation as movements occur within a short time frame. This comes in handy with the mobility of the EEG system which can be used in almost every lab and is quite comfortable for the subjects. Furthermore, EEG bypasses the problem that most robotic devices are not MRI compatible. In addition, although movements induce movement artifacts and sometimes cable artifacts in EEG, these artifacts are not as dramatic as movements in fMRI.

Altogether, EEG serves as a tool to link ongoing processes on the behavioral level to the neural oscillations in the brain (Cohen, 2017). Regarding motor learning research in force field adaptation, the advantages exceed the disadvantages and, therefore, this thesis used EEG as the method of choice to investigate possible effects on the neural level.

Chapter 2

Consequences of unstable memory encoding

> *"The capacity to predict the outcome of future events [...] is, most likely, the ultimate and most common of all global brain functions."*
> — Rodolfo R. Llinás, *i of the vortex*

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Abstract

The motor learning literature shows an increased retest or transfer performance after practicing under unstable (random) conditions. This random practice effect (also known as contextual interference effect) is frequently investigated on the behavioral level and discussed in the context of mechanisms of the dorsolateral prefrontal cortex and increased cognitive efforts during movement planning. However, there is a lack of studies examining the random practice effect in motor adaptation tasks and, in general, the underlying neural processes of the random practice effect are not fully understood. We tested 24 right-handed human subjects performing a reaching task using a robotic manipulandum. Subjects learned to adapt either to a blocked or a random schedule of different force field perturbations while subjects' electroencephalography (EEG) was recorded. The behavioral results showed a distinct random practice effect in terms of a more stabilized retest performance of the random compared to the blocked practicing group. Further analyses showed that this effect correlates with changes in the alpha band power in electrodes over parietal areas. We conclude that the random practice effect in this study is facilitated by mechanisms within the parietal cortex during movement execution which might reflect online feedback mechanisms.

2.1 Introduction

It is widely accepted that practice under highly unstable conditions (random) compared to more stable (e.g. serial, blocked, or even constant) conditions enhances retest and transfer performance in motor sequencing tasks (Shea and Morgan, 1979; Wright et al., 2015). This random practice effect (also known as contextual interference effect) states that interference during practice is the reason for motor benefits, hence, high interference should lead to improved retention performances. This is frequently explained with the elaboration hypothesis (Magill and Hall, 1990) or reconstruction hypothesis (Lee and Magill, 1983), describing either the effect of a parallel (elaboration) or an alternating (reconstruction) motor planning of the different task conditions on motor memory consolidation (stabilization of memory over time). Nevertheless, both hypotheses have in common that retest motor benefits are explained by higher cognitive efforts during movement planning in the practice session (Kantak et al., 2010; Li and Wright, 2000). This leads to the questions if benefits of random practice truly depend on improved mechanisms of movement planning and, thus, on feedforward mechanisms and if these effects are limited to specific motor tasks or represent a general motor learning phenomenon.

It is widely accepted that movements are generated by explicit (aware) and implicit (unaware) components (Huberdeau et al., 2015; Taylor et al., 2014). Both components together enable the execution of complex motor behavior. Furthermore, if benefits of random practice are caused by cognitive effort during the planning period, it is possible that these benefits are caused by explicit but not implicit components (Kantak et al., 2010) and are processed within prefrontal brain areas (Robertson, 2009). This is in line with studies using repetitive transcranial magnetic stimulation (rTMS) showing that non-invasive brain stimulation of the dorsolateral prefrontal cortex (DLPFC) suppresses the benefit of random practice, whereas stimulation over the primary motor cortex (M1) attenuates retest performance after stable practice but not vice versa (Kantak et al., 2010). Studies using neuroimaging techniques revealed similar results showing an increased prefrontal and premotor activation when practicing under unstable conditions (Cross et al., 2007; Lin et al., 2013, 2011). Altogether, the authors of these studies conclude that memory consolidation after highly unstable practice relies on different cortical structures than consolidation after stable practice (Tanaka et al., 2010; Wright et al., 2015). This is explained by a greater involvement of prefrontal and premotor areas during movement planning (Kantak et al., 2010).

However, the above mentioned conclusion is only supported by studies which investigated the benefits of random practice by using skill and sequence learning tasks. Their observations of an increased prefrontal and premotor processing under random conditions are reasonable because these regions are strongly involved in these kinds of tasks (Lin et al., 2013; Pascual-Leone et al., 1996; Schwarb and Schumacher, 2009) and this involvement might increase under unstable task conditions. However, studies targeting at different motor tasks – in which prefrontal (Robertson, 2007) but not necessarily premotor (Hardwick et al., 2013) regions are less involved – are rare. One example would be a motor adaptation task in which subjects adapt their reaching movements to dynamic perturbations (Shadmehr and Mussa-Ivaldi, 1994) – an adaptation task which relies mainly on implicit processes (Shadmehr et al., 1998). Up to now, no study examined if the random practice effect also occurs in such a motor adaptation task and if so, whether this effect can be explained by the involvement of frontal brain regions during movement planning. An alternative explanation for a random practice effect in the motor adaptation task would be that the dynamic perturbations under random conditions are unpredictable and this uncertainty would force subjects to correct their movements during their movement execution. Such a correction would use sensory information and could be described as online feedback mechanisms (Braun et al., 2009; Dimitriou et al., 2013; Yousif and Diedrichsen, 2012). Therefore, random practice would lead to an increased integration of sensory feedback into the motor control system involving the implicit dorsal stream, which should rather affect the activity of the parietal than the prefrontal cortex

(Diedrichsen, 2005; Shadmehr and Krakauer, 2008), and improve the correction of movements during execution. It was recently shown that such a motor control system of reaching movements is located in the posterior parietal cortex of non-human primates (Rathelot et al., 2017).

The aim of this study was to investigate if mechanisms of motor planning or motor execution, can explain the random practice effect in a motor adaptation task. Electroencephalography (EEG) was used to gain deeper insights into the neural processes of the behavioral effect. Previous EEG studies investigating memory processes in general showed that lower and higher frequency bands (theta, alpha, higher gamma) over frontal and parietal areas are linked to memory (Canolty et al., 2006; Roux and Uhlhaas, 2014; Thürer et al., 2016). Therefore, we focused on these learning related lower and higher frequency bands in electrodes over frontal and parietal areas.

We hypothesized that a random compared to a blocked practice schedule leads to an enhanced motor memory consolidation in a dynamic motor adaptation task. Furthermore, if benefits of random practice are caused by motor execution rather than by motor planning mechanisms, this should lead to a stronger involvement of the parietal cortex during movement execution.

2.2 Materials and methods

2.2.1 Participants

We tested a total of 24 (age: 22 ± 2 years; 6 female) right-handed and healthy subjects. Handedness was assessed by the Edinburgh handedness inventory (Oldfield, 1971). All subjects provided written informed consent and had normal or corrected to normal vision. Subjects were naïve to the experimental task and the test-protocol. No subject was excluded from the analysis. The study was approved by the ethics committee of the Karlsruhe Institute of Technology.

2.2.2 Experimental apparatus and task

The experimental task was implemented by using a robotic manipulandum (Kinarm End-Point Lab, BKIN Technologies, Kingston, Canada; Figure 2.1 A) which can produce forces via a handle toward subjects' hands. Position and force at the handle of the manipulandum were recorded at a sampling rate of 1000 Hz.

Subjects were centrally positioned in front of the manipulandum and performed center-out reaching movements in the horizontal plane while grasping the handle of the manipulandum with their right hand. To prevent fatigue, subjects' forearm was

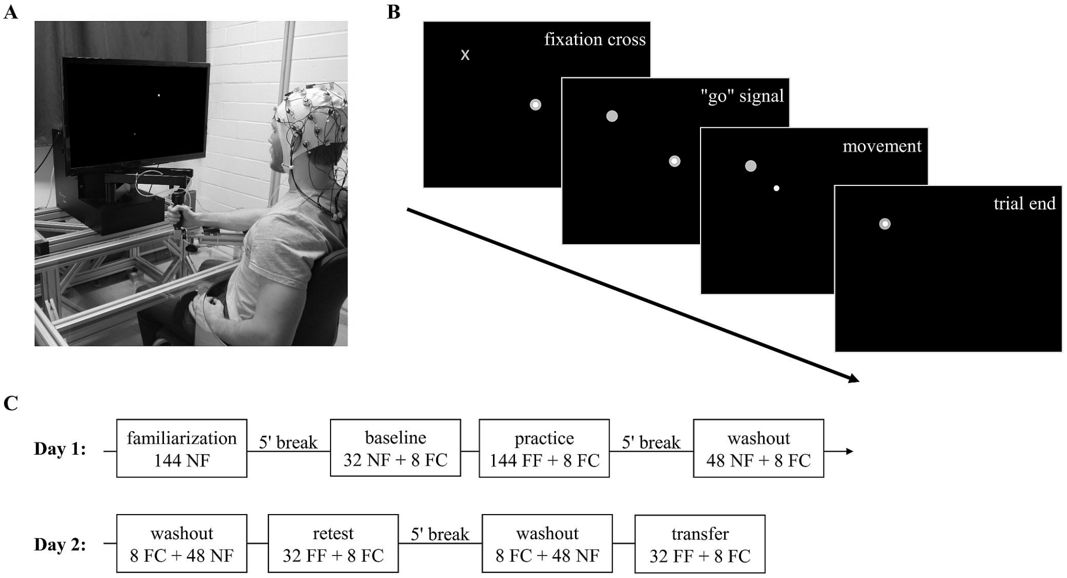

Figure 2.1: Experimental task and procedure. **A** Robotic manipulandum, air-sled system, and EEG. The participant gave permission to publish this Figure. **B** Example display for one trial. Highlighting of a fixation cross which gives the subsequent “go” signal by changing to target. After subjects moved the cursor via the handle and reached the target, the trial ended and the manipulandum guided subjects’ hand back to the center position (not shown). **C** Experimental procedure over the two consecutive days. NF: null field; FC: force channel; FF: force field.

supported by an air-sled system which enabled movements with very low friction (Figure 2.1 A). By handling the manipulandum, subjects controlled a cursor on a screen which was vertically located in front of the subjects. Every trial started by holding the cursor in the center target on the screen. After a fixed interval of 3.6 s, a fixation cross highlighted at the upcoming target position (Figure 2.1 B). Subjects were instructed to fixate their gaze on this cross but not to start their reaching movement. This fixation cross was randomly displayed for a period of 0.8 to 1.5 s and then changed its shape to a circular target. Highlighting of the target served as a “go” signal. Subjects were allowed to start their reaching movements without any pressure of time (no fast reaction times required). After reaching the target, the manipulandum actively guided subjects’ hands back to the center point and, thus, provided the beginning of the next trial to a different target. In total, eight targets were arranged on a circle with a diameter of 20 cm surrounding the center target. Target order was pseudo-randomized so that in every block (one block containing eight movements) every target highlighted just once. The target order was identical across groups.

To ensure similar movement times across trials and subjects, visual feedback about the movement duration was given during the whole experiment. The feedback was displayed after finishing each trial via the target color, which became blue if the movement was too fast (< 450 ms), red if it was too slow (> 550 ms), and green otherwise (Thürer et al., 2016).

We implemented three types of trials: null field trials, force field trials, and force channel trials. In null field trials, the motors of the manipulandum were turned off and subjects performed movements under unperturbed conditions. The robot's motors were turned on for the force field trials and produced a velocity-dependent curl force field in clockwise direction as follows:

$$\begin{bmatrix} F_x \\ F_y \end{bmatrix} = \begin{bmatrix} 0 & k \\ -k & 0 \end{bmatrix} \cdot \begin{bmatrix} \dot{x} \\ \dot{y} \end{bmatrix}$$

where F_x and F_y are the robot-generated forces, k is the force field viscosity with three different gradations ($k = 10$, 15, 20 Ns/m), and $\dot{x}$ and $\dot{y}$ represent the horizontal components of the hand velocity. Under such force field conditions, subjects' movements are perturbed. This typically results in an initially degraded motor performance stimulating motor learning processes (Shadmehr and Mussa-Ivaldi, 1994).

In force channel trials, the manipulandum produced a force channel from the start to the target point. Note that due to this force channel, subjects could only move directly towards the target and experienced no curl force field. This allowed the analysis of forces which subjects produced at the handle to counteract a previously learned force field task. Therefore, these forces provide a good estimation of subjects' force field prediction and allow the measurement of subjects' feedforward motor control (Scheidt et al., 2000; Stockinger et al., 2015). Subjects were not informed about the three different trial types.

Subsequent analyses of subjects' performances were done using the custom made software application ManipAnalysis (Stockinger et al., 2012). To quantify the motor performance of the subjects, we calculated the absolute maximum perpendicular distance (PDmax) between subjects' hand path and a straight line from start to target. This parameter reflects both, feedforward and feedback mechanisms. We computed the mean PDmax of the first (FT) and last (LT) 8 trials of the practice period and of the first 8 trials of the retest and transfer period (practice-FT, practice-LT, retest, transfer). In addition, we were interested in subjects' force field predictions captured using the force channel trials. In these trials, we calculated a force field compensation factor (FFcomp) by linear regression of the measured and the ideal perpendicular force profile (Joiner and Smith, 2008). As subjects do not receive error-feedback in the force channel trials, this parameter reflects mainly movement prediction by feedforward mechanisms. Clearly, we cannot rule out an additional contribution of other control mechanisms (impedance control, reflex modulation) when learning the force field. Finally, we calculated the average FFcomp over 8 consecutive force channel trials (one trial for each target direction).

2.2.3 Experimental procedure

Subjects were equally distributed in a blocked ($n = 12$; 3 female) and a random ($n = 12$, 3 female) group. The study took place on two consecutive days with 24 h between the two test sessions (Figure 2.1 C).

On day 1, subjects were instructed in the behavioral task and the EEG recordings. Both groups performed 144 familiarization trials under null field conditions with two breaks of 30 s after every 48th trial to ensure that all subjects were familiarized to the task, the manipulandum, and that all subjects show the same movement speed. After a five-minute break, all subjects made a baseline measurement which started with 32 null field trials and ended with 8 force channel trials. Then, subjects practiced for 144 force field trials which were divided in three parts of 48 trials with 30 s breaks between two parts. Subjects practiced the three force field gradations either in a blocked (gradation is kept constant over all trials of a part) or random (gradation changes for each trial) order with a mean force field viscosity of 15 Ns/m over the whole practice period. For the blocked group, this resulted in a Latin square design with six different gradation orders, each order practiced by two subjects. At the end of the practice period, all subjects performed 8 force channel trials. Afterwards, subjects had a five-minute break and performed 48 null field trials (washout) with 8 subsequent force channel trials.

On day 2, the experimental procedure was identical for both groups. First, subjects performed 8 force channel trials followed by 48 null field trials (washout). Then, all subjects performed a retest including 32 force field trials and 8 force channel trials. After another washout period of 48 trials, subjects performed 32 force field and 8 force channel trials under transfer conditions. This transfer test was identical to the retest but the manipulandum moved the subjects' hand to the outer targets and subjects performed their reaching movements inwards. Because the eight targets were equally distributed on a circle, the movement directions and the force did not differ between retest and transfer test. The only difference between the retest and transfer test was a spatial offset of 10 cm along the reaching direction. Force field viscosity for retest and transfer test was constantly set at the mean value of the practice period (15 Ns/m).

2.2.4 Electroencephalography

For electroencephalography, we used the actiCHamp system with 32 active-electrodes and the BrainVision PyCorder V1.0.6 (Brain Products, Gilching, Germany). The EEG was synchronized with the manipulandum using a direct link and the data was recorded with a sampling rate of 1000 Hz. A cap with 29 EEG electrodes was used and the electrodes were placed according to the international 10-10 system (Fp1, Fp2, F7, F3, Fz, F4, F8, FC5, FC1, FC2, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, TP10, O1, Oz, O2). In addition, we placed three electrodes below the outer canthi of the eyes and above the nasion to record subjects' eye movements (Schlögl et al., 2007). Electrode impedances were constantly kept below 10 kΩ. The reference electrode was placed at Cz, and electrodes were grounded to the location Fpz.

EEG data were analyzed offline using MATLAB R2015b (MathWorks Inc., Natick, USA) and EEGLAB 13.5.4b (Delorme and Makeig, 2004). Raw data were high-pass filtered using a FIR filter with a cut-off frequency of 0.5 Hz. To remove 50 Hz line noise, we used the cleanline plugin for EEGLAB. Then, the data was resampled to 250 Hz and an automatic subspace reconstruction (ASR) with a "BurstCriterion" of 20 was implemented to remove bad channels and correct for movement artifacts. This step removed on average 2.8 channels (SD: 1.1) in which mostly the EOG channels were affected but in over 60 % of the cases channel TP10 was also affected. Therefore, we removed channel TP10 from the whole analysis of all subjects to avoid subsequent influences on the independent component analysis (ICA). In a next step, electrodes were re-referenced to the average-reference and the signal of the channel location Cz was reconstructed and appended to the data. Then, EEG data was epoched to segments of 7 s ranging from 2 s before to 5 s after the highlighting of the fixation cross. Infomax ICA (Makeig et al., 1996) was performed with several iterations, each done on the principal components of the residual channels. In each iteration, a maximum of 3 components was removed if components showed distinct artifacts in the spatial, spectral, or temporal domain. On average, this procedure removed 8.4 components (SD: 3.2) of the data. Missing EEG channels due to ASR were re-calculated using spherical interpolation (except TP10).

To investigate subjects' time-frequency power, we used complex Morlet wavelet convolution for the frequency decomposition. Therefore, 30 frequencies from 2 to 90 Hz were calculated in logarithmical space with 3 to 16 wavelet cycles changing as a function of frequency. In a next step, we increased the signal-to-noise ratio by averaging across trials. For this purpose, we computed the percentage power across all trials of the practice period (practice-ALL), of the first and last 32 trials of the practice period (practice-FT, practice-LT), and of all 32 trials of the retest and transfer period. The percentage power shows if the power of a certain time-frequency bin in- or decreases according to a fixed reference period (Pfurtscheller and Lopes, 1999). To do so, we determined a fixed reference period from 500 ms before up to the highlighting of the fixation cross. Each time-frequency bin (averaged over trials) was subtracted and divided by the mean reference period and then multiplied by 100. According to our hypotheses, we constrained the percentage power in the time and frequency domain. In the frequency domain, motor learning processes are mostly associated with theta, alpha and gamma bands (Canolty et al., 2006; Gentili et al., 2011; Perfetti et al., 2011; Tombini et al., 2009). Especially theta and gamma bands are correlated with improvements in cognitive learning processes (Canolty et al., 2006) which makes these two frequency bands intriguing in terms of possible cognitive demands during movement planning. Therefore, we averaged the data into lower and higher frequency bands: theta (4-7 Hz), alpha (8-13 Hz), and gamma (60-80 Hz). In addition, we restricted the time domain of the percentage power to a planning (-0.4 s $< t <$ 0 s) and movement (0 s $< t <$ 0.4 s) window, where 0 s indicates movement onset.

2.2.5 Statistics

Regarding the motor performance, we were interested in group (random, blocked) differences and interaction between group (random, blocked) and time (practice-FT, practice-LT) in the adaptation during the practice period. In addition, we were interested in the random practice effect describing an enhanced motor memory consolidation indicated by the interaction between group (random, blocked) and time (practice-LT, retest; practice-LT, transfer). Therefore, statistical comparisons were done using independent t-tests and mixed model ANOVAs.

To investigate effects in the EEG, we used non-parametric permutation testing on the basis of clusters (Cohen, 2014) either across the group dimension using t-tests or across the group and time dimensions using mixed model ANOVAs. Therefore, we computed 2d topographical head plots of the planning and movement window for every frequency band (theta, alpha, gamma) and time period (practice-ALL, practice-LT, retest, transfer). According to the hypothesis that mechanisms of motor planning facilitate the benefits of random practice, we compared groups in the planning window of the practice period. Therefore, we performed a t-test for every pixel of the topographical plot between groups (random, blocked) and stored the t- and p-values. The resulting maps of p-values were then used to create clusters of pixels below the threshold of $p = 0.05$. The t-values within each cluster were aggregated and stored as the observed t-value per cluster. Then, we shuffled the data over the group dimension, re-performed a t-test per pixel and stored the t- and p-values. Once more, clusters were computed on the map of p-values as described for the observed data. The t-values within each cluster were aggregated and, now, only the maximum t-value over all clusters is stored. This step of shuffling and re-computing was repeated 10,000 times resulting in 10,000 permutated maximum t-values. The 95th percentile of the permutated maximum t-values was defined as the threshold for significant clusters. Thus, observed clusters were defined as statistical significant if the observed t-value exceeded this threshold.

These cluster-based statistics were also performed across the group and time dimensions to investigate the random practice effect in the planning and movement window. Therefore, for every pixel of the topographical plot we performed a mixed model ANOVA and stored the F- and p-values of the interaction between time (practice-LT, retest OR practice-LT, transfer) and group (random, blocked). The subsequent steps were similar to the cluster-based statistics across the group dimension besides that, now, the data was shuffled over all dimensions (Edgington and Onghena, 2007).

Finally, we performed Spearman's rank correlations between the behavioral and electrophysiological data. To do so, the difference of the PDmax and the FFcomp is computed for the retest and the last trials of the practice period (retest - practice-LT) as well as for the transfer and the last trials of the practice period (transfer - practice-LT). The same differences were computed for the ROIs alpha band power. Then, each correlation was performed between the difference on the behavioral level and the difference on the electrophysiological level.

For all statistical analyses, the level of significance was a priori set to $\alpha = 0.05$ and Greenhouse-Geisser correction was used if assumption of sphericity was violated. Correction for multiple comparisons was done using false discovery rate and effect sizes were determined using Cohen's d (Cohen, 1988) or partial eta squared η_p^2 (Cohen, 1988; Richardson, 2011). Statistical analyses were done using SPSS statistics 22 (IBM, Armonk, USA) and MATLAB R2015b (MathWorks Inc., Natick, USA).

2.3 Results

2.3.1 No group differences in the motor performance but in the variance during practice

As the blocked and random group performed different schedules of the force field gradations, we were interested in statistical comparisons regarding the motor performance during the practice period. Statistical results of the PDmax revealed a significant effect of time (first trials, last trials) showing that subjects improved their motor performance during practice ($F_{(1,22)} = 93.72$, $p < 0.001$, $\eta_p^2 = 0.81$). No significant group (random, blocked) differences were found indicating similar performances between groups (first trials: $t_{(22)} = 1.39$, $p = 0.179$, $d = 0.57$; last trials: $t_{(22)} = -0.67$, $p = 0.510$, $d = -0.27$). In addition, no significant interaction effects between group (random, blocked) and time (practice-FT, practice-LT) were observed ($F_{(1,22)} = 2.52$, $p = 0.127$, $\eta_p^2 = 0.10$). We also checked for differences between groups in their force field prediction by examining the FFcomp in the force channel trials at the end of the practice period. The results showed no significant differences indicating no differences in the force field prediction between groups ($t_{(22)} = 0.08$, $p = 0.447$, $d = 0.32$).

Furthermore, we performed independent t-tests between the variances of the motor performance (PDmax) between groups for the first, second, and third part of the practice period, each including 48 trials. The results showed a significant effect for the second ($t_{(22)} = -2.61$, $p = 0.016$, $d = -1.06$) but not for the first and last part after correction using FDR (first: $t_{(22)} = -0.39$, $p = 0.696$, $d = -0.16$; third: $t_{(22)} = -1.82$, $p = 0.083$, $d = -0.74$).

Summarized, both groups increased their motor performance during the practice period but no group or interaction effects were observed. However, we found an increased variance in the motor performance for the random compared to the blocked group during practice.

2.3.2 Random practice leads to enhanced retest performance

One of the hypotheses of this study was, that the random practice effect is detectable in a dynamic motor adaptation task. We investigated the PDmax and used a mixed model ANOVA with factors group (random, blocked) and time (practice-LT, retest). The results showed a significant time ($F_{(1,22)} = 74.30$, $p < 0.001$, $\eta_p^2 = 0.77$) but no significant group ($F_{(1,22)} = 0.73$, $p = 0.404$, $\eta_p^2 = 0.03$) effect. Moreover, the interaction effect was significant revealing a high effect size ($F_{(1,22)} = 4.82$, $p = 0.039$, $\eta_p^2 = 0.18$). This clearly shows that although both groups decreased their performances (increase of the PDmax) from the last trials of the practice period to the retest, the random practicing group tends more to a stabilization of the performance (Figure 2.2 A-B).

In a next step, we used mixed model ANOVA to test for a group*time effect comparing the FFcomp at the end of the practice period with the FFcomp at the very beginning of day 2 (first washout period on day 2) and detected no interaction effect ($F_{(1,22)} = 2.16$, $p = 0.156$, $\eta_p^2 = 0.08$). Thus, force field prediction does not explain the observed random practice effect (Figure 2.2 C).

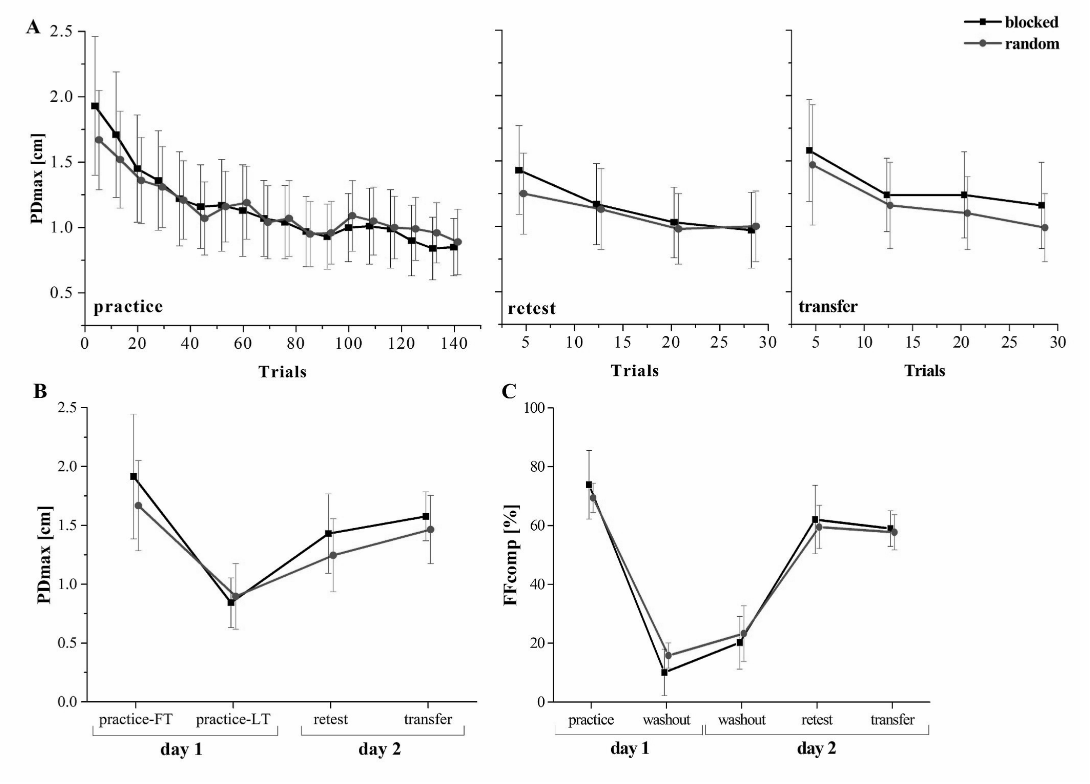

Figure 2.2: Progress of the motor performance over the two consecutive days. **A** Progress of the maximum perpendicular displacement (PDmax) between groups along the practice, retest and transfer tests. **B** PDmax between groups for specific blocks in the experiment. **C** Results of the force field compensation factor (FFcomp) between groups over the entire experiment (Mean ± CI_{95}). FT: first trials; LT: last trials.

It was shown that random practice can also enhance the performance in a transfer test. Therefore, we used the PDmax to perform a mixed model ANOVA with the factors group (random, blocked) and time (practice-LT, transfer). The results showed no interaction effect ($F_{(1,22)} = 1.36$, $p = 0.257$, $\eta_p^2 = 0.05$) and, thus, similar performances between groups over time (practice to transfer).

In summary, our behavioral data show that both groups decreased their performances from practice-LT to retest but this decrease was significantly smaller for the random group which shows the random practice effect. However, this effect is not explainable by increased force field prediction and, thus, feedforward mechanisms.

2.3.3 Changes in the alpha band power coincide with the random practice effect

To deal with high dimensionality of EEG data, we used cluster-based permutation tests and corrected using a maximum statistic. Statistics of the planning window during practice failed to show significant group differences in any of the analyzed frequency bands. The cluster-based statistics of the planning window testing for a group (random, blocked) and time (practice-LT, retest; practice-LT, transfer) interaction effect also did not show significant results. Thus, statistics during the planning window cannot explain the random practice effect on the behavioral level.

Similarly, cluster-based statistics regarding the movement window showed no significant clusters regarding group differences during practice. However, statistics showed significant clusters in the alpha and gamma bands testing for interaction effects with the factors group (random, blocked) and time (practice-LT, retest; Figure 2.3 A, B). No significant clusters were observed in the theta band and no significant clusters were observed comparing for a possible transfer effect (time: practice-LT, transfer; Figure 2.3 A). This shows that the random practice effect which we observed on the behavioral level coincides with percentage power changes in electrodes over the parietal cortex (alpha) and temporal cortex (gamma). Regarding the gamma band, results have to be interpreted with great caution as the statistical results are comparably weak and reflect partly the interpolated activity of the outermost electrodes. In a next step, we built a region of interest (ROI) according to the significant cluster in the alpha band (CP1, P3, PZ) and examined the time-frequency plots of the percentage power between groups (Figure 2.3 C). Time-frequency plots of this ROI showed a decreased alpha band power for blocked and random groups in the practice-LT period. This decreased alpha band power was also present in the retest period but much weaker for the random group. This effect was also confirmed by the progress of the alpha band power for the ROI during the whole experiment (Figure 2.3 D) which showed a significant interaction effect between group and time

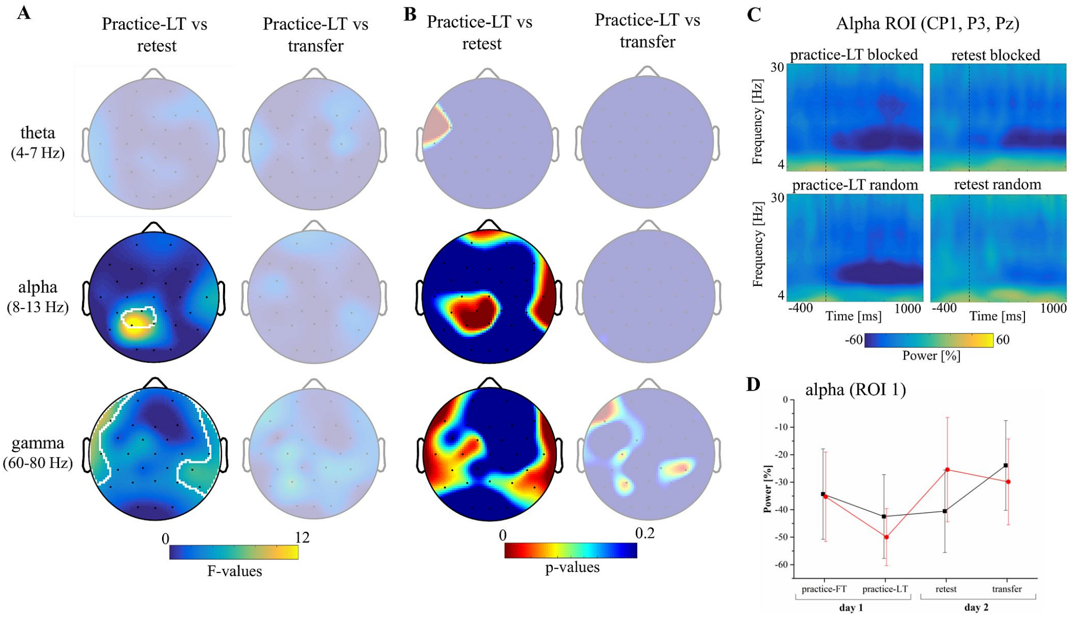

Figure 2.3: Results of the EEG data. **A** topographical plots show the F-values of the cluster-based statistic regarding an interaction effect (group*time) in the movement window for the theta, alpha and gamma frequency bands. Columns show interaction statistics between practice-FT and retest (left) and between practice-FT and transfer (right). Significant clusters, corrected for multiple comparisons, are circled by white pixels. **B** topographical plots of the p-values of the cluster-based statistic. **C** time-frequency plots display the average alpha (ROI 1: CP1, P3, PZ) band power during the practice-LT and retest periods from 400 ms before to 1000 ms after movement onset (dashed vertical lines indicate movement onset). **D** progress of the alpha band power during movement execution over the whole experiment for both groups (Mean ± CI_{95}).

with a high effect size ($F_{(1,22)} = 12.03$, $p = 0.002$, $\eta_p^2 = 0.35$).

In summary, random and blocked groups showed similar alpha power values at the beginning of the practice period but at the end of the practice period, alpha power of the random group showed a stronger decrease in power. However, the random group showed a distinct increase in alpha power from practice-LT to retest whereas alpha power in the blocked group stayed constant.

2.3.4 Changes on the behavioral level correlate negatively with changes in the alpha band

The above-mentioned results are obtained by statistical comparisons either on the behavioral or on the electrophysiological level. To investigate if there is a relationship

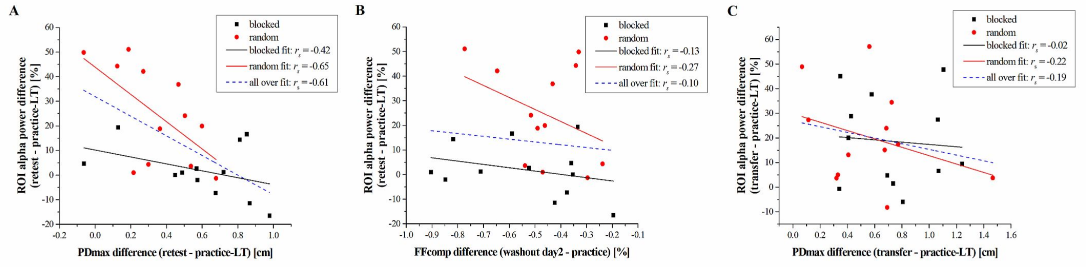

Figure 2.4: Results of the correlation analyses. **A** correlation between the difference of the alpha band power (retest - practice-LT) and the PDmax (retest - practice-LT) for the blocked (black squares) and random (red circles) group. Linear fits are represented by black-solid (blocked), red-solid (random), and blue-dashed (blocked + random) lines. **B** correlation between the difference of the alpha band power (retest - practice-LT) and the FFcomp (washout day2 - practice) for the blocked and random group. **C** correlation between the difference of the alpha band power (transfer - practice-LT) and the PDmax (transfer - practice-LT) for the blocked and random group.

between these results on the subject level, we used spearman correlation analyses between the alpha band power of the ROI and the PDmax or the FFcomp. The differences of these parameters between task periods (retest - practice-LT; transfer - practice-LT) were computed to take the performance change into account. Results across both groups show a significant negative correlation between the alpha band power difference and the PDmax difference from practice to the retest period (r_s = -0.61, p = 0.002; Figure 2.4 A). This negative correlation coefficient decreases even more when taking only the random-practicing subjects into account, although it does not reveal significance after correction for multiple comparisons using FDR (r_s = -0.65, p = 0.026; Figure 2.4 A) due to the reduced sample size. For the blocked group, the correlation coefficient was higher indicating no correlation between the alpha band power difference and the PDmax difference for the blocked group (r_s = -0.42, p = 0.177; Figure 2.4 A). In contrast, no significant correlations are found for the FFcomp (across both groups: r_s = -0.10, p = 0.626; random group: r_s = -0.27, p = 0.404; blocked group: r_s = -0.13, p = 0.683; Figure 2.4 B) and for the transfer period (across both groups: r_s = -0.19, p = 0.378; random group: r_s = -0.22, p = 0.499; blocked group: r_s = -0.02, p = 0.956; Figure 2.4 C).

Summarized, EEG data showed a distinct group*time interaction in the alpha band. This alpha band effect correlates with the performance changes, measured by PDmax, on the behavioral level.

2.4 Discussion

The aim of this study was to investigate if the random practice effect is either facilitated by mechanisms of motor planning or motor execution. We used a dynamic motor adaptation task to quantify the random practice effect on the behavioral level and EEG to identify the underlying neural correlates. The behavioral results confirmed our hypothesis that random practice enhances motor memory consolidation in a motor adaptation task. All results support our hypothesis that the motor benefit is rather caused by motor execution than by motor planning mechanisms.

2.4.1 The random practice effect in a motor adaptation task relies on mechanisms during movement execution

The behavioral data show that practice under random conditions tends to an increased memory consolidation compared to blocked practice conditions. This is in line with the literature (Shea and Morgan, 1979; Wright et al., 2015) and shows that random practice leads to motor benefits even in a motor adaptation task with dynamic perturbations.

We observed the random practice effect in the PDmax, which reflects both feedforward and feedback control, but not in the FFcomp, which reflects mostly feedforward control. This shows that the random practice effect in our data is not caused by a more pronounced improvement in the force field prediction. Previous work showed that subjects adapt to the approximate mean of the task dynamics when they are exposed to unpredictable dynamic conditions (Scheidt et al., 2001). In that way, as the force field viscosity mean value across all subjects and within each group was 15 Ns/m, similar force field predictions between groups at the end of the practice period and at the retests concur with the literature. However, this force field prediction cannot entirely counteract the dynamic uncertainty during movement execution under random force field conditions. Therefore, subjects of the random group must have used either some sort of control strategy (impedance control or reflexive modulation) or online feedback mechanisms to perform similar to the subjects of the blocked group (Franklin et al., 2012; Stockinger et al., 2014). Usage of an impedance strategy would lead to a minor variability in the PDmax and to a decreased reliance on force field prediction in the random group. However, since we did find an increased motor variability for the random group in the second part of the practice period and did not observe any differences in the force field prediction, the usage of online feedback mechanisms is more likely.

The assumption that online feedback mechanisms corrected during movement execution is also supported by the results of the EEG data. Results of the EEG-data failed to find significant differences between groups or a significant interaction effect during movement planning. However, EEG data showed a similar interaction effect in the alpha band power in electrodes over parietal areas during movement execution as for the behavioral data. It should be noted, that this effect also occurred when only 8 trials (like for the behavioral effect) were taken for the analyses (results not shown here). The parietal cortex is a main control center for sensory feedback in the brain. Upstreaming sensory information is filtered and forwarded by the thalamus and reaches the parietal cortex where the relevant information for movement control goes along the dorsal stream and the relevant information for semantic knowledge goes along the ventral stream (Gardner and Johnson, 2013). The coincidence between the random practice effect and the alpha band power indicates such an increased feedback mechanism. This is in line with previous work showing changes in the parietal cortex activity when subjects adapted their reaching movements during movement execution to random target positions or kinematic conditions (Desmurget et al., 1999; Diedrichsen, 2005). Therefore, we suggest that in a dynamic motor adaptation task subjects of the random group are required to rely on online feedback mechanisms more than subjects of the blocked group.

2.4.2 Random practice seems to reflect a general learning phenomenon

Up to now, the literature on the random practice effect mostly used tasks which rely on a strong explicit component (e.g. Battig, 1972; Kantak et al., 2010; Shea and Morgan, 1979). Especially in the motor domain, previous work used skill acquisition tasks (e.g. sequencing task, sinusoid tracing, serial reaction time task) for which it is quite reasonable that random practice shows an increased involvement of prefrontal and premotor areas. As far as we know, only one study (Kim et al., 2015) used a motor adaptation task instead of a skill acquisition task to investigate the effect of random practice on retest. The amount of explicit control should be weaker in such a motor adaptation task, especially using dynamic perturbations (Shadmehr et al., 1998) and, thus, random practice should rather lead to an increased involvement of parietal than prefrontal areas as shown for uncertain kinematic conditions (Diedrichsen, 2005). Therefore, it is reasonable that we found a decreased alpha band power in random compared to blocked groups at the end of the practice period which increased from the practice to the retest condition for the random group but remained constant for the blocked group. These results show that the random practice effect is not specific to a distinct motor task. This is also supported in a study by Debarnot et al. (2015) showing a positive benefit of random practice in motor imagery. This is intriguing as different motor tasks lead to partly different cortical activation patterns but to the same behavioral effect, which is an increased performance after unstable practice. Therefore, it is more likely that the benefit of random practice reflects a general learning phenomenon.

However, there are several studies which did not observe a benefit of random practice and contradict the hypothesis of a general learning phenomenon (e.g. Brady, 1997; Jarus et al., 1997). This could be explained by the generally weak effect of random practice (Battig, 1979).

2.4.3 Decreased alpha band power in parietal electrodes might reveal increased parietal processing

The EEG literature states that an increase of alpha band power reflects an active inhibition of the specific cortical region (Klimesch, 2012; Pfurtscheller, 2006) leading to weak contributions of this region to the current execution of a task. Therefore, the reverse of an increased alpha band power reflects a reduced inhibition of the region so that this region is contributing to the task execution. Using this hypothesis, our EEG data indicate that the parietal cortex is contributing to the motor adaptation task in random and blocked groups. However, the random group shows a slightly more decreased alpha band power at the end of the practice period which concurs with a previous study showing increased hemodynamic responses during interleaved practice (Lin et al., 2011). Despite the decreased alpha band power during practice, the random groups showed an increased alpha power in the retest condition. This observation indicates that the contribution of the parietal cortex decreases from the end of the practice period to the retest whereas it remains constant for the blocked group. This effect is somewhat contradictory to the behavioral data. Assuming a direct link between an increased task contribution of the parietal cortex with increased online feedback mechanisms would indicate that the random group performs better in the retest condition despite reduced online feedback mechanisms. As a direct link between alpha power of the parietal cortex and online feedback mechanisms is quite speculative, future work using neuroimaging techniques is needed.

2.4.4 Parietal alpha band power is negatively correlated with the motor performance

The correlation coefficient show that our results in the alpha band power over contralateral and parietal electrodes are connected to the motor performance. Therefore, the observed effect in the alpha band does not reflect just a coincidence. The correlations were performed on differences between task periods. As all subjects increased their motor performance during the practice session, low differences between task periods reflect a more stabilized performance whereas high differences reflect performance loss. Therefore, the observed negative correlation coefficient indicates that a stabilized motor memory is accompanied by an increase of alpha band power from practice to retest. Independent correlation analyses for each group showed an even more decreased correlation coefficient for the random group compared to the blocked group. However, the reduction of the correlation coefficient accompanied with an increased p-value indicates that this test with only 12 subjects was underpowered.

However, it is not clear if the alpha band power of the parietal cortex is directly involved in the execution or correction of reaching movements or if it represents indirect influences which also could lead to the observed correlation.

2.4.5 Limitations and conclusion

The observed behavioral effects in the PDmax are only observed for the first trials of the retest period. Therefore, the positive effect of random practice in the dynamic adaptation task does not reflect a long term retest benefit. A specific warm-up could lead to similar performances between blocked and random practicing groups.

One could argue that the effect on the behavioral level is quite low because of the low p-value ($p = 0.039$). However, the effect size ($\eta_p^2 = 0.18$) is quite high which suggests that the amount of 24 subjects was too low and, thus, the study was underpowered.

Although the literature states the FFcomp as a measure of feedforward mechanisms, we cannot rule out that other control mechanisms slightly effected the results (impedance control, reflex modulations). Therefore, we cannot entirely rule out that random practice leads to a positive effect due to changes in impedance or feedforward control.

It is not clear if the effect on the behavioral level is facilitated by an increased memory retrieval due to random practice or by a decreased memory retrieval due to blocked practice. The latter could be explained by retroactive inhibition which might influence the retest performance of the blocked practicing subjects negatively. Retroactive inhibition describes the inhibition of memory by the acquisition of a new competing memory (Robertson et al., 2004). According to a blocked practice schedule, it is possible that the acquisition of a new task, or in our case of a new force field gradation, inhibits at least partially the previously learned task (Shewokis et al., 1998). From a theoretical point of view, if this is true, blocked practicing subjects will only be able to recall the last practiced task condition – the other task conditions will be inhibited (at least partially). This would lead to a decreased mean but increased variance in the retest motor performance of the blocked compared to the random group. As this phenomenon of retroactive inhibition is not restricted to dynamic motor adaptation tasks, it is not clear if previous work in the literature is also affected by retroactive inhibition. We are not able to rule this effect out and, therefore, this influence of retrograde inhibition should be carefully considered in future studies which try to compare blocked and random practice schedules.

This work shows a positive effect of random practice in a dynamic motor adaptation task. Furthermore, this improved motor memory consolidation after random practice seems to be facilitated by mechanisms during movement execution and not by motor planning mechanisms. We assume that online feedback mechanisms during movement execution contribute to this phenomenon. The observed effects on the behavioral level are correlated with the alpha band power over parietal regions, suggesting that sensory processes play an important role. Altogether, this study indicates that the random practice effect reflects a task independent general learning phenomenon.

Chapter 3

Sleep and motor memory consolidation

”I love sleep. My life has the tendency to fall apart when I’m awake, you know?”
— Ernest Hemingway

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Abstract

Motor memory is an important learning feature. How its consolidation depends on sleep is still unsolved. Some motor tasks were previously shown to depend on sleep to some extent, whereas pure non-hippocampal dependent motor tasks, like motor adaptation, might not. However, recent research suggests that training schedules might affect the sleep dependency of motor adaptation tasks. This study investigated whether sleep differentially impacts memory consolidation on a motor adaptation task dependent on the training schedule. Healthy men were trained with their dominant right hand on a force field adaptation task and re-tested after an 11-h consolidation period either involving overnight sleep (Sleep group) or daytime wakefulness (Wake group). The Retest session comprised a Posttest and a Transfer test to the left hand. Half of the subjects in each group trained the adaptation to different force field magnitudes in a blocked schedule with low inter-trial variability (Sleep-Blocked; Wake-Blocked), the other half in a random schedule with high variability (Sleep-Random; Wake-Random). EEG records during task performance and overnight polysomnography was obtained. Consistent with the notion that sleep generally does not benefit motor adaptation, memory performance did not differ between Wake and Sleep groups, although Posttest performance specifically correlated with sleep spindles nesting in slow wave upstates. Increased, inter-trial variability at Training produced better performance at the Posttest and Transfer test. This improvement appeared to result from the participants' increased ability to use feedback for ongoing movement corrections, and correlated with EEG alpha power over the left parietal cortex during the task.

Significance statement

This study confirms that consolidation of motor adaptation and generalization to the non-dominant hand benefits from training with higher trial-to-trial variability. The consolidation success was independent of sleep, even if training was scheduled with different amounts of variability. Consolidation benefits of variable training were linked to effective feedback corrections during the ongoing movement and correlated with synchronous activity in the parietal cortex of the trained hemisphere.

3.1 Introduction

The influence of post-learning sleep on motor memory consolidation has been frequently investigated (King et al., 2017). However, the literature shows an inconsistent picture with studies supporting (e.g. Albouy et al., 2013; Fischer et al., 2002; Plihal and Born, 1997) and not supporting (e.g. Donchin et al., 2002; Rickard et al., 2008) sleep dependent motor memory consolidation. Many studies, hence, point to a more complex relationship between specific factors of motor tasks and sleep (Adi-Japha and Karni, 2016), but also see Rickard and Pan (2017). In a recent qualitative literature review, King et al. (2017) identified that motor benefits or stabilizations due to sleep can be seen in explicit sequence learning tasks, specific variants of implicit sequence learning tasks, and specific visuomotor adaptation tasks, with all of these tasks involving hippocampal function to a certain extent. On the other side, it has been suggested that specific non-hippocampal-mediated tasks, like motor adaptation to dynamic perturbations (e.g. force field adaptation; Shadmehr and Mussa-Ivaldi, 1994), reflect a motor memory process that is purely time- but not sleep-dependent (Donchin et al., 2002), although those results, to the best of our knowledge, have not been confirmed so far.

Beyond sleep's dependency on specific task aspects, the effects might also depend on the specific training schedule. Several studies showed that motor training under highly unstable conditions, compared to more stable conditions, enhances posttest and transfer performance, suggesting that depending on the training schedule different memory systems are involved (e.g. Lage et al., 2015; Magill and Hall, 1990; Shea and Morgan, 1979). Furthermore, it has been assumed that specifically benefits after variable training depend on sleep (King et al., 2017). This assumption is derived from a study investigating imaginary training which showed that variable but not constant mental training of a motor task leads to sleep dependent memory improvements (Debarnot et al., 2015). Moreover, other studies revealed that hippocampal dependency of a motor task changes with the schedule and the amount of training (Dick et al., 2003; Martel et al., 2007; Merbah and Meulemans, 2011).

In this study, we assessed the effects of sleep on memory for a force field adaptation task. Specifically, we were interested whether effects of sleep might express depending on the variability of different force fields used during training. For this purpose, subjects were examined either in more stable or highly unstable training conditions, and retested after periods of sleep or wakefulness with the same arm. Since previous work from our lab showed sleep dependent consolidation effects for contralateral transfer (Witt et al., 2010), we also examined transfer performance on the contralateral hand. We recorded EEG correlates during training, intervening sleep, and during retest, and also aimed to characterize the role of online feedback mechanisms in mediating improvements during movement execution.

3.2 Materials and methods

3.2.1 Participants

Forty-eight healthy, male participants recruited from the local university campus were included in the study (age 24.27 ± 0.45 yrs.). All participants were native German speakers with normal or corrected to normal vision and were tested for right-handedness by the Edinburgh handedness inventory (Oldfield, 1971). They reported not to nap habitually or have any sleep disorders and did not take any medication at the time of the experiments. Participants followed a normal sleep–wake rhythm and reported no night shifts during the 6 weeks before the experiment. Participants were instructed to keep a regular sleep schedule, abstain from caffeine- and alcohol-containing drinks for at least 2 days before and on the days of the experiments. Experimental task and task-protocol were new to the participants. All participants provided written informed consent and the study was approved by the ethics committees of the Karlsruhe Institute of Technology and the University of Tübingen.

3.2.2 Apparatus and motor adaptation task

Apparatus and task stem from a previous study (see Thürer et al., 2017, for a detailed description). Participants performed point-to-point reaching movements at a robotic manipulandum (Kinarm End-Point Lab, BKIN Technologies, Kingston, Canada; Figure 3.1 A). The manipulandum sampled position of the handle and forces exerted on the handle at 1000 Hz. Participants' grasped the handle and their forearm was supported by an air-sled system which enabled low friction movements. The task goal was to move a cursor on a screen – controlled via the robot handle – into a target circle (Figure 3.1 B). To prevent movement anticipation, each trial started with a fixation cross and the highlight-duration of this fixation cross varied randomly between 0.8 and 1.5 s. When the fixation cross changed its shape to a target circle, subjects were allowed to start their movement (no fast reaction times were required). After reaching the target, the manipulandum actively guided subjects' hands back to the center point and provided the beginning of the next trial. In total, six targets were arranged on a circle with a diameter of 20 cm surrounding the center target. The target order was pseudo-randomized so that in every block (containing 6 movements) every target highlighted just once. In addition, within each group the target order was different for every single subject so that the mean target direction and the mean force field magnitude across all subjects was identical of each specific trial.

The manipulandum can produce forces via the handle towards subjects' hands. In this study, we implemented three types of trials. In null field trials, no forces were produced and subjects performed movements under unperturbed conditions. In force field trials, the motors of the manipulandum were turned on and produced a velocity-dependent curl force field in clockwise direction with three different viscosity magnitudes of 10, 15, and 20 Ns/m. In force channel trials, the manipulandum produced a virtual force channel from start to target so that the subjects were only able to move along this path directly into the target (Figure 3.1 C). In every single trial, visual feedback about the movement time was given to ensure similar movement times across trials and subjects (< 450 ms: too slow; > 550 ms: too fast).

Offline calculations of dependent variables on the behavioral level were performed using MATLAB R2015b (MathWorks Inc., Natick, MA, United States). For null field and force field trials, we computed the motor error by using the enclosed area (EA) between subjects' hand path and the vector joining start and target (Figure 3.1 C, left). This parameter was averaged over 30 trials for the Baseline, First Training Trials, Last Training Trials, Posttest, and Transfer. To quantify motor performance in force channel trials, we calculated a force field compensation factor (FFCF; Figure 3.1 C, right) by means of the linear regression of the measured and the ideal perpendicular force profile (Joiner and Smith, 2008) and averaged this across each 6 force channel trials. As subjects do not receive error-feedback in these trials, this parameter reflects mainly movement prediction and, thus, feedforward mechanisms (Scheidt et al., 2000). From now on, the term motor error will refer to the enclosed area and the term motor prediction will refer to the force field compensation factor.

3.2.3 Design and procedures

This study compares the effects of random (unstable) vs. blocked (stable) training on motor adaptation and consolidation processes during wake vs. sleep. In a between-groups design, participants were randomly assigned to four equal sized groups ($n = 12$) of comparable age (range 18–30 yrs; $p > 0.45$, for one-way ANOVA between groups) with altered training conditions and retention periods taken place either in the night or during the day. All participants trained with their dominant right hand the motor adaptation task. The task was either trained in a random trial sequence (Random group) or in three randomized blocks, each containing a consistent field magnitude (Blocked group). Participants trained either in the morning (9 am; Figure 1D) and were retested in the evening (8 pm; Wake-Random, WR; Wake-Blocked, WB) or, vice versa, trained in the evening and were retested the following morning

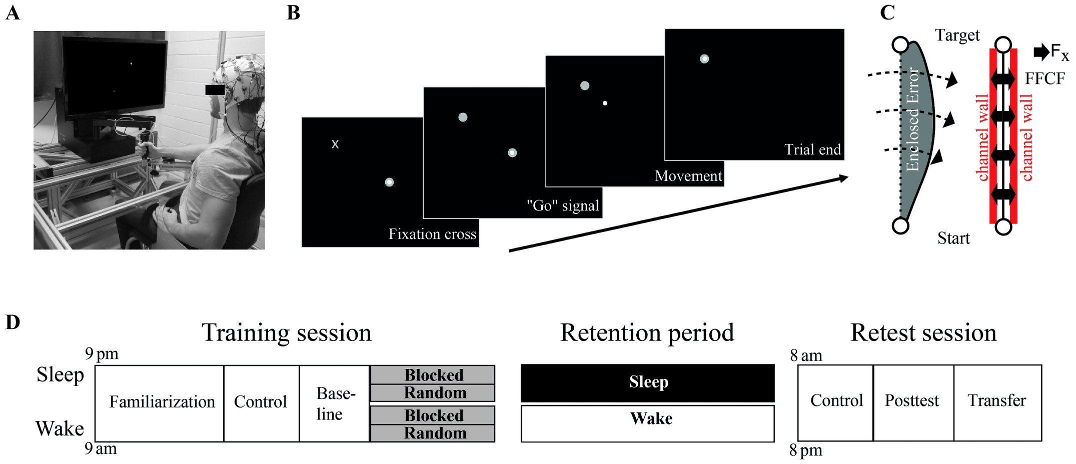

Figure 3.1: Motor adaptation task and experimental design. **A** The motor adaptation task was instrumented by a robotic manipulandum (Kinarm End-Point Lab, BKIN Technologies) with a custom made low friction air-sled system. The robotic manipulandum can induce force fields to perturb participants' hand movements. During the task, participants' EEG is recorded. **B** Example of one trial from highlighting of the fixation cross to trial termination by reaching the target. **C** Sketch of the parameters quantifying the motor error (enclosed area, EA) and motor prediction (force field compensation factor, FFCF). Enclosed area (left) is defined by the area between the trajectory and the direct line between start and target. Arrows indicate the force field direction. The FFCF (right) is computed using the subject's forces (Fx) directed against virtual channel walls and compared to the ideal force profile to cancel out the perturbation. **D** All participant groups had a Training session to train the motor adaptation task with their dominant right hand including Familiarization phase, Control tests (subjective sleepiness, mood, and vigilance), a Baseline, and the force field Training (gray blocks). After a Retention period, Retest performance was quantified in a Posttest and an additional Transfer test on the left hand. Groups differed in their training and consolidation period. The Random groups trained motor adaptation under highly unstable conditions and the Blocked groups under more stable training conditions. The Wake groups trained in the morning and were retested in the evening and the Sleep groups were trained in the evening and retested the following morning after a night of sleep.

after a night of sleep (Sleep-Random, SR; Sleep-Blocked, SB). The retention period between Training and Retest sessions was about 11 hours for all groups. The Wake participants spent their awake time following their usual daily activity and Sleep participants went home after Training to sleep there with polysomnographic home recordings. Retest session contained a Posttest and Transfer test, quantifying the motor performance of participants using their right (Posttest) and left (Transfer) hand (Figure 3.1 D).

Before Training, participants were mounted with a task-EEG and familiarized themselves with the motor adaptation task. During Familiarization, participants performed 144 null field trials with their right hand. Before Training and Posttest, participants were tested on possible confounding effects of subjective sleepiness (Stanford Sleepiness Scale, SSS; Hoddes et al., 1973), mood (Positive Affect Negative Affect Scale, PANAS; Krohne et al., 1996; Watson et al., 1988), and objective vigilance (5-min Psychomotor Vigilance Task, PVT Roach et al., 2006).

Then, participants performed a Baseline measurement using 30 null field trials and 6 additional force channel trials. Training contained 144 force field trials followed by 6 consecutive force channel trials. All participants trained force field trials split into three force field magnitudes (10, 15 and 20 Ns/m) with a mean force field magnitude of 15 Ns/m over all trials. Random and Blocked groups trained the magnitudes under different training schedules that manipulate the training variability of those groups: the Random group trained all trials with force field magnitude switching from trial to trial in a pseudo-random order (unstable); the Blocked groups trained three trial blocks, each containing 48 trials with consistent force field magnitude, with force field magnitude switching only between the blocks. The block order was counterbalanced across participants of each group. The Wake group participants ended the Training session with unmounting of the task-EEG and were given instructions for the daytime until arrival for the Retest session in the evening; the Sleep group participants, however, were additionally prepared for the sleep-EEG and received instruction for the overnight home-polysomnography recording until the next day. The Sleep group started the Retest session with the unmounting of the sleep-EEG.

The Retest session was the same for all participants. Thereby, all participants performed a Posttest of the task with 6 force channel trials, 30 force field trials, and 6 force channel trials. All force field trials were fixed at the mean force field magnitude of the Training (15 Ns/m). Posttest was followed by a Transfer test. Transfer test had the same protocol as Posttest and participants performed the behavioral task with the non-dominant left hand. Note that the force field direction in the Transfer test was still clockwise.

3.2.4 Task-EEG

To record the EEG during task performance we used the actiCHamp system with 32 active-electrodes and used the BrainVision PyCorder V1.0.6 for data recordings (Hard- and software from Brain Products, Gilching, Germany). The task-EEG was synchronized with the manipulandum via a direct link and the data was sampled at 1000 Hz. Electrodes were mounted on subjects' heads with a cap and 29 electrodes were used for the recording of cortical activity using the international 10-10 system (Fp1, Fp2, F7, F3, Fz, F4, F8, FC5, FC1, FC2, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, TP10, O1, Oz, O2). The remaining three electrodes were used to record horizontal and vertical eye movements. Electrode Cz was used as the reference and Fpz as the ground electrode. The impedances of the electrodes were kept below 10 kΩ.

Offline EEG analyses were done using MATLAB R2015b (MathWorks Inc., Natick, MA, United States) and EEGLAB 13.5.4b (Delorme and Makeig, 2004). Raw data of the task-EEG was filtered first by a FIR high-pass filter with a cut-off frequency of 0.5 Hz and then by a FIR low-pass filter with a cut-off frequency of 281.25 Hz. Line noise was removed using the cleanline plugin for EEGLAB. Channels strongly affected by artifacts were removed by visual inspection and the missing channels restored using a spherical interpolation. Electrodes were re-referenced to the average reference and channel location Cz was reconstructed and appended to the data. Then, EEG data was epoched into segments of 8.5 s ranging from 6 s before to 2.5 s after trial start. Principle component analysis (PCA) was performed to compress the data to 99.9 % of the variance and, thus, deal with the reduced rank due to interpolation. Then, infomax independent component analysis (ICA; Makeig et al., 1996) was performed on the principle components. To detect bad ICA components, the components were evaluated in the spectral, spatial and temporal domain. Components showing distinct artifacts were rejected and the data was re-transformed into the channel domain.

We calculated the percentage power in the frequency domain for subsequent statistical comparisons. For this, we used complex Morlet wavelets for the frequency decomposition. We decomposed the data into 40 frequency bins ranging from 2 to 100 Hz in logarithmic space with 5 to 19 wavelet cycles changing as a function of frequency. The decomposed data was averaged over 30 trials and squared, resulting in the average power for: Baseline, First Training Trials, Last Training Trials, Posttest, and Transfer. Then, power was normalized according to the average reference period 250 ms before the highlighting of a fixation cross and the event-related desynchronization / synchronization (ERD / ERS) was calculated (Pfurtscheller and Lopes, 1999).

Data was averaged in the frequency domain into specific frequency bands: theta

(4-7 Hz), alpha (8-13 Hz), beta (14-30 Hz), and gamma (30-45 Hz). The data was also compressed in the time-domain by averaging to two time windows: movement planning (-0.4 s to 0 s) and movement execution (0 s to 0.4 s), where 0 s indicates the trial start.

3.2.5 Polysomnography and sleep-EEG analyses

Standard polysomnography was assessed using a home recording system (Somnoscreen Plus, Somnomedics, Randersacker, Germany) including electroencephalography (EEG) at locations F3, F4, Fz, C3, C4, Cz, P3, P4, Pz (International 10–20 system), electrooculography (EOG) sites around the eyes, electromyography (EMG) with electrodes placed at each musculus mentalis as well as the two electrodes at each mastoids behind the ear. Fpz served as the ground electrode and Cz as the original reference. Data was digitized at 256 Hz and down-sampled to 128 Hz to facilitate computation. Offline manual sleep scoring and automatic basic sleep-EEG analysis was performed using the open-source toolbox SpiSOP (Weber, 2016, http://www.spisop.org, SpiSOP, RRID: SCR_015673). Data of two participants (one from the Blocked, one from Random group) were excluded for these analyses due to technical failures ($n = 22$). Scoring was performed by an experienced rater according to standard criteria (Rechtschaffen and Kales, 1968) and was blind to the participant's conditions. Sleep-EEG analyses, apart from sleep scoring, were performed on EEG channels re-referenced to the average signals from the mastoids. Sleep-EEG parameters were detected using standard settings of SpiSOP (Weber, 2016) and briefly described in the following.

Power spectral analyses of sleep EEG. Power spectra were calculated separately for Stage 2, SWS, non-REM and REM sleep on consecutive artifact-free 10 s intervals of non-REM sleep, which overlapped in time by 9 s. Each interval was tapered by a single Hanning-adapted window (1 s tails follow Hanning window, the other 8 s are 1) before applying Fast Fourier Transformation that resulted in interval power spectra with a frequency resolution of 0.1 Hz. Power spectra were then averaged across all blocks (Welch's method) and normalized by the effective noise bandwidth to obtain power spectral density estimates for the whole data. Mean power density in the following frequency bands was determined: slow-wave activity (0.5–4 Hz), theta (4–8 Hz), spindles (9–15 Hz), alpha (8–12 Hz), slow spindles (9–12 Hz) and fast spindles (12–15 Hz), and beta (15–30 Hz), and log transformed (decibel) prior to statistical testing.

Slow waves. For the identification of slow waves, the signal in each channel during non-REM sleep epochs was filtered between 0.5 and 3.5 Hz. Next, all intervals of time with consecutive positive-to-negative zero crossings were marked as putative slow waves if their durations corresponded to a frequency between 0.5 and 1.11 Hz (zero crossings marked beginning and end of slow oscillation), yet these were excluded in case their amplitude was > 1000 mV (as these were considered artifacts) or when both negative and positive half-wave amplitudes lay between -15 and +10 mV. A slow wave was identified if its negative half-wave peak potential was lower than the mean negative half-wave peak of all putatively detected slow oscillations in the respective EEG channel, and also only if the amplitude of the positive half-wave peak was larger than the mean positive half-wave amplitude of all other putatively detected slow waves within this channel. For each participant and channel, the number of slow oscillations, their density (per min non-REM sleep), mean amplitude, and slopes (down slope, the ratio between value of the negative half-wave peak and the time to the initial zero crossing, up slope, the ratio between absolute value of the negative half-wave peak and the time to the next zero crossing) were calculated.

Sleep spindles. For each EEG channel, the signal during non-REM epochs was filtered in a 2-Hz frequency band centered to the visually determined corresponding power peak (12 to 15 Hz range, 13.32 ± 0.11) in the non-REM power spectrum of each participant. Then, using a sliding window with a size of 0.2 s, the root mean square was computed, and the resulting signal was smoothed in the same window with a moving average. A sleep spindle was detected when the smoothed RMS signal exceeded an individual amplitude threshold by 1.5 standard deviations of the filtered signal in this channel at least once and for 0.5 to 3 s. The threshold crossings marked the beginning and end of each spindle and quantified their duration. Sleep spindle amplitude was defined by the voltage difference between the largest trough and the largest peak. Spindles were excluded for amplitudes >200 mV. We focused the analysis on fast spindles only as slow spindles power peaks could not clearly identified in too many participants. For each participant and channel's absolute spindle counts, spindle density (per min non-REM sleep), mean amplitude, average oscillatory frequency and duration were calculated.

Sleep spindles co-occurring with slow wave upstates. To explore if spindles co-occurring with slow waves possess altered properties and associations with behavior, we identified slow waves that had at least one detected sleep spindle from the lowest trough (down state) to +0.5 seconds after the next positive-to-negative zero crossing (i.e., the slow wave upstate). Only the first spindle with the shortest delay to the down state was considered. Then properties of these co-occurring sleep spindles and slow waves were determined as mentioned above. In addition, the mean delay to the down state as well as the standard deviation of the delay were calculated.

For an exploratory analysis of standard and fine-tuned sleep EEG parameters and their associations with memory consolidation, power density, slow wave and spindle parameters (e.g. density) were averaged per electrode. Pz was excluded from analysis since it went bad in 4 sleep subjects with otherwise good sleep EEG.

3.2.6 Statistical analysis

We used independent t-tests and mixed model ANOVAs with the within factors time (First Training Trials, Last Training Trials), retention (Last Training Trials, Posttest; Last Training Trials, Transfer), and the between factors sleep (Sleep, Wake) and training (Random, Blocked) to test differences in the motor error (EA) and motor prediction (FFCF).

Statistical analysis of task-EEG in terms of a possible sleep effect were done using cluster-based statistics corrected by the maximum permuted cluster values. Therefore, mixed model ANOVAs with factors retention (Last Training Trials, Posttest; Last Training Trials, Transfer) and sleep (Sleep, Wake) were performed for every frequency band during movement planning and execution. Clusters were computed on the channel level according to p-values of the ANOVAs and the summed F-value for each cluster was stored as the observed statistic. Then, permutation testing was done using 1000 iterations. For each iteration, data was shuffled across both dimensions (retention, sleep), ANOVA was computed, and the maximum cluster value was stored. P-values were defined as the account of maximum permutation clusters exceeding the observed statistic divided by the number of iterations.

Furthermore, we tried to reproduce previous findings from our lab (Thürer et al., 2017), targeting the neural basis for the benefits of variable training. Accordingly, independent t-tests between training groups (Random, Blocked) were performed to test alpha band power differences during Posttest and Transfer. In addition, motor error differences between Posttest and Last Training Trials (Training-to-Posttest) and Transfer and Last Training Trials (Training-to-Transfer) were computed for each subject on the behavioral level and correlated with the EEG data during Training using Spearman correlations.

Likewise, to find potential correlates of consolidation success within sleep parameters, we performed an explorative analysis across both Sleep groups using Spearman correlations between behavioral changes over the retention period and all sleep parameters (i.e., total sleep time [TST]; sleep onset delay; duration and percentage of TST sleep in stages like Wake after sleep onset, Stage 1, Stage 2, SWS, non-REM [i.e. SWS+Stage 2]; Power and energy density of each sleep stage in the prominent frequency bands; parameters of slow waves, sleep spindles and their co-occurrence during the slow-wave upstates). Due to the explorative nature in the absence of a behavioral sleep effect we did not corrected these correlations for multiple comparisons.

Threshold for statistical significance was set to $p = 0.05$. Multiple comparisons were either corrected by the maximum statistic (permutation test) or by the False Discovery Rate (FDR; Benjamini and Hochberg, 1995). In the case of FDR, p-values in this study represent the FDR corrected p-value (Benjamini and Yekutieli, 2001).

3.3 Results

3.3.1 Behavioral results

All groups adapted to the dynamic force fields and decreased their motor error (quantified by the enclosed area, EA) during Training (Figure 3.2 A,B, $F_{(1,44)} = 143.05$, $p < 0.001$, $\eta_p^2 = 0.765$, for ANOVA with factor time (First Training Trials, Last Training Trials)) independent of Sleep/Wake conditions ($F_{(1,44)} = 0.06$, $p = 0.801$, $\eta_p^2 = 0.001$) or Blocked/Random training conditions ($F_{(1,44)} = 1.95$, $p = 0.169$, $\eta_p^2 = 0.042$). The Blocked groups adapted faster during Training than the Random groups (time*training, $F_{(1,44)} = 4.50$, $p = 0.040$, $\eta_p^2 = 0.093$; time*sleep, $F_{(1,44)} = 1.29$, $p = 0.262$, $\eta_p^2 = 0.028$, for mixed ANOVA with factors training (Blocked, Random), sleep (Sleep, Wake), and time (First Training Trials, Last Training Trials)). Faster learning was confirmed by FDR corrected post-hoc t-tests on Last Training Trials between Random and Blocked groups ($t_{(46)} = 3.96$, $p = 0.002$, $d = 1.144$).

Random and Blocked groups started with similar Posttest performance (Figure 3.2 A,B), showing that the retention from the Last Training Trials (11 hours earlier) to Posttest was worse for the Blocked compared to the Random groups (Figure 3.2 B, retention*training, $F_{(1,44)} = 6.95$, $p = 0.012$, $\eta_p^2 = 0.136$, for mixed ANOVA with factors retention (Last Training Trials, Posttest) and training (Blocked, Random)), but independent of sleep (retention*sleep, $F_{(1,44)} = 1.68$, $p = 0.201$, $\eta_p^2 = 0.037$). A descriptive benefit of Sleep over Wake among the Blocked groups only from the Last Training Trials to Posttest (Figure 3.2 B) was not statistically supported (retention*sleep or retention*sleep*training, $F_{(1,44)} = 1.44$, $p = 0.237$, $\eta_p^2 = 0.032$, for mixed ANOVA with factors retention (Last Training Trials, Posttest), training (Blocked, Random) and sleep (Sleep, Wake)). The benefit of Random over Blocked training manifested quickly during the Posttest from the 5th trial onwards (Figure 3.2 C). This benefit is also confirmed by Pearson correlation analyses showing that training success (i.e., lower motor error at the end of Training) was inversely related to retention success (percentage of Posttest error related to last Training error, $r = -0.78$, $p < 0.001$, $n = 48$) with this effect weaker in the Random ($r = -0.51$, $p = 0.01$, $n = 24$) than in the Blocked groups ($r = -0.86$, $p < 0.001$, $n = 24$; $p = 0.018$, $z = 2.36$, for the difference using Fisher r-to-z transformation). However, training success in general was moderately predictive and positively correlated with the overall Posttest performance for all groups ($r = 0.29$, $p = 0.044$, $n = 48$; for any

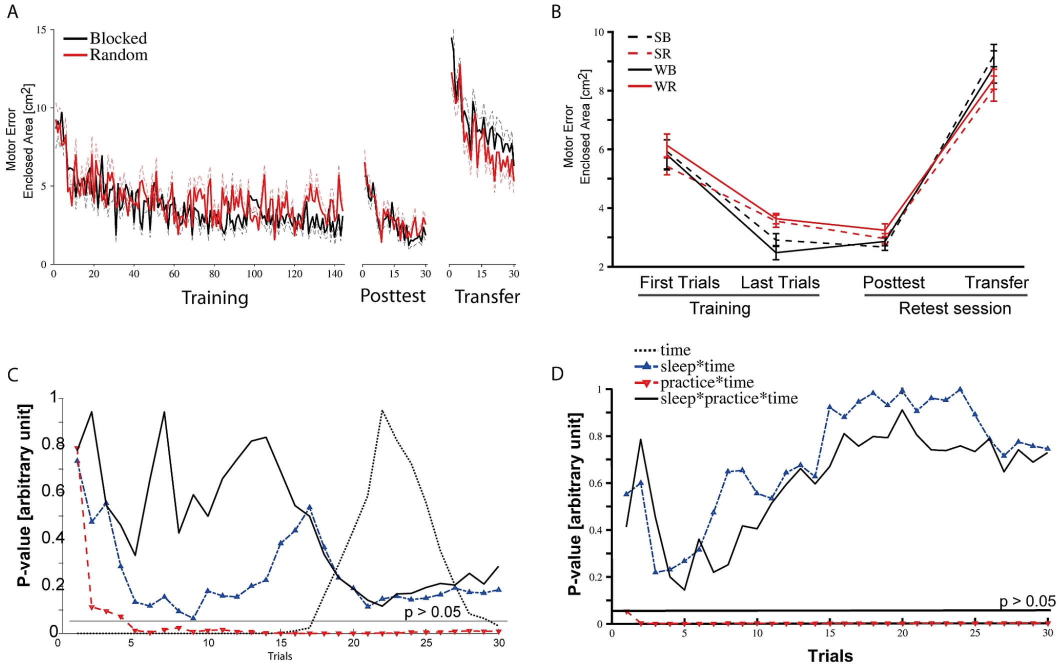

Figure 3.2: Behavioral results. **A** Progress of the mean (± SEM) motor error (enclosed area, EA) for the Blocked (black) and Random (red) groups during Training (left), Posttest (middle) and Transfer trials (right). **B** Mean (± SEM) motor error across 30 trials for each group during First and Last Training Trials, Posttest and Transfer. SB: Sleep-Blocked, SR: Sleep-Random, WB: Wake-Blocked, WR: Wake-Random. **C** P-values of different factors and interactions of the mixed ANOVAs investigating a consolidation effect from Training to Posttest and **D** Training to Transfer.

group r is within 0.167–0.35). This suggests, though initial Training performance might benefit from a blocked training schedule, motor memory retention benefit from a randomized training schedule. These processes were unaffected by sleep.

We further investigated if memory consolidation also enhanced the generalization from the dominant hand (during Training) to the non-dominant (Transfer). As expected, all groups performed worse during Transfer testing as compared to the Last Training Trials, even after averaging across all 30 Transfer trials ($F_{(1,44)} = 483.56$, $p < 0.001$, $\eta_p^2 = 0.917$). In addition, initial Transfer performance of all groups was worse compared to the initial Training performance (First Training Trials; Figure 3.2). This lower initial performance during contralateral transfer learning indicates that participants expected the force field in the opposite direction as during Training (relying on an internal rather than an external representation). This is also supported by the motor prediction (force field compensation factor, FFCF) showing similar force field predictions in the initial Transfer trials for the Blocked and Random groups (Blocked: -15.64 %, SD 16.61 %; Random: -15.62 %, SD 17.85 %, negative sign indicates that participants expected the opposite force field direction). Motor error in Transfer test was lower in the Random than in the Blocked groups (retention*training, $F_{(1,44)} = 16.57$, $p < 0.001$, $\eta_p^2 = 0.274$, for mixed ANOVA with factors retention (Last Training Trials, Transfer) and training (Blocked, Random)) and this effect manifested immediately after the first Transfer trial (Figure 3.2 A,D). Transfer learning effects were independent of sleep (retention*sleep, $F_{(1,44)} = 0.11$, $p = 0.742$, $\eta_p^2 = 0.002$) and not strongly predictive by training success (for all groups $r = 0.12$, $p = 0.42$, $n = 48$; Random group $r = 0.14$, $p = 0.54$, $n = 24$; Blocked group $r = 0.395$, $p = 0.056$, $n = 24$). Likewise, Posttest performance had no strong correlation to Transfer performance ($r = 0.27$, $p = 0.072$, $n = 48$). However, transfer learning was strongly influenced by motor memory retention, that is, improvements over the retention period from Last Training Trials to Posttest were associated with improvements from Last Training Trials to Transfer ($r = 0.84$, $p < 0.001$, $n = 48$), an association that was weaker for the Random ($r = 0.48$, $p = 0.024$, $n = 24$) than for the Blocked groups ($r = 0.88$, $p < 0.001$, $n = 24$; $p = 0.007$, $z = 2.72$, for the difference between correlation coefficients after Fisher r-to-z transformation). This suggests that, in general, an enhanced consolidation from Training to Posttest is strongly connected to an enhanced Training to Transfer consolidation but transfer learning was less hampered by motor memory consolidation after random than after blocked training.

Motor error quantified by EA is affected by both, predictive feedforward and responsive motor feedback. As the feedback responses typically start to compensate for feedforward errors already at 100 ms (Jeannerod, 1988) and the average trial duration across groups was about 550 ms, EA should mostly reflect the feedback responses. Thus, we tested if the observed influences of training conditions also underlie feedforward motor prediction as measured by FFCF. Neither training nor sleep condition influenced motor prediction changes from Training to Posttest (retention*sleep, $F_{(1,44)} = 1.23$, $p = 0.274$, $\eta_p^2 = 0.027$; retention*training, $F_{(1,44)} = 0.56$, $p = 0.459$, $\eta_p^2 = 0.013$) or Training to Transfer (retention*sleep, $F_{(1,44)} = 1.37$, $p = 0.249$, $\eta_p^2 = 0.030$; retention*training, $F_{(1,44)} = 0.41$, $p = 0.524$, $\eta_p^2 = 0.009$). This suggests that the observed effect here is more affected by late feedback than early feedforward responses.

3.3.2 Task-EEG

Explorative analysis using cluster-based statistics for a possible retention*sleep effect (with retention: Last Training Trials, Posttest; Last Training Trials, Transfer) revealed that cortical activity in all frequency bands were unaffected by Sleep vs. Wake. Thus, we focused on further task-EEG analysis regarding the training conditions (Blocked,

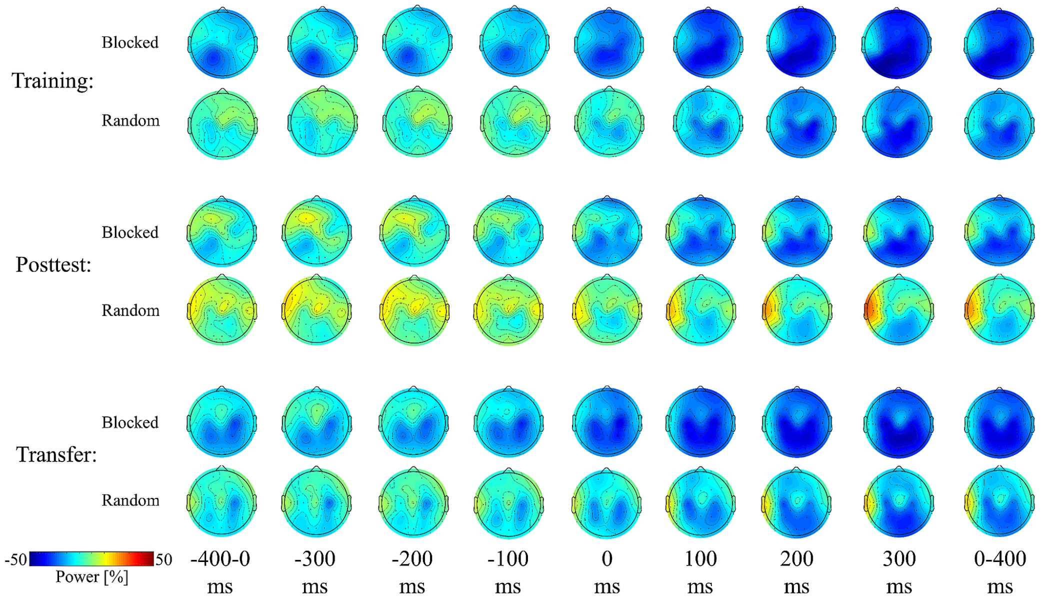

Figure 3.3: Mean alpha band power. Progress of the mean alpha band power for Blocked and Random groups during the Training session and during the Posttest and Transfer test of the Retest session. Leftmost and rightmost topographies represent the mean power across motor planning (-400-0 ms) and execution (0-400 ms). Other plots represent the topographical power at specific points in time (from -300 to 300 ms).

Random).

Analysis of a possible training condition effect was restricted to the alpha band power (Figure 3.3) over parietal areas according to previous work showing a linkage between training effect and force field adaptation only in alpha frequencies (Thürer et al., 2017). Based on these previous findings, we defined a left- and right-hemispheric region of interest (ROIl: CP5, CP1, PZ, P3; ROIr: CP6, CP2, PZ, P4) and found a higher alpha band power for the Random compared to the Blocked groups in the Posttest and a similar effect which did not reach significance in the Transfer test, both during movement execution (Posttest, $t_{(46)}$ = -2.22, p = 0.031, d = 0.642, for t-test of ROIl; Transfer, $t_{(44)}$ = -1.85, p = 0.072, d = 0.543, for t-test of ROIr). Increased alpha band values over ROIl from Training to Posttest during movement execution were associated with better task retention success (quantified by a small Training-to-Posttest difference of the motor error; Figure 3.4) for participants of the Random but not of the Blocked groups (Random, ρ = -0.50, p = 0.031; Blocked, ρ = 0.04, p = 1.0, for Spearman correlations with ρ representing Spearmans rho). This suggests that random training of force fields affects parietal alpha band activity of the Posttest and maybe even of the Transfer test.

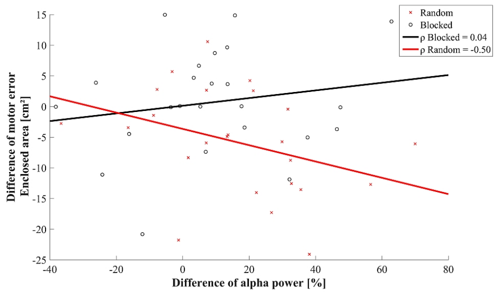

Figure 3.4: Association between Training-to-Posttest difference for motor error and alpha power. Associations between Training-to-Posttest difference of the motor error (quantified by EA) and alpha power for ROIl (CP5, CP1, Pz, P3) during motor execution were tested using Spearman correlation. Each red cross represents the data of a single participant from the Random group and each black circle of a participant from the Blocked group. Lines represent a basic linear fit (red: Random; black: Blocked) and ρ represent Spearmans rho.

Furthermore, we explored if the behavioral retention effects (Training-to-Posttest, Training-to-Transfer), are predictable by the alpha band power during Training. Spearman correlations indicate positive but weak associations from Training-to-Posttest for both groups (Random, Blocked), phases (planning, execution), and ROIs (ROIl, ROIr), which did not reach statistical significance (Figure 3.5; Training-to-Posttest, all ρ for Blocked between 0.22-0.33; all ρ for Random between 0.12-0.18). However, associations of Training-to-Transfer consolidation were strong for Blocked (ρ in all cases between 0.39-0.60) but still weak for Random groups (ρ between 0.04-0.20). These positive correlations for Blocked groups were statistically significant after FDR correction for ROIl (Figure 3.5; planning, $\rho = 0.595$, $p = 0.025$; execution, $\rho = 0.550$, $p = 0.025$) but only during trial execution for ROIr (planning, $\rho = 0.389$, $p = 1.0$; execution, $\rho = 0.486$, $p = 0.050$).

3.3.3 Sleep-EEG

Though sleep during consolidation did not improve the motor performance more than wake-time, we explored which activity during sleep could give an indication of the consolidation processes to happen during the time of sleep. None of the basic sleep stage parameters correlated with consolidation performance (Table 3.1).

Consolidation success was predicted by sleep spindles and their occurrence during up-states of slow waves in a pattern that more sleep spindles during this short time window reflected the improvements from Training to Posttest and Training to Transfer (Table 3.2). This pattern was most pronounced in the left parietal area

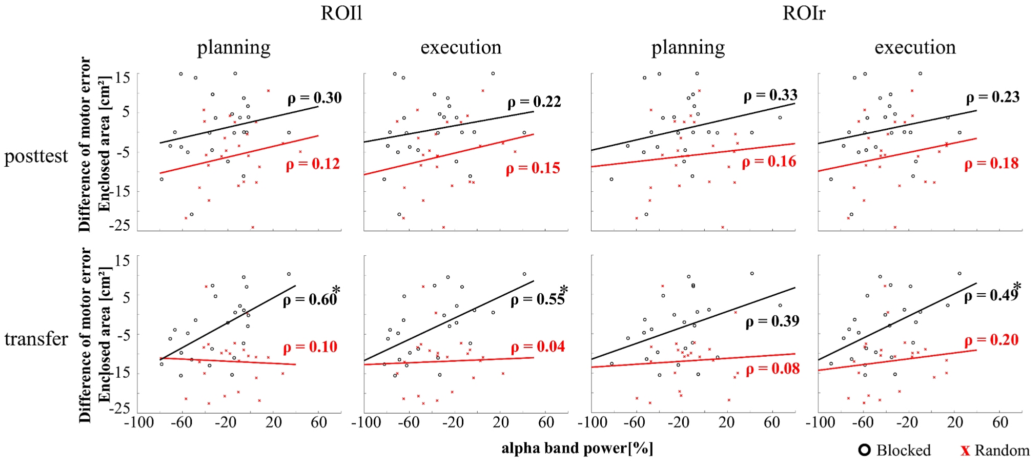

Figure 3.5: Prediction of motor memory consolidation by alpha power during Training. The predictability of motor memory consolidation (Training-to-Posttest or Training-to-Transfer difference of motor error) is indicated. Each plot represents the data points for each participant of the Blocked (black circle) and Random (red cross) groups together with their groups' linear fit. Asterisks indicate a significant Spearman correlation coefficient after FDR correction. Lines represent basic linear fit whereas ρ represents Spearmans rho.

(i.e., P3). This was also reflected in the over-representation of slow-wave activity (power density) during Stage 2 sleep (i.e. an indicator of higher a priori changes for sleep spindles and slow waves to occur) was likewise predictive of improvements from Training to Posttest. Also, longer sleep spindles during slow waves (and in general) predicted improvements from Training to Posttest. A less steep decline in oscillation frequency (i.e. less 'chirp' towards lower oscillation frequency) during such spindles predicted worsening from Training to Transfer, and a generally higher sleep spindle oscillation frequency in fronto-central areas was predictive for the deterioration of the motor performance from Training to Posttest. Higher dispersion of sleep spindles locked to the slow wave down state in Cz (SD of the delay to the slow wave down peak) predicted less improvement during Transfer as compared to Training. No other sleep measures reached significant correlation with consolidation measures.

Table 3.1: Results of the gamma bands testing for consolidation effects between groups.

Sleep parameter (n = 22)				Spearman rank correlations with behavior [ρ]				
Stages				Training	Posttest	Transfer	Posttest - Training	Transfer - Training
TST [min]	435.91	±	8.79	-0.219	-0.338	-0.152	0.160	-0.043
Sleep onset [min]	18.56	±	3.70	-0.092	-0.074	-0.011	0.040	0.179
WASO [%]	2.91	±	0.43	-0.238	-0.043	0.207	0.357	0.433*
Stage 1 [%]	7.09	±	0.60	-0.342	-0.329	-0.152	0.123	0.040
Stage 2 [%]	45.23	±	1.52	0.234	0.342	-0.030	-0.174	-0.073
SWS [%]	27.64	±	1.50	0.043	-0.097	0.025	-0.019	-0.082
Non-REM [%]	72.86	±	0.84	0.420	0.281	0.058	-0.377	-0.172
REM [%]	17.14	±	0.71	-0.051	-0.095	-0.152	0.071	-0.158
Sleep spindle power peak	13.32	±	0.11	-0.500*	-0.163	0.072	0.367	0.363

Means ± SEM for the sleep parameters in the left columns. The right columns show Spearman's rank correlation of sleep parameters with behavioral measures of mean motor error (enclosed area) during end of Training, Posttest, Transfer, as well as changes from Training to Retest (Posttest – Training) and Training to Transfer (Transfer – Training). Note that for Posttest – Training and Transfer – Training a negative correlation is indicative of beneficial relation on consolidation success. Given are the total sleep time (TST), sleep onset (with reference to the time of lights off and beginning of first occurrence of stage 1-sleep epoch followed by stage 2-sleep), and time spent awake after sleep onset (WASO), sleep stage 1, sleep stage 2, SWS, non-REM (S2 + SWS) and REM in percentage of total sleep time. In addition, the sleep spindle power peak in the non-REM sleep power spectra of 12–15 Hz frequency range, Significant correlations are in bold, * $p < 0.05$, uncorrected for multiple comparisons.

Table 3.2: Sleep parameters and events and correlations with motor adaptation learning and consolidation.

Sleep parameter (n = 22)			Spearman rank correlations with behavior [ρ]				
Analysis	Property	Electrode	Training	Posttest	Transfer	Posttest - Training	Transfer - Training
power density (S2)	(0.5-4 Hz)	P3	0.392	-0.112	0.150	-0.439*	-0.161
power density (REM)	(0.5-4 Hz)	F3	0.467*	0.013	0.362	-0.464*	0.048
spindle	duration	C3	0.536*	-0.075	0.204	-0.517*	-0.093
		C4	0.527*	-0.056	0.209	-0.508*	-0.095
		Cz	0.487*	-0.037	0.179	-0.467*	-0.081
		F4	0.470*	-0.137	0.098	-0.473*	-0.180
		P3	0.466*	-0.081	0.249	-0.481*	-0.049
		P4	0.430*	-0.125	0.277	-0.517*	-0.010
	frequency	C4	-0.544**	-0.138	0.077	0.431*	0.407
		Cz	-0.562**	-0.102	0.020	0.470*	0.360
		F3	-0.558**	-0.172	-0.031	0.434*	0.303
		F4	-0.561**	-0.144	0.063	0.464*	0.411
		Fz	-0.573**	-0.141	0.054	0.449*	0.411
	chirp	C3	-0.348	-0.034	0.255	0.318	0.430*
		C4	-0.276	-0.045	0.270	0.371	0.450*
		P3	-0.187	0.089	0.302	0.315	0.450*
		P4	-0.223	0.072	0.266	0.273	0.439*
spindle upstate	count	C3	0.266	-0.189	-0.316	-0.482*	-0.490*
		C4	0.235	-0.203	-0.407	-0.450*	-0.554**
		Cz	0.248	-0.101	-0.434*	-0.399	-0.582**
		F3	0.442*	0.185	-0.237	-0.400	-0.465*
		Fz	0.413	0.082	-0.268	-0.456*	-0.494*
		P3	0.382	-0.100	-0.379	-0.548**	-0.569**
		P4	0.233	-0.058	-0.397	-0.399	-0.480*
	density	C3	0.268	-0.153	-0.295	-0.469*	-0.481*
		C4	0.255	-0.169	-0.378	-0.452*	-0.529*
		Cz	0.296	-0.146	-0.351	-0.499*	-0.548**
		F3	0.436*	0.158	-0.300	-0.412	-0.513*
		F4	0.404	0.155	-0.098	-0.461*	-0.326
		Fz	0.426*	0.129	-0.258	-0.436*	-0.465*
		P3	0.343	-0.091	-0.368	-0.518*	-0.549**
		P4	0.311	-0.008	-0.318	-0.462*	-0.443*
	duration	C3	0.394	-0.198	-0.137	-0.471*	-0.391
		C4	0.471*	-0.299	0.136	-0.599**	-0.139
		Cz	0.455*	-0.231	-0.013	-0.615**	-0.295
		P3	0.369	-0.286	-0.047	-0.505*	-0.252
		P4	0.469*	-0.153	0.016	-0.512*	-0.268
	frequency	Fz	-0.525*	-0.103	0.040	0.436*	0.387
	SD of slow-wave delay	Cz	-0.225	-0.196	0.302	0.125	0.427*

The right columns show Spearman's rank correlation of sleep parameters with behavioral measures of mean motor error during end of Training, Posttest, Transfer, as well as changes from Training to Posttest and Training to Transfer. Only significant relations are listed. All other measures did not reach significance for relations with these two consolidation measures. Significant correlations are in bold, ** $p < 0.01$, * $p < 0.05$, uncorrected for multiple comparisons.

3.4 Discussion

Our results show that Random and Blocked groups adapted to the force field conditions successfully. Subsequent consolidation was influenced by training conditions but unaffected by intervening sleep. Regarding training conditions, although Training outcome was worse for the Random than Blocked groups, all groups showed a similar motor performance in the Posttest and Random groups showed an even more pronounced motor performance compared to the Blocked groups when tested for transfer on the untrained, non-dominant hand. This improvement expressed itself in reductions in motor error (enclosed area), which is mostly affected by responsive feedback corrections, but not in the measure of motor prediction (force field compensation factor).

3.4.1 Sleep does not improve consolidation of force field adaptation

Our behavioral results exclude a substantial profit from sleep on the present motor adaptation task. Task performance and measures of consolidation were independent on whether participants spent awake or asleep during the intervening time between Training and Retest. Thus, our study confirms earlier findings by Donchin et al. (2002) and concurs with some force field studies (Brady, 1997; Shadmehr and Holcomb, 1997) claiming that consolidation of motor adaptation towards dynamic perturbations is time but not sleep dependent. Previous work suggested that force field adaptation represents a non-hippocampal dependent, implicit memory (Brashers-Krug et al., 1996; Rasch and Born, 2013). Accordingly, our negative findings here agree with the assumption that only hippocampal dependent motor processes benefit from sleep (King et al., 2017). However, research showed that hippocampal damage deteriorates the benefits of unstable training conditions (Merbah and Meulemans, 2011), indicating that a motor task might become hippocampal-dependent - and thus would be expected to become sleep-dependent - when trained under highly unstable conditions (Debarnot et al., 2015; King et al., 2017). However, this view is not supported by our behavioral data showing also now sleep effects for the Random groups. The exact extent to which motor adaptation after variable training becomes hippocampal-dependent is unclear and need to be elaborated in future studies.

Despite the lack of a consolidation benefit of sleep over wake retentions, the consolidation success correlated positively with sleep spindle activity during slow-wave upstates. This is at odds with the view that consolidation of motor adaptation learning is completely independent of hippocampal processes, because the coalescence of spindle and slow-wave activity during sleep is thought to benefit consolidation of hippocampal-dependent tasks in particular (Khodagholy et al., 2017; Maingret et al., 2016; Rasch and Born, 2013). Intriguingly, we found task-consolidation-associated alpha activity over parietal brain regions which matches the strong association of sleep-mediated consolidation in the same regions. This concurs with the view that cortical regions that were engaged in learning have a strong local association with spindles and slow waves in subsequent sleep (Pereira et al., 2017) and predict the extent of consolidation (Huber et al., 2004). If such associations are functionally involved in the consolidation process in our data or are merely a reflection of consolidation success of other memories, not tested by our task, is unclear.

3.4.2 Variable training leads to consolidation benefits

This study reproduced earlier findings of the contextual interference effect (Lage et al., 2015; Schmidt and Lee, 2011) in that higher training variability led to a decreased motor performance at the end of Training, but to a performance similar to that of the blocked training groups on the Posttest and to even performance benefits on the Transfer test. As previously reported (Thürer et al., 2017), this gain induced by variable training is only seen in the motor error which is mostly affected by feedback responses. By contrast, motor prediction again did not show this effect. Because subjects do not receive task specific feedback during force channel trials, FFCF is only feedforward dependent (Joiner and Smith, 2008; Scheidt et al., 2000). Therefore, it is likely that the motor benefits of the Random groups were facilitated by feedback corrections during movement execution evoked by the permanent regulation of random, unexpected forces during Training.

Although the Random groups ended their training worse compared to the Blocked groups, their Posttest performance was comparable. This points to unstable training conditions to either prime for better memory consolidation or the formation of memory that is more stable. Also, the generalization to the Transfer test on the left hand was more pronounced in the Random groups. The consistency of this generalization benefit over 30 trials speaks for a stable long-term memory effect. This was confirmed by the significant association of benefits in memory consolidation and the training schedule, that is lower Training performance (in terms of higher motor error) from unstable training also led to better retention performance.

During Transfer testing the participants expected a force field on their left hand that was directed in the opposite direction than force field was during Training of the right hand which explains the initially worse Transfer performance present in all groups when compared to initial Posttest performance. This suggest the generalization did not take place in extrinsic force field transformation but rather in intrinsic, mirror symmetric coordinates, that is, perturbation was expected to come from right on the right hand and from left on the left hand. This agrees with the literature (Shadmehr and Mussa-Ivaldi, 1994) but contradicts the preference of extrinsic coordinates in other studies (e.g. Malfait and Ostry, 2004; Stockinger et al., 2017). The divergent findings of coordinate systems in use for generalization are in line with the recent assumption that representations might occur in a mixture of coordinate systems (Berniker et al., 2014; Franklin et al., 2016). Paradoxically, we do not find an even more decreased initial Transfer performance for Random groups, as would be expected by a more stable intrinsic representation in this group which gives rise to predict the force field in the opposite, 'wrong' direction during Transfer. But the opposite was the case, i.e., the Random groups showed an enhanced Transfer performance compared to the Blocked groups. There are three possible explanations for this outcome:

(1) Generalization was worse for the Random compared to the Blocked groups. Increased motor performance of the Random group might be facilitated by a weaker generalization or consolidation of the generalized memory. However, motor performance quantified by the motor prediction showed similar Transfer performances for all groups, indicating similar generalizations between groups.

(2) Random training favored the formation of a different coordinate system (or mixture of systems; Berniker et al., 2014). The results, however, do not support such explanation as motor predictions were similar between groups. In addition, inspection of single individual data revealed cues for an extrinsic force field representation in only 4 of the 24 participants of the Random groups. This was also the case in 2 of the 24 participants of the Blocked groups.

(3) Random training led to a generally increased ability to use feedback responses. This explanation is supported by the finding that only motor error, which is sensitive to feedback corrections, but not motor prediction showed an increased memory consolidation for the Random groups. In addition, the EEG data shows that parietal but not frontal areas of the brain are involved in the contextual interference effect, with the former known to be specifically implicated in sensory integration (Whitlock, 2017). However, future research should further investigate the influence of variable training on online feedback corrections in motor behavior.

Summarized, variable training leads to benefits in consolidation of a force field adaptation task. This effect is even more prominent when retention is tested on the contralateral hand. We assume that the increased consolidation after highly variable training is facilitated by an increased ability to use online feedback corrections.

3.4.3 Parietal alpha power predicts transfer performance in the blocked groups

The EEG during task performance showed that behavioral changes across the consolidation period after Random training are accompanied with a parallel increase (from Training to Posttest) in alpha band power over parietal areas, which concurs with previous findings from our lab (Thürer et al., 2017). In detail, we were able to reproduce here a negative correlation between changes in alpha power over contralateral parietal areas (ROIl) and motor error during movement execution. An increased alpha band power is frequently discussed as a sign of an active inhibition of the underlying cortical region (Klimesch, 2012). Therefore, a negative correlation might indicate that, for Random groups, a more accurate and, thus, better consolidated motor performance comes in parallel with an increased inhibition of parietal areas.

The results also showed that consolidation in this force field adaptation task can be predicted by the alpha power over parietal areas during Training. Blocked but not Random groups showed significant associations between Training-to-Transfer consolidation and the alpha band power. Thus, high parietal alpha power and, thus, inhibition of parietal cortical areas during Training, might favor a weaker consolidation for the Blocked but not for the Random groups. Intriguing questions arising here are whether the greater efficacy of random training specifically results from its ability to counter the disadvantage of increased parietal alpha power during training and whether parietal alpha power is connected to online feedback corrections of the motor system.

Chapter 4

Neural correlates of memory retrieval

> *"Data! Data! Data!" he cried impatiently. "I can't make bricks without clay."*
>
> — Sherlock Holmes, *Sir Arthur Conan Doyle*

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4.1 Abstract

The retrieval of motor memory requires a previous memory encoding and subsequent consolidation of the memory engram. Previous work showed that motor memory seems to rely on different memory components (e.g. implicit, explicit). However, it is still unknown if explicit components contribute to the retrieval of motor memories formed by dynamic adaptation tasks and which neural correlates are linked to the retrieval of motor memory. We investigated subjects' lower and higher gamma bands with EEG during encoding and retrieval of a dynamic adaptation task. In total, 24 subjects were randomly assigned to a treatment and control group. Both groups adapted to a force field A on day 1 and were re-exposed to the same force field A on day 3 of the experiment. On day 2, the treatment group learned an interfering force field B whereas the control group had a day rest. Kinematic analyses showed that the control group improved it's initial motor performance from day 1 to day 3 but treatment group did not. This behavioral result coincided with an increased higher gamma band power in the electrodes over prefrontal areas on the initial trials of day 3 for control but not treatment group. Intriguingly, this effect vanished with the subsequent re-adaptation on day 3. We suggest that improved re-test performance in a dynamic motor adaptation task is contributed by explicit memory and that gamma bands in the electrodes over the prefrontal cortex are linked to these explicit components. Furthermore, we suggest that the contribution of explicit memory vanishes with the subsequent re-adaptation while task automaticity increases.

4.2 Introduction

Commonly, movements under novel environmental conditions exhibit sparse motor performances which, in turn, lead to a subsequent motor adaptation process (Krakauer and Mazzoni, 2011).It is hypothesized that this encoding of new motor memories relies on at least two components: explicit (i.e. with awareness) and implicit (i.e. without awareness) (Huberdeau et al., 2015). Following this encoding, motor memory is transformed from an initially fragile to a more robust and stable state (Robertson et al., 2004). This memory transformation is called consolidation and refers to a time (Brashers-Krug et al., 1996), sleep (Rasch and Born, 2013), and practice (Stockinger et al., 2014) dependent process. If consolidation was successful, a subsequent retrieval of the motor memory is facilitated (Robertson, 2009).

Studies examining motor memory retrieval after a consolidation period frequently use kinematic (e.g. Krakauer et al., 1999) or dynamic (e.g. Shadmehr and Mussa-Ivaldi, 1994) perturbations to change the environmental conditions and, thereby inducing motor adaptation processes. Neuroimaging studies using dynamic perturbations showed the involvement of cerebellar structures in the motor memory encoding and retrieval (Krebs et al., 1998; Nezafat et al., 2001; Shadmehr and Holcomb, 1997). However, it has been shown that the motor memory encoding and retrieval of dynamic perturbations is not restricted to the cerebellum (Diedrichsen, 2005; Hallett, 2006; Shadmehr and Holcomb, 1997). Yet, it is still unclear which areas of the human brain contribute to the retrieval of motor memory after a period of consolidation of a dynamic adaptation task.

Studies using kinematic and dynamic perturbations have shown that learning of sensorimotor adaptation tasks lead to changes within the prefrontal cortex (Floyer-Lea, 2004; Gentili et al., 2015; Shadmehr and Holcomb, 1997), indicating that the prefrontal cortex most likely plays a prominent role in motor memory processing, too (Gentili et al., 2015; Taylor and Ivry, 2014). In this regard the cognitive control theory (Miller and Cohen, 2001) states that early trials of a task rely predominantly on explicit control involving prefrontal areas. Further repetitions of the task lead to an increased movement automaticity, as the repetitions potentiate existing (or form new) neural pathways. These movements, now exhibiting an increased automaticity, are supposed to rely predominantly on implicit control and, thus, are performed without or less prefrontal activity. This theory is supported by previous neuroimaging studies using adaptation tasks to dynamic (Shadmehr and Holcomb, 1997) and kinematic (Gentili et al., 2015) perturbations. Moreover, recent work indicates that such explicit components contribute also to motor memory retrieval and may serve as one component of long-term motor learning (Haith et al., 2015; Huberdeau et al., 2015). Although there is a large amount of literature investigating motor memory on the behavioral level, changes on the underlying neural level (Wolpert et al., 2011) and the involvement of the prefrontal cortex (Taylor and Ivry, 2014) are not fully understood.

Previous studies using electrocorticography (ECoG) or EEG stated that theta (4-8 Hz), alpha (8-13 Hz), and gamma (>30 Hz) band frequencies might be linked to memory processes (Canolty et al., 2006; Gentili et al., 2015; Perfetti et al., 2011; Roux and Uhlhaas, 2014; Sauseng et al., 2013). While theta and alpha bands are frequently investigated in motor memory studies (Gentili et al., 2011; Kranczioch et al., 2008; Novakovic and Sanguineti, 2011; Studer et al., 2010; Tombini et al., 2009), gamma frequencies are less examined due to their high contamination with eye and muscular artifacts (Croft and Barry, 2000; Goncharova et al., 2003). However, previous work depicted that enhancement of signal-to-noise ratio provides the gamma band examination even of movement tasks Crone et al. (2011); Darvas et al. (2010). Studies which investigated the human gamma band associated changes over frontal areas with explicit components of memory encoding during episodic (Sederberg et al., 2003) and motor (Gentili et al., 2015) memory tasks. To the best of our knowledge, there is no EEG study which examined the human gamma band power in the retrieval of motor memory after subjects' consolidation of a dynamic adaptation task.

Up to now, it is unclear if explicit components contribute to motor memory retrieval of dynamic adaptation tasks and if gamma frequencies are linked to such a contribution. Therefore, the aim of this study was to investigate gamma band power changes within the human EEG in electrodes over the prefrontal cortex during motor memory encoding and retrieval with a period of consolidation in-between. We hypothesized that motor performance improvement in a dynamic adaptation task, after a period of consolidation, (1) coincides with changes in the gamma band power. In addition we hypothesized that such an effect (2) is located in electrodes over the prefrontal cortex and (3) vanishes with the subsequent re-adaptation.

4.3 Materials and methods

4.3.1 Participants

After providing written informed consent, a total of 24 male and right-handed subjects (age: 23.9 ± 3.1 years) participated in this study. Right-handedness was tested using the Edinburgh inventory (Oldfield, 1971). All subjects were healthy and had normal or corrected to normal vision. The experimental task was new to the subjects and the test-protocol was approved by the institutional review board. Subjects were randomly assigned to one of two groups (treatment or control). Each group contained twelve subjects and no subject was excluded from the subsequent analyses.

4.3.2 Apparatus

Subjects sat on an individually adjustable chair in front of a robotic device (BioMotionBot, Figure 4.1; Bartenbach et al. (2013)). The workspace of the robotic device was restricted to the horizontal plane and subjects grasped the handle with their dominant hand. Subjects' hand position was recorded at 200 Hz.

For the EEG recordings, we used an ActiCap system mounted with 13 silver/silver chloride electrodes and the V-Amp amplifier by Bain Products (Brain Products GmbH, Gilching, Germany). All EEG electrodes were placed according to the international 10-20 system over the frontal lobe (Fp1, Fp2, F3, Fz, F4, F8, FC5, FC1, FCz, FC2, FC6, C3, Cz), whereas three additional EOG electrodes were placed above the nasion and below the outer canthi of the eyes (Schlögl et al., 2007). During recording, electrodes were referenced to the location Pz and impedances were kept below 20 kΩ. The amplifier sampled the signal at 500 Hz and electrodes were

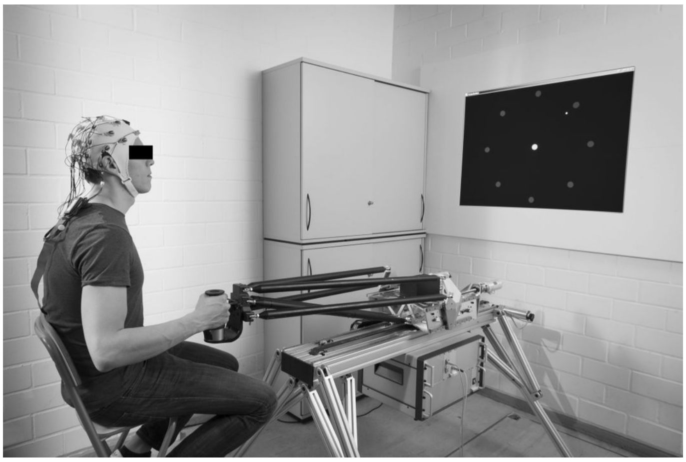
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Figure 4.1: 2D point-to-point reaching movement task. Subjects sat at the robotic device (BioMotionBot; Bartenbach et al., 2013) and performed point-to-point reaching movements in the horizontal plane. A screen in front of the subjects gave full visual feedback of the cursor and target.

grounded to the location AFz. An additional EEG channel recorded a TTL signal (on during movement onset, off otherwise) which was generated by the BioMotionBot to synchronize the systems. Kinematic and EEG data were stored for subsequent offline processing.

4.3.3 Experimental task and procedure

Subjects grasped the handle of the robotic device and performed 2D point-to-point reaching movements. Nine targets (eight in a circle surrounding the ninth) were displayed on a screen in front of the subjects. Targets diameter was 1 cm and the distance between the center target and each surrounding target accounted 10 cm. Subjects had full visual feedback of their hand position and the targets during the whole experiment (see Focke et al., 2013; Stockinger et al., 2014, for details).

The task goal was to make accurate reaching movements between targets. Therefore, subjects started with the cursor in the center target and moved the robot handle to a pseudo-randomized highlighted peripheral target. Every other trial contained the movement backwards to the center target. Thus, subjects performed alternating outward and inward movements. To provide self-timed movement starts, subjects were told that they can stay as long as they want in a target, even though a new target highlighted. To balance all target directions, one set of movements contained all possible 16 movement directions (eight outwards and eight inwards). To avoid target-specific learning phenomena across subjects, each subject performed a different sequence order of targets. Subjects were instructed to perform each trial within 500 ± 50 ms. After movement termination, visual feedback was given during the whole experiment via a colored circle surrounding the target: moving too fast < 450 ms (yellow circle), moving in time (green circle), moving too slow > 550 ms (red circle).

The whole experiment took place over three consecutive days. On day 1 was no difference of the task and schedule between groups. All subjects were instructed to the robotic device and the chair was individually adjusted. Afterwards, the EEG cap was applied to the subject's head. Both groups performed a familiarization block under null field condition (no perturbing forces) that contained 25 sets (400 trials). This block provided that all subjects were able to perform each trial within the requested time. Following this familiarization block, all subjects completed a baseline block with six sets (96 trials) under null field condition. Afterwards, both groups performed a force field block with 16 sets (256 trials) under force field condition A (clockwise-directed). Previous research showed, that practice of an interfering task B, 24 h after the adaptation of task A, could prevent the retrieval of motor memory in a re-test of task A, 24 h after learning task B (Caithness, 2004; Stockinger et al., 2014). Therefore, on day 2, the treatment group performed a force field block, similar to day 1 (256 trials), under interfering force field condition B (counterclockwise-directed). In contrast to the treatment group, the control group had a day rest. On day 3, re-test performance of the force field condition A (256 trials) was tested in both groups. Under force field conditions the robotic device generated a velocity-dependent force field, which perturbed subjects' movements perpendicular to the movement direction, according to the following equation:

$$\begin{bmatrix} F_x \\ F_y \end{bmatrix} = \begin{bmatrix} 0 & k \\ -k & 0 \end{bmatrix} \cdot \begin{bmatrix} \dot{x} \\ \dot{y} \end{bmatrix}$$

where F_x and F_y are the robot-generated forces, k is the force field viscosity (force field A: k = 20 Ns/m clockwise; force field B: k = -20 Ns/m counterclockwise), and $\dot{x}$ and $\dot{y}$ represent the horizontal components of the hand velocity.

Altogether, the session on day 1 lasted about 1.5 h, whereas sessions on day 2 and 3 lasted about 0.5 h. To prevent mental fatigue, breaks, each containing 60 s, were placed after every five sets (80 trials) within each block and, in addition, a 5 min rest period was given between the blocks. The first and last two sets (32 trials) within the baseline and force field blocks contained an intertrial interval of 10 s, which defines the time between the movement offset and the highlight of a new target. This period of time was chosen to enable the development and the recovery of EEG band power between trials (Pfurtscheller and Lopes, 1999). Outside of these EEG analyzing periods, the intertrial interval was 1 s.

4.3.4 Data analyses

Positions of the robot handle were low-pass filtered with a fourth-order Butterworth filter (6 Hz cut-off frequency) using the custom-made software application ManipAnalysis (Stockinger et al., 2012). To average the kinematic data over trials, position data was segmented defining the movement onset as the point of time when the cursor left the starting point and movement offset when the cursor reached the target. Each trial was time-normalized and subjects' reaching performance was quantified as the maximum perpendicular displacement (PDmax) between the hand path and the straight line joining start and target point (Izawa et al., 2008; Shadmehr and Moussavi, 2000).

For the subsequent offline processing of the electrophysiological data, MATLAB R2013b (Mathworks Inc., Natick, USA) and the additional EEGLAB package 13.3.2 were used (Delorme and Makeig, 2004). EEG data was re-referenced to the location Cz and band-pass filtered (low cut-off: 1 Hz; high cut-off: 100 Hz) using a FIR filter. To correct the data for eye movement artifacts, we conducted an automatic correction of ocular artifacts (Schlögl et al., 2007). In addition, artifact subspace reconstruction was applied to the data to correct for muscular artifacts. Then, EEG data was segmented into epochs of 10 s, containing 5 s before and 5 s after movement onset. Afterwards, all artifact corrected channels (EEG and EOG) were manually checked to remove residual artifact-related components using an infomax ICA (Makeig et al., 1996). Due to the previously applied artifact correction, ICA was performed on much cleaner data and, thus, only distinct artifact related components were extracted considering the spatial, spectral, and temporal domain.

According to the power law of EEG data (frequency spectrum reveals decreasing power by increasing frequencies), the amplitude of gamma band power is smaller compared to lower frequency bands. To improve signal-to-noise ratio even of higher frequencies, time-frequency decomposition for the gamma bands was done in accordance with previous studies (Ball et al., 2008; Gonzalez et al., 2006) using a multitaper approach with five Slepian tapers (Mitra and Pesaran, 1999). Each taper accounted a time window of 200 ms with a time step of 50 ms. Using this approach, 40 frequencies were extracted from 2.5-100 Hz and the time-frequency power was calculated. To avoid line noise (50 Hz), gamma bands were defined from 30 to 45 Hz (lower gamma band) and from 60 to 85 Hz (higher gamma band). At this stage, the parameter represents band-specific power and, thus, it is not known if this parameter does or does not depict true neural oscillations (Cohen, 2014). For subsequent analyses, percentage power changes within each frequency band were calculated (Pfurtscheller and Lopes, 1999). In detail, percentage change (PC) describes the comparison of the frequency band power within every sample to the frequency band power within a fixed reference period. This was calculated as follows:

$$PC_j = \frac{A_j - R}{R} \cdot 100$$

where A_j is the power at the j-th sample and R is the median power in the reference period. The reference period for R was determined from -4.5 s to -3.5 s before movement onset. Percentage change of power was calculated within two different temporal windows: -0.5 s < t < 0 s (planning) and 0 s < t < T (execution), where 0 s denotes movement onset and T denotes movement offset. The temporal window of movement execution was time-normalized to ensure the same number of samples in each trial.

4.3.5 Statistical analyses

We observed large artifacts in the very first trial under several conditions. Therefore, the first trial was excluded from both kinematic and electrophysiological analyses. This led to a total of 31 trials for each analyzing period: day 1 first force field trials (D1FT), day 1 last force field trials (D1LT), day 3 first force field trials (D3FT), day 3 last force field trials (D3LT).

Concerning the statistical analyses of the kinematic data, we used independent t-tests to compare reaching performance between groups in the first and last force field trials of day 1. Afterwards, we performed dependent t-tests to check for adaptation (from D1FT to D1LT) and consolidation (from D1FT to D3FT) effects within each group. Finally, a two-way repeated measures ANOVA was conducted to compare consolidation effects between groups containing within-subject factor “time” (D1FT, D3FT) and between-subject factor “group” (treatment, control). Regarding the electrophysiology, we used a two way ANOVA with repeated measures for every frequency band (lower gamma, higher gamma) and every time window (planning, execution) to test for power differences between groups in the first and last force field trials of day 1 and day 3. Within-subject factor “channel” (12 EEG channels) and between-subject factor “group” (treatment, control) were applied to perform these ANOVAs. Finally, we compared the consolidation effects between groups conducting repeated measures ANOVAs for every frequency band and every time window containing within-subject factors “time” (D1FT, D3FT) and “channel” (12 EEG channels) and between-subject factor “group” (treatment, control).

All statistical analyses were conducted using SPSS statistics 22 (IBM, Armonk, USA) and MATLAB R2013b (Mathworks Inc., Natick, USA). The significance level was set a priori to $p = 0.05$ for all statistical tests. Greenhouse-Geisser correction was used if sphericity was violated and false discovery rate (FDR) to correct for type I error (Benjamini and Hochberg, 1995). Cohen’s d (small effect: $d \geq 0.20$; medium effect: $d \geq 0.50$; large effect: $d \geq 0.80$) was used to state the effect sizes in the independent t-tests (Cohen, 1988). In addition, we indicated effect sizes of ANOVAs using partial eta squared η_p^2 (small effect: $\eta_p^2 \geq 0.01$; medium effect: $\eta_p^2 \geq 0.06$; large effect: $\eta_p^2 \geq 0.14$) (Cohen, 1988; Richardson, 2011).

Analyses of fixed time-frequency windows have the advantage to be comparable using complex statistical designs (Multivariate ANOVAs). However, cluster-based statistics provide deeper insights if an observed effect is transient in the time-frequency domain. Whether an effect in the gamma bands is transient or not is an important question because we would expect that a truly brain derived gamma effect is transient in the frequency, time, and spatial domain. Otherwise a possible widespread gamma band effect would likely reflect artifacts. Considering this, we performed cluster-based statistics (Cohen, 2014) on the power values of every time-frequency decomposition between groups using permutation testing (Fraker and Peacor, 2008). To implement this approach, we used the time-frequency decompositions as described in Section 4.3.4 and computed for every subject the difference between the first trials of day 3 and day 1 (D3FT – D1FT). Afterwards, permutation testing was used to account for significant different clusters of pixels between groups on the remaining decompositions. In detail, we computed two-sample t-tests for every time-frequency pixel between groups and assigned significant pixels ($p < 0.05$) to clusters. The summed t-values of each cluster were defined as our observed clusters. Then, we pooled all subjects and assigned them randomly to two groups and performed the former mentioned group differences again. This step was done 10000 times and for every step we stored the maximum summed t-value of all clusters. This led to 10000 permutated maximum t-values. Finally, we computed a threshold to consider observed clusters as significant or not. This threshold was defined by the 95th percentile of the permutated t-values. Thus, if a cluster of pixels reached significance at $p < 0.05$, the cluster was highlighted as significant cluster in the resulting time-frequency plots. This cluster-based statistic was done for every EEG-channel.

4.4 Results

4.4.1 Movement kinematics

On day 1, no significant differences were found in the first and last force field trials between groups (D1FT: $t_{(22)}$ = -0.61, p = 0.548, d = -0.25; D1LT: $t_{(22)}$ = 0.44, p = 0.667, d = 0.19), thus, groups did not differ in their performance of day 1 (Figure 4.2 A,D). Our results showed significant motor adaptations on day 1 for both groups (treatment: $t_{(11)} = 11.18$, $p < 0.001$; control: $t_{(11)} = 11.80$, $p < 0.001$). Testing for consolidation effects between groups, ANOVA revealed significant time ($F_{(1,22)}$ =

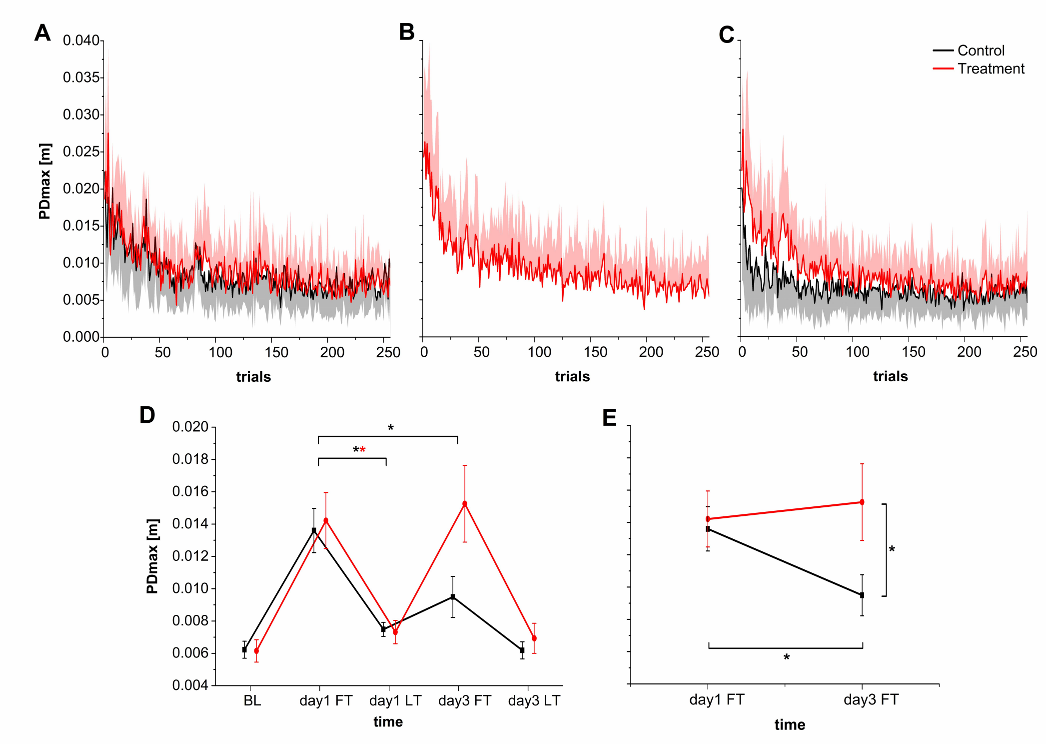

Figure 4.2: Motor performance progression during the whole experiment. All plots (**A-E**) depict the grand average motor performance (PDmax; mean ± CI95) of the control (black lines) and treatment (red lines) groups. **A** 256 trials of force field A on day 1. **B** trials of the treatment group in force field B on day 2. **C** re-test in force field A on day 3. **D** progression between groups across the whole experiment. **E** interaction effect of initial trials of day 1 and day 3 between groups. Asterisks indicate significant differences. BL: baseline; FT: first trials; LT: last trials.

12.19, $p = 0.002$, $\eta_p^2 = 0.36$), group ($F_{(1,22)} = 9.61$, $p = 0.005$, $\eta_p^2 = 0.30$) and time x group ($F_{(1,22)} = 34.45$, $p < 0.001$, $\eta_p^2 = 0.61$) effects (Figure 4.2 E). This interaction effect is confirmed by t-tests checking for consolidation effects within groups (Figure 4.2 C-D). Results revealed significantly increased motor performance in the first trials of day 3 compared to day 1 for the control ($t_{(11)} = 7.48$, $p < 0.001$) but not for the treatment group ($t_{(11)} =$ -1.52, $p = 0.156$).

Summarized, while motor performance of day 1 did not differ between groups, the control group exhibited an increased motor performance in the initial trials of day 3 compared to the initial trials of day 1, whereas motor performance of the treatment group did not change between the initial trials of day 1 and day 3.

Table 4.1: Results of the gamma bands testing for consolidation effects between groups.

			planning			**execution**		
		df	F	p	$\eta_p{}^2$	F	p	$\eta_p{}^2$
Lower Gamma	time	(1,22)	1.44	0.243	0.06	0.35	0.558	0.02
	channel	(11,242)	3.00	0.014*	0.12	2.28	0.062	0.09
	group	(1,22)	3.49	0.075	0.14	1.37	0.255	0.06
	time x group	(1,22)	0.30	0.592	0.01	0.59	0.452	0.03
	channel x group	(11,242)	1.00	0.452	0.04	1.24	0.260	0.05
	time x channel	(11,242)	0.56	0.749	0.03	0.76	0.581	0.03
	time x channel x group	(11,242)	0.34	0.975	0.02	0.81	0.631	0.04
Higher Gamma	time	(1,22)	4.07	0.056	0.16	2.96	0.101	0.12
	channel	(11,242)	2.66	0.023*	0.11	1.21	0.312	0.05
	group	(1,22)	1.52	0.231	0.07	3.53	0.558	0.02
	time x group	(1,22)	8.25	0.009*	0.27	2.62	0.120	0.11
	channel x group	(11,242)	0.86	0.576	0.04	1.52	0.127	0.06
	time x channel	(11,242)	0.43	0.838	0.02	0.62	0.706	0.03
	time x channel x group	(11,242)	0.65	0.785	0.03	0.69	0.752	0.03

* indicates $p < 0.05$

4.4.2 Lower gamma band power

Testing for group differences during movement planning on day 1, the results of the ANOVAs revealed a significant channel effect for the first but not for the last force field trials (D1FT: $F_{(11,242)} = 3.05$, $p = 0.013$, $\eta_p^2 = 0.12$; D1LT: $F_{(11,242)} = 2.16$, $p = 0.057$, $\eta_p^2 = 0.09$). No significant group (D1FT: $F_{(1,22)} = 2.36$, $p = 0.139$, $\eta_p^2 = 0.10$; D1LT: $F_{(1,22)} = 2.55$, $p = 0.124$, $\eta_p^2 = 0.10$) or interaction (D1FT: $F_{(11,242)} = 0.80$, $p = 0.636$, $\eta_p^2 = 0.04$; D1LT: $F_{(11,242)} = 1.52$, $p = 0.125$, $\eta_p^2 = 0.07$) effects were observed in the planning window for the first and last force field trials of day 1. Thus, even though the results of the lower gamma band in the planning window differed between channels, no group differences were observed.

Regarding the movement execution window on day 1, ANOVAs showed no significant channel (D1FT: $F_{(11,242)} = 0.19$, $p = 0.119$, $\eta_p^2 = 0.08$; D1LT: $F_{(11,242)} = 2.09$, $p = 0.108$, $\eta_p^2 = 0.09$), group (D1FT: $F_{(1,22)} = 0.56$, $p = 0.462$, $\eta_p^2 = 0.03$; D1LT: $F(1, 22) = 0.97$, $p = 0.336$, $\eta_p^2 = 0.04$), or channel x group (D1FT: $F_{(11,242)} = 1.45$, $p = 0.150$, $\eta_p^2 = 0.06$; D1LT: $F_{(11,242)} = 1.05$, $p = 0.404$, $\eta_p^2 = 0.05$) effects for the first and last force field trials. Therefore, lower gamma band power during movement execution did not differ between control and treatment groups on day 1.

Table 4.1 gives an overview of all results concerning the tests for consolidation differences (from D1FT to D3FT) between groups. Summarized, ANOVAs only revealed a significant channel effect in the movement planning window. Thus, channels but not groups differed in the movement planning window. We found no significant interactions which indicate different consolidation effects between groups during planning or execution.

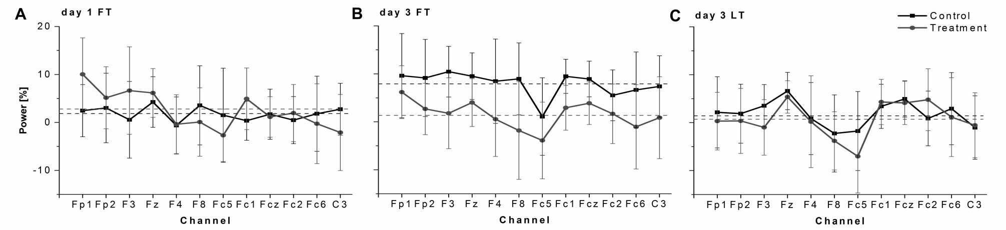

Figure 4.3: Results of the higher gamma band during movement planning. The plots illustrate changes of the higher gamma power (mean ± CI95) from the first trials of day 1 (**A**) to the first trials of day 3 (**B**) and the last trials of day 3 (**C**) for the control (black lines) and treatment (red lines) groups across all channels. Dashed lines indicate the means over all channels.

4.4.3 Higher gamma band power

ANOVAs, testing for group differences in the planning window of the first and last force field trials of day 1, showed no significant channel (D1FT: $F_{(11,242)} = 1.48$, $p = 0.192$, $\eta_p^2 = 0.06$; D1LT: $F_{(11,242)} = 1.05$, $p = 0.388$, $\eta_p^2 = 0.05$), group (D1FT: $F_{(1,22)} = 0.08$, $p = 0.779$, $\eta_p^2 < 0.01$; D1LT: $F_{(1,22)} = 1.19$, $p = 0.288$, $\eta_p^2 = 0.05$), or interaction (D1FT: $F_{(11,242)} = 1.23$, $p = 0.297$, $\eta_p^2 = 0.05$; D1LT: $F_{(11,242)} = 1.51$, $p = 0.197$, $\eta_p^2 = 0.06$) effects.

Similar to the planning window, results of the movement execution window of the first and last force field trials of day 1 also did not reveal significant channel (D1FT: $F_{(11,242)} = 1.33$, $p = 0.260$, $\eta_p^2 = 0.06$; D1LT: $F_{(11,242)} = 0.50$, $p = 0.745$, $\eta_p^2 = 0.02$), group (D1FT: $F_{(1,22)} = 0.19$, $p = 0.666$, $\eta_p^2 = 0.01$; D1LT: $F_{(1,22)} = 0.15$, $p = 0.700$, $\eta_p^2 = 0.01$), or channel x group (D1FT: $F_{(11,242)} = 1.86$, $p = 0.111$, $\eta_p^2 = 0.08$; D1LT: $F_{(11,242)} = 1.56$, $p = 0.188$, $\eta_p^2 = 0.07$) effects. This depicts that higher gamma band power of day 1 did not differ between groups.

Tests for different consolidation effects between groups showed significant channel and time x group effects for the planning window but no significant effects during movement execution (Table 4.1). This reveals that, although higher gamma band power differed not between groups on day 1, higher gamma power differed between groups in the re-test condition on day 3 for the planning (D3FT: $F_{(1,22)} = 5.77$, $p = 0.025$, $\eta_p^2 = 0.21$) but not execution (D3FT: $F_{(1,22)} = 1.97$, $p = 0.175$, $\eta_p^2 = 0.08$) window. In detail, control group showed an increase of higher gamma power from day 1 to day 3 whereas the treatment group did not (Figure 4.3 A,B). Intriguingly, this effect vanished with the subsequent re-adaptation (Figure 4.3 C, Figure 4.4). Thus, the last trials of day 3 showed no differences between groups in the higher gamma band during planning (D3LT: $F_{(1,22)} = 0.19$, $p = 0.665$, $\eta_p^2 = 0.01$) and execution (D3LT: $F_{(1,22)} = 0.01$, $p = 0.916$, $\eta_p^2 < 0.01$).

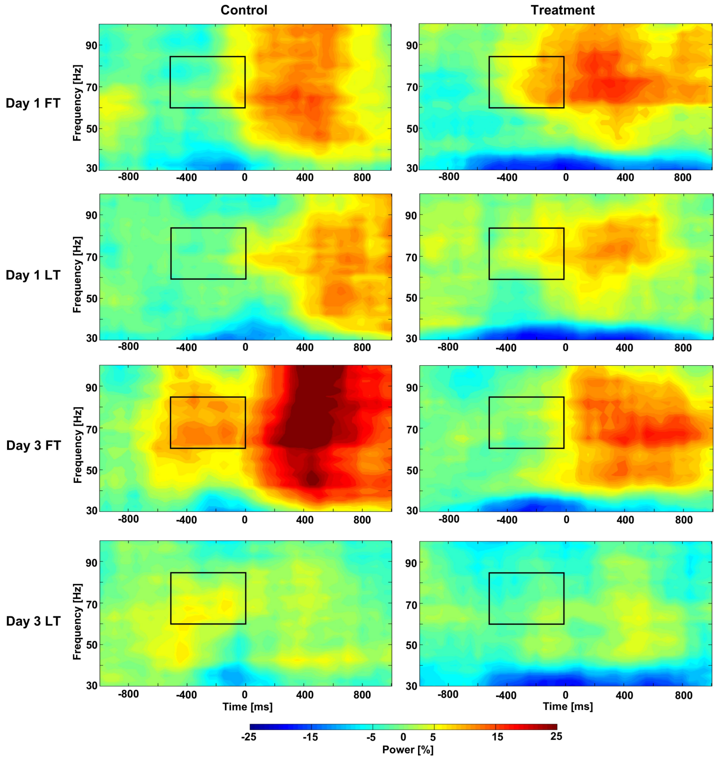

Figure 4.4: Grand average time-frequency plots of channel F3. The plots show the time-frequency power for the first and last force field trials on day 1 and day 3 (rows) and for control and treatment groups (columns). The black rectangle displays the movement planning window for the higher gamma band.

4.4.4 Results of the cluster-based statistics

The before mentioned results (Section 4.4.2, 4.4.3) analyzed the gamma band power over fixed time-frequency windows and used all EEG channels as a dependent factor within the ANOVAs. This is a good approach for complex statistical designs but leads to an inaccurate observation on the time-frequency level. To gain deeper insights into our results, we investigated if the significantly increased higher gamma band power during movement planning reveals a transient or widespread phenomenon in the frequency, time, and special domain. To do this, we performed cluster-based permutation tests (Section 4.3.5). The results showed that significant group difference regarding a possible consolidation effect (D3FT – D1FT) occurred predominantly in a time range of -600 to -100 ms before movement onset and in a frequency range of 60 to 90 Hz (indicated by green and red color in the time-frequency plots of Figure 5). Thus, the observed gamma band effect in our study is a transient phenomenon before movement onset and independent of the gamma band power during movement execution. Intriguingly, although the ANOVA revealed no significant time x channel or time x channel x group interaction, cluster-based statistics indicate that the observed effect in the gamma bands appeared predominantly in electrodes over prefrontal areas with a dependency to the left hemisphere (Figure 4.5). This indicates that the effect is not present over all frontal electrodes as indicated by the ANOVA, but rather in electrodes over the prefrontal cortex. Because cluster-based permutation testing is a powerful statistical approach (Cohen, 2014; Fraker and Peacor, 2008) we summarize that the increased higher gamma band effect in the control group occurred before movement onset, is independent from the movement-related gamma band power during execution, and appears predominantly in a frequency range from 60 to 90 Hz in electrodes over prefrontal areas.

4.5 Discussion

The aim of this study was to examine gamma band power changes within the human EEG in electrodes over the prefrontal cortex due to effects of motor memory consolidation. We hypothesized that retrieval of consolidated motor memory leads to (1) gamma band power changes which are (2) located in electrodes over the prefrontal cortex and (3) vanish with the subsequent re-adaptation.

While our results of the lower gamma band discard with our hypotheses, the results of the higher gamma band confirm all three hypotheses for the movement planning window. As further discussed, these results indicate the involvement of explicit components in the retrieval of motor memory. To the best of our knowledge, this is the first study showing the involvement of specific frequency bands in the

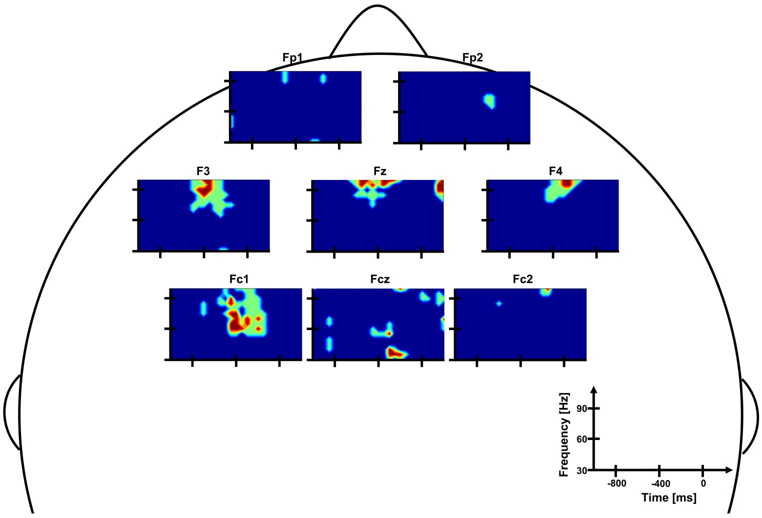

Figure 4.5: Time-frequency plots of the cluster-based statistics. The plots illustrate significant differences (colors indicate cluster-threshold; blue: $p > 0.05$; green: $p < 0.05$; red: $p < 0.01$) between groups in their possible consolidation effects (D3FT – D1FT) using cluster-based permutation testing. Plots of channels F8, Fc5, Fc6 and C3 are not displayed because they revealed no significant clusters. A detailed description of the underlying analyses is given in Section 4.3.5

human EEG during motor memory retrieval of a consolidated dynamic adaptation task.

4.5.1 Movement kinematics reveal memory consolidation of the control but not treatment group

The statistical analyses revealed that motor performance of day 1 did not differ between groups. Both groups showed a similar increase of their motor performance from the first to the last trials and, thus, a similar motor adaptation on day 1. This is in accordance with previous studies investigating force field adaptation (Focke et al., 2013; Gonzalez Castro et al., 2014; Shadmehr and Mussa-Ivaldi, 1994). Therefore, the difference between groups in their motor performance on day 3 is not explainable by differences in their initial force field adaptation.

The increased motor performance on day 3 for control subjects, compared to the first trials on day 1, reveals the motor memory consolidation of task A. However, the treatment group showed not such an effect indicating that task B interfered the memory consolidation even 24 h after the adaptation of task A. These results concur with previous force field studies (Caithness, 2004; Focke et al., 2013; Stockinger et al., 2014) and set the basis for the subsequent electrophysiological discussion.

Regarding our results, it is not possible to distinguish between a retro- or anterograde effect of the inferring task B (Robertson et al., 2004) as we did not include washout trials. Therefore, it is not clear if the observed decreased performance for the treatment group compared to the control group on day 3 is caused by the disruption of consolidation (retrograde) or by the disruption of memory retrieval (anterograde). Thus, the observed effect could also be caused by the inability of treatment subjects to retrieve the consolidated memory of task A due to the anterograde interference of task B.

4.5.2 Higher gamma band during motor planning indicates the contribution of explicit components

Our results showed that the control group exhibited an increased higher gamma band power in the movement planning window of day 3, whereas the treatment group did not. Furthermore, this effect was predominantly observed in electrodes over the prefrontal cortex and, thus, supports our first two hypotheses. Altogether, our results concur with the role of the prefrontal cortex for explicit memory retrieval (Gentili et al., 2015; Miller and Cohen, 2001; Roux and Uhlhaas, 2014) and are in line with the current research suggesting the involvement of gamma bands during working memory encoding and retrieval (Howard et al., 2003; Roux and Uhlhaas, 2014; Sederberg et al., 2003). Thus, our results support our hypothesis that motor memory retrieval affects the gamma bands during movement planning. However, we observed this effect only for the higher but not for the lower gamma band power. This could be explained by the suggestion that lower and higher gamma bands rely on different functionalities (Edwards, 2005).

Intriguingly, the observed effect of increased higher gamma band power for control subjects vanished with the subsequent re-adaptation on day 3. This finding supports our third hypothesis and shows that group differences occurred in the first but not last trials on day 3. If our results reflect a neural correlate of an implicit component, for instance internal model updates (Wolpert et al., 2011), we would not expect that this effect vanishes as long as the adapted perturbation is present and the motor performance stays constant on a comparably high level. Therefore, we do not associate these results with implicit components. Explicit components, however, are described as fast upcoming (after the first trial) components which require a prolonged preparation time (Fernandez-Ruiz et al., 2011; Huberdeau et al., 2015). The fact that power changes in our results occurred only in the movement planning window is, therefore, in line with the literature which shows that the planning phase plays a critical role for explicit components (Haith et al., 2015). With the subsequent repetition of a task, these components vanish and movement automaticity increases (Miller and Cohen, 2001). Therefore, we suggest that the observed increased power of the higher gamma band in the first trials of the re-test on day 3 is linked to explicit components.

This suggestion is also supported by previous studies describing that explicit components of motor planning are located in the prefrontal cortex and supplementary motor area (Bonini et al., 2014; Miller and Cohen, 2001). However, the majority of studies supporting explicit components in the motor memory of adaptation tasks used kinematic instead of dynamic perturbations. Concerning dynamic perturbations, it was suggested that force field adaptation relies on implicit components (Shadmehr et al., 1998), but more recent literature indicates the occurrence of explicit components after force field adaptation (see Krakauer and Mazzoni (2011), for a review). Furthermore, previous research supports the hypothesis that implicit memory can be transformed to explicit procedural knowledge and that this conversion is facilitated by sleep (Drosopoulos et al., 2011; Fischer et al., 2006). According to this, even when the memory encoding of a dynamic perturbation task might rely on implicit components, memory retrieval after sleep might rely on explicit components. In addition, the involvement of explicit components in memory retrieval of dynamic perturbation tasks is also supported by studies using force field tasks (Shadmehr and Holcomb, 1997, 1999). Altogether, our results seem to refer to the involvement of explicit components in motor memory retrieval, yet it is unclear if and how these components contribute to the re-test performance of a force field task. Possible explanations how explicit components might enhance re-test performance are: the prefrontal cortex consolidated a cognitive model of the perturbation (Haith et al., 2015), the prefrontal areas actively inhibit other memory traces (Sauseng et al., 2013), or the prefrontal cortex guides procedural memory of deeper structures to the primary motor cortex (Miller and Cohen, 2001). Moreover, it should be considered that re-test performance is likely facilitated by a contribution of different memory components (explicit, implicit, reinforcement, etc.).

However, as we mentioned in Section 4.5.1, subjects did not perform washout trials. Therefore, we cannot distinguish between the disruption of the consolidation per se or of the memory retrieval. Thus, it is possible that the lack of an increased higher gamma power in the treatment group could also be caused by the disruption of memory retrieval due to the interfering task B on day 2. Summarized, we suppose that increased gamma band power prior to movement onset in electrodes over the prefrontal cortex reflects processes of explicit components. Furthermore, it is possible that these components contribute to the motor memory retrieval even of a dynamic adaptation task. Whether explicit components guide information from deeper structures to the relevant motor areas or directly influence the motor outcome due to cognitive models or strategies of inhibition, belongs to future studies.

4.5.3 Gamma bands during movement execution showed no significant effects

Our results of the lower and higher gamma bands showed no group differences in their consolidation effects during movement execution. As previously mentioned, the absence of an effect could be explained by the critical role of the movement planning and not execution for explicit components (Haith et al., 2015).

Intriguingly, we observed an increased higher gamma power during movement execution in the first trials of day 1 and day 3 for all subjects, but this effect weakened with the further (re-) adaptation to the dynamic perturbation (Figure 4.4). This effect has to be interpreted with great caution due to possible muscular artifacts during movement execution. However, this effect might indicate the involvement of explicit components in motor memory encoding and retrieval (Huberdeau et al., 2015) even during movement execution.

4.5.4 Limitations and conclusion

Although our study is based on a comparable large set of subjects, there are a few limitations. The usage of 13 EEG electrodes is in accordance with previous studies investigating memory encoding (Novakovic and Sanguineti, 2011; Tan et al., 2014) but results in a comparably low spatial resolution. Nevertheless, we assume they were sufficient to record the activity in electrodes over prefrontal areas. However, in a future attempt it is necessary to use high-density EEG to improve the quality of the spatial resolution and the subsequent signal processing.

Regarding our results, we cannot exclude that the observed effect in the higher gamma band reflects a side effect of muscular artifacts or different states of subjects' awareness. It is possible that, during the re-test condition, control subjects were aware of the task A, whereas treatment group was not because they learned two opposing force fields and, therefore, might not allocated the re-test condition to the specific task A. However, we would not expect such a side effect occurs transient in the motor planning phase and, furthermore, we would not expect that control subjects implement a muscle artifact only in the initial trials of day 3.

We conclude that our study supports previous work suggesting the involvement of explicit components in the retrieval of motor memory after a period of consolidation in a dynamic adaptation task. This involvement seems to be reflected by increases in the higher gamma band power in electrodes over the prefrontal cortex in the human EEG. Up to now, it is unclear how the prefrontal cortex contributes to an improved motor performance after a period of consolidation. Therefore, future studies are needed to proof the involvement of explicit components and gamma bands during memory encoding, offline learning inclusive sleep, and memory retrieval.

Chapter 5

General discussion

> *"Do not try and bend the spoon. That's impossible. Instead... only try to realize the truth." [...] "There is no spoon."*
>
> — Spoon boy, *Matrix I*

All studies performed in this thesis investigated motor adaptation under force field conditions in combination with EEG. Variability of force field conditions was implemented either within the same practice period (variable practice effect) or in different practice periods (ABA paradigm). Each study was able to reproduce known behavioral phenomena and gave insights about possible neural mechanisms and even correlates behind these behavioral results. Altogether, the different findings of this thesis can be integrated and summarized in two general statements: (1) interference but not sleep affects motor memory, (2) lower and higher frequency bands are linked to motor memory processes. In the subsequent sections, I will discuss each of these statements according to the literature and its implications for future studies.

5.1 Interference but not sleep affects motor memory

Practicing hand-reaching movements under different dynamical conditions was the experimental paradigm which was used in this thesis. Subjects either adapted to unstable force field magnitudes of similar directions (Chapter 2 and 3) or adapted and re-adapted to different force field directions (Chapter 4). Therefore, all studies in this thesis induced some sort of interference and tested its impact on memory consolidation and memory retrieval.

5.1.1 Positive impact of interference

The experiment of Chapter 2 investigated if unstable practice conditions have a positive impact on the motor performance of a dynamic adaptation task. While the force field conditions in Chapter 4 differed in their direction (clockwise vs. counter-clockwise), here, force fields had the same direction but were of different magnitude (10, 15, or 20 Ns/m). The results concur with the force field adaptation literature, which showed that a random intersperse of null-field trials (catch trials) during force field practice will induce variances and, thus, increase the retest performance (Focke et al., 2013; Overduin et al., 2006; Stockinger et al., 2014). Moreover, for the first time this study was able to reproduce the contextual interference effect in the force field paradigm. According to the contextual interference (Kantak et al., 2010; Wright et al., 2015) and to the force field literature (Dhawale et al., 2017; Overduin et al., 2006), these results demonstrate that interference in motor practice can enhance motor memory consolidation as long as the direction of interference stays constant.

The positive effects of interference were observed in different experimental paradigms (adaptation and skill learning tasks; Lage et al. (2015); Schmidt and Lee (2011)). This leads to the assumption that benefits of variable practice are not specific to a certain skill but might reflect a general learning phenomenon. This is supported by neuroscientific studies (Cross et al., 2007; Kantak et al., 2010; Lin et al., 2013, 2011; Tanaka et al., 2010; Thürer et al., 2017), which showed positive effects of variable practice in different brain areas, especially in frontal and parietal cortical areas. That means, benefits of variable practice are not facilitated by one specific core region but might reflect a general working mechanism of the CNS.

Previous work discussed these benefits of high interference practice schedules with an increased consolidation of the specific motor task's memory. This, however, must not be the case because Chapters 2 and 3 showed that interference might increase the ability to correct the movement execution by feedback integration and, thus, that interference might not lead to motor memory consolidation per se. The assumption that benefits after variable practice come from an increased task consolidation also contradicts the transfer results in Chapter 3. The results showed that subjects who practiced under random force field conditions facilitated an increased left-hand transfer performance compared to the blocked practicing subjects. But the absolute values of the transfer test proofs that all subjects performed worse in the transfer test compared to the practice period - their first force field experience. Together with the dependent variable which purely reflects feedforward mechanisms (force field compensation factor), this proofs that subjects expected an intrinsic generalization of the force field memory from the right to the left hand. In other words, subjects expected changes of the force field direction from clockwise during practice to counter-clockwise during transfer. Since this was not the case, subjects' performance deteriorated. Furthermore, the amount of force field prediction on the left hand during transfer was similar for both groups at -15 %. If unstable force field conditions would lead to an increased memory consolidation of the specific motor adaptation task and generalization would take place in intrinsic coordinates, this should lead to a decreased and not increased transfer performance on the left hand for the random group. Since in Chapter 3 the opposite was the case, benefits after random practice seem to be facilitated by online feedback corrections which could be falsely interpreted as an increased motor memory consolidation.

This assumption of online feedback corrections as the primary mechanism facilitating the contextual interference effect, is also in line with optimal feedback control (Todorov and Jordan, 2002). According to the explanation given in Section 1.2.2, optimal feedback control describes that movements are corrected in task-relevant dimensions to fulfill a specific task goal. Therefore, unstable practice conditions lead to permanent task errors which must be compensated by permanent corrections of the task-relevant dimensions. This might lead to a positive practice effect regarding the processing of this optimal feedback loop, which is then observed in an increased task performance. However, this last aspect is quite speculative and needs further evidence.

5.1.2 Negative impact of interference

The study in Chapter 4 showed that re-adapting to the same force field but this time with a different direction, inhibits the retention performance in the previous force field. This was even the case if there was a 24 h consolidation period between the practice sessions. It is important to note that this phenomenon might reflect an inhibition and not a deletion of the previous memory, as classic conditional studies already showed that responding to conditioned stimuli recovers with the passage of time (Pavlov, 1927). Thus, adapted subjects will fall back into their old, not-adapted motor dynamics (or in conditional studies, into their old habit), when they practice under normal conditions or under conditions in which feedback is excluded (Joiner et al., 2013). This shows that the previous, not-adapted (normal) motor program of reaching is inhibited but not extincted (Berman and Dudai, 2001).

According to the general assumption that consolidated memory is resistant against interference, the consolidation process of force field adaptation, in this study, was not complete. These findings confirm previous work using visuomotor rotation or force field adaptation (Caithness, 2004; Focke et al., 2013) but, however, contradict with older studies which showed that re-adaptation of an opposing force field does not affect retest performance if the time lag between the two practice sessions accounts for at least 5 h (Shadmehr and Brashers-Krug, 1997; Shadmehr and Holcomb, 1997). This discrepancy in the inter-study results is still unsolved and led to several approaches investigating the mechanisms of consolidation behind motor adaptation (e.g. Brashers-Krug et al., 1996; Caithness, 2004; Focke et al., 2013; Krakauer et al., 1999, 2000; Miall et al., 2004; Overduin et al., 2006; Tong et al., 2002). Altogether, these studies showed that the assumption by Shadmehr and Holcomb (1997), that motor memory consolidation purely depends on time, is not true. Time seems to be one factor (apparently a major one) but other factors like practice conditions (Overduin et al., 2006), amount of kinematics or dynamics involved in the motor skill (Tong et al., 2002), or superposition of different learning processes (Smith et al., 2006) seem to impact the behavioral results and memory consolidation as well.

From an interdisciplinary perspective regarding force field adaptation, there may be other theoretical aspects explaining this discrepancy in the motor memory consolidation literature. In particular, two possible aspects, which are barely mentioned in the force field adaptation literature, are of primary interest for the interpretation of consolidation results.

The first aspect is the widely accepted phenomenon of re-consolidation (Nader and Hardt, 2009). Re-consolidation describes that activation of an already consolidated memory leads to a transformation of this engram back into its fragile state (Lewis, 1979). Therefore, after a short period of relearning, the memory engram can be updated and adapted to new conditions. Concerning the whole memory process in ABA paradigms related to the two stage model of memory (Marr, 1971) and hebbian learning theory (Hebb, 1949), practice in force fields will lead to a neural representation of the specific motor task first. Then, during consolidation, weak and task irrelevant synapses will be degraded, whereas strong and relevant synapses remain stable (or might even become stronger in form of a replay, Hanert et al., 2017) - this effect of degraded or stabilized synapses has already been observed during sleep in mice (Diering et al., 2017). This process of stabilization takes time and concurs with the results of Shadmehr and Brashers-Krug (1997), assuming that after a period of consolidation the memory engram for 'A' is resistant against interference. However, re-consolidation could also explain the controversial findings by Caithness (2004). Similarities of task kinematics, dynamics, and goals might hinder the CNS in its creation of an independent memory engram for 'B'. Regarding re-consolidation, the more stabilized the synapses are (due to consolidation), the longer the process of re-activation would take. Hence, with the amount of consolidation, subjects would need to practice more trials of the opposing force field 'B' to re-activate the previous memory and transform this into a new representation. According to Diering et al. (2017), this re-activation would weaken the 'strong' synapses of task 'A' and stabilize the relevant synapses of task 'B'. Future studies will be able to test this assumption empirically. If re-consolidation leads to the addressed discrepancy in the literature, an increased amount of interference trials as a function of consolidation, time would lead to a consistent reduction of retest performance.

The second aspect targets the two-stage model by Marr (1971). Studies investigating motor memory consolidation inherently assume that there is such a two-stage model (Rasch and Born, 2013). However, as explained in Section 1.2.4, it is not clear if motor memory, similar to declarative memory, goes from a short-term to a long-term memory with a period of consolidation in-between. Searching for other theories than consolidation might lead to new ways to explain the inconsistent findings in motor memory consolidation. For instance, a motor learning theory which does not depend on consolidation would picture motor skills and adapted motor skills as more fragile. Therefore, not time but previous movements and their success would influence the retest performance as these are the factors weakening or stabilizing synapses. This speculative assumption is intriguing for it would be able to explain the occurrence of natural variances in kinematics of all movements (Todorov and Jordan, 2002). A fragile motor memory network of synapses would lead to fast remodeling in its connectivity, maybe after every single movement. Therefore, integration of feedback into the ongoing and the future motor plan would be important to generate consistent end-point performances. This aspect of the importance of feedback is in line with optimal feedback control and the assumptions which are made in this thesis (Chapters 2 and 3), since artificially evoked variances would increase errors during movement execution which can be used for movement corrections. Accordingly, the amount of time between practice sessions would not be relevant for the memory engram, as time is not a critical factor, but still, time would influence recall in other ways (e.g. fatigue or recovery). This assumption is quite speculative and does not agree with the results of Shadmehr and Brashers-Krug (1997) but researchers should be open for the possibility that there might not be a classic consolidation period for motor memory.

5.1.3 Sleep does not influence force field adaptation

One of the main purposes of Chapter 3 was to investigate if motor memory adaptation of the force field paradigm depends on sleep. In the literature, there is a big community supporting the assumption that not only declarative but also procedural and, hence, motor memory depends to some extent on sleep (Albouy et al., 2013; King et al., 2017; Plihal and Born, 1997; Stickgold, 2005). However, others were not able to find such an effect for motor adaptation tasks (Donchin et al., 2002; Shadmehr and Mussa-Ivaldi, 1994) and supposed that non-hippocampal-mediated tasks like force field adaptation do not depend on sleep. This latter assumption is widely accepted in the motor adaptation community but studies which reproduced the findings of Donchin et al. (2002) with a proper sleep protocol and flanked by sleep EEG are missing.

This thesis was able to clearly show that force field adaptation does not depend on nocturnal sleep. The results support the previous findings by Donchin et al. (2002) and demonstrate that force field adaptation is not sleep dependent. Furthermore, this study was able to show that sleep dependency is not affected by different practice conditions. Thus, a motor task memory which does not depend on sleep is still unaffected by sleep when it is practiced under unstable task conditions. These findings contradict with previous assumptions (Debarnot et al., 2015; King et al., 2017). However, this should not lead to the assumption that memory consolidation of force field adaptation is purely time dependent for I already pointed out that other factors (e.g. practice conditions) contribute to the memory process. The experimental paradigm in this thesis captured a specific motor adaptation task and does not rule out that memory consolidation of other motor tasks rely to some extent on sleep.

5.2 Frequency bands for correlates of motor memory

All studies in this thesis flanked the behavioral tests with EEG and investigated possible cerebral correlates of motor adaptation and motor memory consolidation. The results show that lower (alpha) and higher (gamma) frequency bands in the EEG might be good candidates for correlates of motor memory processes (this confirms previous findings of other memory tasks, Canolty et al. (2006)). However, as force field adaptation is not affected by sleep, EEG recordings during sleep after practice might not be beneficial in the quest for the underlying neural substrates of force field memory. Therefore, I will focus in the subsequent discussion only on the task-EEG, recorded during the practice, posttest, and transfer sessions.

5.2.1 Gamma band power in motor memory retrieval

The EEG analyses in Chapter 4 showed that subjects which underwent the A-A design and, thus, were not inhibited in their recall of the force field, revealed an increased gamma band power during movement planning in their prefrontal areas. This effect was short-lasting and vanished with further re-adaptation. This effect, its occurrence in motor planning, and the localization over prefrontal areas indicates that this increased gamma band power might be linked to explicit but not implicit task components (Huberdeau et al., 2015; Miller and Cohen, 2001; Roux and Uhlhaas, 2014). Together with the findings of Chapter 3, which showed that this force field adaptation is not sleep dependent, and with the findings by Huberdeau et al. (2015), who showed that long-term motor adaptation memory is facilitated by implicit components, this increased gamma band power might not be a good correlate of the underlying motor memory because it does not capture the implicit part. Furthermore, even if the gamma band power is linked to the explicit components, it is not clear if such explicit components are task relevant and reflect specific explicit strategies, useful for task completion. Regarding the internal model theory, it is highly unlikely that the gamma band effects observed here reflect benefits of an updated internal model, since it is suggested that internal model updates are represented in a long-lasting and implicit process (Mazzoni, 2006; Taylor and Ivry, 2014).

Chapter 2 used exploratory statistical to examine the underlying neural mechanisms of the positive effects after unstable practice. This study also showed significant gamma band power changes but their location was over temporal and not prefrontal areas. Deeper investigations of the power spectra revealed that this effect represented movement artifacts. In the study of Chapter 3 no significant effects of the gamma band power related to unstable practice have been found. Therefore, although gamma band power might be related to explicit components during retrieval, it is not linked to the motor benefits of random practice and consolidation of motor memory. Because of that, EEG's gamma band power might be a good candidate to investigate initial explicit strategies (future work is needed to proof that) but not to investigate motor memory mechanisms or possible internal model updates.

5.2.2 Alpha band power correlates with behavioral performance

Chapters 2 and 3 investigated if benefits of unstable practice correlate with neural substrates captured by EEG. The results indicated a left-hemispheric (contralateral), parietal area of interest in the alpha band which correlated with the behavioral results. This involvement of lower frequencies in learning mechanisms confirms previous work (Canolty et al., 2006) and shows that lower frequencies are important for learning mechanisms.

In Chapter 3, parietal alpha band power during practice was able to predict the subsequent performance difference from practice to transfer in blocked practicing subjects. In detail, increased alpha band power during practice in the blocked group led to a worsened motor consolidation. That means, subjects' correlation between the alpha band power and the motor behavior is not just a coincidence, since correlation analyses indicated that the alpha band power during practice is associated with the memory consolidation from practice to transfer. Therefore, alpha frequencies might be a good neural correlate for motor memory consolidation. This assumption makes sense because it is widely accepted that an increased alpha band power reflects the inhibition of the targeted area (Klimesch, 2012). In so far, for some unknown reasons motor relevant areas are partly inhibited which inversely correlates with the transfer performance. However, this effect was only seen for the blocked practicing subjects, indicating that random practice can overcome this limitation. I speculate that such a benefit of random practice might be facilitated by the increased ability to use online feedback to correct the ongoing movement.

Another possibility is that the observed effects represent changes in the subjects' attention due to different task protocols. Since it is assumed that attentional mechanisms of the visual system are linked to EEG's alpha frequencies over parietal areas (Sauseng et al., 2005), the findings in Chapters 2 and 3 could be affected by attention. Although I cannot rule out such a potential influence, the high effect sizes of the statistics combined with the cortical location pointing more to the posterior parietal cortex (PPC) and the high standardization for confounding attentional effects (especially in Chapter 3), lead to the suggestion that results are evoked by sensory processing and not by attentional mechanisms.

The findings of an parietal area of interest together with the assumption that online feedback corrections might have affected the performance differences between unstable and stable practicing groups concurs with an quite old assumption that the PPC has direct access to the motor output of hand movements (Mountcastle et al., 1975). Recently, a study by Rathelot et al. (2017), examining non-human primates, was able to confirm this hypothesis. They showed that PPC influences interneurons which, in turn, are able to directly inhibit the motor output patterns of hand movements. Furthermore, this study was able to show that PPC's route to access motor outputs exceeds the route of the premotor areas. Future studies investigating motor benefits of variable practice conditions should investigate these possible aspects, for instance by inhibiting the PPC using TMS.

Altogether, the EEG findings in this thesis show that EEG is a good tool to investigate motor memory under laboratory conditions. This thesis was able to show that frequencies within the alpha range seem to be associated to motor memory but the details of this association are still unclear. The reproducibility of the alpha band findings over parietal areas in Chapters 2 and 3 support the conclusion of the behavioral discussion that parietal feedback mechanisms are facilitating the benefits of unstable practice conditions. Recent neuroscientific studies support the view that parietal areas can directly influence reaching movements (Rathelot et al., 2017). Obviously, motor memory and its consolidation reflects a complex mechanism which is not only explainable by an in- or decrease in power of one specific frequency band in a specific brain region. In addition, EEG is not able to detect cerebellar or sub-cortical mechanisms which are involved in motor control (see Section 1.2.1). Therefore, I suggest that the findings of this thesis do only reflect one small piece of the whole mystery of motor memory representations in the human brain.

5.3 Limitations and implications for the future

5.3.1 Impact of retrograde inhibition on the random practice effect

The work in Chapters 2 and 3 showed motor benefits after variable practice confirming the contextual interference effect. But these studies cannot rule out possible confounding effects of retrograde inhibition in the blocked practicing subjects (see Section 4.5.1 and 2.4.5). Thus, blocked practice might lead to a chain of subsequent retrograde inhibitions in which, with every practice of a force field block, the memory of the previous force field block is inhibited. If that is the case, retest performance of blocked practicing subjects mainly depends on the last practiced force field magnitude of the practice session. To control this potential effect of retrograde inhibition, the experimental design of a certain study must consider every possible order of the magnitudes during practice in combination with the retest magnitude. In the case of three different force fields magnitudes or three different motor tasks, this would lead to 18 different combinations. However, with 18 combinations there is only one force field magnitude or motor task retested for each subject in the retest session. Testing for the retention of all three magnitudes or tasks would lead to 36 possible combinations (6 possible combinations during practice multiplied by 6 possible combinations during retest). To the best of my knowledge, there is no study controlling for this possibly confounding effect with at least 18 or 36 subjects per group.

To examine if retrograde inhibition affects the contextual interference effect in motor adaptation, a recent study is conducted in our lab (Thürer et al., 2018, *in preperation*). Preliminary results showed only small affects of retrograde inhibition on the retest performance in force field adaptation. Therefore, retrograde inhibition does have an impact on the contextual interference effect, at least in force field adaptation tasks, but this effect is far too weak to explain the effect sizes shown in Chapters 2 and 3.

5.3.2 Do online feedback corrections facilitate the random practice effect

The studies conducted in this thesis and its general discussion lead to the suggestion that online feedback corrections facilitate the benefits after variable practice. This suggestion is based on the results of specific dependent variables which have been used to quantify the motor performance. However, these variables do not directly measure online feedback mechanisms. The findings in Chapters 2 and 3 are not able to proof that online feedback corrections are responsible for the behavioral effect. Therefore, the suggestion of online feedback corrections here is based on indicators coming from different findings on the behavioral and the neural level, together with the reproducibility of the results. Future studies are needed which investigate the relevance of feedback and the involvement of the parietal cortex for the contextual interference effect. To do so, future studies should perturb feedback in different sensory systems (visual or proprioceptive) to test its impact on the behavioral retention performance. Furthermore, studies should examine if inhibition of the parietal cortex with transcranial magnetic stimulation (TMS) hinders the behavioral effects.

If these future studies are able to confirm the relevance of feedback and if inhibition of the parietal cortex hinders this effect, EEG's alpha frequencies would be the main signal to analyze. This thesis was already able to show that the observed alpha band effects are not just a coincidence and that they were reproducible in different subjects by using a different preprocessing schema. With high density EEG and source localization, in future studies it would be possible to detect the direction of information flow of the alpha frequencies within the brain. Measures of brain connectivity would be able to detect if signals in the alpha domain during movement execution flow in a feedforward (parietal to frontal) or feedback (frontal to parietal) direction.

However, reproducibility of the parietal cortex's involvement in this thesis contradicts previous work which used different motor tasks and found prefrontal brain areas involved in the contextual interference effect (e.g. Kantak et al., 2010). It is still possible that the observed brain areas do only reflect the increased neural effort in these areas due to different practice conditions. Thus, prefrontal and parietal brain regions must not be directly connected to motor memory or memory consolidation. Future studies are needed to investigate why different brain areas are involved in different motor tasks but both leading to the same behavioral phenomenon (motor benefits after variable practice).

5.3.3 Discrepancy in ABA paradigm studies

The discrepancy in the findings of ABA paradigm studies using force field adaptation is still unsolved. In Section 5.1.2, I introduced the suggestion that this discrepancy might be solved if the amount of trials in the interference session 'B' is set as a function of consolidation time (and in more detail as a function of time and practice condition). This assumption is derived from the hebbian learning theory in combination with the theory of re-consolidation. Consolidation strengthens relevant synaptic connections but weakens non-relevant connections. If there is enough time for consolidation, more trials must be completed under the 'new' interfering task condition to rebuild the former non-relevant (but now relevant) synaptic connections and to weaken the former relevant (but now non-relevant) connections.

However, previous studies examining the ABA paradigm in force field adaptation set the amount of trials regardless of the amount of time between test sessions and, furthermore, the amount of trials in the interfering session 'B' was similar to the initial session 'A' (e.g. Caithness, 2004; Focke et al., 2013; Shadmehr and Brashers-Krug, 1997; Thürer et al., 2016). Future studies should properly increase the amount of trials and / or induce variable practice conditions in the interfering session 'B' and test its effect on the retest of the former force field 'A'.

5.4 Conclusion

The aim of this thesis was to gain deeper insights into the behavioral and neural processes during and after different interfering practice conditions. Three studies were conducted to fulfill this aim. The main findings of these studies were:

(1) Interfering practice conditions can enhance the consolidation and generalization performance.

(2) Consolidation and generalization of force field adaptation tasks do not depent on sleep.

(3) Interference induced by a different practice session with an opposing motor task can re-consolidate the previous memory even after a retention period of 24 h.

The synopsis of the findings (1) and (2) and their integration into the scientific literature led to the suggestion that online feedback correction of the parietal cortex facilitates the benefits of the contextual interference effect in force field adaptation tasks. However, further proof is needed regarding this assumption. Another remaining question is if alpha band frequencies over parietal areas are directly connected to feedback mechanisms and the behavioral performance. The interpretation of finding (3) led to the open question if different amounts of trials in the interfering practice session as a function of consolidation time would lead to different results in the ABA paradigm.

In general, this thesis showed that motor memory is a complex research field which is far from being understood soon on the behavioral, computational and neural level. Much more effort in the future years and decades will be needed to completely understand motor memory in order to improve motor training in rehabilitation, sports, or everyday life.

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Statutory declaration

Hiermit erkläre ich, dass ich die vorliegende Dissertation mit dem Titel:

"Towards cerebral and behavioral representations of motor learning and its interaction with interference and sleep"

selbstständig angefertigt habe und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt sowie die wörtlich oder inhaltlich übernommenen Stellen als solche kenntlich gemacht und die Satzung des Karlsruher Instituts für Technologie (KIT) zur Sicherung guter wissenschaftlicher Praxis beachtet habe.

Karlsruhe, den 13. Februar 2018