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Influence of Mental Preparation Tasks on TMS-Induced Motor Potentials

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Contents

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Outline

The study at hand fits into the field of motor-cognition which is an attempt to root cognition in the body. Theories of motor-cognition state that much of the processing of perceptions as well as meaning happen within the motor system. They acknowledge that actions have a goals or a purposes that are present to the actor at the time of the action. Another dimension of motor cognition is that it is fundamentally social. Research in the field has concluded again and again that the representations of understanding actions of others overlap with the representations of action execution. This means that we understand the intentions of others by knowing our own agency. We, however, also learn how to act by observing actions of others and deriving their intentions from those observations. In a broader sense, motor cognition aims at providing insight into one of the many aspects of the subject of agency and self-consciousness, which in recent years have increasingly favored an interdisciplinary approach instead of discussing them from a rational perspective exclusively, as philosophy did for centuries. Both in the sciences (e.g. cognitive neuroscience), as well as recent developments in cognitive science (e.g. enactivism) the body plays an increasingly important role for agency.

This research can be understood as adding to the endeavor of regarding agency and self-consciousness from an interdisciplinary perspective with an emphasis on the importance of the body. In more concrete terms, this thesis is concerned with the interaction of the volitional and the executive aspects of movement. It is a well-known and evident fact that we can guide and regulate our movements according to certain

goals. Clearly, there is an association between the thoughts that we think, the plans we have and the actions we take. In most cases, this has a positive character, i.e., we decide to do something and then do it. However, the negative aspect of movement is often overlooked, namely that we are capable of actively inhibiting movements. This again seems quite intuitive, since it is usually us who are responsible for the movement and we are hardly ever in situations where a movement is being executed without us being the initiator of it. Transcranial magnetic stimulation (TMS) enables us to do exactly that. A movement is induced in a person without him or her ever "taking action". It has been reported, however, that it is possible to influence the intensity of these induced movements by simple volitional tasks. The dissociation of the volitional and the execution aspect of movement can hence be studied using TMS in appropriate experimental designs. A paper by Bonnard et al. (2009) tested whether people could decrease or increase a TMS-induced motor twitch of the wrist and concluded that subjects were able to do so. In the present master thesis, the assumptions of this preceding study were challenged through several methodological modifications and improvements which led to results and interpretation that diverge from those of previous studies.

In the first chapter, a brief introduction into some basic background concepts that are important for the experiment described in a later part of the thesis is provided. In a first step, I outline how TMS works and how it can influence electrophysiology. I also discuss how some electrophysiological properties of the nervous system can be assessed by electromyography (EMG). However, I focus on those aspects of TMS and EMG that are relevant, firstly, for understanding later parts of the theoretical chapters of the thesis and, secondly, for the experiments conducted for the thesis at hand. In chapter 2, I provide evidence that both assisting as well as resisting the induced movements, is possible. For that purpose, I discuss the capacity to simulate, observe and prepare for actions. With these arguments I want to show that it should be expected that subjects can mentally prepare for an increased response to a TMS

pulse. I later argue that these findings can be extrapolated to the experiment at hand. I summarize two papers of Bonnard et al. (2003, 2009) in chapter 3 and based on the chapter before argue why parts of their conclusions are, firstly, unexpected and not in line with neurophysiological evidence and, secondly, why some of their conclusions cannot be drawn from the experiment they conducted. Based on this criticism, the research question and the hypotheses that follow from it are formulated. The aim of chapter 4 is to take a close look at the design and methodology of the study and to describe the modifications to the initial experiment of Bonnard et al. (2009). In chapter 5, the results are presented and discussed. Discussion mainly focuses on the interpretation of the differences of the results of this study and its predecessors, mainly by examining the variability present in TMS experiments.

It cannot be avoided that for the knowledgeable reader these elaborations fall short in many instances. While I do not try to pretend that all these shortcomings are by choice, I want to explain myself at least in one regard. I have decided not to include any information on the influence of the basal ganglia on cognitive as well as motor aspects of movement production. This decision was based on the fact that the research conducted within the scope of this thesis can at best draw inferences on the functional aspects of the cortical motor system. Hence, the main focus is on the neocortex throughout the thesis.

Chapter 1

Introduction

1.1 TMS

This chapter introduces several necessary conceptual and methodological basics of transcranial magnetic stimulation (TMS). For a thorough analysis of the plethora of issues that come along with TMS research and treatment, the interested reader is referred to Wassermann et al. (2008).

1.1.1 Physics and Biophysics of TMS

TMS was invented by Barker et al. in 1985 and is a non-invasive, safe and comparably comfortable way to induce electric currents in brain tissue via electromagnetic induction. TMS uses strong magnetic field pulses to excite or inhibit neurons in the brain. This is done by sending high voltage through a plastic-shielded wire coil, in which a magnetic field is generated. The coil receives electric current for a short period (600 μs) from a capacitor, which is charged from a power source (Figure 1.1). The "magnetic field pulse [...] induces electrical fields, and hence currents, [...] which are proportional to the rate of change of magnetic field (dB/dt)" (Barker and Freeston, 2007, para. 6).

For stimulation, the coil is put on the scalp and the magnetic field can penetrate the

bone to reach into the outer layers of the cortex. Once the magnetic field reaches the neurons, it can depolarize neurons which serve as a conductor and therefore trigger action potentials. The term "magnetic" stimulation suggests that the method is distinct from electrical stimulation. This, however, is only true to some extent. While the delivery of electrical stimulation and magnetic stimulation is, in fact, distinct, the effect on the neuronal level is actually the same for both. Neurons are excited by the exact same neuronal mechanisms that are used when implanted or surface electrodes inject electrical current directly (Barker and Freeston, 2007).

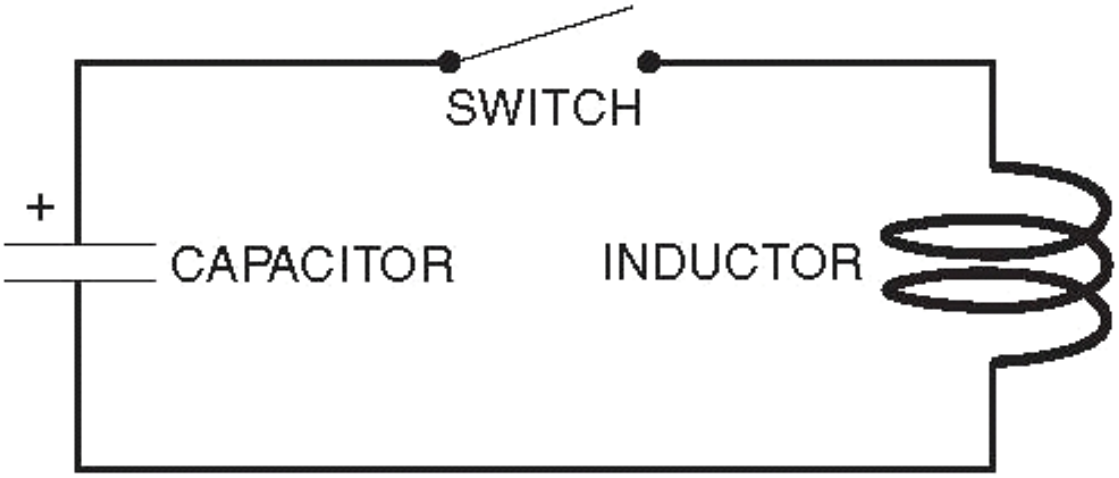

Figure 1.1: Simplified TMS circuit. The capacitor is first charged to a high voltage, and then discharged into the inductor (the stimulation coil) when the switch is closed. Reproduced from Epstein (2008a).

Brain tissue is conductive and can serve as a conductor for externally applied magnetic fields. The conductivity of different kinds of brain tissue varies greatly, which also poses problems for finding the ideal hotspot for stimulation. Additional constraints for stimulation are anisotropy and head geometry (Miranda et al., 2003; Wagner and Al., 2007; Baumann et al., 1997).

The big advantage of TMS over electrical stimulation is, that it is painless. Due to its low frequency, the magnetic field can pass through the skull easily, with close to no attenuation. Additionally, the pulse also passes through the skin without exciting

pain nerve fibers in the skin, since the strength of the magnetic field reaches its maximum only several millimeters to centimeters away from the coil, and the strength is therefore decreased close to the coil (Barker and Freeston, 2007).

1.1.2 TMS Coils and Pulse Forms

TMS coils can have various shapes, which can be used for different stimulation aims. All coils have advantages and disadvantages, typically representing a trade-off between stimulation depth, focality and stimulation intensity, and hence are suitable for different research and clinical applications. Because of the limited scope of this thesis and for reasons of relevance, I will briefly discuss only the two most common coil types, the circular and figure-of-eight coil.

Circular Coils

The classical and historically earliest form is the circular coil (Figure 1.2). It is comprised of a wire coil of between 8 to 15 cm in diameter. The electric current running through the coil is opposite to the direction of the magnetic field induced. Although the magnetic field as well as the electric fields are more or less symmetrical, the largest effect on brain tissue is not observed beneath the center of the coil. This was shown by stimulating motor cortices of both hemispheres by placing the coil over the vertex. It was found that motor-evoked potentials (MEPs) were larger for the hemisphere that received the input from the side of the coil where current flows in a posterior to anterior direction (Rösler et al., 1989). Whether this effect is due to specific properties of the primary motor cortex (M1) alone is not yet clarified. However, the lack of knowing what exactly it is that one is stimulating in motor studies, greatly reduces the applicability of circular coils in these studies (Epstein, 2008b).

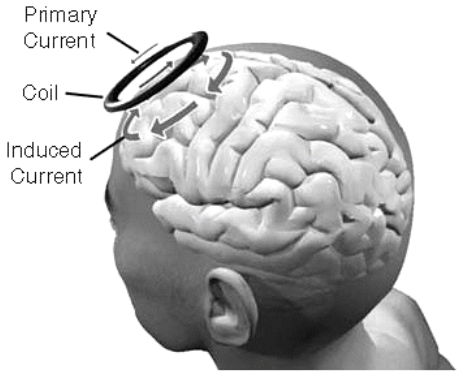

Figure 1.2: Circular stimulation coil showing opposite directions of primary coil current and induced brain current. The size of the arrows does not reflect the size of the current, which is many orders of magnitude greater in the coil than in the brain. Reproduced from Epstein (2008b).

Figure-of-Eight Coils

The most commonly used coils in TMS studies are figure-of-eight coils or butterfly coils (Figure 1.3). In contrast to the circular coil, the figure-of-eight coil does not face the problem of uncertainty of actual stimulation site to the same extent as the circular coil does. Basically, figure-of-eight coils are two circular coils placed next to each other, partially overlapping.

The currents flow in the same direction in both coils and add up in the center of the coil, thereby generating a stronger magnetic field at the middle junction, approximately twice as strong as the magnetic fields of the individual coils (Barker and Freeston, 2007; Epstein, 2008b). Higher focality is achieved by the differences in the magnetic field of both coil types can be seen in Figure 1.4.

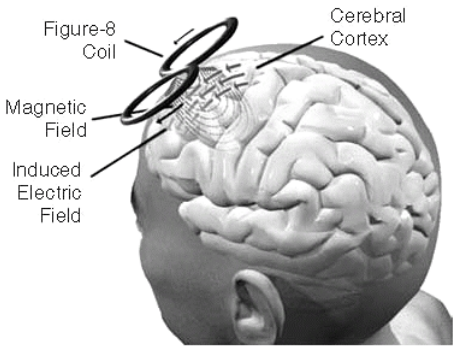

Figure 1.3: Magnetic and electric fields produced by a figure-8 coil over left prefrontal cortex. The two narrow black arrows show the current directions in the two side loops, which will sum at the coil junction. If the anterior-posterior coil orientation is defined by the plane of the coil junction, the magnetic field (small gray arrows) lies at right angles to that plane, extending from the center of one side loop to the center of the other. The induced electric field (large gray arrows) is in the plane of the coil orientation, and is largely constrained to lie parallel with the cortical surface. Reproduced from Epstein (2008b).

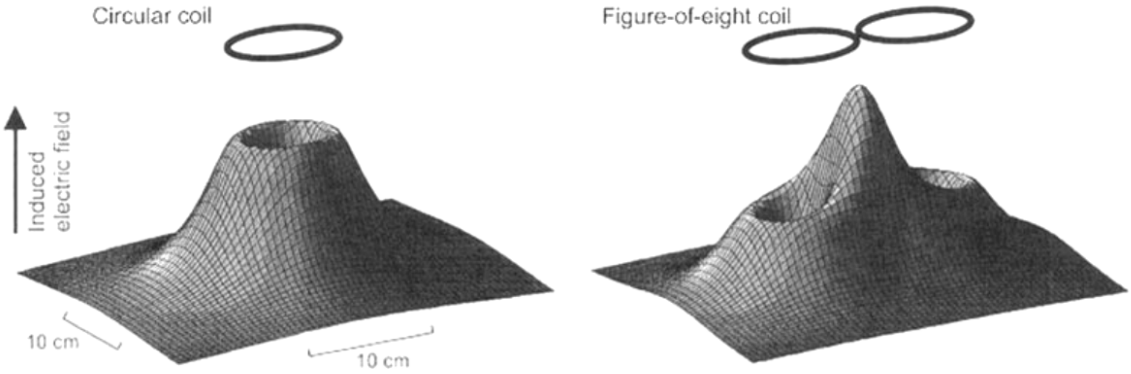

Figure 1.4: The strength of the electrical field induced below a circular (*left*) and figure-of-eight coil (*right*). Reproduced from Ilmoniemi et al. (1999).

Pulse Forms

Two different wave forms can be outputted by the TMS machine, and they have different effects on the stimulated brain tissue. *Monophasic* pulses consist of a single steep quarter cycle, *biphasic* pulses, on the other hand, show a second and a third cycle (Figure 1.5) (Bohning, 2000; Di Lazzaro et al., 2001). These differences in the magnetic field are due to differences in the rate of change of the induced current (Sommer and Paulus, 2008).

Monophasic pulses yield a higher motor threshold (see next section) than biphasic pulses (Niehaus et al., 2000; Kammer et al., 2001; Sommer et al., 2006). This has led to speculation as to whether the latter two cycles substantially add to the net effect of stimulation, but the exact mechanism for these differences remains unknown to this date (Sommer and Paulus, 2008).

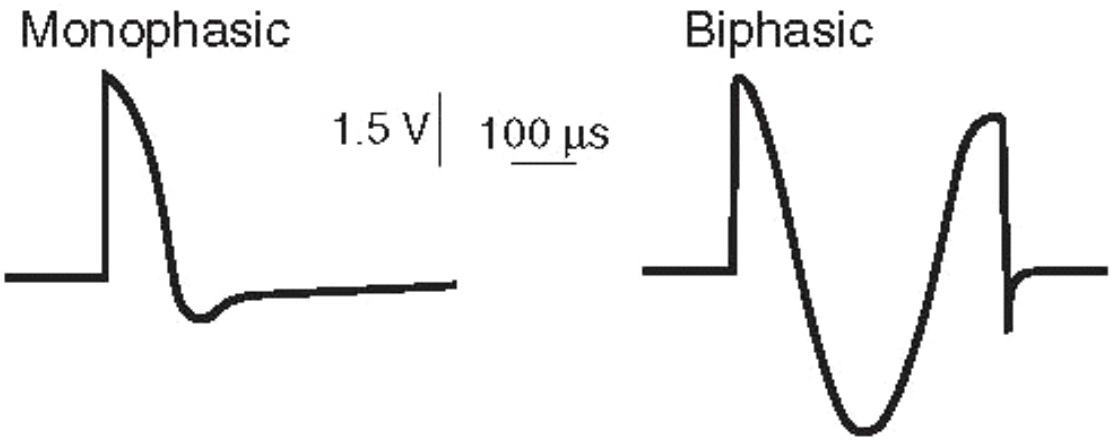

Figure 1.5: Current induced in a probe coil of 1 cm diameter by different types of transcranial magnetic stimulators, recorded and stored by an oscilloscope. *Left*: Waveform induced by a MagPro stimulator in the "monophasic" mode. *Right*: Waveform induced in the "biphasic" mode. For all graphs the same Dantec MagPro stimulator and the same MC-B70 coil were used [sic]. Reproduced from Sommer and Paulus (2008).

Most commonly, monophasic pulses are used because of their higher accuracy and the

fact that they produce fewer coil heating and less acoustic artifacts. These features are generally more valued than the increased efficiency of biphasic wave forms. Biphasic pulses are widely used in studies in which a train of pulses is delivered to the brain, because the energy from the earlier pulse can be recovered to be used in the following pulse (Hovey et al., 2006).

1.2 TMS Protocols

Many different stimulation protocols are available for assessing a multitude of motor and cognitive features. Here, I will outline the basics of a few of the most common ones.

1.2.1 Single-Pulse TMS and Related Measurements

Many clinical and research settings only need to send a single pulse to the cortex in order to directly test for simple electrophysiological responses. The main research applications of TMS are studies which test for various motor function by stimulating M1. Due to its relatively easy excitability and its major part in movement execution, most studies focus on the area of the primary motor cortex (M1), which represents the hand and especially the finger muscles and movements. Several measurements are available to researchers to inspect the many aspects of the motor system.

MEPs

First and foremost, motor-evoked potentials (MEPs) give an insight into the excitability of the cortex (Figure 1.6). To measure these potentials, two electrodes are mounted on the belly and the tendon of the muscles, several centimeters apart. This technique of detecting electric potentials from skeletal muscles is known as electromyography (EMG). Once the TMS-induced action potential has traveled from the central to the peripheral motor pathways and into the muscle cells, it is picked

up by the first and then by the second electrode, which gives insight into amplitude and delay and hence conduction speed of the action potential. The two main aspects of the MEP, i.e., MEP amplitude and latency, give insight into electrophysiological features of the healthy and diseased nervous system.

Simple MEPs are recorded by administering pulses at 120% of the resting motor threshold (RMT), which is obtained by finding the percentage of the maximum stimulator output (MSO) that can elicit a MEP in 5 out of 10 trials. MEP amplitudes increase with a rise in stimulation intensity. For some measures it is beneficial to adjust stimulation intensity by measuring the active motor threshold (AMT), which is obtained by the same method as RMT but with subjects contracting the muscle at 10% of maximum voluntary contraction (MVC).

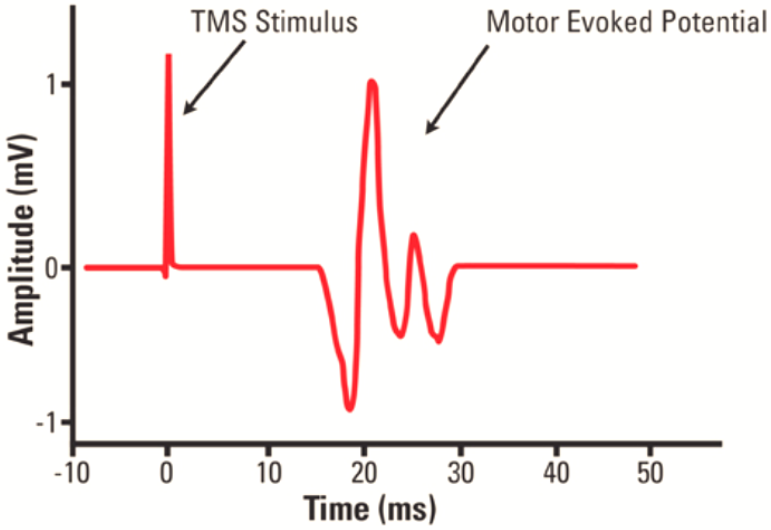

Figure 1.6: A motor evoked potential MEP, with the artefact from the TMS pulse.

Input-Output Curves

Many studies also use a method called "input-output curves". Before a specific drug or another type of treatment is administered, MEPs are recorded at different percentages

of stimulator outputs. MEPs increase with increasing MSO. This is thought to be due to more nerve fibers being recruited when higher intensities are applied, although this relation is not as straightforward as in the stimulation of peripheral nerves and might be obscured by several factors (Rösler, 2008). After the administration of the treatment, this measure is repeated to see whether the excitability has changed, i.e., whether the same intensities as before the treatment yield the same, higher or lower MEP amplitudes. Based on these changes, inferences about the effect of the treatment on excitability can be drawn.

Cortical Silent Period

Yet another measurement is the "cortical silent period" (cSP) or simply "silent period" (SP) (Figure 1.7). When the muscle is active (commonly activity is gauged to 10% or 20% of MVC of the muscle), there is a short period of about 100-300 ms after the end of the MEP where the background activity reaches close to zero mV. The duration of the cSP gives valuable information about inhibitory processes in the cortex and is known to be altered in various diseases, like Parkinson's disease (Cantello et al., 1991) or dystonia (Filipović et al., 1997; Rona et al., 1998).

The silent period is not a homogeneous phenomenon and can be subdivided into a former and a latter part. The former part, up to 50 ms, is due to changes in spinal inhibitory circuits. The latter part, however, is thought to be the result of a prolonged period of inhibition in the cortex that follows the strong magnetic perturbation (Inghilleri et al., 1993; Roick et al., 1993).

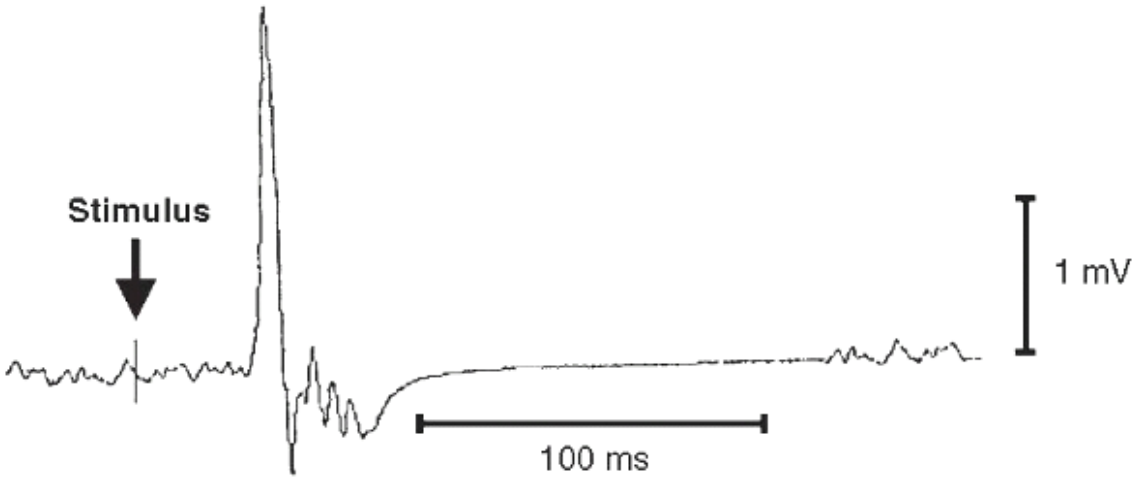

Figure 1.7: Single-trial electromyogram recording of a physiological cortical silent period (cSP), elicited by focal TMS of the motor cortical representation of the contralateral first dorsal interosseous muscle during tonic contraction with 20% of maximum voluntary strength. Stimulus intensity, 1.2 times of the resting motor threshold; arrow, time of the TMS pulse. Reproduced from Wolters et al. (2008).

1.2.2 Paired-Pulse TMS

Measures like simple MEPs and silent period are obtained by delivering a single pulse to the respective movement representation in M1. But it is also possible to deliver two pulses in varying close temporal proximity to test how the first (conditioning) stimulus modulates the response to the subsequent (test) stimulus. Most commonly, the conditioning stimulus is delivered in an intensity below RMT or AMT (70-80%), the test stimulus above RMT or AMT. Depending on the inter-stimulus interval (ISI), the conditioning stimulus either facilitates or inhibits the MEP elicited by the subsequent test stimulus. Here, I will briefly mention the four most widely used intervals and their effects.

ISIs from 1-5 ms have an inhibitory effect on MEPs. This is referred to as "short-interval intracortical inhibition" (SICI).

Another type of modulation can be observed when ISIs are between 10-15 ms. In this case, MEP responses to the suprathreshold test stimulus are facilitated. Thus,

protocols that make use of these ISIs are called intracortical facilitation (ICF). Figure 1.8 shows the modulatory effects of SICI and ICF.

When a conditioning stimulus with threshold intensity or higher is used, an increase in MEP amplitude can be observed for intervals between 1-1.5 ms. This effect is called short intracortical facilitation (SICF).

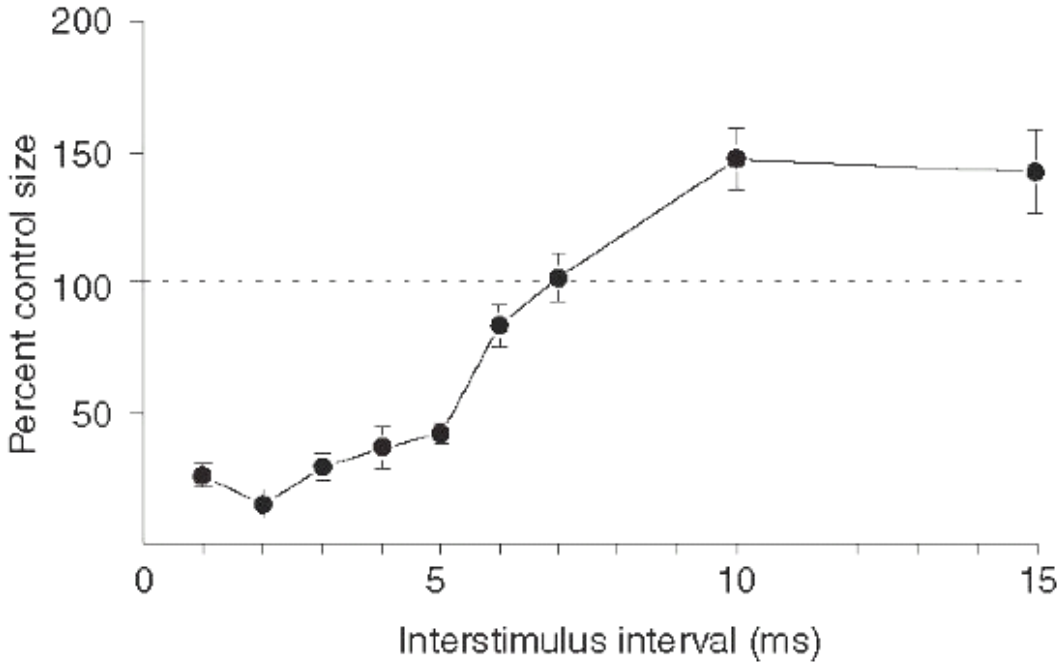

Figure 1.8: Paired-pulse stimulation to test short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) (Kujirai et al., 1993). [...] The average time course of the paired stimulation effect obtained from 10 normal subjects. The ordinate indicates the percentage of the conditioned MEP size to the control MEP, and the abscissa the interstimulus interval (ISI). At ISIs of 1-5 ms, significant inhibition was obtained. The inhibition is followed by facilitation at ISIs of 10 and 15 ms. Reproduced from Hanajima and Ugawa (2008).

1.2.3 Repetitive TMS and Theta Burst Stimulation

Protocols in which a train of pulses is delivered are referred to as repetitive protocols. In research, repetitive TMS (rTMS) is widely used to study brain plasticity, since

the induced effects are persistent beyond the duration of the actual stimulation. Another common use is the use of rTMS for temporary disruption of local neural circuits. By these means, "artificial lesions" can be induced that allow the study of structure-function relationships. Of the various rTMS protocols the two most common ones are the simple (1 Hz) stimulation and theta-burst stimulation (TBS). Simple protocols have a depressing effect on cortical excitability, with the strength of the effects depending on stimulation intensities and duration and the effects lasting up to 30 minutes (Chen et al., 1997b; Muellbacher et al., 2000). At lower stimulation intensities, an increase of RMT can be observed, even if MEP responses show no decrease in amplitude (Fitzgerald et al., 2002). Interindividual differences are large, with some subjects even responding with an increase in MEP size (Maeda et al., 2000). The reason for these differences is not yet understood.

Theta-burst stimulation refers to protocols where short trains of pulses are delivered in theta frequency, i.e., 5 Hz. Two protocols are widely used for research and therapeutic purposes. First, intermittent TBS delivers trains for 2 seconds, every 10 seconds for a total of 190 seconds. In continuous TBS (cTBS) protocols, three TMS pulses are delivered in 50 Hz frequency, repeated in the theta frequency for a total of 20s. Stimulus intensity for both is subthreshold at 80% AMT. While iTBS has a strong facilitatory effect on MEP amplitudes, effects of cTBS are inhibitory (Figure 1.9).

The main advantage of TBS over conventional rTMS is that a short TBS treatment duration yields results that in rTMS would require much longer rTMS administration.

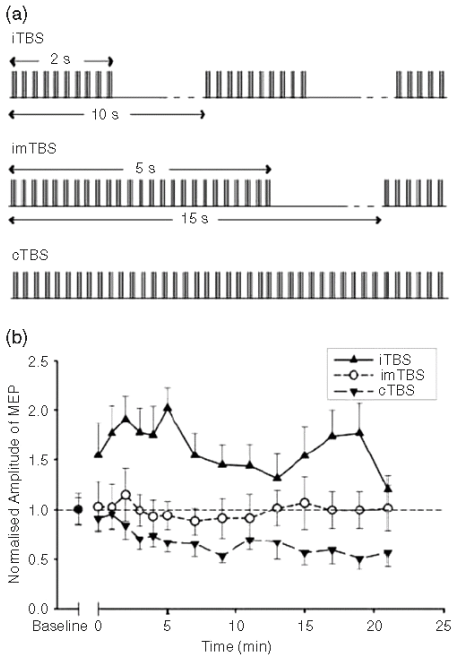

Figure 1.9: Theta-burst stimulation (TBS). (a) Illustration of the three stimulation paradigms used. Each paradigm uses a TBS pattern in which three pulses of stimulation are given at 50 Hz, repeated every 200 ms. In the intermittent (i)TBS, a 2 s train of TBS is repeated every 10 s for a total of 190 s (600 pulses). In the intermediate (im)TBS paradigm, a 5 s train of TBS is repeated every 15 s for a total of 110 s (600 pulses). In the continuous (c)TBS paradigm, a 40 s train of uninterrupted TBS is given (600 pulses). (b) Time course of changes in MEP amplitude following conditioning with iTBS (closed up-triangle), cTBS (closed-down triangle), or imTBS (open circle). There is a significant facilitation of motor-evoked potential (MEP) size following iTBS lasting for approximately 15 min, and a significant reduction of MEP size following cTBS lasting for nearly 60 min. Intermediate TBS produces no significant changes in MEP size. Reproduced from Classen et al. (1998).

Other than application in studying electrophysiology, rTMS is nowadays also widely used for various therapeutical purposes in depression (George et al., 1995), migraine (Lipton and Pearlman, 2010), schizophrenia (Lee and Park, 2005), chronic pain (Fregni et al., 2007), epilepsy (Loo and Mitchell, 2005), addiction(Amiaz et al., 2009), stroke (Lefaucheur, 2006), Parkinson's disease (Hamada et al., 2008) and autism (Sokhadze et al., 2012).

1.3 Safety Issues

TMS is generally considered a safe, non-invasive method to probe the CNS (for a metareview see e.g. Janicak et al. (2008)) when some guidelines are upheld (Rossi et al., 2009). TMS poses a potential threat to electronic devices like deep brain stimulation systems or cochlear implants, and subjects should be screened for having such devices in their body before any administration of TMS. For protocols that use trains of pulses (such as rTMS or TBS), there is a chance of heating of the coil in long stimulation sessions. This problem can be prevented by alternatively using two coils before any overheating occurs.

Subjects should be made aware of possible side effects before undergoing any TMS administration. These side effects are generally very mild as compared to techniques that aim at similar results, but are using other means to induce them, such as electroconvulsive therapy or transcranial electrical stimulation. Subjects in TMS studies have reported to feel discomforted by the noise produced by the discharging coil, especially when the stimulation site was close to the ear. Furthermore, some subjects complained about slight headaches or slight local pain at the sight of stimulation during or after the session. Again, the fact that TMS might be experienced as unpleasant or in some cases even painful should be disclosed to the subjects (Machii et al., 2006).

There have also been reports of sporadic cases of seizures in response to TMS. Machii

et al. (2006) also reported a small amount of instances of psychotic reaction to rTMS over the dorsolateral prefrontal cortex in patients with depression. These incidents (seizures and psychosis) were reported exclusively for high-frequency stimulations and not in response to single- or paired-pulse protocols. Nevertheless, subjects have to be screened for a history of epilepsy and other neurological diseases in their past or their immediate family prior to single pulse TMS.

Another issue that can occur is spontaneous syncope or brief fainting (vasovagal syncope) due to reflex decrease of blood preasure and/or heart rate. These adverse effects are commonly thought to occur in relation to anxiety and psycho-physical discomfort. The presentation of syncope can be very similar to the one of epileptic seizures and may include "tonic stiffening, jerking, vocalizations, oral and motor automatisms, brief head or eye version, incontinence, hallucinations, and injuries from falling" (Rossi et al., 2009, p. 2021). One marker to distinguish syncope from an actual seizure is the duration of the impairments, with the duration of syncope lasting only for a couple of seconds and seizures lasting up to several minutes. All of the more severe adverse effects are extremely rare, considering the large number of participants subjected to TMS on a daily basis.

1.4 Limitations and Problems of TMS

One issue in TMS research and its clinical application is a high amount of variability. Differences cannot only be observed inter-individually but also occur in different trials in the same subject. There are many potential reasons for those differences, including positioning and tilting of the coil, background activity of the muscles in question or possibly even the affective state of the subject. Even if all these factors were taken into account, some variability would still remain that poses difficulties for generalizations and statistical analysis. The problem with this residual variability is that it is essentially random, resulting from "constant, rapid, spontaneous fluctuations

in corticospinal and segmental motoneuron excitability levels" (Kiers et al., 1993, p. 415). While this does not constitute a big problem for studies that compare patients with healthy controls or treatment with non-treatment groups, this variability might obscure small effects in studies that compare different conditions within a single subject group (Sandbrink, 2008).

This chapter just begins to scratch the surface of the multitude of possible applications of TMS, since a comprehensive discussion of the various topics would be well beyond the scope of this thesis. A comprehensive review of most topics like biophysics, application (therapeutic and research) and shortcomings can be found in Wassermann et al. (2008).

1.5 Influence of Cognitive Functions on Motor Performance

> "The classical view of the primary motor cortex (M1) holds that it is an area devoted to transferring motor execution messages that have been elaborated upstream in the cerebral cortex. Anatomically, M1 is the site of the convergence of inputs from the premotor cortex and basal ganglia; it is also the main site of the origin of the pyramidal tract and of direct cortico-motoneuronal connections. Early functional studies using direct cortical stimulation had concluded that the role of the motor cortex is limited to selecting the proper muscular addresses and encoding muscular force for executing a movement" (Riehle, 2005, p. 241).

Despite the major function of movement execution, M1 handles more than mere executive tasks. It is also involved in functions like motor preparation, observation and simulation of actions. In this context, the question of how motor, sensory and cognitive functions interact arises. This chapter deals with these more cognitive features of the motor system.

When performing an informed action in a complex environment, a great deal of information from sensory and cognitive modalities is required. Especially important in this regard is the influence of vision on movements. Losing one's sight indirectly results in a diminished repertoire of motor actions. The kicking movement in playing football, for example, is not possible without the required visual information.

According to earlier theories, the brain was organized in a highly modular manner, where each cortical area was responsible for a specific task or faculty (Fodor, 1983). In earlier days, the visual system, for example, was thought to be restricted to the occipital lobe, which recruited neurons in the parietal and temporal lobe to process information a little further. From there, the already processed information was believed to be forwarded to areas in the frontal lobe, which are responsible for planning and selecting goals, which in turn projected the output of their *computation* to the motor system, which executes the appropriate movements accordingly. Each processing step was thought to be confined to a specific structural area and the different regions were believed to communicate with each other by sending back and forth the results of the completed calculation.

However, this view has been relativized since: Modularity remains, however, in a much less strict sense than previously thought; strict modules, in the sense that one single region is instructed with the handling of one single function, do not exist anywhere in the brain (Grossberg, 2000). Although it is still ACCEPTED that inputs come from the occipital visual system to the executive motor system, the pathway turned out to be a lot more intertwined along the way than earlier, simple models suggested. This holds especially true for pathways required in ecological behavior in complex environments.

Compelling evidence for a non-homogeneity of processing in regard to motor-vision binding comes from lesion studies. It was found that patients with lesions in the ventral stream (which results in visual agnosia), while unable to recognize size, orientation and location of objects, were still able to grasp them with appropriate

grip and hand position (Farah, 2004; Goodale et al., 1991). An opposite effect was observed in patients with optic ataxia, which results from lesions of the dorsal stream in the posterior parietal cortex. These individuals are unable to grasp or reach for objects, although their recognition of these objects remains unimpaired. A very interesting feature of these lesions is that patients not only lose the capability to use visual (spatial) information to guide their actions, but also hand and finger positioning seem to be impaired (Perenin and Vighetto, 1988). One case study with a patient who suffered from Balint's syndrome because of bilateral parietal damage was reported by Jakobson et al. (1991). The patient was able to recognize line drawings of objects, but was not able to position her fingers with conventional ease, in order to grasp them. While getting closer to the object many adjustments were observed in the patient which were not present in healthy individuals.

Corroborating evidence for these motor features of the dorsal visual stream comes from studies on responses of single neurons in the posterior parietal lobe. Interestingly, the responses of these neurons show a dependency on the behavior of the animal in relation to the stimulus. Some subsets of neurons respond to visual fixation, saccadic eye movements, eye-hand coordination, and visually guided reaching movements (Goodale and Milner, 1992).

These studies suggest that while information might be available for verbal reporting and description, it need not be available for the guidance of action, and vice versa. In any case, there seems to be a part of the visual system that is directly responsible for whether or not an individual is capable of using his or her limbs appropriately to interact with the environment.

Although studying overt movement impairments is very informative, the link between cognition and movement also becomes apparent in studying the effect of mentally simulating, observing and preparing for movements. One of several useful tools to do so is TMS.

1.5.1 Mental Imagery

Mental imagery is the process of imagining moving parts of one's body, without any actual overt movement. It also includes imagining how one would manipulate an object (e.g. using tools, grasping, kicking, or any other interaction that requires motor actions) and is closely related to observing a movement of somebody else and mental practice.

Experiments using TMS were able to show that mental simulation of movement of specific muscles decrease motor threshold and hence increase contralateral cortical excitability for specific muscles. MEPs are generally enhanced only for those muscles that would actively take part in the overt movement (Facchini et al., 2002; Izumi et al., 1995; Kiers et al., 1997). Although there have been claims that activity during motor imagery is restricted to areas anterior to M1, i.e., premotor and supplementary motor area, there is evidence that also M1 itself is active during tasks that require motor simulation (Porro et al., 1996; Roth et al., 1996).

Fadiga et al. (1998) conducted an extensive study on the specificity of motor imagery. In their study, they report two separate experiments. The first investigated whether there are differences in MEP facilitation patterns for different muscle and imagery tasks.

In a first session, they tested EMG activity in the right biceps brachii (BB), the agonist for elbow flexion, and opponens pollicis (OP), responsible for the adduction of the thumb towards the index finger. A non-motor visual imagery task in which subjects were asked to mentally generate expanding/shrinking light bar served as a control condition. MEPs were increased for BB when subjects had to mentally simulate a flexion of their right elbow, but remained at baseline for simulation of elbow extension (Figure 1.10). EMG showed no significant difference for both simulation tasks in the OP muscle (Figure 1.11).

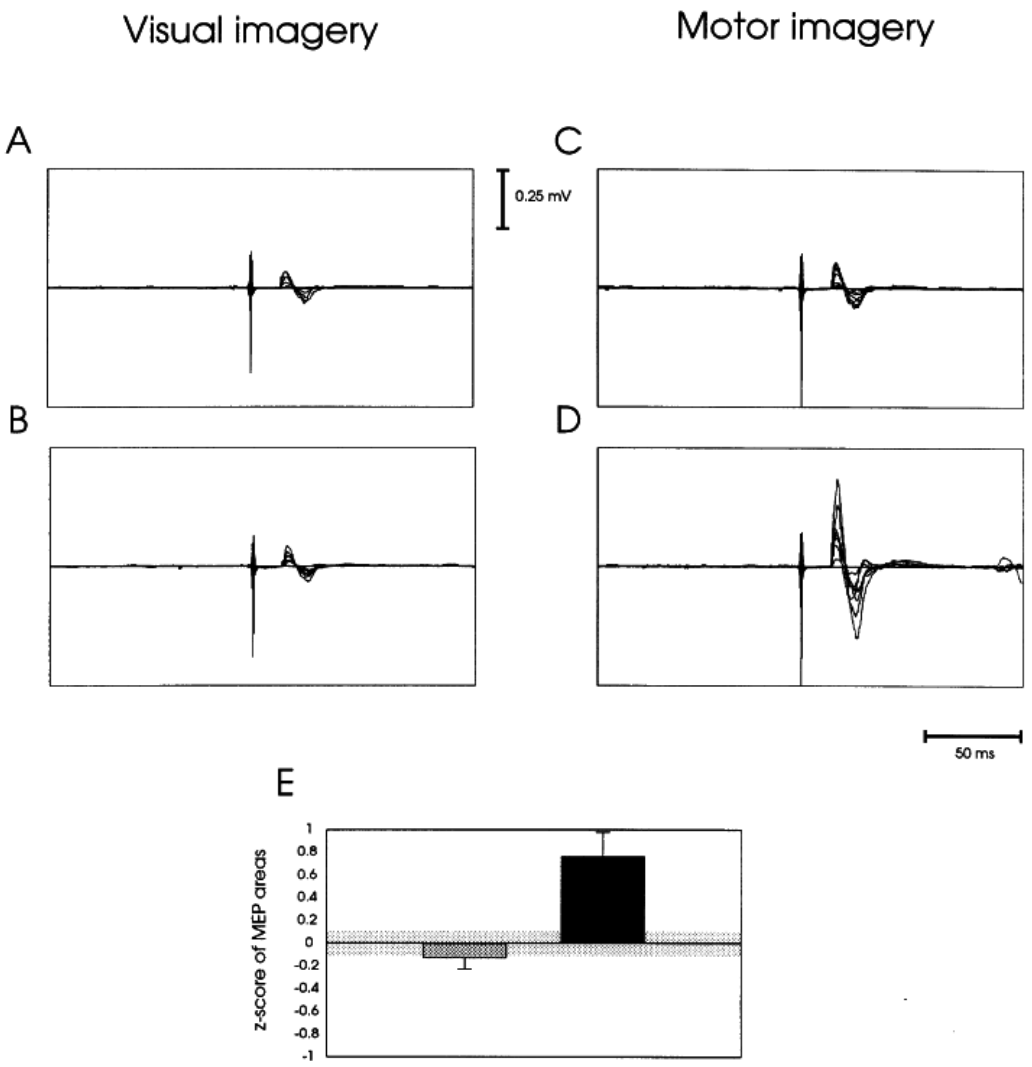

Figure 1.10: Effects of motor imagery of forearm extension and flexion on motor evoked potentials (MEPs) of Biceps Brachialis muscle. In A, B, C, D the MEPs of one subject are presented. A B: visual imagery of expanding and shrinking bar, respectively. C D: motor imagery of forearm extension and flexion, respectively. Each panel shows all superimposed responses (n = 8) evoked from the muscle in one condition. Traces are aligned with the magnetic stimulus onset (magnetic stimulus artifact is visible at the center of recordings). E: Mean values (± 2 S.E.) of MEPs for all subjects in the two experimental conditions. Grey bar, imagined forearm extension; black bar, imagined forearm flexion. Ordinates: z-score of MEP total areas. Data are represented as difference from the control condition, whose standard error is shown by the grey strip across the orizontal [sic] axis (mean values of control condition 0.09 ± 0.12). Reproduced from Fadiga et al. (1998)

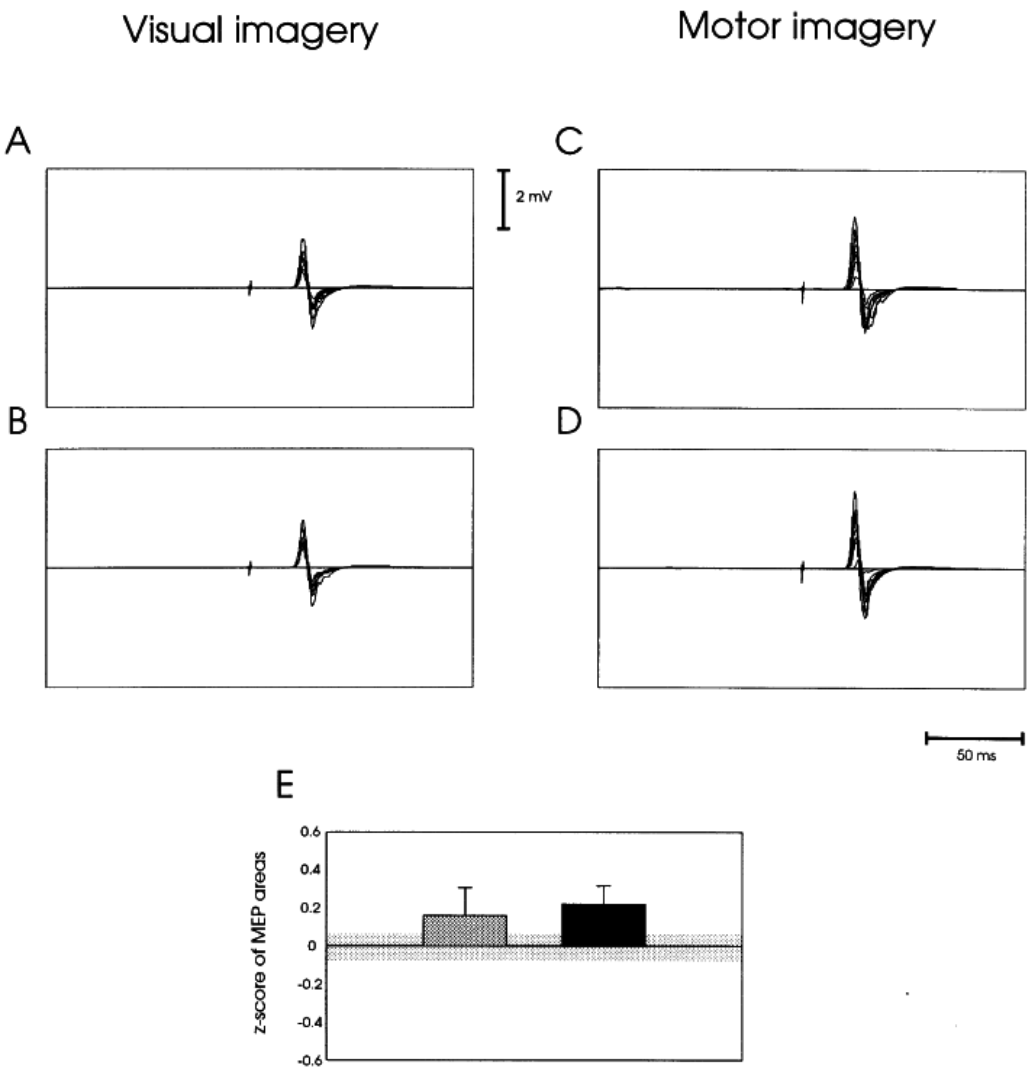

Figure 1.11: Effects of motor imagery of forearm extension and flexion on motor evoked potentials (MEPs) of Opponens Pollicis muscle. In A, B, C, D the MEPs of one subject are presented[A, B visual imagery of expanding and shrinking bar, respectively. C, D: motor imagery of forearm extension and flexion, respectively. E: Mean values (± S.E.) of MEPs for all subjects in the two experimental conditions. Grey bar, imagined forearm extension; black bar, imagined forearm flexion. Ordinates: z-score of MEP total areas. Data are represented as difference from the control condition, whose standard error is shown by the grey strip across the orizontal axis (mean values of control condition] 0.09 ± 0.14. For other conventions see Fig. 10. Reproduced from Fadiga et al. (1998)

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In a second session, activity for distal hand muscles were tested. EMG was recorded from the extensor digitorum communis (EDC) and OP muscles. EDC is an agonist of the hand opening movements and an antagonist of hand closing. In contrast, OP is an agonist of hand closing and an antagonist of hand opening. Subjects were asked to perform mental imagery tasks of opening and closing their right hand. As hypothesized, it was found that MEPs were larger for OP when people imagined hand-closing than for hand-opening. Reversely, MEPs in EDC were higher for the hand-opening than for the hand closing imagery task, although the differences were below significance. These results indicate that imagery of proximal and distal movements, selectively increases MEPs only in the respective muscles.

In a second, separate experiment, TMS was delivered to both the left and the right hemisphere, while subjects had to imagine opening and closing the right and left hand alternately. The influence of motor imagery conditions on activity recorded from needle electrodes in OP were tested. Results showed that MEP sizes increased for contralateral and ipsilateral motor imagery of hand closing, but neither for contralateral nor for ipsilateral imagery of hand opening. Additionally, MEPs were larger for contralateral imagery of hand closing, but were reduced for contralateral imagery of hand-opening (Figure 1.12). A similar hemispheric asymmetry was also found when the left and right finger movements were executed (Kim et al., 1993). Also, rTMS of the left hemisphere interferes with the execution of left and right hand movements, while stimulation of the right hemisphere only interferes with contralateral executive tasks (Chen et al., 1997a).

Together, these results suggest a strong isomorphism of overt and covert movement and that the mental task of imagining a movement has a highly specific effect on M1 excitability.

The excitability of M1, however, might be modulated by the adjacent supplementary motor (SMA) cortex and the premotor cortex. This was shown by the experiments of Abbruzzese et al. (1996), who asked their subjects to perform four different tasks.

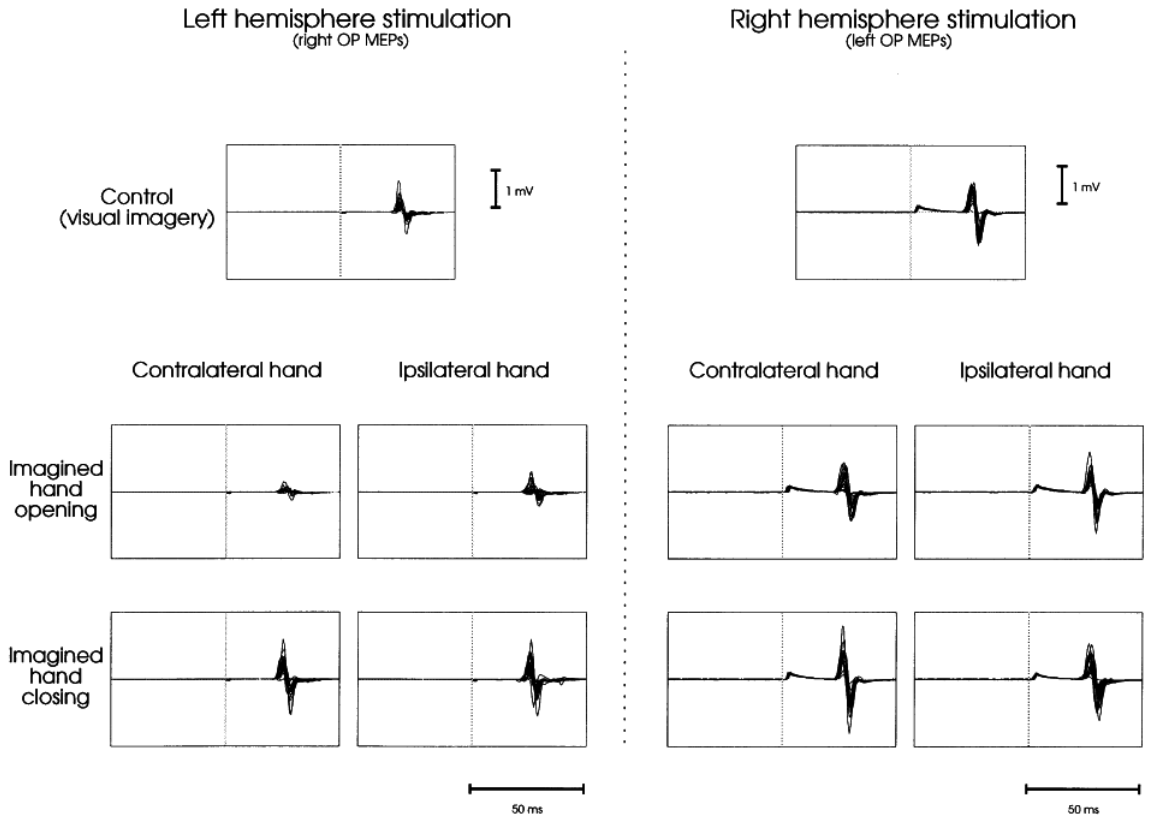

Figure 1.12: Effects of motor imagery of hand movements on motor evoked potentials (MEPs) of Opponens pollicis muscle. The MEPs of one subject are presented. Each panel shows all superimposed responses (n = 20) evoked from the muscle in one condition. Traces are aligned with the magnetic stimulus onset (grey line across traces). Reproduced from Fadiga et al. (1998)

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They were either instructed to 1) perform overt *repetitive* thumb-to-index-finger movements with their left hand, 2) mentally simulate the same task in their right hand, or 3) perform overt *sequential* thumb-to-index-finger movements again with their left hand, or 4) mentally simulate the sequential movements with their right hand. Compared to MEPs at rest and a mental calculus control condition, the results showed that MEP increases were only present for sequential, but not for repetitive movements of the thumb, both for overt and covert conditions in both recorded muscles. Since SMA is thought to be a major processing site of non-routine motor behavior, the study concluded that activation of SMA has a direct facilitatory effect on M1.

1.5.2 Observation

Observing movements to decipher plans of other living creatures in one's immediate surroundings is absolutely crucial for living in a social world. In this section, I will briefly summarize a few aspects of the mechanism that let us interpret other actors' movements and their intentions by utilizing our own motor system.

Rizzolatti et al. (2010) have argued that instead of investigating the motor system based on the assumption that it is responsible for movements, it would be more fruitful to shift the focus to what they call "actions" or "motor acts". Actions are necessarily goal-directed and are defined by expectation, whereas movements are common components of different actions that lack these goal-directed features. Movements simply execute actions. The motor system, in this view, is not just in charge of movement execution, but "also plays an important role in matching the external reality on their internally produced actions" (Rizzolatti et al., 2010, p. 539). Evidence for an intimate link between movement observation and execution comes from primate studies. In monkeys, a set of neurons in area F5 of the premotor cortex is activated during the grasping of an object, but also when observing such behavior in other creatures with the same or a similar motor repertoire, i.e., other

monkeys and human experimenters (di Pellegrino et al., 1992; Rizzolatti et al., 1996). These neurons are commonly referred to as "mirror neurons" and are thought to be involved in understanding motor events and plans of other animals. Area F5 is located in the ventral-rostral part of Broadman Area 6 and is related to hand and mouth movements (Figure 1.13). Its organization is roughly somatotopic, and the representations of hand and mouth are located in the dorsal and ventral parts of the premotor cortex, respectively (Hepp-Reymond et al., 1994; Rizzolatti et al., 1981; Rizzolatti, 1988).

F5 neurons have two major properties. Firstly, they posses *motor properties* which are highly specific to certain actions. Most neurons in this set discharge selectively for movements like grasping, holding or manipulating objects. Although some neurons fire preferentially for specific muscle groups, many also discharge preferentially for specific actions, like precision grip, finger or whole-hand prehension (Jeannerod et al., 1995; Rizzolatti, 1988; Rizzolatti et al., 2010). Many neurons fire, e.g. if a grasping movement is performed, with the left or the right hand, or even with the mouth (Figure 1.14).

The second type of properties are *sensory properties*. Many neurons fire when the animal sees a gripping action performed by a peer, or an idle 3D object that can be manipulated. Depending on the size of the object, and hence the appropriate grip position of hand and palm, different patches show activation (Jeannerod et al., 1995; Matelli et al., 1994). Due to these features, area F5 has been called an observation/execution matching system. It is responsible for representation of movement, whether this movement is executed or not (Rizzolatti et al., 1996).

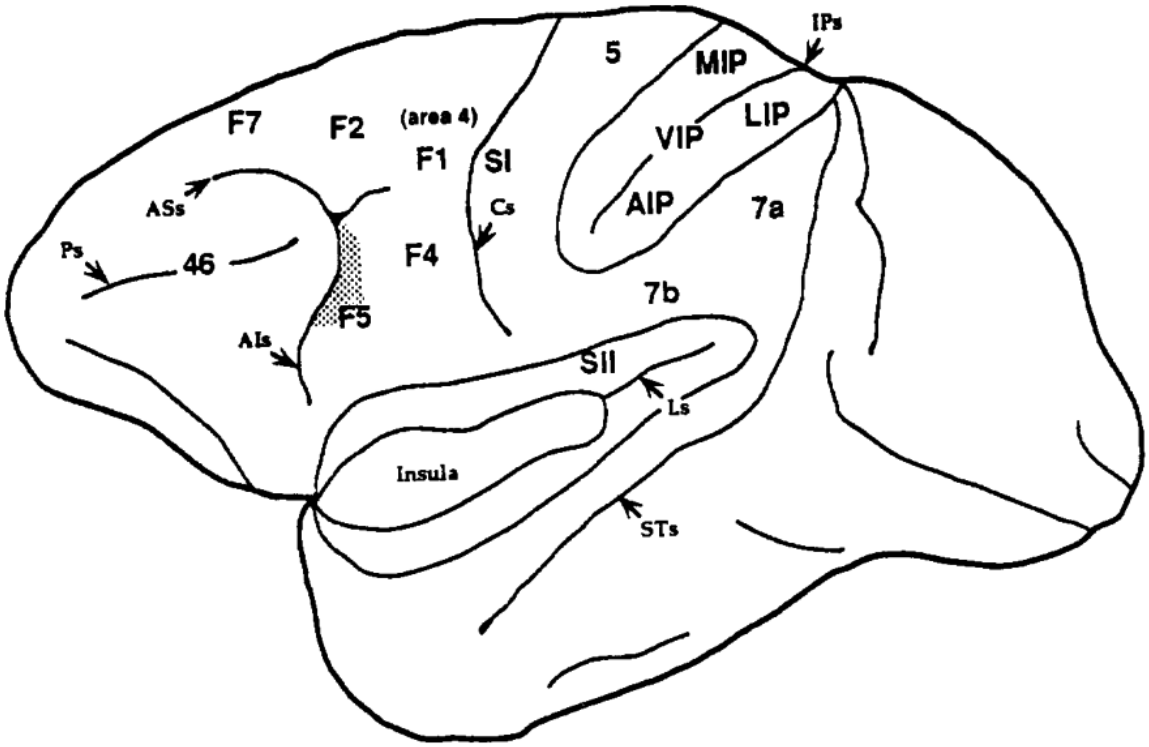

Figure 1.13: Lateral view of the monkey brain. [...] Frontal agranular cortical areas are classified according to Matelli et al. (1985). Abbreviations: AIP, anterior intraparietal area; AIs, inferior arcuate sulcus; ASs, superior arcuate sulcus; Cs, central sulcus; IPs, intraparietal sulcus; LIP lateral intraparietal area; Ls, lateral sulcus; MIP, medial intraparietal area; Ps, principal sulcus; SI primary somatosensory area; SII, secondary somatosensory area; STs, superior temporal sulcus; VIP, ventral intraparietal area; Note that IPS and Ls have been opened to show hidden areas. Adapted from Rizzolatti et al. (1996).

Analogous to the organization of F5, parts of the late dorsal visual pathway, which are a major source of input to F5, show strikingly similar features. The anterior intraparietal (AIP) area , located in the inferior parietal lobule - a part of the dorsal stream of the visual system, which is responsible for spatial awareness and guidance of action, is of special interest in this regard (Jeannerod et al., 1995; Matelli et al., 1994). Most neurons in the AIP area preferentially discharge for observing stimuli with specific types of hand grip (Figure 1.15). Neurons in this area can be classified into roughly three distinct population (Taira et al., 1990):

Motor-dominant neurons discharge, no matter if the animal can see (light in the room) or cannot see (no light in the room) the three-dimensional object it was currently grasping. These neurons also do not fire when the animal is only fixating its gaze on the object without overtly interacting with it.

Motor and visual neurons fire more strongly when the animal can see the object, but show reduced activation when the object is not visible. This cell-population is also referred to as "hand-movement-related neurons".

Visual-dominant neurons discharge exclusively when lights are on in the room. Activation of these neurons is similar during overt manipulation and object fixation.

Hence, portions of the posterior parietal cortex and especially the AIP seem to be involved in the visual guidance of movement, in a similar way to area F5.

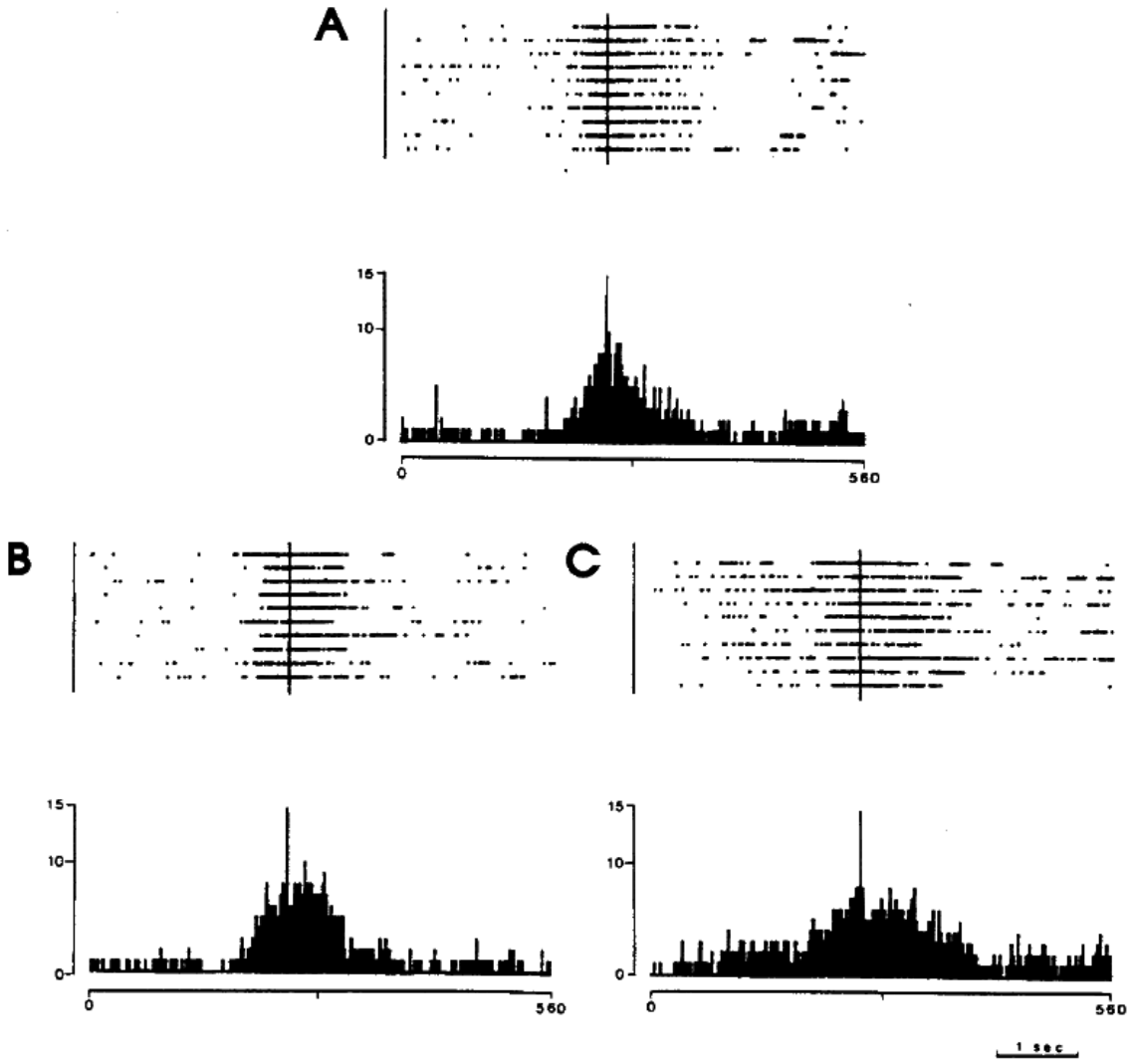

Figure 1.14: Example of a "grasping-with-the-hand-and-the-mouth" F5 neuron. (A) Neuron discharge during grasping with the mouth. (B) Neuron discharge during grasping with the hand contralateral to the recorded hemisphere. (C) Neuron discharge during grasping with the hand ipsilateral to the recorded hemisphere. Rasters and histograms are aligned with the moment in which the monkey touched the food. The histograms are the sum of ten trials. Abscissae: time expressed in bins. Bin width: 10 ms. Ordinates: spikes/bin. Reproduced from Rizzolatti et al. (2010).

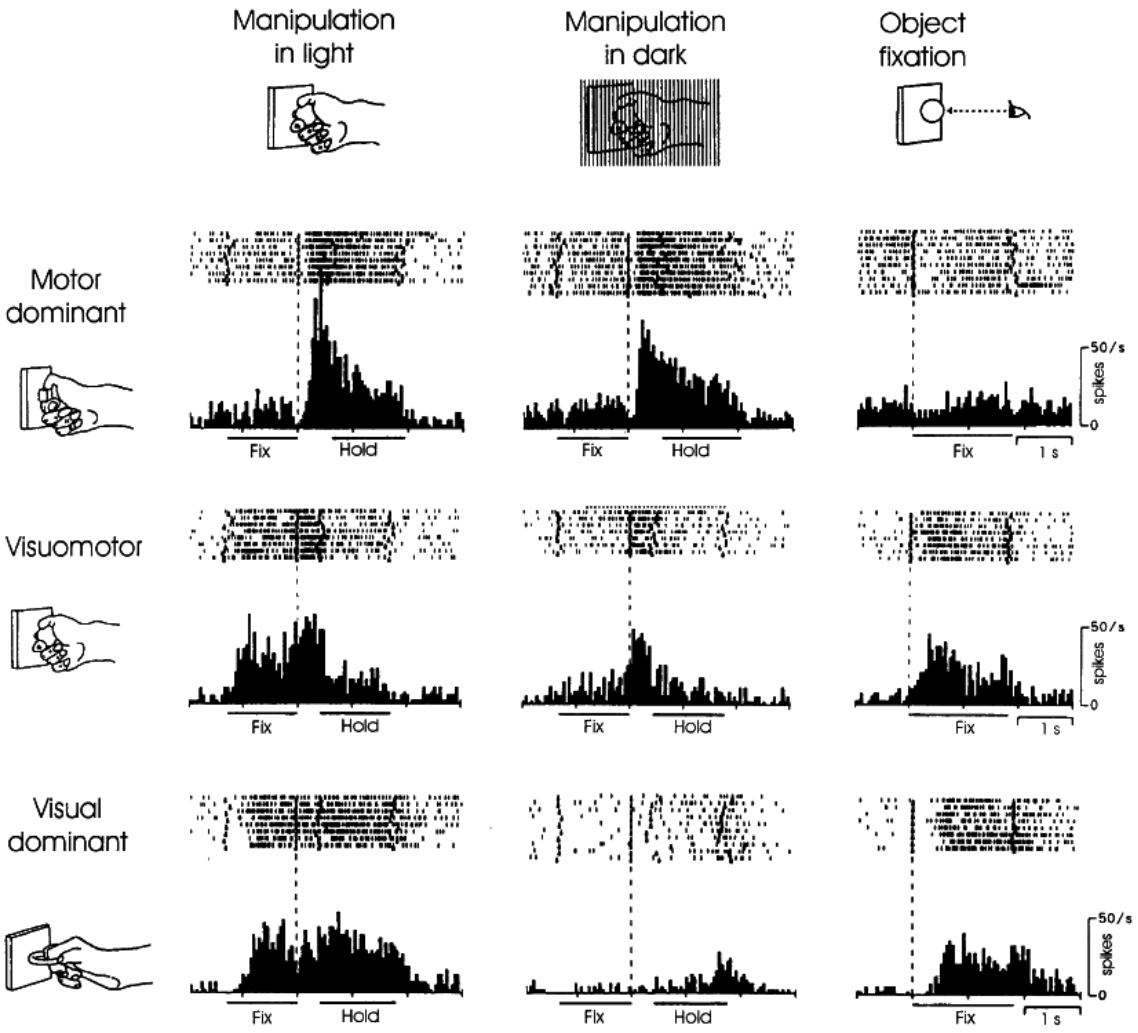

Figure 1.15: Examples of Different Categories of AIP Neurons.
The experimental paradigms in the manipulation in light and in object fixation conditions were the same as those of object grasping and object fixation [...]. In the manipulation in dark condition, after a first trial in which the object was grasped with the box illuminated, the light inside the box was turned off and the following trials were executed in complete darkness. The objects were presented in blocks. Rasters and histograms are aligned with go signal in manipulation conditions and with the task onset in the fixation condition (modified from Murata et al. (2000)). Adapted from Rizzolatti and Luppino (2001).

Similar binding between execution and observation was also found in humans, and evidence for their interaction has been brought forth by studies using EEG (Cochin et al., 1999), EMG (Järveläinen et al., 2001), fMRI (Calvo-Merino et al., 2006), PET (Grafton et al., 1996) and TMS. One experiment by Fadiga et al. (1995) used TMS to test for the influence of observation of movements on motor execution. Subjects were presented with a set of stimuli where they had to observe 1) how the experimenter grasped an object, 2) the object without any manipulation, 3) arm movements of the experimenter or 4) dimming of light, as a control condition that tested for attention of subjects. TMS was administered shortly before the stimuli disappeared. MEPs were recorded from four muscles (EDC, Flexor Digitorum Superficialis, First Dorsal Interosseous, OP). Additionally, a subset of the participants also had to perform these actions overtly, in order to see whether there are similarities between the activities resulting from observation and execution. The results (Figure 1.16) showed that the MEP sizes increased for all three observation conditions, as compared to the dimming-light-detection control task in all muscles that participated in the actual movement. In addition, the findings were constant for both subjects who were told that there would be overt movement tasks after the TMS experiment and subjects who did not receive such instructions. Observing actions of another actor, therefore, seems to modulate M1 excitability, regardless of whether it is in expectation of actual movement or not. % As discussed above, the premotor cortex seems to be involved in the modulatory effect. In agreement with this hypothesis, one group was able to show that cTBS of the dorsal premotor cortex produced a decreasing effect on MEPs after single-pulse stimulation of M1, similar to the effects observed after direct cTBS stimulation of M1 (Huang et al., 2009).

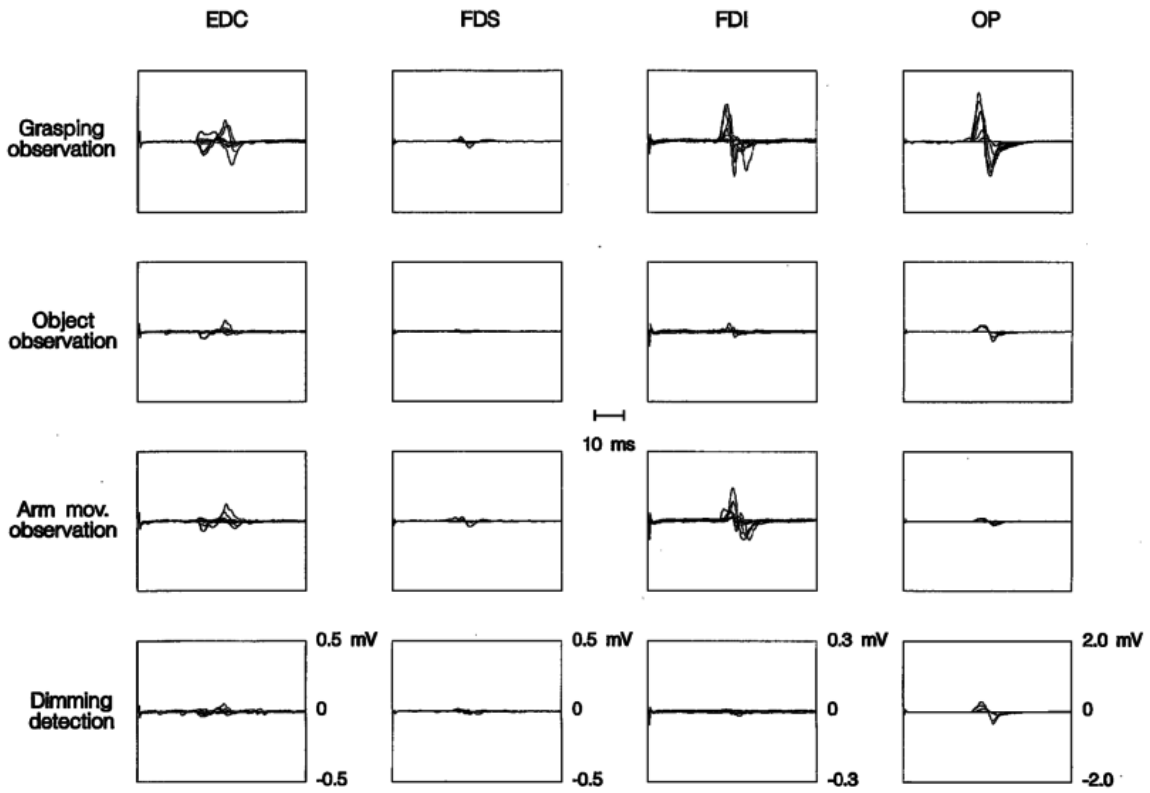

Figure 1.16: Effects of observation of hand and arm movements on the magnetic evoked potentials. The MEPs of one subject are presented. Each panel shows all superimposed responses (n = 8) evoked from the indicated muscle in one condition. Traces are aligned with and shown from the stimulus onset. Reproduced from (Fadiga et al., 1995).

It was also found that motor acts are coded in a time series. In premotor area F5, there exist mere motor neurons as well as the mirror neurons mentioned before. Interestingly, different sets of neurons are being activated in different segments of the grasping action (Rizzolatti, 1988). Some subsets seem responsible for the initiation of grasping, others for holding on to the object, again others for letting go of it, etc. These properties, however, are likely not restricted to the visuomotor neurons. An experiment with TMS showed that observation of a video clip showing a finger aperture would increase MEPs for that specific motor act. This effect was not present for finger closing. By delivering TMS pulses at different times during the

clip, Gangitano et al. (2001) concluded that the facilitation is tuned in different ways during the appearance of different phases of the grasping movements. Activation specificity in both the spatial as well as the temporal domain suggest that both processes are highly similarly represented in the cortex and that there is a large amount of isomorphism between overt and covert action representation (Buccino et al., 2001).

Two possible theories have been put forward to explain the ability to recognize the movements of another agent. Either the mirror system simulates the actual motor commands that would be necessary to act out the movement or the information relies on the visual features of the observed movement, codes it perceptually and infers their intention afterwards. Early studies on the mirror neuron system did not clarify if the activation truly reflected motor representations or if it was due to more general perception-inference-theory building processes. One study investigated male and female ballet dancers who had the same visual knowledge about a set of moves. However, these moves were part of the motor repertoire of one gender group, but not the other. Investigation with fMRI showed increased activity in premotor, parietal, and cerebellar regions for observed dance moves which were part of the gender-specific motor repertoire. These results indicate that there is a pure motor component in the mirror system (Calvo-Merino et al., 2006).

Besides activity in the motor system during mentally simulating and observing movements, similar activity has also been found when subjects were asked to look at pictures of tools. Results from an fMRI study showed selective activation of the left ventral premotor cortex and the left posterior parietal cortex in these tasks (Chao and Martin, 2000). These findings are in line with primate studies, which show that storage of visual information about graspable objects activates portions of the ventral premotor cortex (Murata et al., 1997). In contrast, no such activity was found while subjects were looking at pictures belonging to other categories. This means that

pictures of tools which require a specific movement of the hand elicit activity in frontal[1] areas that are known to process information about motor-based properties. An additional aspect of the cognitive-motor binding is the reverse influence, i.e., the biomechanical constraints of the body and their representation in motor areas guide and put restraints on how we perceive objects that can be manipulated. In an experiment by Jeannerod and Frak (1999), a glass was shown to subjects, which had indications of where to put the thumb and index finger. Participants then had to decide if, for various indications, it was impossible, difficult or easy to lift the glass and pour its contents into another container. It was found that the reaction time for the observing condition was similar to the one in overt movement trials. Reaction times increased with difficulty of the task. This indicates that the physical restrictions the effector puts on a movement influence cognitive tasks that are related to that effector. Unlike classical mental rotation tasks, where the speed for rotation in any direction is always the same, it seems that mental imagery of hand and arm movements is restricted by the biomechanics of the joints required in the movement.

1.5.3 Preparation of Movement

Where does movement preparation[2] begin? Requin and his colleagues argue that

> "[...the reaching movement of the arm may be described as preparatory to the target movement of grasping a glass. The preparatory phase of this action is quite similar to the reaching movement, executed in, for example, picking up a pencil. However, if one observes the moving hand carefully, one can see that the fingers are already positioned to grasp either a glass or a pencil before the reaching movement starts. This prepositioning

[1] Activity is not restricted to the frontal parts (premotor cortex), but was also found to be significantly increased in the left posterior parietal cortex.

[2] The literature in this field is less abiding to a common taxonomy as compared to motor imagery and observation . Similar studies discuss the same concepts under different terminology. For the purpose of this thesis, I will use "motor preparation" and "motor planning" synonymously.

> of the fingers according to the shape of the target to be grasped even before the target is reached identifies a preparatory component of the reaching movement. Moreover, the extension of the arm to reach the glass is accompanied and even preceded by a backward movement of either the trunk or the whole body that compensates for the change in spatial distribution of body weight, thus making the projection of the center of gravity on the ground stable. These postural adjustments that anticipate the equilibrium perturbation resulting from voluntary movements form an important aspect of motor preparation" (Requin et al., 1991, p. 359).

Consequently, they point out that every movement is always a preparation for another movement. Hunting is a preparation for eating, which in turn serves as a metabolically necessary precursor for hunting. From this perspective, natural behavior is always preparatory in some sense, which results in an inflated and hence diminished meaning of the term. Investigating preparation of movement experimentally, however, requires a more concise and reduced meaning of preparation.

Experiments which want to elucidate the underlying processes of the preparation of movement typically focus on the duration of the execution of intended movement. What most experimental paradigms have in common is that subjects are instructed to respond as quickly as possible to a stimulus. Reaction time (RT) to the stimulus, i.e., the time between stimulus onset and initiation of overt movement, is then indicative of motor preparatory processes. Mean RT for responding to a visual stimulus is around 190ms (Kosinski, 2008) and decreases with additional information, such as exact knowledge of the location or time at which the stimulus appears and what response will be asked for. If uncertainty is high, such as in conditions where the stimulus occurs at random times or locations and invokes more than one potential response, RT increases. Three main paradigms that draw on the concept of RT have been described in the literature (Kosinski, 2008; Miller and Low, 2001):

Simple Paradigms consist of at least one stimulus that requires only one response. Commonly, a stimulus is shown in a previously denoted location, and RT is measured. An example for this kind of task would be to respond with a key press with the right hand to any letter appearing on the screen.

Recognition or Go/No-Go Paradigms include different types of stimuli. One of them requires the response, similar as in simple paradigms, whereas the others serve as distractors. For example, subjects would be asked to respond to an ✕ with a right hand key press, but not to a ❍.

Choice Paradigms: Subjects are presented with different stimuli and have to respond by different motor acts. Subjects would, for example, be asked to respond with a right-hand key press to an ✕ and with a left-hand key press to an ❍.

Donders (1868) noted in his early hallmark work on the speed of mental processes that recognition reaction time was longer than simple reaction time, but shorter than choice reaction time.

One assumption underlying RT paradigms is that within the preparatory period discrete stages of processing take place in a serial manner and that the different factors in processing simply add up to produce RT (Sternberg, 1969). However, the assumption that this model holds true in all cases was more recently challenged by theories of parallel-distributed processing (McClelland, 1986; Requin et al., 1988). It is possible that stages overlap in their temporal signature and that they cannot be held apart as the "additive factor method" suggests. An additional problem arises in choice tasks. RT increases logarithmically with the number of options the subject has to choose from[3].

Despite these problems, RT experiments remain a very informative methodology, used by various disciplines. The following reasoning is common to all RT experiments. In a simple paradigm, there would be only two necessary stages. First, signal detection (1)

[3]This effect is known as Hick's Law (Hick, 1952).

occurs and based on that motor execution (4) is initiated. In a go/no-go paradigm, the additional stage of stimulus discrimination (2) and in choice tasks a response selection (3) must be present. This model seems to intuitively explain different response times for the different tasks. Given the total duration T, the duration of the three stages could be calculated or at least estimated by a subtraction method. The "subtraction procedure" assumes that (1) and (4) are equal in all paradigms and that, therefore,

(T) – (1) – (4) provides you with the duration of (2). In turn,
(T) – (1) – (4) – (2) provides you with the duration of (3).

Miller and Low (2001) tested the assumption that motor execution is the same for all three tasks. Early experiments by Ludwig Lange in 1888 suggested that the duration of the stages was not as invariant as would be necessary for the subtraction method to work properly (described by Boring (1950)). Lange observed that the duration of T differed in two separate simple paradigms in which subjects were instructed to either concentrate on the performed movement or on the presented stimulus. Hence, the duration of the stages is at least dependent on specific task instructions. This finding was extrapolated to all stages, including motor execution. Miller and Low point out that while Lange's findings support the possibility of differences in motor execution for the different paradigms, this does not follow necessarily. Additional evidence for differences in the executive stage comes from Ulrich et al. (1999). They measured whether the force of the responses in simple, go/no-go task, and choice task was identical. Interestingly, they found that while force was the same for simple and choice tasks, go/no-go tasks were followed by responses with larger force. Although this indicates general differences in the executive stage for the different tasks, it can not be inferred from these findings that the time requirements of the stages in the different tasks differ as well. Duration might be just the same, even if forces of the responses differ.

The rationale that motor preparation is different in conditions in which people know

what action they will have to perform (e.g. simple tasks) and conditions in which they do not initially know what action will be required (e.g. left or right hand movement in a choice task) seems legitimate. When people are instructed in a way that provides them with a way to know which response is more likely to be asked of them, reaction time decreases. For example, in a paradigm where two fingers on each hand are required to make responses, information about what hand will have to be used makes the subjects' reaction significantly faster (De Jong et al., 1988).

Miller and Low (2001) modified Donders' classic simple, go/no-go and choice tasks in a way that allowed for their maximum comparability. Arrows cued the participants with 80% validity whether the left or the right hand would be required in the consecutive trial. In simple tasks, subjects had to respond with the cued hand to any test stimulus that appeared on the screen (80% of trials) or remain unresponsive when no test stimulus was presented (20% of trials). In go/no-go tasks, subjects were asked to respond with the cued hand when the frequent (80% of trials) test stimulus appeared, but to withhold the response when a distractor (20% of trials) was shown. In choice tasks, the frequent stimulus required a response with the cued hand (80% of trials), whereas subjects had to use the other hand when a distractor was displayed (20% of trials). Differences in response were therefore only required in the case of the distractor stimuli, but responses to the frequent ones remained identical in all three conditions. This allowed for an ideal comparison of the three conditions.

Besides EMG, also EEG was recorded and analyzed for several components. Most importantly, the study investigated whether the movement-related lateralized readiness potential (LRP) showed differences in their temporal course for the different tasks.

LRP is recorded from both hemispheres and is characterized by increased negativity over the contralateral hemisphere when subjects perform a motor task or when they prepare for it (Coles, 1989). When the experimental procedure denotes in advance which hand will be required to make a response after the appearance of a test stimulus,

LRP can be detected before test stimulus onset (Eimer, 1998). Results showed that neither EMG nor LRP could provide evidence that motor preparation differed for the three conditions. These findings lend support to the idea that differences in RT are due to different cognitive stages and that the time for movement execution is equal in all three tasks, as disussed above.

TMS has been used to demonstrate increases in MEP responses when delivered during movement preparation. Within the RT paradigm, a TMS pulse can be delivered at different times in regard to the cue. This provides insights into processing speed of cortical motor system.

In an experiment by Schneider et al. (2004) subjects were asked to flex their ankles when a auditory stimulus occurred at random intervals, either with their muscle contracted at 10% MVC or at rest. During the RT period, TMS was delivered to the leg area of M1. They found that MEPs were facilitated in the contralateral leg during preparation, with the highest facilitatory effect taking place around 12.8 ms before the overt reaction. EMG background activity was monitored to be equal throughout the trial, which led the authors to conclude that the increase is due to changes in motor-cortical excitability during movement preparation.

Chen et al. (1998) compared preparatory processes of self-paced with externally paced (simple RT task) thumb abduction movements, by delivering TMS at different times before movement onset. It was found that although both tasks increased MEP responses to a single TMS pulse, increases were present 20 ms earlier in the condition where movements were voluntary (i.e., self-paced) than when they were paced by the RT experiment. Also, if TMS was delivered after EMG onset, a decrease in excitability was observed for both self-paced and externally paced movements, again with a larger decrease in the self-paced condition.

Movement preparation is also closely related to *anticipatory processes*. Compared to reflexes, the processes that link sensory information and motor execution take a lot of time. Nevertheless the organism is able to infer from previous experiences and learned

responses what motor actions will be required in a specific situation (Slater-Hammel, 1960).

If a baseball player who has to hit a ball flying at him with great speed would wait for the ball to be at the point where hitting it was required, he would miss it every time. What enables him to hit the ball is that he can anticipate when it will be at the appropriate spot, to ensure an ideal hit. Considering how much time it takes for processing, around 150ms for simple reactions to simple stimuli as shown in simple RT experiments, it may seem odd that we are accurate with our reactions quite frequently. One way to study these anticipatory processes is to interrupt already planned movements in different intervals before an overt response is required. Paradigms which use this rationale are referred to as "Stop-Signal" paradigms. In their 1949 paper, Hick and Bates coined the term "transit reaction" to refer to reactions that require anticipation of where a target will be, in order to react to it appropriately. Examples for transit reactions would be shooting at a moving target or hitting a baseball coming towards you (Hick and Bates, 1949).

Slater-Hammel (1960) has pointed out two conceivable ways to respond to a stimulus. Suppose a subject is seated in front of a clock with a revolving marker and is asked to press a key, but release that key when the marker reaches a designated position. The subject could either wait for the coincidence where the marker reaches the designated position to time her response, or she could attempt to make the marker stop at the exact time it coincides with the designated position. If the first strategy is used, the subject will inevitably be late by one reaction time, which she would avoid if she were relying on coincidence anticipation.

> "[T]he decision to respond must be taken at least one reaction time *before* coincidence, and, moreover, must be based upon judgments of the velocity of approach, the distance between objects, and the subject's own reaction time, as known to him from previous experience. In other words, it is

> a case of responding to a combination of misalignment and the rate of change of misalignment" (Hick and Bates, 1949, p. 21).

In summary, it appears that subjects show different modulatory effect of motor-cortical excitability when engaged in a cognitive task such as imagery, observation, or movement preparation. What is common to most results of the reported experiments is that this modulation is mostly positive, i.e., M1 excitability is up-regulated by the imagining, observing or preparing for the overt movement.

Chapter 2

Research question and hypotheses

Another line of experiments attempts to dissociate the cognitive influence on motor execution by trying to examine the effects of the subjects' voluntary or intentional state on the TMS perturbation. Bonnard et al. (2003) asked participants to periodically flex and extend their wrist and delivered a TMS pulse that always coincided with the flexion. Subjects were then asked to perform either an active or a passive mental task. For the passive part, they had to "let go" or simply not intervene in the increased flexion that was a result of the TMS pulse. For the active part, they had to compensate for the perturbation by thinking about decreasing the elicited movement without using their muscles.

The results showed that the degree of wrist flexion was significantly higher in the non-intervention as compared to the compensation instructions. Based on phase-plane trajectories of the moving wrist, trials were divided into successful and unsuccessful ones. Successful trials were those which either deviated from the initial steady state of the unperturbed trials in the compensation condition or were within the range in the non-intervention condition. Conversely, trials which showed to be close to the unperturbed trials in the compensation or deviated from them in the non-intervention trials were deemed unsuccessful. It was found that in successful trials, flexions of the wrist were significantly bigger when people were idle than when they were mentally

counteracting the TMS pulse. Additionally, the influence of the two instructions on MEP amplitudes was measured. The same division into successful and unsuccessful trials was used. For the flexor carpi radialis muscle (FCR) it was found that for the successful trials MEPs were significantly higher in the nonintervention than in the compensation condition and for unsuccessful trials lower in the nonintervention than in the compensation condition. In the antagonistic extensor carpi radialis muscle (ECR), the situation was reversed, although no significant effects were found for the two instructions, neither for successful nor for unsuccessful trials.

A successive experiment tested whether there were differences in peak-to-peak amplitudes when subjects were instructed to mentally assist or resist a TMS-induced movement (Bonnard, 2009). It was found that the evoked potentials were smaller for the resist than for the assist task, but only in the flexor muscle. Also the silent period was longer in the flexor muscle when subjects tried to resist the induced movement. Neither amplitudes nor SP duration showed any significant differences in the extensor muscle. Besides the myographic data, Bonnard et al. (2009) also attained electroencephalographic data (EEG) to investigate the cortical reaction to the TMS perturbation. Two signals were of interest to the study. To examine the effect of the mental task on the cortex, the contingent negative variation (CNV) was measured and analyzed for the 100 ms before TMS onset. CNV is a form of *readiness potential* and reflects a preparatory effort of the cortex. It was found that CNV amplitude was decreased in the resist condition when compared to the assist condition in those electrodes that were closest to M1. In a second EEG measurement, the TMS-evoked N100 component (the negative peak at approximately 100 ms) was used as a marker of cortical inhibition. Results showed that N100 was significantly bigger in the resist than in the assist condition. Furthermore, a negative correlation of the CNV and the N100 was shown to be present in six of the eight subjects. Bonnard et al. (2009) give the following summary of their experiment:

> "[The] experiment was designed to study how prior intention can tune the excitability of the primary sensorimotor cortex. We used the ability of human subjects to prepare themselves cognitively to **resist** a TMS-evoked movement by anticipatory selective modulation of corticospinal excitability." [emphasis added] (Bonnard et al., 2009, p.7)

What both of the experiments (2003 and 2009) have in common is the instruction to mentally prepare to decrease the TMS-induced movement, but although the instructions of non-intervention (2003) and assisting (2009) can be seen as two different sets of instructions, interestingly, the relation of both of them were similar regarding compensating and resisting, respectively. On the basis of the experiments, however, it cannot be conclusively asserted that the two instructions have the same effect. Bonnard et. al. used similar but not identical experimental paradigms to examine the difference of resisting (or compensating) and non-intervening (2003) *or* assisting (2009). The possibility that assisting and non-intervening are different therefore remains untested. Because this implicit assumption remains untested, there are two different possible influence of instructions that can account for the findings of both studies: If the assisting and non-intervention were in fact identical, this would indeed indicate that, just as Bonnard concluded, people are merely able to mentally resist a subsequent TMS pulse. If on the other hand the two instruction sets led to different outcomes and both conditions were to show a significant difference when compared to resisting, it would be possible that assisting increases the movement, resisting decreases the movement and the condition of nonintervention serves as a baseline for both. Differences in CNV and N100 could not exclusively stem from the effective diminishment of cortical excitability, but might as well be a result of its active amplification. The observed increase of the N100 potential after resisting the TMS pulse might also be interpreted as a decrease of inhibitory activity when assisting the induced movement. In short, the question whether the assist condition really does coincide with the baseline condition of non-intervention remains unanswered in the

two experiments of Bonnard and colleagues.

Given what was discussed in the chapters above, it seems conceivable that the assist instruction can be seen as similar to mental imagery and movement preparation. When the subject sees the instruction cue for assisting the movement, he or she could, for example, prepare for the movement by visually imagining the hand movement. Bonnards experimental paradigms are close to but not identical with those made on movement preparation, since they requires a "tonic" increase of motor cortex excitability for an extended period of time and not a mere preparation for a previously known point in time where the movement will be required. Nevertheless, it seems reasonable to anticipate a positive effect on MEP amplitudes when people intend to assist the induced movement. The possibility of an alternative interpretation of the experiments of Bonnard (2003 and 2009) cannot be excluded without merging all three conditions into one experimental paradigm. To put it more conservatively, the interpretation that subjects are able to positively influence the excitability of their cortex is just as likely (if not more) than the interpretation that they are able to negatively influence it. Given the evidence that observation, simulation and preparation change the excitability of M1 (as presented previously in this thesis), the assumption that assisting and non-intervening are identical seems surprising.

The experiments conducted in the scope of this master thesis, therefore, challenge the assumption that subjects are rather capable of mentally decreasing than increasing a TMS-induced motor twitch. The experimental paradigms of Bonnard et al. (2003, 2009) were adapted and modified in a way that tests whether the instructions of non-intervention and assistance have the same or a different influence on M1 excitability, by comparing both conditions to an assist condition.

The hypothesis of this thesis is that the assist and control conditions are not identical. Furthermore, it is postulated that subjects are able to resist as well as assist the TMS-induced movements and that the control condition lies between the two conditions. Explicitly stated, 1) the peak-to-peak amplitude in the flexor muscle

should be largest in the assist condition, smallest in the resist condition and 2) the amplitudes of the control condition should lie between them. Differences in the extensor muscle, if any, should be 3) reversed for the assist and resist condition, because ECR serves as an antagonist of the flexion movement, but 4) the control condition should remain between them. Further, the cSP is expected to show an equal relationship for the 3 conditions. In the flexor muscle, 5) SP duration should be longest for the resist and shortest for the assist condition, with 6) the control condition again in between. Again an inverse effect (if any) is expected for the extensor muscle. SP duration should be 7) shortest for the resist and longest for the assist condition and of intermediate length for the control condition.

Chapter 3

Methodology

3.1 Subjects

12 right-handed subjects (5 male, mean age 31.8 $\pm$ 5.7, and 7 female, mean age 29.6 $\pm$ 3.5) were examined for the study. All of them were screened for safety regulations and filled out a TMS safety screening questionnaire (see Appendix). They were warned about possible inconveniences, e.g. slight pain, headache or boredom, and informed that their participation could be terminated at any time, without giving any reasons to the experimenter. Subjects were recruited either through personal solicitation in and around the medical faculty in Ljubljana or through the website of the Neurological Clinic, where people could sign up after reading a short summary of the research. The restriction of accepting only right-handed subjects was introduced, because the activation patterns for left-or mixed-handed subjects are not as straightforward as those of right-handed people and mixing right and left handed people both might result in uncontrollable factors and less comparability.

In general, the sample mainly consisted of medical or psychology students, which were informed about the purpose of the experiment prior to its start. The purpose of the experiments was disclosed to spark interest and thereby increase motivation and because it was assumed by the experimenters that this would have no bias effects,

due to the very physiological nature of the study. The study was approved by the National Medical Ethics Committee of the Republic of Slovenia.

In addition to the 12 subjects that were analyzed, three more were recruited but had to be discarded. Two subjects were excluded because the experimenters were not able to get a clear signal from the extensor carpi radialis (ECR) and/or the flexor carpi radialis (FCR) . Interestingly, both of them reported to be regular climbers. Another session was terminated prematurely because the subject did not respond well to the removal of her insulin pump. Although she claimed that she regularly goes without the pump for periods exceeding the duration of the experiment before to the beginning of the session, she reported to feel dizzy and slightly nauseous. In the first place, the pump was removed to guarantee no electronic damage to the device.

3.2 Experimental Setup and Design

This experiment was based on research recently conducted by Bonnard et al. (2009) and was supplemented with several modifications.

Subjects were seated comfortably in an armchair with their right hand fixed to an armrest in a way that allowed the wrist to be moved upwards and downwards. Angle and pointing directions were variable between subjects because the length of the experiment demanded a position maintainable over a long period of time. In some subjects the hand was almost horizontal, in others it was inclined upwards, again in others downwards. Also the pointing direction was very different for all subjects. In some cases it was more suitable to have the hand pointing rather proximally, others preferred it to point rather distally and some had it pointing straight. Due to the long duration of the experiment, great care was taken in preparation of the position before the beginning of the experiment to maximize the comfort of the subject and to minimize any potential fatigue effects.

3.3 Experimental Procedure

Subjects were facing a 15" screen from a distance of approximately one and a half meters. The stimulus presentation lasted 12,5 seconds per trial. The default position was that subjects had their right arm resting on the armrest of the chair, with their hands hanging down in a supine or close to supine position without making any effort. At trial start a fixation cross appeared on the monitor, which told the subject to align the right hand horizontally with their forearm. After 4 seconds, a 500-ms-long instruction cue was presented that signaled the mental task the subject had to perform. Either a red, green or gray circle was shown as cue:

> If a **GREEN circle** was presented, the subject had to mentally ASSIST (ASS) the TMS induced motor twitch, i.e. increase the intensity of movement, solely by means of their mental powers.
>
> If a **RED circle** was presented, the subject was told to mentally RESIST (RES) the TMS induced motor twitch, i.e. reduce the intensity of the movement, solely by means of their mental powers.
>
> Additional to these two conditions, which were also present in Bonnard (2009), subjects were presented with a third CONTROL condition:
> If a **GRAY circle** was presented, the subject didn't have to perform any mental task at all.

It was made clear on several occasions that the task should only be performed mentally and that any use of muscles was prohibited. The disappearance of the cue was followed by a preparatory phase of three seconds, in which the fixation cross reappeared. The preparatory phase was concluded by a single TMS pulse to the forearm representation of M1. Subjects were instructed to return to the alignment after the TMS induced deflection and to be as precise as possible in keeping the same angle and force before

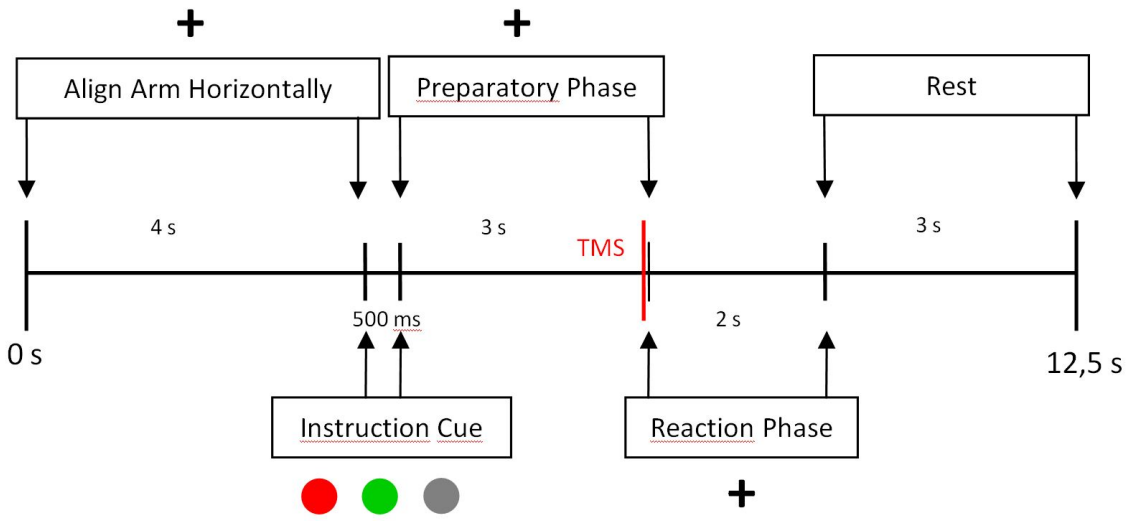

Figure 3.1: Experimental Paradigm. Subjects were asked to have their right hands aligned when a fixation cross (+) was present. The red, green and gray circle indicated whether or not they had to mentally ASSIST, RESIST or do nothing, respectively. In the absence of the fixation cross, the hand was to be left hanging with no effort.

and after. It was also made clear that alignment should be as similar as possible over trials. The period of alignment after TMS was two seconds, after which the fixation cross disappeared, signaling that the arm should go back into the default resting/hanging position (Figure 3.1). The resting period between trials was 3 seconds.

The three conditions were presented in a fully randomized fashion, on average 117 times per condition and subject. The experiment consisted of one practice block, in which the experimenter gave instructions for improvement based on the visible muscle contraction visible in the online EMG data, and 8 blocks of 39 fully randomized trials. Experimental procedure, including setting-up the equipment, instructing the subjects, recording and the breaks between the blocks took between three and a half to four hours on average. To further improve effects resulting from fatigue, subjects were allowed to take one longer break. They were asked not to consume any sugar or caffeine before or during the experiment.

3.4 Modifications of the Original Experiment

Several modifications were made to the original experimental design of Bonnard et al. (2009), due to theoretical as well as practical considerations:

1. An additional control condition was introduced:

   The most noteworthy essential modification of this experiment is the introduction of the baseline condition. The reasoning and rationale for this modification have been discussed at length in previous Chapters.

2. A direct result of the introduction of the baseline condition was that the experiment took substantially longer to run. Additionally, more blocks and more trials were added to the original paradigm. Contrary to Bonnard et al. (2009), the experiment did not have 50, but 39 trials per block. Instead of 4 blocks, the modified version of the experiment had 9 blocks. This had two main advantages. First, subjects had to hold their concentration over shorter periods of time, arguably reducing possible fatigue effects towards the end of each block. Second, since a neural navigation system was not available for this research, it was necessary for the experimenter to stabilize the coil by hand. This was physically demanding for the experimenter, who was holding the coil for approximately 8 consecutive minutes. The decreased duration of the blocks arguably reduced the fatigue of the experimenter considerably and hence guaranteed less variation of stimulation location.

3. The sample size in this study was larger than in the original study. Instead of just 8 subject, we collected data from 12 subjects. Together with the increased number of trials, our data set was substantially larger than in Bonnard et al. (2009).

4. One major methodological improvement was that we looked for the hotspot for wrist muscle stimulation in a more systematic way than usually reported

in the literature. A 10x15 linen grid with 1x1 cm squares was mounted on an EEG cap, which had the electrode holders removed at the TMS stimulation site. The search for the hotspot was started at the omega point, 5 cm between vertex and ear. The experimenter then moved the coil along the grid in distances of 1 cm to test whether the EMG response increased or decreased. Once a seemingly optimal point was found on the grid, the experimenter would continue moving the coil between the edges of the grid in steps of 0,5 cm to optimize the stimulation site even more. The final point was then marked with a permanent marker and an indication line that showed the extension of the pointing direction of the coil was drawn. The hotspot was found using 70% of MSO in all subjects. This technique was developed in the scope of this study and has many advantages as compared to the conventional technique found in the literature, where the hotspot is found by unsystematically moving the coil around on the scalp until a seemingly ideal hotspot is found.

3.5 TMS

For TMS stimulation, a Magstim Bistim 200 (Magstim Co., Whitland, UK) with a figure-of-8 coil was used, which was placed tangentially to the scalp over the left motor cortex. The figure-of-eight coil was chosen for its specific characteristics. The magnetic field that is delivered is more focal in comparison to other coils and has the highest precision for targeting specific neurons for the desired movement. It nevertheless cannot achieve a complete isolation of a single muscle and always activates neighboring neurons, but to a substantially smaller degree when compared to coils with different shapes. Figure of eight coils are the most commonly reported in research that tries to isolate single muscles. The handle was pointing backwards in a 45 degree angle away from the midline, resulting in a perpendicular stimulation in M1, and hence was ideal for a transsynaptical activation of the corticospinal pathways.

(Brasil-Neto et al., 1992; Kaneko et al., 1996).

Stimulation intensity was set to 120% of RMT, which was determined by finding the percentage of MSO that elicits no MEP and increases MSO by 1 percent until an activation of at least 50 microvolts in 3 out of 6 trials was present. The outputted pulse had a monophasic wave form.

For stabilization, a knee joint arm was mounted on the recording chair to hold the coil during trials. Extensive pilot testing determined that this was the best way to reduce variability induced by the movement of the experimenter. Initially, the splitting of the total amount of trials into 5 blocks, which lasted 13 minutes respectively, resulted in muscle tiring and consecutive hand movement for the experimenter holding the coil. Even with the reduced length of 8 minutes per block, this effect was still present when the pulses were administered while holding the coil. In addition to the loss of the hotspot, another issue was that the effect of the inclination and tangentiality of the coil and therefore the MEP responses differed greatly with the manual holding procedure. In contrast, the method of having the coil fixed with with a knee joint arm and adjusting the head by hand to fit the before marked point turned out to guarantee a sufficient amount of precision in both regards, location and inclination. It could also minimize differences between the 3 experimenters and was of little inconvenience to the subject, as compared with the more radical approach of mounting the head in a fixation tool.

A custom-made cable connected the computer, which presented the stimuli in E-Prime 3.0 software (Psychology Software Tools, Pittsburgh, PA), with the TMS stimulator and triggered TMS pulses 3.5 seconds after instruction cue onset.

3.6 EMG Data Acquisition

Recording electrodes were connected to a D360 Pre-Amplifier Headstage, which was connected to a D360 8-channel Patient Amplifier System (Digitimer Ltd., Cambridge).

In a further step, the analogue data were sent to a 4-channel Micro 1401-3 (Cambridge Electronic Design Limited, Cambridge, UK) analogue-to-digital converter (ADC) for digitization. The digitized data were then fed into a PC and depicted and saved in Spike2 (Cambridge Electronic Design Limited, Cambridge, UK) for online and offline analysis. Marker codes were additionally collected directly from the stimulus presentation in e-prime and stored in a separate file for later identification of condition, time of TMS administration, as well as trial start and end for later epoching.

Two pairs of Ag-AgCl EMG electrodes were placed with a belly-tendon montage on both FCR and ECR. The distance between recording and reference electrode was roughly 1.5 cm in all subjects. The cables of the EMG electrodes were bundled as many times as possible in order to reduce noise originating from the environment. Data was sampled with 5000 Hz, amplified by 1000 and filtered using a 20 Hz low-cut and 2000 Hz high-cut filters. The collected data were fed into Matlab 2012b (The MathWorks, Inc., Natick, Massachusetts, United States) for pre-processing. In a first step, trials were epoched from 6000 ms before to 1000 ms after the TMS pulse. In a further step, data were analyzed in more depth in Python 3.5. Peak-to-Peak (P2P) amplitudes were defined to be the difference between the highest and lowest peak of the MEP.

3.7 Exclusion Criteria

Trials were excluded along two lines. First, those trials that showed a difference in the root mean square of the signal in the intervals 1.5 seconds prior to condition cue (more than two standard deviations) and either the 1.5 s interval after cue presentation and/or the interval 1.5 s prior to the TMS pulse. Based on this criteria, approximately $6.1 \pm 5.3\%$ of trials were excluded. In a second step, of the sorted P2P amplitudes 10% of the bottom and the top were excluded to reduce outliers. This had the additional

benefit of being a first step towards getting the data closer to a normal distribution as seen by QQ-plots (Figure 3.2). After this second exclusion, 24.0 ± 4.3% of trials were excluded in each subject altogether.

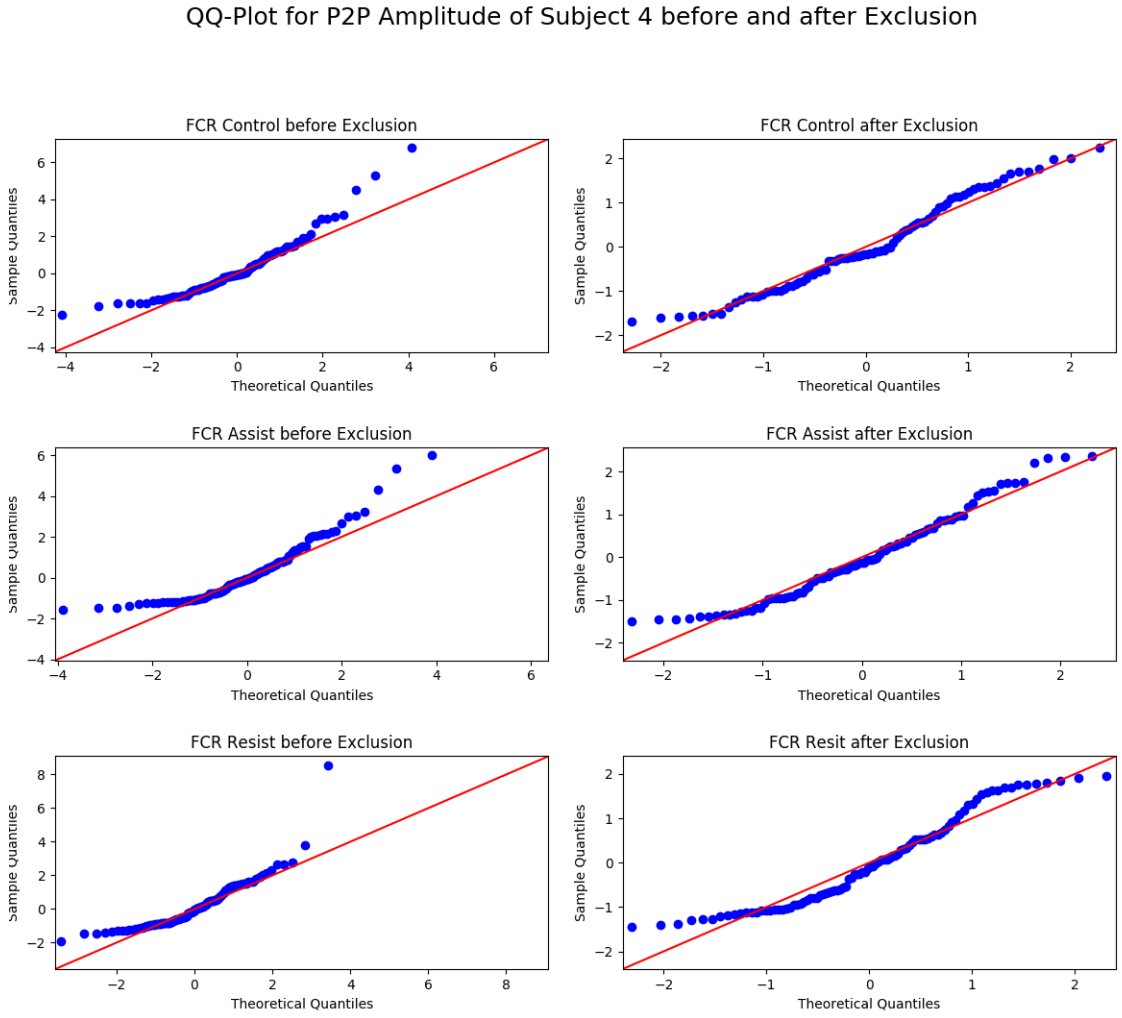

Figure 3.2: QQ plot of the distribution of P2P amplitudes of FCR of subject 4 before (left) and after (right) the application of the second exclusion criterion. The graph shows how outliers are removed and the distribution becomes closer to normal distribution.

3.8 Silent Period Detection Algorithm

The silent period was detected by a specifically designed algorithm. An illustration of the algorithm can be seen in Figure 3.3. In a first step, the cumulative sum of the signal was calculated. The generated signal was then lowered to the x-axis at around 150 ms (green line). In a next step, a time interval for each subject and muscle was determined in which a silent period was always (or nearly always) present (vertical black lines). A tangential curve was then fitted to this interval (diagonal red line). The difference between the value of the fitted line and the cumulative sum of the signal was compared at each data point of the interval. The mean and standard deviations were calculated for the difference between fit and signal. SP was defined to be the point where the difference between the two lines reached a critical level, i.e 20 times the standard deviation of the difference within the individual's initial interval (vertical red line). The silent period was measured for 9 out of the 12 subjects, since the remaining 3 did not show a sufficiently pronounced SP (Figure 3.4).

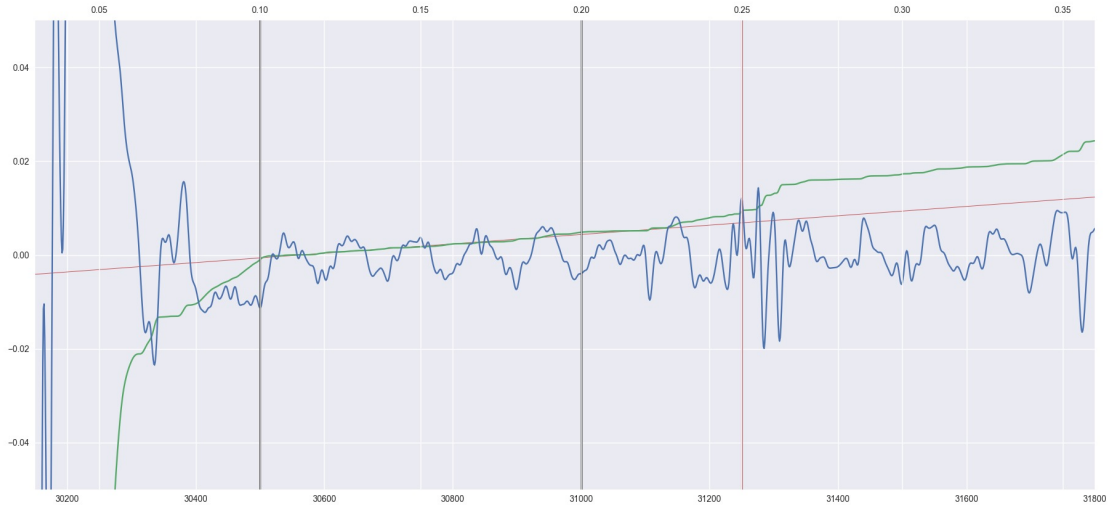

Figure 3.3: An example of a properly detected SP. The interval that is used for detection is denoted by the two black lines. The cumulative sum of the original signal (blue) is shown in green. The horizontal red line is the function fitted to the interval. The vertical red line denotes the point where the algorithm detects the silent period by an assessment of the difference of the cumulative sum and the fit function.

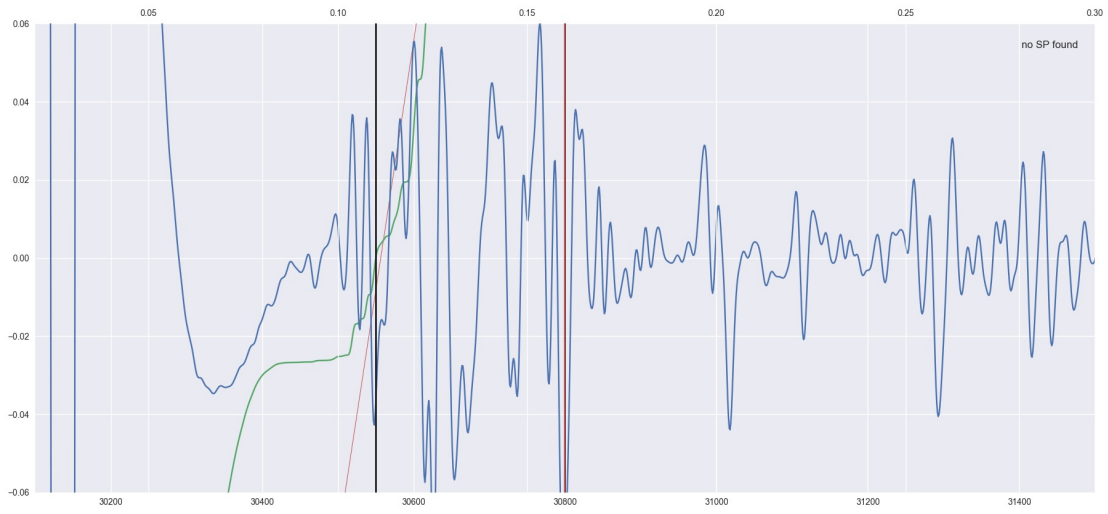

Figure 3.4: An example of an SP of a subject which was excluded from the analysis. No clear SP was detected.

Chapter 4

Results

4.1 MEP Amplitudes

MEP amplitudes of the 12 subject were on average 0.97 ± 0.63 mV for FCR (assist condition: 1.0 ± 0.66 mV, resist condition: 0.96 ± 0.61 mV, control condition: 0.95 ± 0.62 mV) and 2.48 ± 1.86 mV for ECR (assist condition: 2.44 ± 1.87 mV, resist condition: 2.657 ± 1.86 mV, control condition: 2.35 ± 1.86 mV). However, variability between (Figure 4.1) and within (Figure 4.2) subjects was high in terms of P2P amplitude, its shape and latency. In some subjects assist had higher amplitudes than resist, in others the other way round. In some subjects the control condition yielded the highest MEPs.

To test for normality, the Shapiro-Wilk test was used. All in all, 72 groups can be defined for the collected data given that there were 12 subjects, 3 conditions and 2 muscles. Only 18 out of these 72 groups tested positive ($p > 0.05$) for the assumption of normality, with 13 of the 18 being from the extensor muscle. The distribution ranged from highly skewed to both the left and right to bimodal (see distributions of the assist condition in FCR in Figure 4.3 as example). Only two subjects (subjects 9 and 12), and both just in one muscle (ECR), showed a normal distribution in all three conditions. Interestingly, left skewness was only found in FCR and clear

MEP Amplitudes

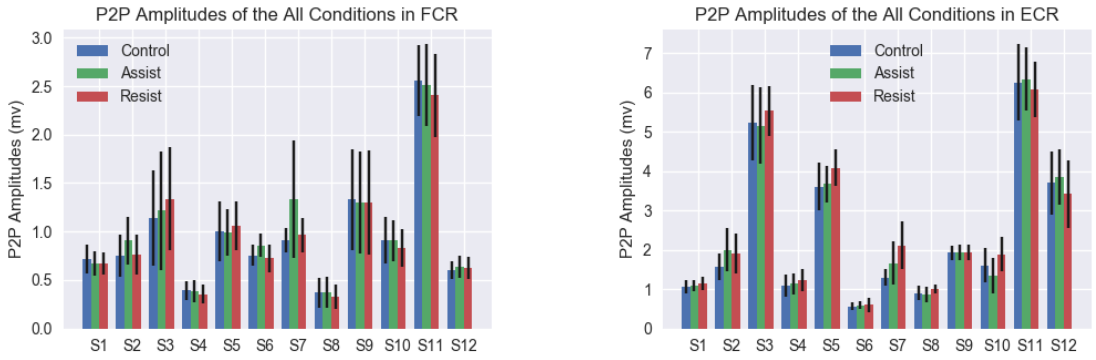

Figure 4.1: Intersubject variability of MEP amplitudes was high, with no clearly visible patterns of consistency of which condition has the highest amplitudes.

bimodality only in ECR. All in all, there was no clear pattern of distribution across subjects in either muscle.

A one-way repeated measures analysis of variance (ANOVA) was conducted to compare the effect of the three different instructions on peak-to-peak (P2P) MEP amplitudes, attained while assisting, resisting, or being idle. This statistical test was performed on both muscles independently. The assumption of sphericity was tested with Mauchly's test, which yielded non-significant results in both muscles. In the flexor muscle, there was no significant effect of instruction on amplitudes, $F(2,22) = 1.89$, $p = 0.17$.

For the extensor muscle, there was also no significant effect of instruction on amplitudes, although the test was close to the chosen significance level (alpha = 0.05), $F(2,22) = 3.13$, $p = 0.06$. Due to the fact that the test was nearly significant in ECR, Tukey's Post Hoc Test was performed. Pairwise comparison indicated that there was a significant difference between the amplitudes in the resist ($M = 2.66$, $SD = 1.86$) and the control ($M = 2.35$, $SD = 1.86$) conditions ($z = 2.38$, $p = 0.04$). However, the assist condition did not significantly differ from either the control or the resist condition (Figure 4.4).

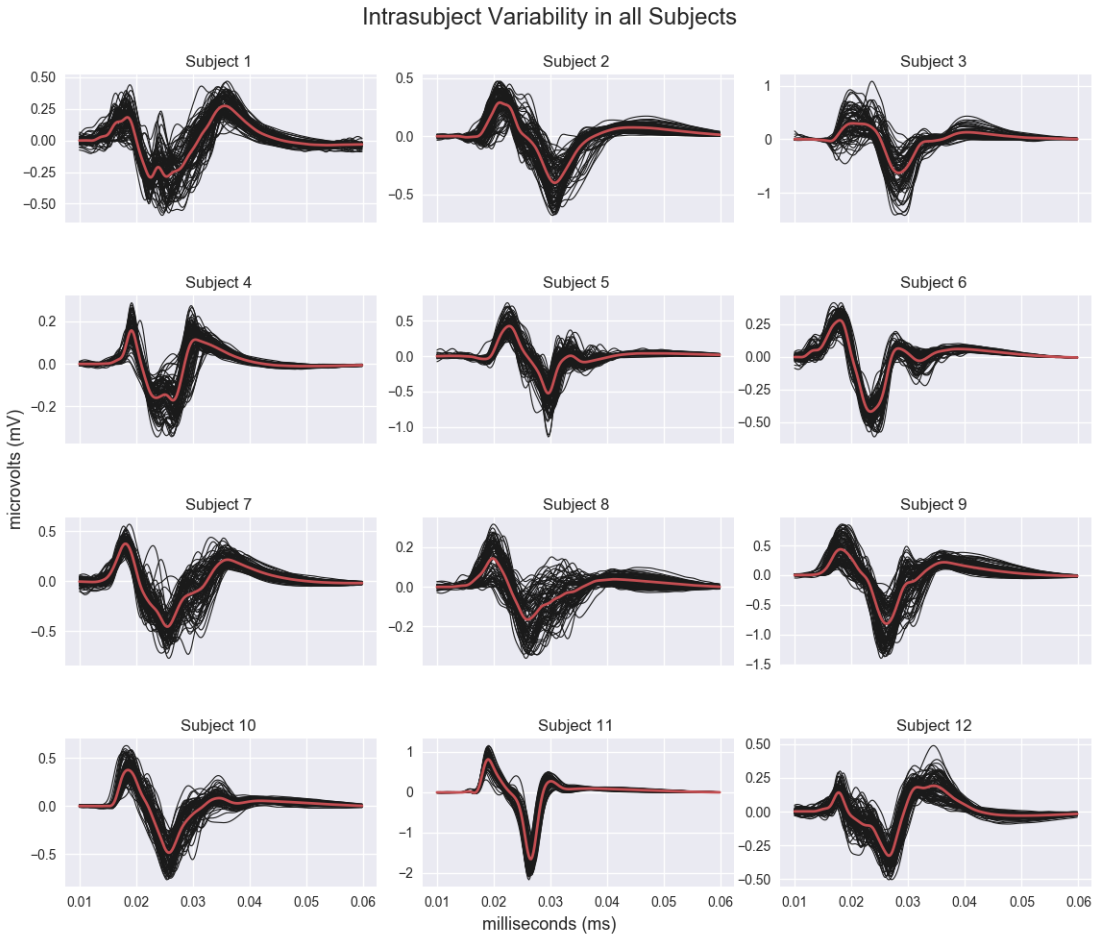

Figure 4.2: Different shape of wave forms of MEPs visible both in all trials (black lines) and average wave form (red line). The MEPs were taken from the control condition and the flexor muscle.

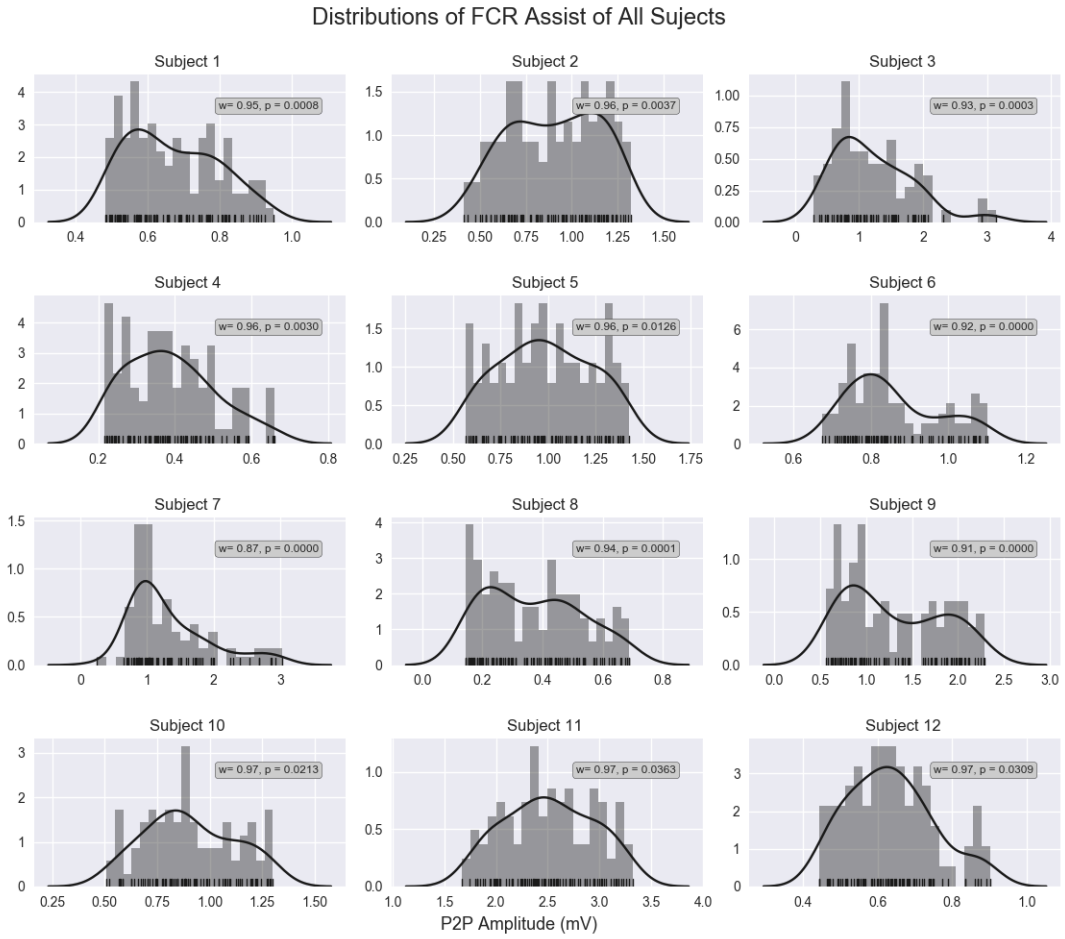

Figure 4.3: Distributions of the assist condition in FCR of all 12 subjects. The graphs show different distribution forms, for example, heavily right skewed distributions in subjects 3 and 7 and heavily bimodal distributions in subjects 8 and 9.

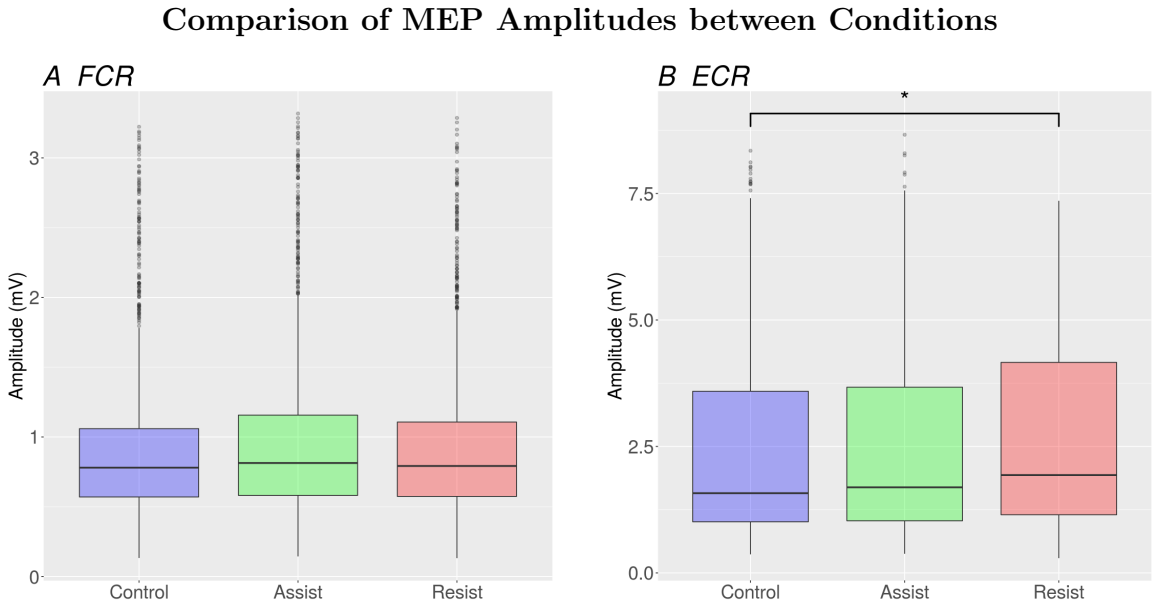

Figure 4.4: Comparison of MEPs in the three conditions in FCR (A) and ECR (B). Significant differences between conditons were found in ECR between the control and resist condition as revealed by Tukey's Post Hoc Test.

4.2 Silent Period

SP duration of the 9 subject that showed acceptable SPs were on average 191.0 ± 24.6 ms for FCR (assist condition: 191.62 ± 24.92 ms, resist condition: 188.6 ± 24.49 ms, control condition: 192.88 ± 24.41 ms) and 201.96 ± 35.86 ms for ECR (assist condition: 200.57 ± 35.62 ms, resist condition: 200.77 ± 37.43 ms, control condition: 204.53 ± 36.54 ms). As for MEP amplitudes, SP duration also showed inconsistencies across and within subjects with some subjects having longer SPs for the assist than the resist condtion and some showing longest duration for the control condition (Figure 4.5).

The same statistical procedure was chosen for the analysis of the silent period. One way repeated measures ANOVA was conducted to compare the effect of instruction on duration of SPs in both muscles, attained while assisting, resisting, or being idle. Again, Mauchly's test for sphericity was non-significant for both muscles. In FCR,

SP Duration

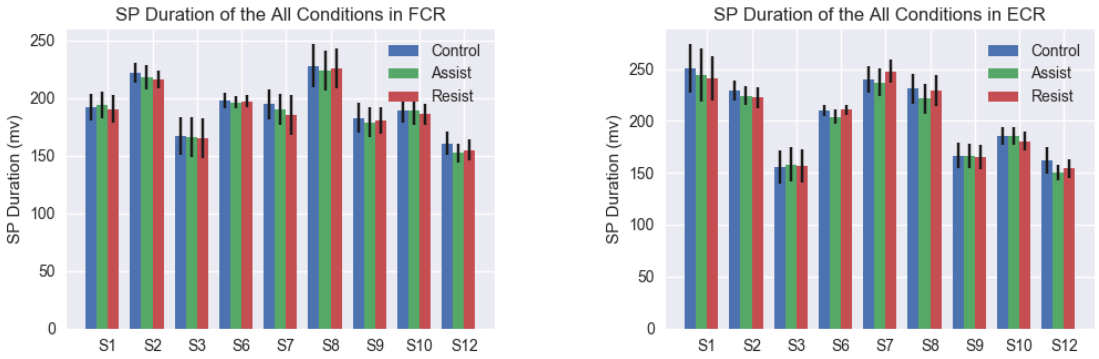

Figure 4.5: Also duration of SPs is highly variable among subjects with no clear patterns of consistency of which condition has the longest SPs.

differences in SP duration for the three groups were statistically significant, F(2,16) = 8.12, p = 0.04.

Tukey's Post Hoc Test revealed that differences between the control (M = 192.9, SD = 24.41) and the resist (M = 188.60, SD = 24.49) conditions were statistically highly significantly, (z = -3.9, p ¡ 0.00) and that there was also a significant difference between the control (M = 192.9, SD = 24.41) and assist conditions (M = 191.62, SD = 24.92). No significant difference between the assist and the resist conditions could be detected by the post hoc test.

The repeated measures ANOVA for the ECR muscle showed a close-to-significant trend, F(2,16) = 3.49, p = 0.55. Therefore, a post hoc test was also performed for this muscle. Tukey's Test showed that there was a statistically significant difference between the control (M = 204.53, SD = 36.54) and the assist (M = 200.6, SD = 35.62) conditions, z = -263, p = 0.02 (Figure 4.6).

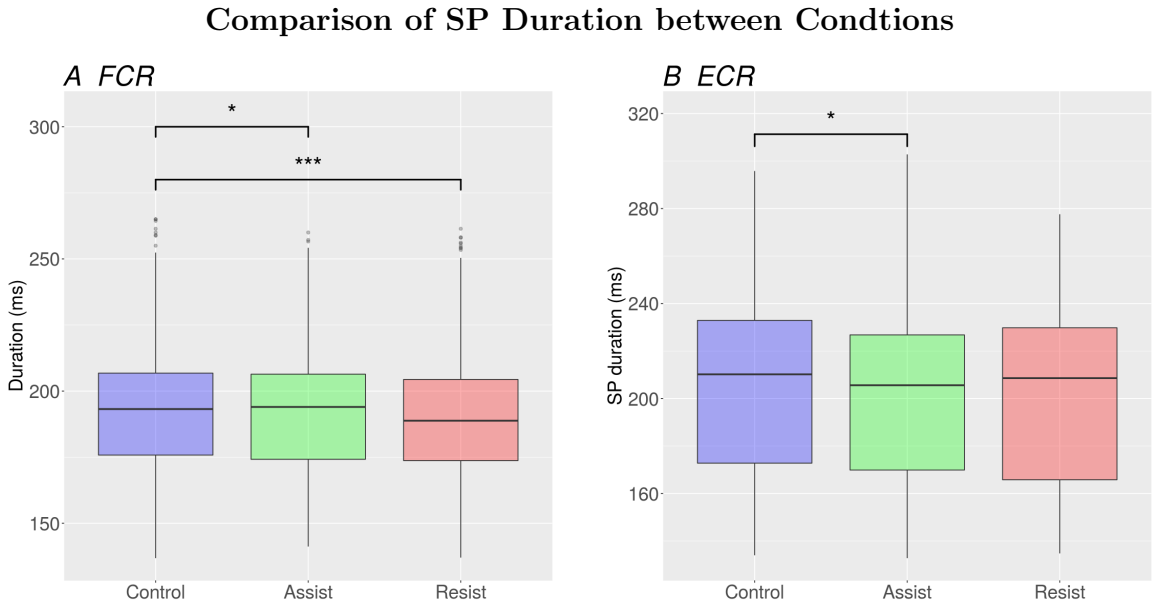

Figure 4.6: Comparison of the three conditions in FCR (A) and ECR (B). Significant differences between conditions were found in ECR between the control and resist conditions as revealed by Tukey's Post Hoc Test

4.3 Replication of Bonnard

Differences between only the assist and resist conditions were also analyzed in order to see if the data collected for this study matched the data of the original study of Bonnard (2009). As a first step, it was checked whether or not the MEP data met the prerequisites for the tests used by Bonnard et. al. Since in the original study paired T-Tests were used to compare the two conditions, the assumption of normality had to be moderately satisfied (if N>50, then T-Tests are relatively robust to deviations from normality) and the variances of the two groups should be homogeneous. To test for normality, Shapiro-Wilk Tests were used. Distributions were normal in only one third of the cases. 12 cases out of 48 were normally distributed according to Shapiro-Wilk tests (see asterisks in Figure 4.7).

Another important prerequisite for T-Tests is homogeneity of variances among the two groups. In order to validate this assumption, Levene's Test was used, which

Results of Shapiro-Wilk Tests for P2P Amplitudes

	Subject 1			
	ECR		FCR	
	w	p	w	p
Assist	0.966	0.015	0.949	0.001
Resist	0.956	0.004	0.976	0.075*

	Subject 5			
	ECR		FCR	
	w	p	w	p
Assist	0.955	0.003	0.963	0.013
Resist	0.96	0.004	0.948	0.001

	Subject 9			
	ECR		FCR	
	w	p	w	p
Assist	0.973	0.051*	0.909	0
Resist	0.992	0.808*	0.879	0

	Subject 2			
	ECR		FCR	
	w	p	w	p
Assist	0.917	0	0.958	0.004
Resist	0.9	0	0.947	0.001

	Subject 6			
	ECR		FCR	
	w	p	w	p
Assist	0.978	0.116*	0.921	0
Resist	0.938	0	0.931	0

	Subject 10			
	ECR		FCR	
	w	p	w	p
Assist	0.981	0.25*	0.966	0.021
Resist	0.971	0.106*	0.967	0.019

	Subject 3			
	ECR		FCR	
	w	p	w	p
Assist	0.948	0.002	0.928	0
Resist	0.959	0.001	0.969	0.012

	Subject 7			
	ECR		FCR	
	w	p	w	p
Assist	0.875	0	0.866	0
Resist	0.976	0.131*	0.943	0.001

	Subject 11			
	ECR		FCR	
	w	p	w	p
Assist	0.987	0.444*	0.973	0.036
Resist	0.974	0.056*	0.98	0.15*

	Subject 4			
	ECR		FCR	
	w	p	w	p
Assist	0.965	0.012	0.957	0.003
Resist	0.936	0	0.928	0

	Subject 8			
	ECR		FCR	
	w	p	w	p
Assist	0.962	0.003	0.94	0
Resist	0.94	0	0.945	0.001

	Subject 12			
	ECR		FCR	
	w	p	w	p
Assist	0.979	0.238*	0.967	0.031
Resist	0.982	0.427*	0.961	0.009

Figure 4.7: Only one quarter of the cases (12 of 48) showed a normal distribution (*) of amplitudes according to Shapiro-Wilk.

Results of Levene's Tests for P2P Amplitudes

Subject 1			
ECR		FCR	
w	p	w	p
3.23	0.074*	1.83	0.178*

Subject 5			
ECR		FCR	
w	p	w	p
0.053	0.819*	0.71	0.4*

Subject 9			
ECR		FCR	
w	p	w	p
0.002	0.968*	0.801	0.372*

Subject 2			
ECR		FCR	
w	p	w	p
1.361	0.245*	4.249	0.041

Subject 6			
ECR		FCR	
w	p	w	p
24.308	0	1.54	0.216*

Subject 10			
ECR		FCR	
w	p	w	p
0.144	0.705*	0.487	0.486*

Subject 3			
ECR		FCR	
w	p	w	p
17.981	0	1.252	0.265*

Subject 7			
ECR		FCR	
w	p	w	p
2.718	0.101*	30.253	0

Subject 11			
ECR		FCR	
w	p	w	p
0.515	0.474*	0.031	0.86*

Subject 4			
ECR		FCR	
w	p	w	p
3.027	0.084*	1.649	0.201*

Subject 8			
ECR		FCR	
w	p	w	p
21.775	0	8.365	0.004

Subject 12			
ECR		FCR	
w	p	w	p
1.947	0.165*	0.043	0.836*

Figure 4.8: Only three quarters of the cases (18 of 24) showed homogeneous variances of the assist and resist conditions (*).

in comparison to the frequently used Bartlett's test is robust to deviations from a normal distribution of the data.

Due to the violations of the assumption of homogeneity of variance in some cases (see Figure 4.8), the paired student' T-Test was calculated with only those cases that showed no such violation. For each muscle, 3 subjects (ECR: 2,6,8; FCR: 2,7,8) were excluded from the statistical analysis. Neither FCR ($t_{11} = 0.7$, $p = 0.5$) nor ECR ($t_{11} = -1.21$, $p = 0.26$) showed any statistical differences between assisting and resisting. Since it is not clear whether the violation of the homogeneity assumption was due to a measurement error in the affected subjects or caused by factual variability within these subjects, an additional non-parametric approach was taken, that is not affected by violations of the two prerequisites that have to be satisfied for the student's T-Test. For this approach, the Wilcoxon Rank-Sum Test was used on all 12 subjects. Again no indication for a statistical difference between the two conditions was found in either FCR ($Z = 0.4$, $p = 0.69$) or ECR ($Z = -0.35$, $p = 0.69$).

A similar situation was found for SPs. Normal distributions were found only in 11 of 36 (Figure 4.9) and homogeneity of variance in 12 of 18 cases (Figure 4.10). T-Tests were performed on those subjects in whom the variances of the assist and resist conditions were found to be homogeneous. Neither FCR ($t_8 = 0.36$, $p = 0.73$) nor ECR ($t_8 = 0.37$, $p = 0.72$) showed any significant differences between conditions. The additional Wilcoxon test, performed on all subjects regardless of normality and homogeneity, also found no significant difference in both muscles (ECR: $Z = -0.16$, $p = 0.87$; FCR: 0.16, $p = 0.87$).

Results of Shapiro-Wilk Tests for SP Duration

	Subject 1			
	ECR		FCR	
	w	p	w	p
Assist	0.931	0	0.968	0.038
Resist	0.926	0	0.951	0.005

	Subject 6			
	ECR		FCR	
	w	p	w	p
Assist	0.972	0.091*	0.972	0.106*
Resist	0.972	0.102*	0.973	0.126*

	Subject 9			
	ECR		FCR	
	w	p	w	p
Assist	0.876	0	0.934	0.001
Resist	0.893	0	0.973	0.085*

	Subject 2			
	ECR		FCR	
	w	p	w	p
Assist	0.972	0.076*	0.934	0.001
Resist	0.954	0.007	0.972	0.076*

	Subject 7			
	ECR		FCR	
	w	p	w	p
Assist	0.938	0.003	0.934	0.001
Resist	0.966	0.063*	0.959	0.017

	Subject 10			
	ECR		FCR	
	w	p	w	p
Assist	0.957	0.019	0.975	0.155*
Resist	0.973	0.231*	0.964	0.028

	Subject 3			
	ECR		FCR	
	w	p	w	p
Assist	0.93	0.001	0.948	0.01
Resist	0.933	0	0.929	0

	Subject 8			
	ECR		FCR	
	w	p	w	p
Assist	0.957	0.005	0.911	0
Resist	0.983	0.409*	0.894	0

	Subject 12			
	ECR		FCR	
	w	p	w	p
Assist	0.867	0	0.931	0.001
Resist	0.887	0	0.898	0

Figure 4.9: Only about one third of the cases (11 of 48) showed a normal distribution (*) of SP duration, according to Shapiro-Wilk.

Results of Levene's Tests for SP Duration

Subject 1			
ECR		FCR	
w	p	w	p
1.373	0.243*	0.054	0.816*

Subject 6			
ECR		FCR	
w	p	w	p
5.977	0.016	0.037	0.848*

Subject 9			
ECR		FCR	
w	p	w	p
0.017	0.896*	2.657	0.105*

Subject 2			
ECR		FCR	
w	p	w	p
1.347	0.248*	6.898	0.009

Subject 7			
ECR		FCR	
w	p	w	p
4.02	0.047	6.733	0.01

Subject 10			
ECR		FCR	
w	p	w	p
0.345	0.558*	8.226	0.005

Subject 3			
ECR		FCR	
w	p	w	p
0.144	0.705*	0.154	0.695*

Subject 8			
ECR		FCR	
w	p	w	p
0.248	0.619*	0.051	0.821*

Subject 12			
ECR		FCR	
w	p	w	p
4.226	0.042	0.697	0.405*

Figure 4.10: Less than half of the cases (11 of 24) showed homogeneous variances of SP duration in the assist and resist conditions (*).

Chapter 5

Discussion

This study was not able to conclusively confirm its hypothesis, nor did it achieve a replication of the results of Bonnard (2003, 2009). No clear conclusions can be drawn from the results. It seems that MEPs were larger in the resist condition in the extensor muscle, which could be interpreted as an active effort to decrease the elicited muscle response. However, no such activity was found in either the compensation condition in Bonnard et al. (2003), or the resist condition in Bonnard et al. (2009).

No significant differences were found in evoked amplitudes in the flexor muscle. However, a non-significant trend shows that the control condition is different from both assist and resist and that subjects seem to have increased amplitudes when assisting, which is in line with the reports of Bonnard et al. (2009). Another non-significant trend was present in ECR. The assist condition seems to be closer to the control condition, which would indicate that subjects can in fact resist the TMS pulse.

What is particularly interesting in the results of the SP duration is that in FCR, the control condition has the longest SPs and significantly differs from both assist and resist. SP duration is an indicator for cortical inhibition and should be prolonged when subjects are mentally resisting. Interestingly, the resist condition had the

shortest SPs for all three instructions. The reported effect in Bonnard et al. (2009) that SPs were different in the assist and resist conditions, was again not confirmed. There are several possible reasons for the two circumstances that the replication of Bonnard (2003, 2009) failed and that the hypotheses were not confirmed:

The acquired data for this study seems to differ considerably from its predecessor study in terms of variability. Upon inspection, many details of the data, like the relationship between the two muscles, the size of MEPs in general, and the consistency of MEP sizes within and between subjects, were different in the two studies. These differences further translate into the requirement of different statistical tests, as data for this study does not allow to repeat the statistical tests that were used by Bonnard et. al. In the following each of these points will be discussed individually.

As a first difference, it has to be noted that while in Bonnard et al. (2003) MEP amplitudes in FCR were larger than those in FCR, in the present study the roles of the muscles were reversed. ECR had higher MEP amplitude responses to the TMS than FCR. This was consistent in all subjects, except subject 6 (see Figure 5.1). One possible reason for this could be that signals were actually recorded from the bigger and close Musculus Brachioradialis, which is partially covering ECR.

Compared to Bonnard et al. (2003), intersubject variability was higher in the present study. Upon visual inspection, Figure 5.1 shows that consistency between conditions was higher in both muscles in the study of Bonnard et al.: In their study, the nonintervention (NINT) condition was consistently higher in each subject in the flexor muscle. In comparison, in this study MEPs in the assist condition were bigger in FCR in 7 out of 12 subjects and in the resist condition in 2 out of 12 subjects. Additionally, 3 out of 12 subjects showed virtually no difference between the two conditions. For the extensor muscle, intersubject variability was comparable for the two studies. In Bonnard (2003), 5 out of 8 subjects showed higher MEP amplitudes for the compensation condition. In comparison, 8 out of 12 subjects had higher

MEPs in the resist condition, and only one subject had highly similar amplitudes for both types of instruction.

Factoring in the control condition, it has to be noted that for FCR the control condition produced the highest amplitudes in 5 of the 12 subjects, lowest amplitudes for 4 of the 12 subjects and was between the two conditions in the remaining 3 subjects. It is especially surprising that the lack of cognitive modulatory effort produces MEPs that are higher than those where such an effort is present. In the extensor muscle, variability was less pronounced than in the flexor. None of the subjects had the highest mean amplitudes in the control condition, but in 7 of the 12 cases MEPs were smallest. In 4 subjects, amplitudes lay between assist and resist. One subject showed virtually no difference for any of the instructions. The results of the previously reported repeated measures one-way ANOVA are in line with these observations.

This variability is a likely cause of the different results in Bonnard et. al. and this study. A possible source of it might be the implicit assumption that all subjects perform the mental task in the same or at least a similar way. "However, intersubject variability might result from subjects engaging different degenerate neuronal systems that are each sufficient for task performance. This would produce a multimodal distribution of intersubject variability"(Noppeney et al., 2006, p. 885). Another reason for the variable results across subject might be the individual arm position that was chosen to make the long experiment more endurable for the participants. Ginanneschi et al. (2006) were able to show that shoulder position has a direct effect on ECR and FCR excitability.

Besides intersubject variability, also variability stemming from within subjects was an issue. Again variability within subjects was also different for every subject. Several subjects had clear-cut MEP responses, highly similar for all trials, whereas in other subjects trials differed greatly in terms of MEP responses. Also variations in the shape of the wave form were found; compare, for example, Subjects 1 and 8 to subject

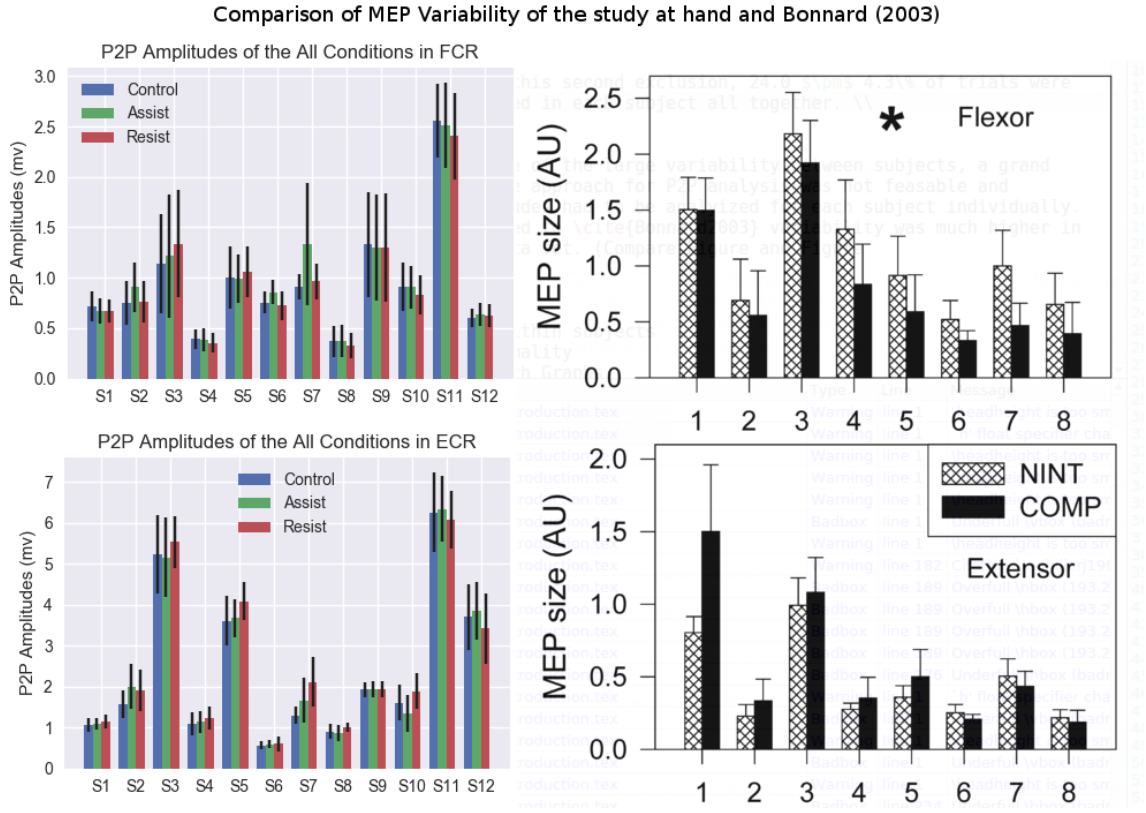

Figure 5.1: Comparison of MEP amplitudes and intersubject variability in the data collected for this thesis (left) and the reported MEPs in Bonnard et al. (2003).

11 in Figure 4.2. Since the procedure of attaining the MEPs was highly standardized for all subjects and no deviation from the procedure occurred in any instances, this intrasubject variability most likely reflects differences in "constant, rapid, spontaneous fluctuations in corticospinal and segmental motoneuron excitability levels" (Kiers et al., 1993, p. 415).

An additional source of the difference to the previous studies was the variability of the distribution of amplitudes within each subject. As mentioned above the distribution of the data was not normal in most cases (Figure 4.3). To increase the fit of the data to a desirable Gaussean distribution that is one of the prerequisites for the tests used by Bonnard, several transformations had been attempted before analysis.

Four different transformations were put to the test: three logarithmic transformations (with the natural logarithm and logarithms with the base 2 and 10) and the Box-Cox transformation. Of the four, the Box-Cox transformation was the only one that considerably improved normality of the data. From the 72 groups, 41 responded positively to the Shapiro-Wilk Test after the Box-Cox transformation. Effectiveness of the transformation was variable between subjects, for example, in subject 3 all 6 groups (3 conditions in 2 muscles each) were initially not normal, but were transformed into a normal distribution. On the other hand, only one group was transformed into normality for subject 8. Another effect that was observed after transformation was that some groups showed a strong platykurtic distribution in the ECR muscle; see for example subject 3 in Figure 5.2. Interestingly, the transformation still yielded a positive ($p > 0.05$) result on the Shapiro-Wilk Test in some of those cases. All in all, also the Box-Cox transformation was deemed insufficient and the entire analysis was performed on the untransformed data and with tests that do not require a normal distribution.

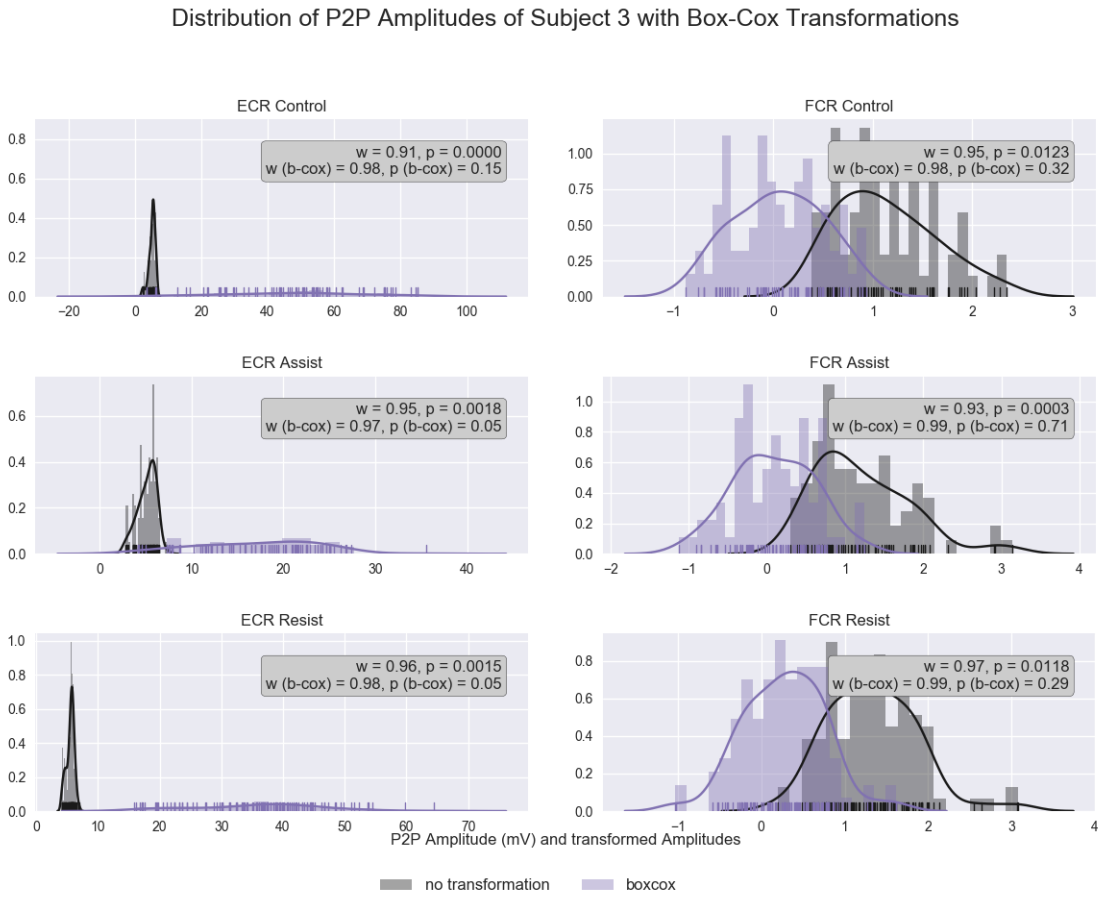

Figure 5.2: Distributions of P2P amplitudes before (black) and after Box-Cox transformation. Note that in ECR the transformation resulted in a normal (according to the Shapiro-Wilk test) yet platykurtic distribution in all three conditions. This effect of the transformation was found in 9 groups.

Conclusion

This study challenged the assumption that has been present in two previous experiments by Bonnard et al., namely that people are rather capable of resisting than assisting a TMS-induced twitch of the forearm. In order to do so, the experimental paradigms of the two studies were combined, with the hypothesis that subjects would have the capacity to assist as well as resist the induced movement and that, unlike implicitly assumed in the previous studies, the assist condition would be identical or at least close to performing no mental task. This hypothesis was corroborated with arguments, laid out in the previous chapters. Since subjects show increased excitability of M1 when simulating, observing and preparing for a movement, mentally assisting a TMS-induced forearm twitch should have similar modulatory effects and should be distinct from being idle. Unfortunately, the experiments did not yield results to confirm this hypothesis. Neither did the results allow for a preproduction of the results of the previous studies. The reasons for this may lie in a high inter- and intrasubject variability that was not present in this form in the data of Bonnard. Intersubject variability might be due to different task realization in different subjects or due to differences in arm position. Variability within single subjects is likely caused by spontaneous fluctuations in cortical excitability. Ultimately, however, the reasons for both forms of heterogeneity found in this dataset remain a matter of conjecture.

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Appendix

Safety Screening Questionnaire

Name:
Date of Birth:
ID-Number of participant:

1. Are you being treated for epilepsy or ever had any kind of seizure? ◯ Yes ◯ No
2. Have you ever lost consciousness or fainted? ◯ Yes ◯ No
   If so, please describe what happened:
3. Have you ever had a serious head injury accompanied by loss of consciousness? ◯ Yes ◯ No
4. Do you have any hearing problems (such as tinnitus)? ◯ Yes ◯ No
5. This question is short ◯ Yes ◯ No
6. Do you have any metal particles in the brain or skull (except for particles of titanium), for example, fragments or pieces of metal after surgery? ◯ Yes ◯ No
7. Do you have auditory implants (cochlear implant) in the ears? ◯ Yes ◯ No
8. Do you have any implanted device for stimulation of the central nervous system (such as deep brain stimulation / DBS, vagus nerve stimulator)? ◯ Yes ◯ No
9. Do you have a pacemaker or other devices implanted in the heart or elsewhere in the body? ◯ Yes ◯ No
10. This question is longer, and will probably wrap to the next line ◯ Yes ◯ No
11. Do you have a device for drug infusion implanted? ◯ Yes ◯ No
12. Are you taking any medication? ◯ Yes ◯ No
    Please list:
13. Have you ever had surgery performed in the spine? ◯ Yes ◯ No
14. Have you ever participated in a study with TMS? ◯ Yes ◯ No
15. Have you ever been a participant in magnetic resonance? ◯ Yes ◯ No
16. Did you use drugs or alcohol in the past 24 hours? ◯ Yes ◯ No
17. Have you ingested caffein during the past 6 hours? ◯ Yes ◯ No

Date and signature of the participant:

Date and signature of the experimenter:

5.1 Abstract

This thesis deals with motor cognition by examining the effect of motor plans on movement execution. EMG recordings were used to determine whether participants are able to increase or decrease a TMS-induced motor twitch of the right wrist merely by actively thinking of influencing the movement. Several methodological modifications to an existing experimental paradigm by Bonnard et al. (2009) were made to test the implicit assumption that subjects can rather resist than assist. It was reasoned that without comparing both conditions to a baseline, it is not possible to draw this conclusion. Based on research examining the positive effect of imagination, observation and preparation of movement on neural activity in the motor cortex, it was hypothesized that subjects would rather be capable of assisting than resisting the induced movement, when measured against a baseline condition. It was found that the data recorded for the purpose of this thesis does not allow for the statistical tests that were used in the previous research by Bonnard et al. (2009). Data did not show a normal distribution, and three different logarithmic as well as the Box-Cox transformation could not remedy this fact. Different statistical tests were hence used that, however, could not replicate the effect found by Bonnard et al. (2009). It was argued that the cause for this might lie in inter-subject and within-subject variability present in the data recorded for this study.

5.2 Zusammenfassung

Diese Arbeit handelt von Motorkognition und untersucht den Effekt von Motorplnen auf die Bewegungsausfhrung. EMG-Aufnahmen wurden verwendet um festzustellen, ob die Versuchsteilnehmer eine durch TMS ausgelste Bewegung des rechten Handgelenkes durch aktives Nachdenken vergrern oder verkleinern knnen. Es wurden mehrere methodische Modifikationen zu einem bereits existierenden Versuchsaufbau von Bonnard et al. (2009) hinzugefgt, um die in frherer Forschung implizite

Annahme, dass Teilnehmer die Fhigkeit haben die ausgelste Bewegung zu verkleiner anstatt zu vergrern, zu testen. Es wurde dargelegt, dass diese Annahme ohne beide Konditionen mit einer Baseline zu vergleichen, nicht haltbar ist. Auf der Basis von Forschungsergebnissen bezglich der positiven Effekte von Vorstellen, Beobachten und Vorbereiten von Bewegungen auf neuronale Aktivitt im motorischen Kortex wurde die Hypothese aufgestellt, dass es Versuchsteilnehmern ehermglich sein sollte die ausgelste Bewegung zu verstrken als sie zu verringern. Es wurde gezeigt, dass die Daten, die fr den Zweck dieser Arbeit erhoben wurden, jene statistischen Tests, die in der vorherigen Studie von Bonnard et al. (2009) verwendet wurden, nicht zulassen. Die erhobenen Daten zeigten keine statistische Normalverteilung und drei verschiedene logarithmische sowie die Box-Cox Transformation konnten daran nichts ndern. Daher wurden andere statistische Tests verwendet, die allerdings die gefundenen Effekte von Bonnard et al. (2009) nicht replizieren konnten. Es wurde argumentiert, dass Variabilitt zwischen sowie innerhalb der Subjekte der Grund dafr sein knnte.