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## Neural entrainment in coordination dynamics

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## Chapter 1

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# General introduction

*All men can do is to move things...  
whether whispering a syllable or felling a forest*

Sherrington



## 1.1 Brain and behavior: synchronization serves coordination

The human body finds itself permanently confronted with a myriad of challenges. At virtually every instant it has to adapt to a largely unpredictable and continuously changing environment, as proper adjustment is often a matter of survival. Most tasks are performed seemingly effortlessly, as we step out of bed, operate the coffee machine (certainly a matter of survival), steer our bicycles to work and greet our colleagues. When confronted with unexpected difficulties, however, it often seems that the 'man in the machine' refuses to collaborate: we may struggle fumbling our keys in the door, dropping piles of paper and spilling coffee on our desk. The more of such experiences are listed, the more astonishing it becomes that our movement apparatus operates so well in the first place: how is it that we can act and move so effectively, most of the time staying ahead of troubles and in full control of our body? Through centuries of perseverance, the empirical sciences have provided a plethora of findings about the neural correlates of voluntary movement. Nonetheless, the precise workings of motor control largely remain to be disclosed. Evidently, movement needs to be properly organized and ordered in space and time to be effective. Many components participate in movement, including the central nervous system and the muscular-skeletal system, and implies that voluntary movement requires extensive coordination.

Coordination is essential for our daily functioning, and it has to be rapid and reliable but also flexible and resourceful. *Coordination implies an integration of parts.* To be more precise, coordination refers to the functional integration of parts of the body that is achieved through the exchange of information between relevant neural sites and sensori-motor components. The strength and timing of the signals that carry and transfer information across our body can indeed be viewed as key ingredients for the generation of smooth muscle control and, hence, for proper movement. In particular the timing of signals along the neural axis appears to rely on what is referred to as neural orchestration, *i.e.*, the concerted activity of neurons involved in the control and production of voluntary movements.

Motor behavior like walking, swimming, or catching a large object often requires bilateral execution of homologous limbs. Furthermore, many everyday tasks, especially when executed with the arms, hands, or fingers, do require an intricate interplay between (homologous) muscles and limbs. These can provide seminal paradigms for studying the aforementioned integration of parts and the corresponding motor-related information transfer. In my thesis, I employed bi-manual movements to study the integration of accompanying neural activities in both the central nervous system and in the spinal cord and muscle. In doing so, I sought to determine how the neural correlates of qualitative changes in movement coordination can be characterized in terms of the activity and interactions of the participating neural networks.

We often see that movement of a limb or even the activation of a single muscle interferes with the movement of its homologous counterpart. In an experimental setting, this interference can be revealed when assigning distinct tasks to each limb. For example, repeatedly stroking ones right hand back and forth, while moving the other hand in circles, is rather challenging for most of us. On a neural level this interference between the two sides of our body suggests a cross-talk between the left and the right hemispheres of the brain, possibly supplemented by biomechanical or perceptual factors, or by feedback mechanisms in the spinal cord. The cross-talk in the central nervous system is of pivotal interest in my thesis as it provides an excellent opportunity to investigate general ways of communication in the nervous system. The focus on cross-talk between hemispheres offers important insights into the control mechanisms underlying (or at least accompanying) bilateral interlimb coordination. Of course, the two participating limbs should generally be able to execute the same tasks, since otherwise the resulting asymmetry may obscure the homologous co-activation. Note that one may suspect that bilateral activation is caused by a single unit controlling both left and right end-effectors simultaneously. However, left versus right performance can substantially differ in skill and, indeed, muscles innervating both limbs are to a large degree controlled by distant brain areas. That is, bilateral integration is not merely employed at the anatomical level, *i.e.*, by a single neural controller, but changes dynamically dependent on task circumstances and demands. The left/right integration is thus realized at a functional level such that it critically depends on the aforementioned information transfer.

Time-varying activities can always be modeled as dynamical systems. Coordination dynamics provides a framework in which descriptive models for interlimb coordination are developed in interplay with empirical, and often behavioral, observations. For instance, when looking at rhythmic movements the corresponding state variables are modeled as self-sustaining oscillators, reflecting the modular organization of the whole system and its resilience against external perturbations. The pattern generated by the rhythmic movement of a finger is then fully described by the amplitude and frequency of its oscillation. While such an oscillation in itself may already account for complex phenomena, it is particularly interesting when studying interactions between oscillators — think of homologous limbs for which the interaction describes the left/right cross-talk and interference. These interactions are captured by coupling functions describing a time-varying response of each variable with respect to the state of the others. A synergy between homologous muscles may then result from coupling different state variables. Importantly, the stability of a movement pattern may drastically change as a consequence of alterations in the strength of the coupling (*e.g.*, through changes in the corresponding coupling parameters). A seminal example of this approach in the context of behavioral studies is Scott Kelso's 'finger wiggling' experiment from the early 1980s. In this experimental set-up, the index fingers are paced by a metronome, starting at a slow pace in an anti-phase pattern, in which activities of homologous muscles alternate such that the fingers move in parallel. An increase in tempo usually yields an involuntary, spontaneous transition to an in-phase pattern, in which homologous muscles are simultaneously active, resulting in mirror-symmetric finger movements. This transition is induced by a loss of stability of the anti-phase pattern that is brought about by a drop in coupling strength, presumably because of a decrease in the movement amplitude with the increase in movement frequency. In my thesis such movement instabilities and spontaneous transitions are described in Chapter 5. As argued below in more detail, changes in stability can provide important insights into the dynamics of complex systems — here the motor apparatus and its 'controller'. In Chapters 2–4 experiments are reported in which subjects had to learn certain movement patterns. Conducting unknown and untrained movement patterns often yields largely unstable performances and, thus, motor learning can be considered as the emerging or increasing stability of the targeted movement patterns similar to the (spontaneous) switches around movement instabilities.

The brain activity that correlates with movement parameters can be discerned through electrophysiological recordings. In the case of bimanual rhythmic movements, the movement frequencies of both fingers become manifest in the spectral density functions of primary motor cortices. However, neurons do not behave like fingers and the recorded signals are hence not restricted to oscillations at the movement frequencies. Neural activity displays by far more complicated dynamical characteristics than macroscopic, kinematic quantities, even when looking at gross behavior of (reasonably) large but local neural populations or more general cell assemblies<sup>i</sup>. This neural activity is typically oscillatory by nature, which allows for categorization in terms of its spectral contents. There is indeed plenty of evidence that various rhythms can be associated with distinct brain functioning; note that a low-frequency amplitude modulation may directly correspond to finger movements (Chapters 2–5). Interactions between brain areas in general and interhemispheric communication between motor areas in particular require that the neural activity generated by the underlying networks can be adjusted in a rapid and robust manner. Since the to-be-adjusted activity is oscillatory, synchronization of activity is of crucial importance. For the sake of argument, assume that the oscillatory activity can be described in terms of limit cycle oscillators and that the interactions between the corresponding phases give rise to significant synchronization properties<sup>ii</sup>. Under such conditions, the (fast) rhythmic activity generated by these neural populations allows for the global communication that is needed for proper information transfer in the nervous system.

In fact the synchronization between distant neural populations might be especially relevant in the neural components of the *motor system*, ranging from the cortex to the spinal cord, which yields a network that will be briefly summarized in Section 1.3. To investigate this network I capitalized on the fact that movements are accompanied by characteristic changes in the aforementioned oscillatory activity that can be distilled from encephalographic and electromyographic signals. Synchronization phenomena between the underlying neural populations were estimated via the analytic signal computed according to the Hilbert transform, which yields a (relative) phase distribution that can be analyzed further using circular statistics. Given the central role of these methods I will summarize their main characteristics in Section 1.4. Guided by a number of research questions that are listed below, I conducted several experiments exploiting these methods in order to probe various aspects of the motor system.

## 1.2 The present thesis: aim and outline

I employed rhythmic bimanual movements to study the integration of neural activity in the context of motor control and asked how the neural correlates of the behavioral changes in the stability of movement patterns can be characterized in terms of the accompanying neural activity and the interactions between neural sites. In two experiments, the stability of behavioral performance was challenged to answer the following overarching question:

**Is neural synchronization linked to motor performance?** If neural synchronization plays a functional role in stabilizing or improving motor performance, then quantitative associations between local synchrony or long-range synchronization and performance may be found. In defining the task, I restricted the spatial organization: the index fingers produced either a smoothly varying isometric force (Chapters 2–4) or a tapping movement (Chapter 5). Complex movement patterns were performed requiring the production of polyrhythms, where the movement frequencies stand to each other as relatively prime integers other than 1, *e.g.*, in a ratio of 2:3 and 5:8. By manipulating experimental parameters as movement speed and amount of practice, changes in (the stability or quality of) motor performance were induced. The studies presented here confirmed the leading hypothesis that neural synchronization is linked to motor performance.

In the first experiment, I investigated the underlying neural motor network involved in the acquisition of a complex motor skill. The task to be learned involved isometric sinusoidal force production with the right and left finger in a 3:2 frequency ratio. In the initial analysis, I focused on differences between control conditions that were repeated pre and post learning, using the practice trials as intervention. The motor network was identified based on maximal differences in spectral power in pre and post control conditions. Event-related patterns of local and long-range synchronization in the so-defined components were studied. Building on this study, I continued by studying changes in these synchronization patterns in the course of motor learning. The following detailed research questions were addressed:

**Does learning induce long lasting changes in the functional organization of the motor network?** By studying power changes in the  $\alpha$ -,  $\beta$ - and  $\gamma$ -frequency ranges (7–11 Hz, 20–30 Hz and 40–70 Hz, respectively) between control condi-

tions before and after learning, I assessed the differential involvement of brain areas. Using correlation analysis I addressed the question of whether these changes were an effect of sustained practice or were related to the learning process. These results are described in Chapter 2 and partly in Chapter 4.

**Does learning lead to changes in the timing properties of this network?** In Chapter 3, I focus on the role of phase-locked activity in cortical motor areas in the course of learning. To this end, the role of  $\beta$ -activity in the timing of movement was assessed by its event-related amplitude. Using principal component analysis the strength of  $\beta$ -amplitude modulation at the target movement frequencies was tested.

**Do these changes transfer to the periphery of the nervous system?** In Chapter 4 event-related patterns of cortico-spinal dynamics during learning are the central topic of interest. Using correlation analysis, changes in cortico-spinal synchronization between motor units innervating the flexor digitorum and contralateral motor cortex at the  $\beta$ -frequencies were associated with motor performance.

In the second experiment, I investigated neural activity and neural interactions associated with tempo increase, and with behavioral instabilities in particular. The task involved tapping a 5:8 polyrhythm while the target frequency was increased, leading to movement instabilities. In this context, the predictions of a qualitative mathematical model describing interhemispheric cross-talk were tested (Daffertshofer et al., 2005). I aimed for disentangling the relative contributions of coordinative and neurophysiologic constraints to cortical and cortico-spinal dynamics. The following detailed research questions were addressed:

**Are there consistent changes in neural activity with respect to increases in movement tempo?** Specifically, changes in the pattern of desynchronization and synchronization of  $\beta$ -activity accompanying movement were inspected during the increase of movement frequency. By comparing unimanual and bimanual performances, I assessed the extent to which these changes are important to coordination. The findings suggested that coordination is constrained by the underlying neurophysiologic mechanism, as described in Chapter 5.

**Do characteristic patterns in neural connectivity exist close to the movement instability?** The aforementioned model predicts changes in interhemispheric cross-talk around movement instabilities. In order to assemble evidence in sup-

port of this model, this cross-talk between the motor cortices was indexed as the ratio between the amounts of spectral power at both movement frequencies. The results of comparing the amount of cross-talk at different instances relative to the movement instability are also presented in Chapter 5.

### **1.3 The motor system: distributed processing**

Voluntary movement results from the control over tens or even hundreds of muscles (Bernstein, 1967). For a muscle to contract, its fibers must be stimulated by an alpha-motoneuron in the spinal cord. Afferent neural pathways convey impulses toward the brain or spinal cord, and efferent pathways convey impulses from such nerve centers to the muscle. Movement emerges as the result of the spatiotemporal properties of impulse sequences that originate in the cortex. The vital ability for fine control of fingers and hands has resulted in specialized cortical areas devoted to the muscles controlling these body parts. The most direct and powerful connections from cortical neurons to spinal motoneurons arise from the primary motor cortex (M1). In combination, the muscles, the spinal cord and the cortical motor output areas form the core of the motor system responsible for the execution of voluntary movement. Revealing the control mechanisms of muscle activity along this pathway is, however, complicated by the fact that many M1 neurons have to interact properly for movement to be executed as desired. Through what mechanisms does the cortex bring various combinations of muscles into play at different times (*i.e.*, for distinct movements)?

The leading research hypothesis of the present thesis is that neural synchronization is a primary vehicle in bringing about functionally coherent and adequate patterns of human movement. In this section I will further unfold this hypothesis conceptually by discarding the notion of sparse coding in favor of distributed coding of information, and by focusing on the concepts of synchronization and synergetics. Questions as to how the brain represents information in general and what the role of these two principles of coding might be in the processing of such information will be further addressed in the Epilogue. The theoretical framework to be introduced now will be supplemented in the next section with methodological considerations motivating the choice of recording techniques and analytical methods as used in the thesis.

### 1.3.1 Neurons and networks

The primary building block for nervous information transfer is the neuron. A neuron is a cell that is able to receive, transform, and send electric pulses (Koch, 1999). At rest, a neuron maintains a fixed electric potential difference across its cell membrane. This potential difference can be modified by incoming electrical and biochemical events received through the neuron's dendrites. If the difference reaches a critical threshold, an action potential is generated which travels along the axon to the terminating synapse. Neurons and muscle cells are thereby excitable units capable of summing and magnifying small changes in their membrane potential. While the membrane returns to its original state, at the synapse the action potential causes a release of chemical messenger molecules that induce subsequent changes in the membrane potential of postsynaptic neurons. Depending on the direction of the potential change, the synapse is called either inhibitory (decrease) or excitatory (increase). Multiple interconnected neurons can, by repeated transmission and feedback, exhibit seemingly spontaneous activity, which can evolve into a rhythmic pattern (Buzáki, 2006).

Anatomically, cortical neurons are arranged in neural masses, which have been categorized by size in terms of minicolumns ( $10^{-3}$  mm), corticocortical columns or modules ( $10^{-1}$  mm) and macrocolumns (1 mm) (Mountcastle, 1997), with the aim to seek a generic mapping between anatomy and neural functioning. Although the column is an attractive concept, it has thus far failed to serve as a unifying principle for understanding cortical function (Horton, 2005). By contrast, anatomical connectivity may be able to provide this link and, hence, to 'explain' (the origin of) brain function. In general, the probability of a direct connection between two neurons decreases with increasing distance between their cell bodies, although axons with a length of up to a meter exist (Jirsa and McIntosh, 2007, p.152). Most axons span short distances (10–30 mm) within one hemisphere, while only 2% of the axons spanning long distances (30–170 mm) cross the midline via the corpus callosum (Kandel et al., 2000). On average each neuron has synaptic connections with several thousands of other neurons (Drachman, 2005). Because neurons are so well connected, they can rapidly (*i.e.*, without detours) transfer signals even if accounting for finite chemical transmission times and substantial synaptic delays. The existence of billions of neurons ( $\sim 10^{15}$ ), several millions of connections and continuing external input are qualifying char-

acteristics of the central nervous system as a highly complex entity. Patterns in neural activity have been recognized at different levels in space and time (Nunez, 1995; Kelso, 1995). Coherent activity of a cluster of neurons may spontaneously emerge by virtue of the intrinsic dynamic behavior of its individual components and synapses. Namely, since neurons are excitable, electric activity traveling recurrently through brain tissue gives rise to localized self-sustaining oscillations in the electric potential (Buszák, 2006; Wilson and Cowan, 1972). Such local oscillations induce rhythmic processes in individual neurons, and the temporal information contained in their firing patterns seems an effective means of signal transmission within the system (Koch, 1999). Then, large-scale behavior results from the concerted action of these putative groups of oscillatory electric units, *i.e.*, local neural populations or even distributed *cell assemblies* (Nunez, 1995). Cell assemblies indicate any group of neurons or neural masses for which preferential actions persist over time intervals of several ten to hundred milliseconds, a slightly slower time scale than is employed at the level of the individual neuron. The coordinated activity of these temporary units is, *ex hypothesi*, established through synchronization mechanisms and underwrites the intended behavior.

### **1.3.2 Neural synchronization and synergetics**

The large-scale intricacy of the human nervous system calls for treating it as a complex system. Complex systems can exhibit certain dynamic behaviors at multiple spatial and temporal scales, which are manifested in the brain as cell assemblies and their experimentally observed, mutual synchronization. This hierarchical organization of spatiotemporal dynamics with interactions between all levels can be conveniently studied within the framework of *synergetics* (Haken, 1995). The governing principle of this theory of self-organization of complex systems is the emergence of ordered spatio-temporal structures or macroscopic patterns out of interactions between structures at different levels of organization and time-scales.

At the bottom level, we find the fast, microscopic components of the system: the electro-chemical activities of the individual neurons. Which activities are specifically realized at this microscopic level does not necessarily determine their collective behavior, which is an emergent property of their interaction. At the mesoscopic level, the organizational units are cell assemblies, formed by the collective behavior of the microscopic elements. Finally, the emerging patterns in space and time that determine behavior ultimately constitute the slowly evolving macroscopic level. The dynamical quantities (variables) that cover this macroscopic level are referred to as *order parameters* and their (slow) dynamics hence describes the change of the system's macroscopic collective patterns. Often, these patterns can be described parsimoniously in terms of a low dimensional dynamical system; this is always the case as long as the system under study undergoes an instability. Note that such a description corresponds to a strict separation of time scales, *i.e.*, close to an instability there will always be (a few) dynamical quantities that evolve significantly slower than all others, which marks them as the aforementioned, slowly evolving order parameters.

Changes in the order parameters yield changes in the entire system at all levels ('slaving principle'). To quote Kelso:

*"Dynamic instabilities provide a way to find new quantities to capture the coordination of living things as a self-organized phenomenon. In summary, if coordinated action [or: brain dynamics] is based on functional synergies and if functional synergies are indeed self-organized, most if not all of the critical features of self-organized, synergetic systems should be found in behavior itself."*

(Kelso, 1995, p.43). To find a proper description of the system at the macroscopic level, the system is therefore best studied (and ultimately modeled) around such instabilities.

For example, if the average electric activity in a neuronal cluster is considered as a dynamical variable in a mean field approach, then the variables of the ensuing reduced dynamics are order parameters presuming, as said, the presence of an instability at which these mean values evolve significantly slower than the constituent micro-components. Likewise, the mean phase in a synchronized cluster can be considered as a collective variable (Winfree, 1980) and often takes on

the role of an order parameter (Jirsa and Fuchs, 1998; Frank et al., 2000)). This motivates the description of the collective dynamics of a synchronized neural population by a single limit cycle oscillator. This oscillator is typically self-sustaining and stable, *i.e.*, after a (small) perturbation it returns to a closed periodic orbit, the limit cycle. Thereby, the amplitude may be viewed as a ‘passive’ variable, and does otherwise not play a functional role (however, strictly speaking, changes in the amplitude dynamics occur when the parameters are changed). The (relative) phase, when related to that of another, similarly oscillating neural population, reflects the coupling between those units. In consequence, the focus on phase dynamics can provide important insights into how interactions and, thus, information transfer<sup>iii</sup> between synchronized neural populations and cell assemblies are manifested and caused.

## 1.4 Methods: recordings and analysis

How do the concepts of synergetics apply to the study of neural activity and how can this approach be effectuated experimentally? To begin with the latter, one can record electric activity at every level of organization in the brain. Intracranial recordings via the electro-corticogram (ECoG) or deep-brain electrodes pick up local field potentials, which appear to be good approximations of the localized activity of neurons. An inevitable drawback of these techniques is, however, that the system, *e.g.*, the living brain, is irritated by these fairly invasive measurements. Besides ethical constraints, this certainly limits the usefulness of these techniques, unless one wants to assess pathological neural activity. The non-invasive alternative, surface encephalography, is particularly sensitive to neural activity occurring at the mesoscopic level, *i.e.*, the level of aggregated activity of several tens of thousands of neurons. Neural populations, *e.g.*, in the (neo)cortex, generate electric and magnetic fields, which are measurable on the scalp as electric potentials (electroencephalography, EEG) or within some small distance from the scalp as magnetic flux (magnetoencephalography, MEG). These fields and potentials reflect the superposition of numerous intracellular primary (dendritic) currents (in MEG) or extracellular return currents (in EEG) that result from both active inhibitory and excitatory synaptic activity. Since the neural activity of the underlying neural populations is often oscillatory in nature (see

below), the appearance of measurable macroscopic aggregates signifies the presence of synchronization in the underlying array of coupled neurons. In addition, for instance for MEG which records the dendritic currents, dendrites have to be aligned in space to avoid cancellation due to the superposition of contributions originating from currents along different directions.

### 1.4.1 Oscillations and neural populations

The first observations of Hans Berger were synchronized neural oscillations at frequencies around 10 Hz (Berger, 1929). These so-called  $\alpha$ -oscillations are visible in the encephalogram by the naked eye, at least when the recorded subjects close their eyes. In this case  $\alpha$  oscillations clearly dominate the power spectrum of the electric signals picked up at the scalp. While Berger merely reported this observation, Eccles (1953) was the first to submit that the origin of the oscillatory EEG components resides in synchronous electric activity of neural populations in the cortex. The most prominent and well-studied oscillations in cortical sensorimotor areas are arranged within the so-called  $\mu$  (8 Hz–12 Hz – which agrees in frequency contents with the aforementioned  $\alpha$ -oscillations) and  $\beta$ -rhythms (15 Hz–30 Hz). During movement planning and initiation, the amplitude of  $\beta$ -oscillations within the sensorimotor area decreases; this synchronization phenomenon is attributed to a reorganization of neural activity (Pfurtscheller and da Silva, 1999). After movement termination, synchronization increases above baseline ( $\beta$ -rebound), which is attributed to decreased cortical activation because it coincides with reduced cortico-spinal excitability of motor cortex neurons (Chen et al., 1998). Because these changes in synchronization are most prominent in relation to events external to the brain, defined by, *e.g.*, the muscle activity accompanying the movement, these processes are termed event-related desynchronization (ERD) and synchronization (ERS). While the electric discharges in muscles had been discovered already at the end of the nineteenth century, the ability to generate synchronized rhythms has only received increased attention in the second half of the twentieth century (Conway et al., 1995). While it is well established that the individual firing frequency of a motor unit is directly related to the force that is generated by the fibers it comprises, the significance of coherent activity of groups of motor units is debated. This coherent activity can be observed at different frequency ranges and, remarkably, at the aforementioned  $\mu$ - and  $\beta$ -rhythms it appears to

synchronize with neural activity in sensorimotor areas (Baker et al., 1999; Boonstra et al., 2009b; Houweling et al., 2010).

Cortical stimulation in early animal studies showed that stimulating particular brain sites can result in twitch contractions (the muscle's response to a single action potential) of the corresponding muscles. By systematically studying this phenomenon in canine motor cortex, Fritsch and Hitzig (1870) mapped cortical stimuli to muscle activation, resulting in a motor map for areas posterior to the central sulcus. Likewise, recording brain activity in response to stimulation of different body parts provided a sensory map, for regions anterior to the central sulcus. This spatial organization of the mapping from the nervous 'input' and 'output' to the body's end-effectors is preserved all along the spinal cord. The somatotopic arrangement of these maps in sensory and motor areas has led to the term 'cortical homunculus' (Penfield and Boldrey, 1937). However, the attractively simple concept that limbs are separable into smaller units which are all independently controlled by different parts of the motor cortex became less appealing after the finding that regions controlling different fingers overlap (Bernstein, 1967; Schieber and Hibbard, 1993).

Nowadays, the emphasis in brain studies has slowly shifted to studies of function in the context of neural dynamics. That is, instead of searching for a bijective mapping between functional units and distinct anatomical/chemical/-physiological levels, approaches emphasizing and explaining intrinsic mechanisms of functional integration came to the fore. While the development is ongoing, a major breakthrough was established with the discovery that neurons in primary motor areas in monkeys show selective activity depending on movement parameters like direction (Georgopoulos et al., 1982). This process was catalyzed both by the development of new and more sophisticated neuroimaging methods for both data acquisition and data analysis, as well as the scientific trend to study self-organization in complex (living) systems. Thereby, the concept of one particular neural structure (*e.g.*, supplementary motor area) responsible for bimanual coordination has shifted to the idea of distributed processing within the motor system (Swinnen, 2002; Riehle and Vaadia, 2005).

At least six cortical motor areas are densely interconnected: bilateral premotor areas, primary motor cortices and supplementary motor areas. The corpus callosum interconnects primarily homotopic areas between hemispheres. These fibers

are formed during the first year of life, but their organization is continuously subject to change (Aboitiz et al., 2003). The sparsity of transcallosal connections between cortical hand motor representations in primates (Gerloff et al., 1998) does not preclude the possibility of a neurological origin of the observed interferences between hands and arms during perceptual and/or motor tasks. Indeed, callosal cross-talk may explain the preference for homologous muscle activation (Schöner and Kelso, 1988) and the tendency towards spatial symmetry (Franz et al., 1991), motor irradiation, which may or may not result in an inability to suppress mirror movements induced by task demands (Carson, 2005), or even the existence of pathological mirror movements (de Oliveira, 2002).

Additional brain areas that are connected to the primary motor areas consist of the cerebellum and primary sensory areas. Several neurons in the hand area of the primary motor cortex receive proprioceptive input from the muscles to which they project (Boudreau and Smith, 2001). These anatomical facts, *i.e.*, the density and diversity of connections, as well as experimental evidence in a dynamical setting, *e.g.*, the early experimental findings of Georgopoulos and colleagues, suggest that the primary motor areas play a significant role in motor control, instead of acting as low-level executable units as traditionally thought by, *e.g.*, Penfield and disciples. More recently, it has been shown that the motor cortex is involved in motor adaptation through motor learning (Andres et al., 1999; Boonstra et al., 2007) and is therefore subject to considerable plasticity.

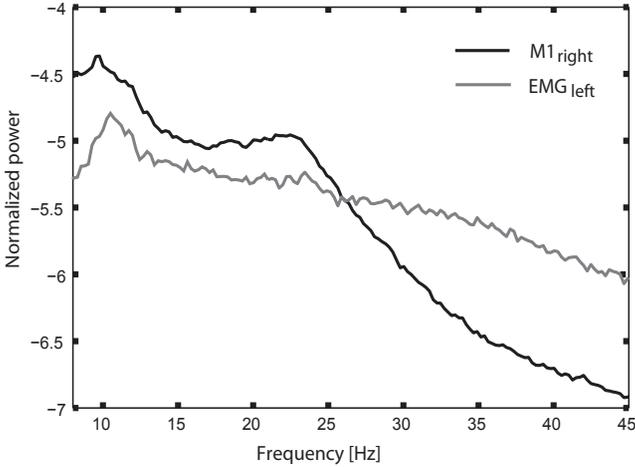
Encephalography is well suited for studying the brain at the mesoscopic level, *i.e.*, the level of aggregated activity of several tens of thousands of neurons. In addition, MEG appears to provide a better spatial resolution than EEG as it suffers less from confounding volume conduction (Hämäläinen et al., 1993), which is of particular importance when looking for the underlying source activity (see Subsection 1.4.2). In the experiments presented here the magnetic activity was recorded using a system with 151 SQUID sensors that were placed in a halo-shaped dewar encapsulating the subjects' head. Additionally, I used surface electromyography (EMG) to measure the summed activity of the motor units inducing the corresponding muscle activity. While all these methods are non-invasive and, hence, readily applicable in healthy subjects, the distant gross recordings yield very noisy electrophysiological data that are above all rather susceptible to artifacts, whose sources range from movement and (other, non-target) muscles to

magnetic interference from external fields. To give an indication, the meaningful signal in MEG ( $\sim 10^{-15}$  T) is in the order of a billion times smaller in amplitude than the Earth's gravitational field ( $\sim 10^{-6}$  T). This means that many observations of the system are needed to capture the neural signal. Fortunately, rhythmic movement is, by definition, repetitive, so that a fair number of by and large identical motor events can be easily generated experimentally within a tolerable time span.

### 1.4.2 Time and frequency domain analysis

To assess the oscillatory activity of neural populations transforming signals to the frequency domain appears advantageous. Indeed, neural activity covers a broad range of frequencies. For instance, the movement frequency is visible as a component in the power spectrum and, in fact, it often dominates the spectrum. Various other features of the power spectrum that are considered functionally relevant in neuroscience surface during movement. This includes the aforementioned spectral components in the  $\mu$  ( $\sim 10$  Hz) and  $\beta$  ( $\sim 20$  Hz) frequency ranges, as illustrated in Figure 1.1. Thereby, changes in spectral properties allow for locating the sources that participate in these rhythms (see Subsection 1.4.3). Besides these specific movement-related aspects another striking, more general feature of electrophysiological signals is a slow decrease in power with increasing frequency<sup>iv</sup>.

As said, in order to obtain a reliable estimate of the power spectrum a rather large number of samples is needed, and the temporal resolution of frequency domain analysis is in the order of seconds (Bendat and Piersol, 1971). The main drawback of this analysis is, however, that timing information (*i.e.*, information on the phases) is lost. Wavelet analysis may increase the temporal resolution but suffers from the same drawback. Since we are interested in the dynamics of motor control, the most advantageous approach is to use the Hilbert transform (Gabor, 1946) to analyze the instantaneous amplitude and phase in the time domain. Transforming the time series with a bandpass filter with small bandwidth prior to this analysis ensures the focus on select frequency components<sup>v</sup> (see Subsection 1.4.4).



**FIGURE 1.1: Spectral power in muscle activity and motor cortex during motor performance.** Power spectra for the EMG of the left extensor digitorum (grey line) and contralateral motor cortex (straight line) displayed on a logarithmic scale. Subjects produced rhythmic, isometric force with their right and left index fingers in a 3:2 ratio during 40 minutes ( $N = 7$ ; Hanning window: 4096, window overlap: 75 %).

### 1.4.3 Source localization

Magnetic fluxes and electric potentials recorded at sensors are linear superpositions of activities at the generating sources. Different distances between sources and sensors as well as inhomogeneous and anisotropic conductance, capacity and inductivity of the surrounding tissue cause source activities to contribute with unequal weights to the sensor signals (Nunez, 2000). The *inverse problem* in neuroscience refers to the problem of reconstructing the aforementioned (primary) electric currents from extracranial measurements. Because the number of possibly contributing sources of current (in 3D) is much larger than the number of sensors at the surface, this problem is ill-defined. Hence, to find an approximate solution nevertheless, requires additional constraints with which the inverse problem becomes well-defined. However, the additional constraints also require some a priori assumptions (or models) about the form, shape and/or type of source activity so that all approaches should be considered (biased) approximations to the inverse problem.

In the literature various methods have been proposed to reconstruct linear combinations of the sensors representing local activity at every position in the brain. Most methods can be categorized within one of three approaches: dipole fitting (Scherg and Berg, 1991), spatial scanning or beamforming (*e.g.*, Mosher and Leahy, 1998) and algorithms within a Bayesian framework (*e.g.*, Pascual-Marqui, 2002). In order to estimate the sources of the motor network, I adopted a beamforming approach (Vrba and Robinson, 2001); this approach originates from radar engineering (Van Veen and Buckley, 1988). In short, beamforming can be thought of as a spatial filter. The brain is divided into a number of voxels representing what is referred to as *source space*. Linear combinations of the MEG sensors are constructed for each voxel and optimized by means of their contribution to the signal variance (which is considered the meaningful part of the signal) while suppressing signals from other voxels. To this end, a simulation of the field distribution for a current dipole in the corresponding volume conductor is used, solving the quasi-static Maxwell equations (known as the *forward problem*)<sup>vi</sup>. Based on the power in a certain frequency band, the voxels showing greatest differences between certain time intervals are considered relevant to the underlying network. The intervals used for these contrasts can be defined by a difference in the experimental conditions (Chapter 2) or by a different onset relative to an external event (Chapter 5). The weight distribution (*i.e.*, the beamformer) corresponding to a particular voxel is used to project the MEG sensor signals to its source signal. An advantage of this approach is that spatial properties of the signal sources that generate the recordings can be addressed, while we can concurrently study the interactions between these separate underlying brain networks on a millisecond scale.

#### **1.4.4 Interaction between sources**

In the present thesis, I study interactions between two functionally relevant clusters of neurons by means of synchronization measures<sup>vii</sup> between the corresponding projected time series. Traditionally, synchronization is defined in agreement with classic spectral decompositions (*i.e.*, Fourier analysis): identical frequencies (apart from small *detuning* effects) define frequency locking (Pikovsky et al., 2001, p.52). Even though the frequency of an oscillation can be defined as the rate of change in its phase, the concept of frequency is only meaningful when studying complete cycles. Defining synchronization in terms of the (Hilbert) phases, also

referred to as instantaneous frequency, is more appealing because it allows for an instantaneous description of synchronization. The most common case, 1:1 phase synchronization, occurs when the difference between phases remains bounded, and implies frequency locking. Two weakly coupled oscillators usually exhibit phase synchronization if their natural frequencies are not too far apart (Pikovsky et al., 2001)). Depending on the coupling function and the intrinsic properties of the oscillators, synchronization can be an asymmetric process by which one oscillator adjusts more than the other. In that case, one speaks of *entrainment*. More general forms of phase synchronization can also appear, as in  $n:m$  phase synchronization where the difference between multiples (at a fixed ratio) of the phases remains bounded (Rosenblum et al., 2001). The behavior of general self-sustaining oscillators can amount to even more complex forms of phase synchronization, but these are difficult to detect and to exploit (Tass, 1999).

For time series, a nonlinear measure of functional similarity is obtained, starting from the approach of Gabor (1946). The aim is to disentangle the signal's amplitude and phase by computing an instantaneous phase function  $\phi(t)$  and corresponding amplitude function  $A(t)$  from the analytic signal  $a(t)$ . Thereby,

$$A(t) = |a(t)| \quad \text{and} \quad \phi(t) = \tan^{-1} \left( \frac{\Re \{a(t)\}}{\Im \{a(t)\}} \right).$$

Computed from the Hilbert transform  $x_H(t)$ , the analytic signal is given by

$$a(t) = x(t) + ix_H(t) = x(t) + PV \left\{ x(t) * \frac{1}{t} \right\}.$$

The convolution integral (denoted by  $*$ ) has to be interpreted as the Cauchy principal value, to be defined for  $t = 0$  also. From the instantaneous phase  $\phi(t)$  the phase uniformity of relative phases is calculated to assess phase synchronization (Rodriguez et al., 1999; Mormann et al., 2000). This measure is equivalent to the phase locking index, the phase locking factor and phase coherence. The phase uniformity is thereby defined as 1-circular variance (abbreviated to  $1 - cv$ ) of a set of phases  $\{\phi_1, \phi_2, \dots, \phi_N\}$ ,

$$cv = 1 - \sqrt{C^2 + S^2} \quad \text{where} \quad C = \frac{1}{N} \sum_{k=1}^N \cos \phi_k \quad \text{and} \quad S = \frac{1}{N} \sum_{k=1}^N \sin \phi_k.$$

High uniformity therefore indicates strong phase locking, *i.e.*, the relative phase remains bounded.

Phase uniformity is computed from a set of phase differences for a fixed time within the movement cycle. Varying this time instance, phase synchronization can be assessed with high temporal resolution, and episodes of high uniformity evidence strong phase locking between the two processes studied. This analysis is not restricted to cortico-cortical interactions, but also cortico-spinal synchronization will be studied thereby. As mentioned above, we transformed the signals with narrow-band filters prior to computation of the analytic signal to distinguish activity at different frequencies.

## Notes

<sup>i</sup>The terms neural population, neural ensemble and cell assembly are not interchangeable. Whereas the first usually refers to a group of neurons without further qualification, the neurons within a neural ensemble exhibit statistically similar behavior. The term cell assembly is even more restrictive and describes a group of neurons whose behavior is functionally related.

<sup>ii</sup>Note that in encephalographic recordings of the human brain oscillatory activity at many different frequencies can be observed (Buszák, 2006). These neural oscillations do show slow modulations in their amplitudes, which may reflect a dynamical function of the amplitude in addition to the phase. If desirable, such amplitude modulation is achieved through, *e.g.*, modeling changes in the parameters of the limit cycle oscillator.

<sup>iii</sup>Pinpointing possible mechanisms of information exchange in oscillating systems is, however, a challenging enterprise, in particular in the context of nervous activity since we do not have a clear concept of which entities represent information in the nervous system (Koch, 1999, p.373). Starting from information theory one may use the concept of Shannon information to study the capacity for meaningful interactions between systems (Shannon, 1948). This concept is closely related to the thermodynamical definition of (dis-)order, namely entropy, from which ideas have been developed on how information may be represented by synchronous clusters (Haken, 2000; Tass, 1999). Here, I sketch a conceptual approach by which information transfer may be realized by means of phase interactions. We will attempt to understand the process of information transfer in oscillating systems in terms of mutual information between two random variables  $X$  and  $Y$ . Recall that the uncertainty we have about  $X$  is expressed by entropy  $H(X)$  (Cover and Thomans, 1991). The conditional entropy  $H(X | Y)$  is then a measure for what  $Y$  does not tell us about  $X$ . Mutual information is the difference between these two measures, and can be interpreted as a measure for how well  $Y$  predicts  $X$ . Let  $X$  be the space of messages that can be sent over a noisy channel, and  $Y$  the space of messages that can be received. The channel transfers information reliably if most messages from  $X$  are matched correctly to messages in  $Y$  after transmission. That is, its capacity is optimally utilized when the dis-

tribution of  $X$  is chosen such that the mutual information is maximized. Now let  $X_t$  consist of the phases of a first oscillator, *e.g.*, from a number of trials of the same event  $t$ , and  $Y_t$  of the phases of a second oscillator. When  $Y$  now becomes entrained by  $X$ , its phase becomes a more reliable predictor of the phase of  $X$ . In other words: the mutual information between  $X_t$  and  $Y_t$  increases, which means that information is transmitted. Moreover, stronger phase synchronization (*i.e.*, a smaller bound on the relative phase) results in higher mutual information and thus more efficient signal transmission. Hence, phase synchronization between two self-sustaining oscillators provides a flexible and robust mechanism to either facilitate or even realize (if information is encoded in the phase) the transfer of information.

<sup>iv</sup>The striking aspect is of course, that the decrease in power is slower than one would expect for a well-behaved stochastic process. In particular, the variance of the time series (the integral of the power spectral density) is infinite. The reason for this peculiar inverse relation between frequency and amplitude in the spectral distributions is unknown. Note that if activity at lower frequencies is more synchronized or is produced by larger assemblies (Section 1.2), this would result in higher sensor and scalp amplitudes. Indeed, slowly oscillating cell assemblies are believed to both comprise more neurons and are likely to be spatially more extended than rapidly oscillating cell assemblies (Singer, 1993). Nunez argues that, considering the EEG dynamics in terms of traveling waves, the dispersion relation in nondispersive waves (*i.e.*, faster oscillations travel faster) causes phase differences of coherent, distributed activity which lead to decreases in power in the recorded signals (Nunez, 1995, p.371). This might be one way to explain the phenomenon. However, most neurons in cerebral cortex fire seemingly randomly (Koch, 1999). Their behavior can be captured by a Poisson process. The power spectrum of a recording consisting of the summation of the simulated activity of a large group of cells exhibits such a slow decay, and this offers another explanation. Whether the inverse amplitude-frequency relation is directly generated by the brain or a consequence of inherent properties of the processes involved, is yet unknown (Boonstra et al., 2009a).

<sup>v</sup>In general, it is uncertain whether changes in one filtered time series are independent of the time series filtered at other, distinct frequencies. For nonlinear systems interactions between different frequency components are expected and complicate the analysis and subsequent interpretation. For example, changes in the composition of power spectra have to be considered due to a complex interplay of various processes which cannot be described by a straightforward transfer function.

<sup>vi</sup>The volume conductor is represented by the conductivity distribution of the different tissues through which the field is transmitted (Brookes et al., 2007). The forward problem concerns the question of how the magnetic field and electric potential arise from a known source distribution. This is solved by the standard forward model: the contribution to electric and magnetic fields from electric currents at different head locations are assumed to add up linearly, weighted by the properties of the volume conductor.

<sup>vii</sup>In principle, the correlation coefficient is a proper measure of temporal coincidence, but it fails in the case of two oscillators synchronized with phase difference  $\pi/2$ . In this case coherency, *i.e.*, the complex correlation in the frequency domain, may provide a more suitable measure, at least at first glance. However, this is still a linear measure and as such amplitude effects cannot be separated from phase effects.