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Epilogue
Oscillations, synchronization and functional connectivity have been the central concepts of this thesis. These three concepts are strongly interrelated and I have even used them interchangeably whenever that did not cause confusion. All three ascribe a major role to the (relative) timing of neural activity. Strictly speaking, however, functional connectivity does not require synchronization and synchronization may occur without oscillations. Yet functional connectivity mediated by oscillatory synchronization is omnipresent in the brain and deemed to play a very important role in neural communication.

In my thesis I have focused on the functional role of neural synchronization in controlling voluntary movement. A brief introduction to this topic has been provided in Chapter 1 together with the main research questions for the work reported in the thesis. I summarized the current state of research in Chapter 2 in an extensive literature overview. There I concluded that, although synchronization plays a fundamental role throughout the motor system, it is not the only means for information transfer in the brain. In order to interpret synchronization patterns, it could be essential to look at conjoint changes in firing rate and to combine findings from different recording techniques.

Chapters 3-5 in the second part of this thesis described three experimental studies addressing specific research questions. In Chapter 3 I showed that an up- and downregulation of beta synchronization is used in response selection not only on a cortical level, but also in the interaction between motor cortex and spinal cord: while an increase in cortiospinal beta synchronization serves to suppress motor output, movement preparation is accompanied by a decrease. In Chapter 4 I investigated the involvement of ipsilateral motor cortex in unimanual force production. Beta synchronization patterns in ipsi- and contralateral motor cortex showed subtle differences, indicating that the activity in ipsilateral motor cortex does not reflect a mere cross-talk from contralateral motor cortex but involves additional neuronal processes likely related to interhemispheric inhibition. Chapter 5 revealed that brain tumors affect the oscillatory activity in M1 both in rest and during movement by causing a shift in spectral frequency content towards lower frequencies. Since patients in this study did not (yet) experience any motor deficits, the disturbed synchronization patterns may act as a precursor that could help to determine the need for surgical removal.

Finally, the third part of the thesis was devoted to two methodological approaches that have recently been introduced to the neurosciences for the study of functional and effective connectivity. On the one hand, graph theory is very suitable to describe the organization of complex networks. However, Chapter 6 revealed major obstacles when comparing graph measures between networks although at first glance it appears a very suitable and elegant approach for studying topologies of complex
networks in an entirely unbiased fashion. In contrast, dynamic causal modeling builds on specific hypotheses concerning effective connectivity in small networks. In Chapter 7 its application to time-frequency modulations during mental hand rotation was demonstrated. With graph theory being (solely) data-driven and dynamical causal modeling being (more) model-driven, these two methodologies form largely complementary approaches. In the following, I will discuss the implications of these studies in more detail while revisiting the main research questions of my thesis.

8.1 Functional role of neural synchronization in the motor system

Before recalling my research questions listed in Chapter 1 I first would like to address one that may be considered to precede the other questions:

• Does neural synchronization have a functional role in the motor system?

The many experimental findings of modulations in M1 oscillations and corticospinal synchronization suggest a strong link between neural synchronization and movement. Whether these relations are also causal is difficult to prove, and certainly impossible by only empirically observing their correlation. It could actually be the case that the modulations are merely epiphenomenal to the ‘real’ generating neural mechanism. One way to test this is by interfering with normal brain activity. As discussed in Chapter 2, Pogosyan and coworkers (2009) entrained beta oscillations in M1 with transcranial alternating-current stimulation at 20 Hz and instructed participants to make fast, goal-directed movements. During periods of stimulation, beta oscillations were stronger and movements were executed slower. Likewise, Chen and coworkers (2007) showed that deep-brain stimulation at 20 Hz slows movement execution. The same type of stimulation at much higher frequencies (100-180 Hz) is being used in patients with Parkinson’s disease to break down excessive beta synchronization of which the effect is correlated with improvement of their bradykinesia (Kuhn et al. 2006; Weinberger et al. 2006; Kuhn et al. 2008; Ray et al. 2008; Kuhn et al. 2009). These studies indicate that oscillations indeed play a functional role in motor control.

Synchronization between regions per se may not be sufficient for proper transfer of information as the specific relative timing – i.e., the inter-regional relative phase – should also be considered. According to the binding-by-synchrony hypothesis, the impact of input arriving in an favorable time window will be strengthened and weakened when arriving in an unfavorable window. Unfortunately the term ‘synchronization’ is often identified with in-phase synchronization, i.e., zero-degrees phase locking – this probably stems from the fact that in single cell studies (a
traditional field in experimental neuroscience) synchrony is often defined as mere spike coincidence. The binding-by-synchrony hypothesis, however, allows for a more general scenario of fixed but finite, non-zero phase relations. Nonetheless there is still a bias in experimental research to detect in-phase synchronization for both invasive and non-invasive studies. To what extent phase locking at a relative phase different from zero contributes to functional interactions in the motor system remains to be established.

Synchronization is not the only way in which neurons communicate. The firing rate of neurons may be used to convey task-relevant information as well, referred to as rate coding. These two mechanisms are not mutually exclusive and may act conjointly. In fact, Riehle and coworkers (1997) showed that synchronization that is not accompanied by alterations in firing rate is associated with the processing of internal cognitive events and the concurrent modulation of synchronization and firing rate with the processing of external events. The combination of multiple neuronal mechanisms increases the brain’s capacity for information transfer. This might also be the reason for the existence of multiple frequency bands as they might – to some extent – operate in parallel. It is likely that the brain optimizes its performance by exploiting all means for neuronal communication available. This brings me to my first research question:

- **Are both increases and decreases in synchronization used to control motor output?**

This question goes back to the so-called idling hypothesis that has been put forward by Adrian and Matthews (1934b) and later by Pfurtscheller and others (1996). According to this hypothesis ongoing alpha and beta oscillations represent an idling state (e.g., during rest) whereas a decrease in these synchronized oscillations reflects an active state of processing. In line, the event-related synchronization after movement termination is associated with decreased corticospinal excitability (Chen et al. 1998). Increased levels of beta oscillations hence impede movement generation. More recent studies provided evidence that M1 beta synchronization can be actively upregulated to suppress unwanted motor output (Androulidakis et al. 2007). The results from Chapter 3 illustrate that this mechanism extends to the interaction with the spinal cord. Corticospinal beta synchronization increased when the non-selected response hand had to maintain the same constant force output. Likewise, both beta band cortical power and corticospinal synchronization were enhanced when muscle force had to be kept constant around a certain target level with high precision (Kristeva et al. 2007; Witte et al. 2007). Put differently, the preparation and execution of new movements is associated with a decrease in beta power, while an increase in synchronization accompanies the stabilization of current motor output. Also these
general correlations suggest that neural synchrony plays a functional role in motor control, but is there also more specific evidence available regarding the encoding or decoding of movement parameters and action plans?

- **What movement-related information is encoded by synchronization?**

As discussed in detail in **Chapter 2**, the time course of mu and beta ERD and ERS relates to several motor parameters: “More forceful movements are accompanied by stronger mu and beta desynchronization (Stancak and Pfurtscheller 1996; Stancak et al. 1997; Mima et al. 1999) and longer ERS (Stancak et al. 1997). The type of movement seems not to influence beta ERD but increases ERS when more muscle mass is involved, as demonstrated by stronger ERS for wrist compared to finger movement (Pfurtscheller et al. 1998) and shoulder compared to finger movement (Stancak et al. 2000). Movement duration has little to no effect on both ERD and ERS (Stancak and Pfurtscheller 1996; Cassim et al. 2000). However, with increasing movement frequency the beta ERD becomes stronger and the ERS less pronounced until the ERD and ERS peaks become almost indistinguishable (Toma et al. 2002; Houweling et al. 2010a). Also, ERD increases with complexity of sequential finger movements (Manganotti et al. 1998; Hummel et al. 2003).”

The interpretation of synchronization patterns is complicated by the fact that there is no one-to-one relation between the activity of a population and the single neuron level. For instance, an increase in amplitude could either mean that more neurons are activated or that their activity is more synchronized while the overall activation level remains constant. Moreover it is, at least at present, difficult – if at all possible – to differentiate between inhibitory and excitatory activity when looking at large-scale activity. On top of that, (large-scale) oscillations may just reflect mere fluctuations in membrane potential without the occurrence of spikes. Revealing how synchronization patterns link to activity of single neurons may thus require the use of additional recording techniques. I emphasized this important point in **Chapter 4** by arguing that the beta power decrease observed in ipsi- and contralateral motor cortex during unimanual force production might reflect different neuronal processes. Fortunately, invasive recordings of local field potentials and spike activity of single neurons did prove to be helpful in clarifying the neural encoding of movement parameters.

Unlike for the visual system, a distinction of movement-related features encoded by neural populations with a particular functional specialization, i.e., neural assemblies, is not directly apparent. Instead the focus has rather been on **population coding** when it was found that certain neurons showed directional tuning in terms of firing rate for a preferred movement direction (Georgopoulos et al. 1982). Each neuron contributes to a so-called population vector depending on the difference in movement
direction and its preferred direction. By this construction the combined activity of all neurons determines the direction in which movement will ultimately take place. In addition, the discharge of single neurons relates to movement displacement, velocity, acceleration, and force (Fu et al. 1993; Ashe and Georgopoulos 1994; Ashe 1997; Moran and Schwartz 1999). In order to verify the existence of neural assemblies in M1, it would be of interest to know whether synchronization occurs between neurons with similar preferred directions. This possibility is fueled by the observation that neurons with similar preferred directions do have excitatory synaptic connections, whereas neurons with opposite preferred directions are connected via inhibitory synapses (Georgopoulos et al. 1993). This may form the basis of synchronization between neurons that share functional properties.

One of the challenges for future research will be to tie the ideas around ERD/ERS patterns and those of population coding together. Fortunately, deciphering movement parameters from (non-)invasive recordings is a very active area of research as it is linked to the development of brain-computer interfaces to restore communication and motor function in, e.g., tetraplegic patients (Jerbi et al. 2011). Recent findings already indicate that directional tuning can also be observed in amplitude modulations of oscillatory activity, measured with LFPs (Rickert et al. 2005) and ECoG (Leuthardt et al. 2004; Ball et al. 2009). However, despite the large modulations in mu and beta oscillations, most directional information seems to be bound to the gamma band (40-160 Hz) and low-frequency components (<4 Hz) (Mehring et al. 2003; Schalk et al. 2007). The latter can also be observed using M/EEG (Waldert et al. 2008). However, although synchronous discharges between cell pairs show directional specificity, it turns out that this does not parallel their directional tuning curves based on firing rate (Hatsopoulos et al. 1998). That is, rather than a mediating mechanism for population coding, synchronization might be an additional means to convey information about movement direction.

A few additional hints for binding of movement features by synchronization in the motor cortex exist. Synchronization between pyramidal tract neurons does occur between cell pairs that project to the same muscle fields as opposed to cell pairs with non-overlapping fields (Jackson et al. 2003). This is important for generating coherent output to the spinal cord and building up corticospinal synchronization. Interestingly, coherence between cortical representations of different muscle fields may arise when they cooperate in the same task, hence forming a ‘functional ensemble’, i.e., a neural assembly. Brown and Marsden (2001) demonstrated this for phasic wrist flexion and extension movements using ECoG recordings. No such coherence was found when the same types of muscle contractions were executed separately. Stark and coworkers (2008) reported another remarkable finding on motor binding residing at a more representational level. They recorded single and multi-unit activity in premotor areas
of two monkeys while they prepared for a prehension movement with specified reach direction (one out of six) and grip type (precision or opposition). Most neurons showed a preference for reach direction and, to a lesser extent, grip type but not so much their combination. However, pair-wise cross-correlation between multi-unit activity did reveal specificity to the combination of reach direction and grip type. This might be a prime indication for a role of binding-by-synchronization in the representation of action plans.

Synchronization may also promote sensorimotor integration (Mackay 1997). Invasive recordings revealed increased synchronization between pre- and postcentral regions during motor performance compared to rest (Aoki et al. 2001; Brovelli et al. 2004; Witham et al. 2007). Classen and coworkers (1998) found an increase in beta band coherence between motor and visual cortex during visuomotor integration. The binding of sensory and/or motor-related information may require higher precision than the broad-band frequency modulations. Using ECoG recordings, Brown and Marsden (2001) indeed detected task-specific narrow band synchronization between motor areas and surface EMG. Moreover, it was recently discovered that the peak frequency of LFP beta oscillations in M1 reflects information on the behavioral context (cue expectancy versus movement preparation) and movement direction (Kilavik et al. 2011). The exact function of synchronization might hence depend on its center frequency, even within single frequency bands.

- **Is there a 1:1 mapping between synchronization patterns and movement?**

Modulations in synchronization accompany the control of voluntary movements. But are they also uniquely related to movement, i.e., in a one-to-one fashion? Multiple synchronization patterns that – under equal circumstances – lead to the same movement outcome might be a sign of redundancy in the neural system. Conversely, when the same modulation in synchronization may give rise to different behavior there should be a predictable relation with the context-dependent state of the neural system for motor output to be controlled. One intriguing phenomenon in this context is the effect that preceding movement may have on the strength of corticospinal synchronization. Riddle and Baker (2006) showed that the amount of digit displacement preceding isometric muscle contraction correlates with corticospinal coherence. In a similar vein, Omlor and coworkers (2011) showed that corticospinal coherence is strongly increased during isometric muscle contractions following a period of dynamic force production compared to a period of rest. More corticospinal synchronization is needed to perform the same task following higher involvement of the motor system in the preceding action.
Pharmacological alteration of synaptic properties may induce changes in oscillations and synchronization. Baker and Baker (2003) showed that administration of diazepam, which enhances inhibitory post-synaptic potentials via $\gamma$-aminobutyric acid A ($\gamma$-aminobutyric acid A) receptors, causes M1 beta oscillations to double in amplitude. However, this barely affected corticospinal synchronization and did not obstruct the subjects’ ability to perform the (simple) motor task under study. Conversely, the administration of carbamazepine resulted in an increase in corticospinal coherence and EMG power, while leaving M1 power unaffected (Riddle et al. 2004). This might have occurred due to altered muscle spindle afferents induced by the drug. These findings underscore that motor output is not fully determined by the strength of synchronization but also depends on synaptic properties, which may (partly) underlie the inter-subject variability in synchronization strength.

Synchronization patterns may also be perturbed due to pathological conditions. The glioma described in Chapter 5 may be seen as a perturbation of normal brain activity. Although this caused significant changes in spectral content of activity in resting state and during movement, the specific movement-related activity seemed unaffected. The absolute amplitude of beta oscillations in M1 therefore seems less important than its modulations for movement generation. Nonetheless, disturbed resting-state levels of synchronization can have profound consequences for motor functioning, as illustrated by the elevated beta activity in the basal ganglia of patients with Parkinson's disease. There, similar slowing of M1 activity is correlated with impairment of motor function (Vardy et al. 2011). The patients in Chapter 5 did not have any obvious motor deficits. Whether the altered synchronization levels due to glioma impede more complex motor behavior remains to be established.

The brain's plasticity allows for anatomical and functional adaptations to changes in the environment or within the body. Synaptic connections may be strengthened or weakened, created or removed. It is thus very likely that also movement-related synchronization patterns alter during development and aging. Also on shorter time scales, the learning of a new motor skill might result in a reorganization of synchronization within and between regions (Andres et al. 1999; Schieber 2002; Serrien and Brown 2003; Boonstra et al. 2007a; Houweling et al. 2008; 2010b). To conclude, the relation between observed synchronization patterns and motor behavior depends on context and task experience. This flexibility may also be essential to allow for the acquisition of new motor skills and to protect against a loss of motor function due to pathology.
8.2 Prospects of graph theory in neuroscience

Grasping the complexity of the brain is a daunting challenge. Throughout my thesis I stressed that studying specific regions in isolation is clearly not sufficient to understand how neural activity leads to and supports behavior. Each region is embedded in a network and influences the activity of other regions. These networks can be small or large, depending on the task at hand. A more global network perspective may be required to comprehend the neural organization underlying higher-order functions like intelligence and cognition. Graph theory provides very elegant and feasible concepts for the characterization of network structures. For instance, a very efficient organization is readily created by adding a few random connections to a highly clustered network, resulting in a ‘small-world’ network topology. This organization can be optimized further by adding a few nodes with a large number of connections that act as central hubs in the network. Simple models based on preferential attachment can explain the emergence of those central hubs and, in consequence, an overall scale-free structure of the network. There is accumulating evidence that the brain uses these organizational principles – small-worldness and scale-freeness – to enable functional specialization while still allowing for effective communication between regions.

Normal network organization can be disturbed by various diseases states, often yielding a more random organization (Stam and van Straaten 2012). For example in Alzheimer’s disease one can observe a loss of connectivity that eventually leads to impaired cognitive functioning, possibly due to damage of connections to major network hubs (Stam et al. 2009). The malfunctioning of hubs might have large consequences on the performance of the entire network because of their strong connectivity. Likewise, the large degree of hubs might lead to hyper-excitability of the network that may evoke epileptic seizures in pathological conditions (Morgan and Soltesz 2008). Furthermore, schizophrenia is associated with a loss of modularity (Alexander-Bloch et al. 2010) and attention-deficit/hyperactivity disorder with a shift from a global to a more local organization (Wang et al. 2009b). Graph theory provides ‘simple’ topological measures to quantify these alterations in network organization and relate them to normal and disturbed brain functioning.

I consider the merits of graph theory in neuroscience to be:

1) Network topologies can be described by just a few scalar measures
2) Topological properties can be unraveled that are not obvious by eye
3) There is a thorough mathematical background
4) The approach is modality independent
5) Assumptions about regions of interest are not required
6) It is relatively easy to apply

These are certainly strong points but, unfortunately, they come with potential drawbacks when applied without sufficient thought. Put differently, although the field of graph theory is well established in mathematics, the application to real-world networks requires careful consideration. An example of a problem that is not easily solved are the difficulties outlined in Chapter 6 to obtain an unbiased assessment of differences in graph measures between experimental conditions and/or subject populations. It is only meaningful to compare values of graph measures when the underlying network type is known – or reliably classified – because in that case the effect of different numbers of nodes and edges can be taken into account. In practice, these effects can be difficult to uncover because empirical networks do typically not follow one of the archetypes described in theory.

Comparing network topologies is not the only methodological concern when applying graph theory to empirical data. Assumptions have to be made already with regard to the initial steps in the analysis. To begin with there is the definition of a node. Obviously, it is unfeasible to record the activity of all individual neurons in the brain. Non-invasive recording techniques can only measure the combined activity of many thousands of neurons. For M/EEG, the recording sites are usually considered as nodes and follow standard layout systems. But this configuration does not necessarily have to be optimal for capturing the underlying, activity generating neural network. Moreover, M/EEG primarily pick-up cortical activity, i.e., they are ‘blind’ to large parts of the brain’s activity.

In Antiqueira et al. (2010) we investigated how downsampling a large brain-like network with surface electrodes may affect the estimation of its topology (see Figure 8.1). Starting from a 4000 node small-world network distributed in a semi-sphere, we downsampling this network by assigning each of the nodes to the closest sensor on the surface of the sphere. A downsampling network was reconstructed by summing the connections between nodes that were assigned to different sensors (weighted by the inverse distance from the sensor). After that, a threshold was applied to obtain a network with a fixed degree. This was repeated for surface networks of 600, 500, ..., 100, and 32 nodes and 100 simulations. For each original and downsampling network a total of 14 graph measures was calculated and used to classify each network as one of four simulated archetypical networks (small-world, scale-free, random, and lattice) that matched in size and degree. While the original network was correctly classified as a small-world network, subsequent downsampling versions more closely resembled that of a random network. In practice, the classification of downsampling networks might be different compared to these simulations due to our simple approximation of
a brain-like network and downsampling scheme, and the presence of volume conduction might introduce a bias towards finding small-world networks. However, this does not affect our central outcome, i.e., the network estimated via surface recordings may not be representative of the underlying network in the brain.

Figure 8.1. Is the network estimated with M/EEG recordings representative of the underlying brain network? M/EEG has by far fewer recording sites than the number of neurons in the brain and is mostly sensitive to collective neural activity from cortical areas. In Antiqueira et al. (2010) we investigated the effect of downsampling on network topology. A) A brain-like network was simulated with 4000 nodes and a Newman & Watts small-world organization. B) M/EEG recordings were mimicked by assigning each of the brain nodes to the closest sensor on the scalp. C) Networks on the sensor level were constructed by adding connections between nodes assigned to different sensors. D) The original and downsampled networks were compared against four network archetypes using canonical variable analysis of 14 graph theoretical measures and a nearest neighbor classification. While the original network was correctly classified as small-world, the downsampled versions more closely resembled a random network.

The finding that downsampling may influence network topology further complicates the estimation of size-effects in experimental data sets. Indeed, graph measures may differ significantly between networks constructed from the same data but using different numbers of nodes (Hayasaka and Laurienti 2010; Zalesky et al. 2010; van Wijk et al. 2010; Romero-Garcia et al. 2012; Joudaki et al. 2012). Both the dependency on size and the effect of downsampling are difficult to estimate and hence to correct for. To avoid biases as much as possible, it is probably best to analyze networks at the largest resolution available.
The definition of edges is equally problematic as that of nodes. Edges can be directed or undirected and weighted or binary. Once the type of edges is chosen, a wide variety of connectivity measures is available to estimate statistical dependencies between the time-series of nodes. Volume conduction effects should be avoided as much as possible, while true in-phase connections should preferably be included in the network. As explained in Chapter 6, networks generally vary in connectivity density. Setting a fixed threshold that determines the minimum correlation between two nodes needed to form an edge may result in large differences in average degree that obscure unbiased comparisons, whereas choosing a fixed degree for each network can introduce connections in the network that are purely due to noise or leave out important significant interactions. Decisions on these definitions will strongly influence the topology of the network and, by this, subsequent conclusions and interpretation.

One may wonder whether describing the connectivity of the whole brain with just a handful of measures is not an oversimplification. The repeatedly found small-world properties of the brain do not seem to come as a surprise as rarely any network in nature is completely regular or random (i.e., the brain is neither an ideal crystal nor an ideal gas). More relevant information might be contained in local network properties because profound differences may exist between global and nodal measures. After all, not all regions are involved to an equal degree in processing task-relevant information. This may give rise to sub-networks (modules) related to different functions, of which the different default mode networks in resting state are a well-known example (Damoiseaux et al. 2006). These modules might be organized in a hierarchical manner (Meunier et al. 2010). In addition, the consistency of hub locations between behavioral tasks or disease states can be of relevance. A focus on local network properties might also ease interpretations in terms of known regional functional specialization.

Finally, differences in connectivity density between networks are certainly not a mere confounder. On the contrary, these differences emerge for a reason and should be seen as one of the primary findings of the study. Graph theory offers a toolbox to aid the analysis of connectivity patterns.

8.3 Data-driven vs. model-driven approaches to study brain connectivity

Part III of my thesis focuses quite strongly on methodological aspects of studying brain connectivity. The two chapters are concerned with rather different approaches. On the one hand, graph theory, as just explained, is an unbiased approach because it requires no a priori assumptions on anatomy or function but simply describes the
network organization of all – even physiologically less plausible – pair-wise interactions between recording sites. On the other hand, more explicit knowledge of how neural regions respond to input in the form of a generative model is used to infer connectivity between specific sources in dynamic causal modeling (DCM). This dichotomy gave raise to my final research question:

• What methodology should be used to study connectivity in the brain?

Most studies, including the ones presented in Chapters 3-6, employ correlation-like measures to estimate functional or effective connectivity between brain regions. These include cross-correlation, (bi- or partial) coherence, phase locking, phase lag index, Granger causality, the directed transfer function, mutual information, synchronization likelihood, and so on (for an earlier overview see Pereda et al. 2005). These measures can be applied to study isolated (mostly pair-wise) interactions, or all possible combinations of recorded signals. As said, the latter forms the network that can be analyzed in graph theoretical terms. I will refer to these approaches as ‘data-driven’. In contrast, approaches based on a generative model that provide estimates of coupling parameters by fitting that model to observed data (like DCM) will be called ‘model-driven’.

Modeling work is invaluable in neuroscience. This is underscored by the broad field of computational neuroscience. For instance, models helping to determine neural activity from BOLD responses recorded via fMRI, to define the mapping between sensor and source space in M/EEG, to integrate signals from different modalities (Valdes-Sosa et al. 2009), and to understand disease states (Adeli et al. 2005; Wendling 2008; Schiff 2010). Recently, neural mass models have been used to study the relation between structural and functional connectivity (Rubinov et al. 2009b; Ponten et al. 2010; Daffertshofer and van Wijk 2011), and to infer connectivity patterns (Riera et al. 2005; Ursino et al. 2007; Kiebel et al. 2009).

A wide range of models is available that describe neural activity from micro-scale to whole brain dynamics. Typically, the larger the scale of modeling, the less biophysiological detail is incorporated in the model. Starting at the level of single neurons, the generation of action potentials is for example described by (leaky) integrate-and-fire models, the renowned Hodgkin-Huxley equations, or the more detailed Morris-Lecar model. When assuming that all neurons within a population have similar properties, the population dynamics at meso-scale can be approximated using mean-field models. When only looking at the average population activity, neural mass models like those of Jansen and Rit or Wilson and Cowan can be employed. The distribution of neural activity within the population can be described with diffusion equations for neural ensembles, like the Fokker-Planck equation. Modeling of whole-
brain dynamics can be achieved by coupling multiple mean-field models. On a more local spatial scale, neural field models describe the spatial-temporal propagation of waves. For an overview of a number of commonly applied models see, e.g., (Deco et al. 2008; Breakspear et al. 2010). The aim of the research often determines which scale to look at and which computational model to use.

The advantage of using a model is that it assists in inferring things that cannot be observed directly. Depending on the level of detail, one can estimate various physiological parameters down to, e.g., the specific synaptic gains from LFP or M/EEG data (Moran et al. 2011a; 2011b). Of course, a proper model does not only help to interpret data but can also predict novel outcomes by modifying physiological parameters. However, the reliability of results strongly depends on the validity of the model. Models are typically approximations of the ‘true’ neurophysiology. The use of a generative model that does not adequately describe the neural dynamics under study can easily lead to erroneous conclusions.

Much insight into connectivity has been obtained via data-driven methods and many of these methods have become standard. I consider model-driven methods to study large-scale brain connectivity very promising. Of course, future studies will have to improve and extend the currently applied models. Given their potential however, I do believe that this development will be of great importance. Data-driven and model-driven approaches should always go hand-in-hand. After all, data-driven methods enable us to explore unknown scientific terrain and, once some basics are known, the predictive capacity of model-driven approaches helps to unravel specific mechanisms and direct novel exploratory strategies.

8.4 Concluding remarks and future outlook

The overarching research question in this thesis has been:

- What is the functional role of neural synchronization in the motor system?

Synchronization plays a key role in the initiation of new movements, the stabilization of current motor output, and the encoding of movement parameters. This is often not limited to synchronization within a single brain region but extends to synchronization between regions. Different roles can be ascribed to distinct frequency bands. Both increases and decreases in synchronization can be employed in a task-relevant way. Synchronization acts conjointly with rate coding, which enriches the number of neural mechanisms available for information transfer.
The interpretation of synchronization patterns measured with M/EEG undoubtedly benefits from other modalities, be it through supplementary information about anatomy and metabolism via fMRI or through invasive recordings and their more detailed information about accompanying physiological processes. Although the combination of recording techniques can be a challenge and often asks for more involved experiments, the potential additive value should not be underestimated. Fundamental research should opt for this combination whenever possible. Likewise, as causal relations between synchronization and behavior are difficult to prove by mere observation, interfering normal brain activity with, e.g., (rhythmic) TMS will be a valuable approach. In addition to data-driven methods, the use of model-driven methods to estimate effective connectivity provides a very valuable direction of research.

The experiments in my thesis employed motor tasks that can be considered as simple. Evidently, the motor system is capable of much more complex behavior, including motor skill learning and bimanual coordination. This also involves cognitive aspects like action selection, movement planning and initiation. It also links to the issue of perception-action coupling. For example, the mirror neuron hypothesis extends the function of the motor system towards that of action recognition. I trust that understanding the neural foundation of simple force generation will certainly help advance these fields as well. Without a doubt, the diversity of the motor system will guarantee research topics for years to come.