Neural synchronization within and between regions of the motor system
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Summary

How does the nervous system generate voluntary movements? The motor system comprises a number of intricately connected regions containing numerous neurons. The main output to the spinal cord originates from the primary motor cortex (M1). The activity in M1 and other regions of the motor system contains rhythmic components (‘oscillations’) that vary in amplitude while controlling motor output. Typical modulations that can be observed with M/EEG include a decrease in mu (8-12 Hz) and beta (15-30 Hz) band oscillations prior to and during movement, and sometimes also an increase in gamma (>30 Hz) activity around movement onset. It is currently believed that, in addition to the firing rate of individual neurons, the precise timing of action potentials contributes to neural communication. Neurons that are active within a population often fire in synchrony. This gives rise to the just-mentioned modulations in distinct frequency bands in a given region. In fact, different populations are considered to be ‘functionally connected’ when synchronized activity is shared among them. This is exemplified by the binding of stimulus features represented by different populations in visual cortex through synchronization. Importantly, the strength of synchronization both within and between regions may modulate with the behavioral task performed. The thesis concentrated on the functional role of synchronization within and between regions of the motor system. An introduction to this topic was presented in Chapter 1 including a description of two important methods that were used in subsequent chapters: the estimation of synchronization between regions (using ‘relative phase uniformity’) and the reconstruction of source activity from sensor signals (using ‘beamformers’).

Part I – Literature

Chapter 2 provides an extensive literature overview of the current knowledge on synchronization in the motor system. Key findings are discussed regarding movement-related synchronization in M1, between M1 and the spinal cord, between cortical regions, as well as abnormal synchronization patterns in a number of motor disease states. While reflecting on these studies, it seems that in order to understand how modulations in synchronization patterns can lead to (coordinated) movement, it is necessary to combine the outcomes of encephalography with those of invasive recordings of single neuron activity. Moreover, modulations in synchronization should always be interpreted in combination with changes in firing rate.
Part II – Experimental observations

Certain aspects of the functional role of synchronization in the motor system were examined in three experimental studies. In the study in Chapter 3 it is asked whether synchronization in the beta band can be both down- and upregulated in a task-relevant manner. It is generally agreed upon that beta band desynchronization in M1 is involved in movement preparation and execution. However, only very recently it became apparent that also an increase in synchronization might be actively employed, but in this case to impede the initiation of new movements by stabilizing current motor output. Our EEG study confirmed that these mechanisms are implicated not only in M1 but also in the interaction between M1 and the spinal cord. The hypothesis was tested that response selection is accompanied by a decreased beta synchrony for the selected response hand and an increased synchrony for the non-selected response hand, as correlates of movement facilitation and inhibition, respectively. To build up levels of corticospinal synchronization, each trial required a constant force production with both hands. A pre-cue was either informative or non-informative about the upcoming response signal that indicated which hand had to make a ballistic movement while the other hand had to maintain the same force output. Corticospinal synchronization raised above baseline for the non-response hand after the informative pre-cue, while beta power in M1 showed only a brief decrease for the selected response hand. Similarly, the decrease in cortical power and corticospinal synchronization during movement preparation was stronger for the response hand compared to the non-response hand. These findings show that a combined down- and upregulation of cortical and corticospinal synchronization is used during response selection.

Although movements of distal muscles are primarily controlled by the contralateral hemisphere, activity in ipsilateral motor cortex can be frequently observed during unimanual movement. It is still debated whether this activity reflects a ‘cross-talk’ from contralateral motor cortex (hence facilitating bimanual movement) or results from an interhemispheric inhibition to prevent unwanted movement of the passive hand. The role of ipsilateral beta desynchronization during unimanual force production is discussed in Chapter 4. In the corresponding MEG experiment, significant ipsilateral beta desynchronization occurred only during unimanual dynamic force production and not during static force production. A comparison of event-related ipsilateral and contralateral synchronization patterns revealed a bilateral ERD, whereas ERS was confined to contralateral M1. These subtle differences in synchronization patterns suggest that ipsilateral activity does not merely reflect a cross-talk from contralateral hemisphere but that additional processes are likely to be involved in unimanual force production. Based on observations reported by others
using either fMRI or invasive recordings, it is speculated that different neuronal activation patterns might underlie the beta desynchronization in ipsi- and contralateral M1.

One way to gain insight into brain function is by ‘artificially’ perturbing its activity. This can be done deliberately, e.g., using transcranial magnetic stimulation, or involuntarily as in the case of pathologies. The MEG study reported in Chapter 5 focused on the effect of glioma (a specific type of brain tumor) on oscillatory activity in M1 during movement and in resting state. Glioma may grow excessively over time while damaging surrounding gray and white matter. Abnormal low-frequency oscillations can be typically observed around the tumor border. In addition, the disruption of white matter fibers might in principle cause alterations in activity at more distant locations because of altered connectivity between regions. The movements performed by the patients in this experiment involved a rhythmic opening and closing of the left or right hand. Despite the presence of a glioma around the central sulcus, the source location of the motor activity could be identified. Subsequently, the spectral power in M1 located in the tumor hemisphere was compared against that of M1 located in the healthy hemisphere. The amplitude of beta oscillations turned out to be smaller and that of alpha oscillations larger in the tumor hemisphere compared to the healthy hemisphere, both in rest and during movement. No such ‘slowing’ of activity was observed when looking at specific movement-related power modulations. As no motor deficits were manifest in the patients who participated in this study, the results are also indicative for the flexibility of oscillations underlying normal motor functioning. A longitudinal study monitoring the progression of alterations in spectral power in combination with a quantitative evaluation of motor function might help to determine the appropriate time for surgical removal of the tumor in future cases.

Part III – Data-driven versus model-driven approaches

The third part of the thesis has a strong focus on methodology to study connectivity in the brain. Two methods are evaluated that recently became very popular in the neurosciences. The first one is graph theory, which provides a powerful framework to describe the complex structure of networks with just a few (scalar) topological measures. It shows that simple organizational principles can give rise to very efficient networks that enable functional specialization while still allowing for effective communication between regions. There is growing evidence that brain connectivity has indeed characteristics of both ‘small-world’ and ‘scale-free’ networks. This efficient network organization appears disrupted in various disease states, often in the direction towards a more randomly connected network. Prior to applying graph
measures, networks are constructed by correlating measured activity from all pair-wise combinations of recording sites. It is therefore a very explorative method that does not require a priori information about which regions are anatomically connected or actively involved in the task. The application of graph theory to empirical networks, however, poses a number of challenges. One of the problems is the comparison of topologies between networks that differ in the number of nodes and/or connections because graph measures do not only depend on network structure but also on the size of the network. Empirical networks in general have differences in either one or both, hence rendering an unbiased comparison problematic. Chapter 6 explicates this issue while evaluating the methods that have been applied in the literature to compare network topologies.

The second method, \textit{dynamic causal modeling (DCM)}, takes a very different approach. In contrast to graph theory, which might be considered as more data-driven, DCM makes use of generative models to estimate effective connectivity in a typically quite small network of task-involved sources. Such a model describes how the activity in one region responds to input from other regions, its intrinsic dynamics and (if appropriate) an external stimulus. The differential equations could be based either on neurophysiology or model directly the dynamics of a specific feature of the data. Guided by our anatomical knowledge, a number of models are constructed that differ in their configuration of connectivity. These models are fitted to the observed data and their performance is compared. The model that provides the best fit is selected and its parameter values are assessed to infer the coupling strength within and between regions. Chapter 7 demonstrates the capacity of DCM to model time-frequency modulations and inferring directional cross-frequency couplings between sources. MEG data were used from an experiment in which subjects used motor imagery in the form of mental hand rotation to identify the laterality of a presented hand drawing. The task was accompanied by a strong increase in gamma activity in visual areas, together with a decrease in alpha and beta activity in both visual and motor areas. Using DCM we showed that trials with a long reaction time were characterized by a less effective suppression of gamma and beta modulations in the visual cortex due to altered connectivity strength from the visual cortex to motor areas, as well as in the reverse direction.

Finally, the epilogue constituting Chapter 8 reflects on the main findings in this thesis and their implications for our understanding of the functional role of neural synchronization in controlling voluntary movement. The results of all studies are discussed along the following research questions: are both increases and decreases in synchronization used to control motor output? What movement-related information is encoded by synchronization? Is there a 1:1 mapping between synchronization
patterns and movement? What methodology should be used to study connectivity in the brain? Synchronization plays a key role in movement initiation, the stabilization of current motor output, and the encoding of movement parameters. This is effectuated through different frequency bands and synchronization both within and between regions. Synchronization patterns are not fixed in relation to motor output but may alter due to pathologies, learning a new motor skill, and even depend on immediately preceding movements. Modulations in synchronization strength operate conjointly with modulations in firing rate, hence enriching the number of available mechanisms for information transfer in the brain. The interpretation of synchronization patterns benefits from studies using a combination of recording techniques as well as experimental perturbations to normal brain activity. Only in this manner it becomes feasible to disclose causal relations between synchronization and behavior. Without a doubt, the use of model-driven approaches to infer connectivity continues to be a valuable direction of research that will certainly bring many new insights in the years to come.