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Chapter 6

Epilogue

It is this potential for plasticity of the relatively stereotyped units of the nervous system that endows each of us with our individuality.

Eric R. Kandel

6.1 Summary of main results

The preceding chapters presented studies that addressed the various methods, concepts and ideas outlined in **Chapter 1**. The overarching hypothesis was that neural synchronization has functional significance for movement control.

Chapter 2 focused on the neural changes that occurred between unimanual and isofrequency control conditions that were conducted before and after a motor learning session. The to-be-learned task involved polyrhythmic force production. The largest changes in power were found in the left and right motor cortices and both cerebellar hemispheres. These changes were broadband, *i.e.*, they ranged from α -, via β - to the γ -band, while no differences were observed between left and right cerebellar areas. For the right motor cortex, however, effects were larger than for the left motor cortex. Event-related analyses revealed β -amplitude modulation in motor cortices and α -amplitude modulation in cerebellar hemispheres. The α -modulation increased after learning and, simultaneously, the coupling between bilateral motor areas increased around the movement frequency reflecting improved (*i.e.*, more effective and more efficient) motor timing. Furthermore, the interhemispheric γ -synchronization between primary motor areas decreased, which may reflect reduced attention and attentional demand after learning. The changes in synchrony between distant neural populations were not a mere by-product of sustained performance as they were clearly related to the learning process though they were only weakly correlated with performance improvement. Interestingly, the decrease and increase of local synchrony of β -activity in the motor cortex during the movement cycle did become more pronounced as performance improved. This was particularly evident in the motor cortex contralateral to the slow hand. The findings in **Chapter 3** led to the conclusion that increased β -modulation in general displays an improvement of the neural mechanisms involved in movement timing. Accompanying the increase in cortical β -amplitude, a brief episode of increased cortico-spinal synchronization between EMG and contralateral motor cortex was found. In **Chapter 4** I could further show that improvement of task performance correlates strongly with increased synchronization between the ensemble of cortical motoneurons

and alpha-motoneurons of the muscles involved. This finding suggested that precise timing in muscle control benefits from a mechanism that employs cortico-spinal synchronization.

In **Chapter 5** I described how the accompanying pattern of desynchronization and synchronization of β -activity (corresponding to the 'on/off' cycles of motor activity) in motor cortex during the movement cycle changed while the tempo increased. The β -modulation decreased and, by the same token, the temporal distance between the episodes of desynchronization and synchronization diminished. Based on these findings, I argued that coordination is limited by certain constraints of the underlying neurophysiologic mechanism. That is, the time required to build up local changes in synchronization within a neuronal ensemble could limit the central control of the muscles involved. Presumably, the time scale of this mechanism has quite general repercussions for the interactions between the cerebral hemispheres: the movement instability is accompanied by an increased cross-talk, indexed as the ratio between the amounts of spectral power at both movement frequencies, between the motor cortices. In the experiment this cross-talk occurred at the movement frequency, suggesting that the bilateral phase locking over movement cycles is mediated by high-frequency (β) oscillations and constrained by its phase dynamics.

In this thesis I presented empirical support for the functional role of neural synchronization in and between neuronal ensembles distributed (widely) across the nervous system. In the next section I will argue that this kind of neural synchronization may support the notion of motor binding, *i.e.*, the integration of the building blocks of movement into a smooth and continuous execution. Thereby, I attempt to show that the framework of phase oscillators may offer a unified approach to bridge the various temporal and spatial scales involved. This ultimately leads to a number of suggestions for future research that are briefly sketched in the concluding section.

6.2 Problems of neural organization: a perspective

When trying to understand the neural organization accompanying voluntary movement, several important problems are encountered. To mention a few, one first needs to address the representation of movement in the nervous system. Where

and how is information about movement execution stored and processed? Is there a finite arsenal of not fixed but adaptive building blocks ('motor primitives', see Mussa-Ivaldi and Bizzi, 2000) with which all possible movements are realized, *e.g.*, coordinative movement patterns (Kelso, 1995)? Is each movement unique and constructed on the fly using a number of generic processing units, *e.g.*, the schemata in generalized motor programs (Schmidt, 1975) or muscle synergies (Bernstein, 1967)? Related to this is the second problem, namely that of the 'neural code'.

For decades scientists have been trying to understand how information is represented, transported and stored in the nervous system, or, in brief, to "crack the neural code" (*e.g.*, van Hemmen and Sejnowski, 2006). This code is supposed to facilitate both the transformation of sensory inputs into efferent neural signals, the inverse transformation of afferent neural signals into motor outputs, as well as the internal code used by billions of nervous cells during the intermediate information processing. To infer such a code, interactions between neural units have been studied. To describe these interactions with an emphasis on semantic content, the term *neural mechanism* has been loosely defined as a (dynamical) process that can induce changes in brain states and thereby reorganize neural function. A neural mechanism is therefore not functionally relevant per se, but may be employed for functional purposes¹. Many such mechanisms have been proposed or discovered. On the level of cell assemblies we find synaptic plasticity and synchronization mechanisms: how are these related to the neural code and its function? The concept of plasticity, which can be viewed as an activity-dependent reorganization of cortical connectivity, is primarily implemented through anatomical or spatial changes. It is thought to underlie central learning (Hebb, 1961). It is adaptive and integrative, but relatively slow by definition. In contrast to this, neural synchronization usually occurs on a faster time scale, as it is characterized by specific temporal relations between the activities of neuronal cell populations. In fact, synchronization has been proposed to provide a means to solve the (perceptual) binding problem (von der Malsburg, 1985; Singer, 1993). Thereby, cells respond selectively to different properties of a perceived object by adapting their temporal code, and as such their integrated activity forms the neural representation or 'correlate' of the object. In its most extreme form, a single dedicated cell

¹Informally speaking, we can conceive neural mechanisms as the 'hardware' of the brain and the neural code as the 'programming language' in which the 'software' is written.

represents or reacts upon a specific perceptual stimulus. However, this so-called notion of the *grandmother cell* (Connor, 2005) seems too simple to be true (in view of the amount of cells needed to represent all concepts in the external world). Even though on the lowest level activity in primary sensory neurons relates unambiguously to specific quantities in the external world (detected by their receptive fields), most brain cells are involved in many tasks. Since the inputs a neural unit receives have to be interpreted by taking into account their origin ('part of the message is in the sender'), this means that the functional role an individual neuron is playing is determined both by its locus and by dynamical aspects, in particular in relation to other neurons. Binding then seems to be a dynamical and context-sensitive phenomenon, which renders its analysis involved.

The binding hypothesis is difficult to reproduce in motor system theory: while in the visual system it has been shown that specific attributes of perceived objects are coded by individual cells, in the motor system there are multiple working hypotheses as to what properties of movement are encoded (Georgopoulos et al., 1982; Bizzi et al., 1991; Rickert et al., 2009). Hence, to transfer the concept of binding to the motor domain remains a challenge (Farmer, 1998; Sanes, 2003). Recent evidence suggests that the activity of cells in primary and supplementary motor areas is related to physical properties of movement as force, direction and posture (Georgopoulos et al., 1982), but the "functional characterization of the input of motor structures" (Singer, 1993) remains largely unknown. However, as Sanes and Truccolo (2003) have argued, the control of movement has particularly useful features in determining the functional significance of neural synchronization. That is, in contrast to studies in perception "where only one output variable can be assessed", movement provides an extensive repertoire of experimental variables. Consequently, it is much more feasible to assess motor control experimentally in a direct, controlled and quantitative way.

As argued throughout this thesis, phase synchronization is a mechanism at the mesoscopic level of neural activity that may serve binding in the motor system. The experimental studies presented here show that the framework described in Chapter 1 provides valuable clues as to the principles, components and activities involved in this mechanism. Note that, traditionally, questions of movement coordination are asked in terms of optimal control theory in which feedback loops form the core of the matter (dating back to Wiener's cybernetics, 1961). Al-

though this approach is valuable, the synchronization approach allows addressing these questions more naturally within the framework of synergetics, where the building blocks of controlled movement are dynamic patterns (Kelso, 1995). In contrast to control-theoretic approaches where goal states ('set points') need to be assumed, these patterns are formed through self-organization. Thereby, the problem of goal-setting is avoided and it is possible to describe movement without the assumption of a man in the machine (*kybernetikos*). In the next section, I will present some guidelines to extend this work.

6.3 Implications and Future directions

Model: validation and extension

The dynamical model outlined and discussed in the light of an experiment summarized in Chapter 5 only offers a qualitative description, which renders model validation and verification rather difficult at this stage. In addition, in the analysis of my experiment I did not account for the activities of the premotor areas, which form the second stage of the purported model. Indeed, premotor and motor areas play distinct roles during movement execution (Wheaton et al., 2005; Liuzzi et al., 2009), but the spatial resolution of the here implemented beamformer method did not allow for discriminating between sources that are so close to one another. In a future approach, this may be overcome by repeating the experiment using a larger number of sensors yielding higher spatial resolution. Alternatively one may identify premotor areas through additional analysis. The here adapted method was rather simplistic indeed: relevant components in the motor network were identified by only looking at maximal changes in power. This alleviated the main drawback of the beamforming method, namely that significant changes may be entirely due to covariation of two (or more) true sources (spatial mixing due to linear superposition and geometric effects, generally denoted by the term *volume conduction*). To study information transfer between close sources one may try to distinguish genuine nonlinear interactions from linear 'cross-talk' (as in electrical engineering, where this denotes the undesirable electromagnetic spill-over from adjacent cables) in a more sophisticated way.

Interestingly, some contrast images, generated using comparisons between different conditions, were remarkably similar in that they both seemed to contain

clusters incorporating bilateral primary, secondary and supplementary motor areas (see Fig. 6.1). This hints at the existence of additional, active sources within this cluster. Can we localize these sources? Note that ‘interactions’ due to spatial mixing may be readily distinguished by their projections since a linear mixing of sources leads to phase relations of 0 or $\pm\pi$ (Nolte et al., 2004; Stam et al., 2007). Accounting for these effects, we can identify these tentative sources and study their functional connectivity (Bullmore and Sporns, 2009; Muskulus et al., 2009). The connectivity within and between these areas has recently been studied using diffusion tensor imaging (Kim et al., 2010), EEG (Gross et al., 2005; Wheaton et al., 2005) and MEG (Schoffelen et al., 2008). Kim and colleagues study revealed that the density of anatomical connections varies significantly between motor areas, whereas the encephalographic studies emphasized the event-related functional connectivity during movement preparation and execution. As my studies confirmed the prominent role of β -activity in motor control, we may expect to gain more insight into these inter- and intrahemispheric connections and the active sources involved, by investigating β -synchronization between individual voxels in these ‘activation clusters’.

Based on the findings in Chapter 5, one may moreover hypothesize that the β -oscillations accompanying rhythmic movement are distinct from (or: give rise to) oscillations at the movement frequency. Model-wise, this may be accomplished by representing the primary motor areas as two separate, limit-cycle β -oscillators (one for each hemisphere) that are modulated at the movement frequency via the ipsilateral premotor areas. Accordingly, while these oscillators are primarily concerned with cortico-spinal entrainment, their dynamics influences the effective coupling between the primary motor areas. Whereas the premotor areas are associated with motor planning, and therefore modeled explicitly at the movement frequency, the primary motor areas are associated with execution at a lower level. Instead of describing them in terms of behavioral variables, *i.e.*, oscillating at the movement frequency, it seems more realistic to assume a β -rhythm carrier signal (Hoppensteadt and Izhikevich, 1998). The premotor areas perturb this rhythm, and this modulation is experimentally manifest while the synchronous β -background is less easily detected. Incorporating these ideas into the model of Daffertshofer et al. (2005) might create a more detailed, and perhaps more realistic, model of interhemispheric interactions.

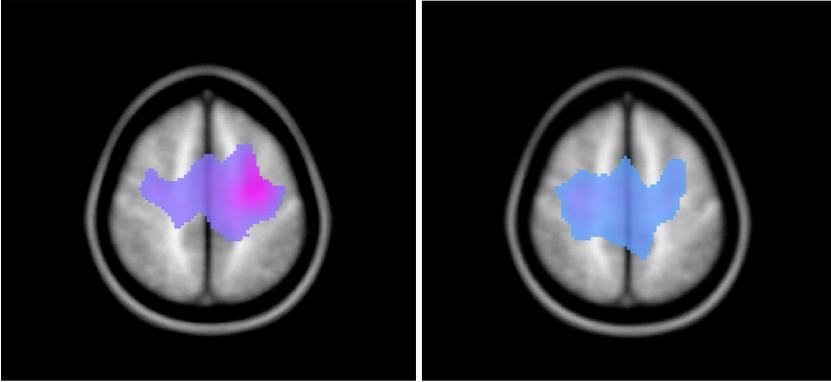


FIGURE 6.1: Power differences in the β -band. Thresholded statistical image after contrasting β -power during movement (left panel) and rest (right panel) conditions in the same experiment ($N=13$). The left panel shows differential effects between unimanual and bimanual 5:8 tapping. The right panel shows differential effects in 30 second rest recordings before and after five blocks (ten minutes each) of 5:8 tapping.

Experiment: motor learning and development

Motor learning is generally conceived as a process that entails rather permanent changes (Newell and Ranganathan, 2009). Whether behavior has permanently improved is often assessed by means of a retention test: the performance of the to-be-learned task is not only measured during and right after the practice phase, but also some considerable time (varying from minutes to months) later. In doing so, mere transient performance improvements may be dissociated from long-term learning (Schmidt and Wrisberg, 2000). Evidently, the neural processes involved in motor learning play different roles in the acquisition, consolidation and ultimately the automatization of a given motor skill (Doyon and Benali, 2005). For example, a sequential order of motor tasks results in better performance right after practice than a random order (Shea and Morgan, 1979). However, when tested several days later, the random order yields the better performance. A similar effect has been observed for (non-invasive) cortical stimulation: three months after practice, performance is better when stimulation has been applied during the practice phase (Reis et al., 2009). Some neural processes are hypothesized to be auxiliary; such effects can only be detected in the course of learning. The purpose

of other processes is considered to consist solely of memory consolidation; these are most prominent right after the learning stage. Therefore, considering the (unknown) different time scales of the (unknown) nervous structures, disentangling the relative contributions of these processes is not a straightforward task. The neural correlates of motor performance improvement I have reported in this thesis may provide useful indications for the design of experiments directed to this goal. Their significance stems from the fact that they have been monitored continually during learning, in contrast to most other studies which, at best, measured brain activity at a few time points only.

Even though the role of consolidation in the learning of motor skills is still under debate, there is structural evidence that bimanual skills benefit from overnight sleep (Brawn et al., 2008). The basic question we might then ask is the following: are the neural changes and their localization in distinct brain structures that were related to performance improvement also responsible for consolidation of the motor task? In particular, do the practice-related cerebellar changes persist after the practice phase? Further, by distinguishing appropriate phases of 'early learning' and 'late learning', can we disentangle the contributions of different components? Recent studies imply that the cerebellum is more involved in early learning (Penhune and Doyon, 2005), an idea which is inspired by its computer-like error correcting role in motor timing tasks (Arbib et al., 1998). The results in Chapter 4 about increased α -power in the cerebellum suggest that one should study particular frequency bands and their involvement in different learning stages. Involvement of the motor cortex in memory consolidation has been reported (Reis et al., 2009) and it may be hypothesized that one of the neural correlates reported (of either practice or learning) facilitates this process. Additionally, not only central processes, but also peripheral changes may accompany performance improvement. As reported in Chapter 4, cortico-spinal synchronization is tantamount to accurate timing. If such a process as the consolidation of timing exists, this should be reflected in persistent β -amplitude modulations, and, since these cortical changes carry over to the spinal cord, in persistent β -synchronization after practice.

To which extent interhemispheric interactions play a role in the improvement of bimanual motor performance remains an open question. A reflection of performance improvement in the primary motor cortices is not necessarily a conse-

quence of improved control. In other words, if performance improves, then one expects to see this reflected in the brain activity. The model of Daffertshofer et al. (2005), referred to in Chapter 5, helps to construct testable hypotheses addressing this issue, and will hopefully leave us with a satisfying explanation of the chain of causality between brain activity and behavior. If β -oscillations underlie the observed movement frequency, as the findings in the second experiment suggested, the interhemispheric cross-talk at the movement frequencies should be constrained by their phase dynamics.

Finally, extending the investigations on functional changes in neural activity and interactions on the time scale of hours or beyond, one enters the realm of developmental neuroscience, *i.e.*, one may look at neural changes during the development of motor behavior. Placing the model of interhemispheric inhibition in a developmental setting, one may hypothesize that the motor areas in the 'untrained' brain are strongly coupled and that this coupling needs to be refined in order to achieve proper motor behavior. In fact, infants, during their first year of life, show changes in behavior that are suggestive of underlying changes in the interhemispheric interactions between motor areas. That is to say, a decrease in the spatiotemporal 'coupling' between the hands occurs between the ages of 3–4 months and 11–12 months (Goldfield and Michel, 1986). Presumably, this shift is the result of an altered (effectively decreased) coupling between the motor areas in both hemispheres. Identifying these shifts is not a trivial task, and measuring the brain activity of infants even less so. Interlimb 'coupling' may be indexed by, *e.g.*, the frequency of unimanual and bimanual hand movements in reaching and grasping, the occurrence of mirror movements in the non-moving hand during unimanual reaching, or the spatiotemporal similarity between (the movement traces of) both hands during bimanual reaching. Assessing the accompanying brain activity may be achieved by easily applicable EEG nets containing 128 electrodes. This seems an ambitious yet feasible project whose results will cast light upon the neural processes underlying developmental aspects of motor behavior.