Summary

Each year about 15 million people suffer a stroke worldwide. While 5 million patients do not survive the initial injury, another 5 million are permanently disabled. The most common recognized impairment caused by stroke is motor impairment. Motor impairments gravely affect an individual’s ability to perform activities of daily living (ADL) and to participate in everyday life situations. In particular, the outcome of ADL independence is associated with the severity of upper limb paresis. Consequently, a wide range of interventions has been developed to improve upper limb function. As outlined in the Introduction of this thesis, two therapeutic concepts stand in stark contrast among these interventions: unilateral and bilateral upper limb training. The first concept deliberately prevents the use of the non-affected upper limb and has been implemented in a variety of ways since over several decades. At present, Constraint-induced movement therapy (CIMT) is the most prominent version of unilateral upper limb rehabilitation interventions based on this concept. The second concept dictates utilization of the non-affected upper limb to enhance motor function in the paretic limb. Bilateral arm training with rhythmic auditory cueing (BATRC) is an example of the second concept.

The success of an intervention may depend on the severity of the upper limb paresis. Following a proposed algorithm based on prognostic research, unilateral training has been suggested to be more beneficial for patients with a mild upper limb paresis, as indicated by residual distal extension of the paretic wrist and fingers (reflecting functional corticospinal tract (CST) integrity). On the other hand, bilateral training has been suggested for those with little or no evidence of CST integrity, thereby exploiting ipsilateral pathways from the contralesional hemisphere and disinhibition of the ipsilesional hemisphere through interhemispheric interactions.

The main goals of the present thesis were to investigate the relative effectiveness of unilateral and bilateral upper limb training after stroke at a group level and as a function of patient characteristics, and to investigate what changes in underlying mechanisms are associated with functional improvement. To this end, five studies were conducted: two systematic reviews, one on training devices and one on previous RCT’s comparing unilateral and bilateral arm training, a randomized clinical trial (RCT) with equally dosed unilateral, bilateral, and conventional interventions, a study of the changes in bimanual coupling strength following these three interventions, and an investigation of the relation between observed and perceived upper limb recovery in a subset of the participants of the RCT.
Chapter 2 entails a systematic review of bilateral upper limb training devices. In total, 6 mechanical and 14 robotic training devices were evaluated in terms of the degree of active involvement of the paretic upper limb (passive, assisted, active) and targeted part of the paretic upper limb (proximal, distal), as well as their potential for clinical applications as a function of the available clinical evidence and commercial availability. While the mechanical characteristics of some of the devices, like BATRAC, are relatively simple and easy to implement, most other, mainly robotic devices, involve complex forms of control and are therefore deemed less proficient for implementation in clinical practice. The available evidence for the clinical efficacy of bilateral upper limb training devices is rather limited and not yet of such caliber that the devices in question and the concepts on which they are based are firmly established. Rather, the initial clinical outcomes indicate that bilateral upper limb training and the accompanied devices may provide a useful extension of the available forms of therapy.

Chapter 3 reports a meta-analysis of the data and outcome measures of previous RCTs comparing the effects of unilateral and bilateral upper limb training. Nine RCTs, comprising a total of 452 patients, were included. Separate quantitative analyses were applied with regard to two key factors: severity of upper limb paresis and time of intervention after stroke. There were no significant differences between the two approaches except for patients with a mild upper limb paresis starting the intervention in the chronic phase (i.e., more than six months) after stroke. For this group of patients a marginally positive effect in favor of unilateral training was found on upper limb function [as assessed with the Action Research Arm Test (ARAT) and the Wolf Motor Function Test, but not the Motor Assessment Scale] and perceived upper limb function [as assessed with the Motor Activity Log (MAL)]. However, the obtained effects were small and below the conventional threshold judged as clinically meaningful. There were no RCTs comparing unilateral and bilateral upper limb training in patients one to six months after stroke.

Chapter 4 describes the applied study protocol of the Upper Limb Training After stroke (ULTRA-stroke) translational research program, which entailed an RCT recruiting sixty patients with an upper limb paresis one to six months after a first-ever stroke in one of the hemispheres. All patients showed at least 10° of active wrist extension, 10° of active thumb extension/abduction and 10° of active extension in at least two fingers of the paretic upper limb. Consequently, all patients had an initial favorable prognosis for paretic upper limb functional outcome. This RCT compared the relative effectiveness of equally dosed modified CMT (mCMT) as unilateral intervention and modified BATRAC (mBATRAC) as bilateral intervention, and a dose-matched conventional treatment (DMCT). In addition, neurophysiological changes and changes in bimanual coupling induced by these interventions were
assessed. All patients received one-hour therapy sessions, three times per week for six weeks. Clinical, neurophysiological, and bimanual coupling assessments were performed the week before, the week after, and six weeks after the intervention period.

The clinical results of the ULTRA-stroke trial are presented in Chapter 5. The Action Research Arm Test (ARAT), measuring motor performance of the paretic upper limb, served as primary outcome measure, and together with the secondary outcome measures all three levels, (I) body functions and structure, (II) activity, and (III) participation, of the World Health Organization International Classification of Functioning, Disability and Health were covered. All groups demonstrated significant improvement on the ARAT from baseline to post-intervention, which sustained from post-intervention to follow-up. Clinically, there were no significant differences between intervention groups in change scores on the primary and secondary outcome measures. Furthermore, after the pretests, the patients were stratified into lower- and higher-functioning subgroups. Consequently, besides the group analyses, additional analyses on these subgroups could be performed. No indications were found that unilateral training had a larger positive impact on upper limb function in the higher-functioning group and that bilateral training had a larger positive impact on upper limb function in the lower-functioning group. However, the power of these subgroup analyses was limited by small sample sizes. Overall, these results indicate that mCIMT and mBATRAC are not superior to DMCT or each other in improving upper limb function, in line with the results of the meta-analysis of previous RCT’s on the topic.

Chapter 6 reports a more detailed investigation of intervention-induced changes in bimanual neural coupling strength associated with the sensorimotor changes observed in the ULTRA-stroke program. To this end, a series of bimanual coordination tasks were used to discern intended and unintended neural coupling effects between the hands. Modified BATRAC was expected to have the additional advantage of improving bimanual coordination, more than mCIMT and DMCT, thanks to reliance on neural coupling during training. However, no significant between-group differences in change scores from baseline to post-intervention and from post-intervention to follow-up were found regarding intended and unintended bimanual coupling. Additional analyses of the harmonicity and amplitude of the paretic hand movements revealed significant between-group differences in the control of the paretic hand. Patients assigned to the mBATRAC intervention showed greater movement harmonicity and larger amplitudes with the paretic hand after training than patients who received mCIMT and DMCT. Although these improvements may indicate a beneficial influence of bimanual coupling, a more likely explanation may be found in the fact that mBATRAC involved rhythmic hand
movements that were very similar to those required in the various tasks, suggesting that the improvements were merely due to practicing rhythmic movements with the paretic hand. Moreover, these significant improvements in control over the paretic hand did not translate into better outcomes on clinical measures in favor of bilateral training as presented in Chapter 5.

The focus of Chapter 7 is on the relation between observed and perceived upper limb recovery, rather than the contrast between unilateral and bilateral upper limb training. In a subset of thirty-nine patients, who completed the intervention and follow-up periods in the ULTRA-stroke trial, it was examined whether objectively meaningful improvements in upper limb motor capacity were matched by subjectively meaningful improvement in upper limb performance. As capacity measure the ARAT was used, which measures motor performance of the paretic upper limb. Subjective change was measured with the MAL quality of movement (MAL-QOM) subscale and the Stroke Impact Scale hand domain (SIS-Hand). The MAL is a standardized (semi-)structured interview intended to examine how much and how well the subject uses the paretic upper limb outside the laboratory. The SIS is a stroke-specific, self-report health status measure of which the hand domain is one of the eight domains in total. A significant association was found between improvements on the ARAT and MAL-QOM, but not between the ARAT and SIS-Hand. Subsequently, determinants for the (non)matchers on the ARAT and SIS-Hand were modeled using a logistic regression analysis. None of the characteristics directly related to the upper limb could be used as determinant for the (non)matchers. Conversely, the concord and disagreement between meaningful changes could be predicted based on the knowledge of the patient’s level of education and mood at baseline. Patients with a lower level of education and a mood score higher than the normative score showed significantly more often a match between the ARAT and SIS-Hand. The relevance of the predictive values of these two determinants remains speculative and requires further investigation.

In the final chapter, the main findings are summarized and reviewed with respect to the communalities and differences between unilateral and bilateral upper limb training after stroke. Furthermore, methodological considerations and important issues of upper limb training after stroke beyond the discrepancy of unilateral and bilateral training are discussed. This Chapter concludes with the implications of the research presented in the present thesis and recommendations for future study directions.