CHAPTER 1

General introduction
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Worldwide 15 million people suffer a stroke each year, resulting in about 5 million deaths. Of the remaining stroke survivors, another 5 million are permanently disabled. Nearly 90% of all strokes are ischemic, the remaining 10% are hemorrhagic. Anterior circulation strokes represent over two thirds of all ischemic strokes and thereof 96% involves the middle cerebral artery (MCA). After an MCA stroke, approximately 80% of survivors have motor impairments. These motor impairments gravely affect an individual’s ability to participate in activities of daily living (ADL). In particular, the outcome of ADL independency is associated with the severity of upper limb paresis.

Recent developments in post-stroke upper limb rehabilitation have provided a plethora of treatment methods for the paretic upper limb. Remarkably, within this collection two therapeutic concepts figure prominently that represent diametrically opposed views as to how the use and function of the paretic upper limb may be improved. On the one hand there are therapies that deliberately prevent the use of the non-paretic upper limb, such as Constraint Induced Movement Therapy (CIMT). On the other hand there are therapies that advocate utilization of the non-paretic upper limb to enhance motor function in the paretic limb, such as Bilateral Arm Training with Rhythmic Auditory Cueing (BATRAC). This dichotomy between unilateral and bilateral approaches of upper limb training after stroke is an interesting subject for research for several reasons. First, unilateral upper limb training, in particular CIMT, is an established rehabilitation intervention, which is recommended in various therapeutic guidelines, whereas bilateral upper limb training is only making its mark in the past 15 years. Second, both approaches have different theoretical backgrounds, while serving the same, ultimate goal, i.e., lasting improvement of upper limb function after stroke. The main goal of the present thesis was to investigate the relative effectiveness of unilateral and bilateral upper limb training after stroke and to delineate the functional and neurophysiological changes that are engendered by these interventions.
Improvement in upper limb function in terms of the International Classification of Functioning, Disability and Health

The World Health Organization International Classification of Functioning, Disability and Health (WHO-ICF) serves as a common language for describing health, disability, outcomes, determinants, and changes in health status and functioning for a clear communication and understanding among scientists and health care professionals. It also provides a well-defined framework that can be used to classify the consequences of stroke (and the changes thereof) in terms of functions, activities and participation (Figure 1.1). All clinical measures presented in this thesis can be classified as pertaining to one (or cutting across two) of these three levels of description. At the end of this chapter, a brief list of definitions used in this thesis following the WHO-ICF terminology is provided.

Unilateral training: Constraint Induced Movement Therapy

At present, CIMT is the most prominent unilateral upper limb rehabilitation intervention. The theoretical framework for CIMT has its origin in Edward Taub’s basic research on deafferented monkeys and the behavioral theory of learned non-use, i.e., the conditioned suppression of the use of the affected limb. From this theoretical perspective it is deemed possible to reverse the phenomenon or even to prevent it from happening by constraining the non-affected upper limb and thus enforcing the daily use of the upper deafferented limb (i.e., forced use). Positive initial results supporting this conceptual notion motivated its introduction and associated techniques in stroke rehabilitation in humans.

The signature protocol for CIMT contains three main elements: (I) repetitive, task-oriented practice of the paretic upper limb for 6 hours a day for 10 consecutive weekdays; (II) adherence-enhancing behavioral methods designed to transfer the
Unilateral versus bilateral upper limb training after stroke

Bilateral training: Bilateral Arm Training with Rhythmic Auditory Cueing

Although bilateral upper limb training is by no means a new form of stroke rehabilitation, it has a relatively short history in rehabilitation research and arose partly serendipitously and partly from insights gleaned from the motor control literature. In this literature, the motor-coupling (or interaction) between the upper limbs has been investigated extensively in rhythmic interlimb coordination studies involving healthy subjects. In this field of research it is well established that humans show a basic tendency towards in-phase (i.e., mirror symmetrical movements) or anti-phase (i.e., alternating movements) coordination, with a prevalent 1:1 frequency locking mode for upper limb bilateral movements. The tendency towards these patterns reflects the neural coupling between the upper limbs.

Bilateral upper limb training after stroke is based on the premise that movement of the non-paretic upper limb may support movement of the paretic upper limb when performed simultaneously. In bilateral upper limb training, movement commands are shared bilaterally by means of crosstalk between both sides of the central nervous system through intact connecting structures, such as the corpus callosum. In this manner, the two upper limbs are coupled and controlled as a single unit. This coupled, unitary activation may result in disinhibition of the ipsilesional hemisphere, allowing for an increase in excitability of the ipsilesional hemisphere. Besides transcallosal pathways connecting both hemispheres and other connections crossing the neural axis at the brainstem and spinal level, there are also ipsilateral projections from the contralesional hemisphere to the paretic upper limb that may be exploited in bilateral upper limb training.

A prominent protocol that relies on interlimb coupling is BATRAC. While in BATRAC, the paretic upper limb has to be used repetitively as well, the obvious difference between BATRAC and CIMT is the use of the non-paretic upper limb as a fundamental component of the training. In the original BATRAC protocol reaching movements are actively mimicked with both upper limbs (i.e., shoulders and
that only constrains movement direction (i.e., the transverse plane perpendicular to the patient). A metronome is used to cue the rhythmic movements, inspired by the beneficial effects of auditory cueing in gait training\textsuperscript{26} and upper limb training\textsuperscript{27}. Bilateral movements are trained for 5 minutes followed by 10 minutes of rest. Training occurs 3 times per week for 6 weeks. A single training session lasts 1 hour, implying that the patient achieves a total of 20 minutes of active bilateral upper limb training per session.

**Distal control and the corticospinal tract**

As the effects of a given therapy depend on patient characteristics, it is conceivable that differential effects between unilateral and bilateral upper limb training after stroke vary as a function of such characteristics. One specific property often discussed in relation to CIMT is the severity of the upper limb paresis.\textsuperscript{5,10} Conventional criteria for the application of CIMT related to distal control of the upper limb are very stringent: patients must possess at least 20° of active wrist extension and 10° of active extension of each finger of the paretic upper limb.\textsuperscript{28,29} The preservation of distal control reflects the integrity of the corticospinal tract (CST),\textsuperscript{30-34} and finger extension in particular is known to be a good predictor of functional improvement in the paretic upper limb.\textsuperscript{35-38} Accordingly, the success of CIMT is often ascribed to the restrictive selection of relatively mildly impaired stroke survivors.\textsuperscript{5}

Based on prognostic research, Stinear and colleagues developed an algorithm for predicting the potential for recovery of upper limb function after stroke.\textsuperscript{32,38,39} Following this algorithm, assessment of CST integrity by testing finger extension\textsuperscript{39} and/or neurophysiological and neuroimaging tests\textsuperscript{32,39} provides information on the functional potential for upper limb recovery. With the help of this algorithm feasible rehabilitation goals can be set\textsuperscript{32,39} and adequate intervention types can be selected.\textsuperscript{32,40} It has been suggested that patients who retain voluntary finger extension (reflecting a high degree of CST integrity) should receive unilateral training (targeting the ipsilesional hemisphere) and that patients with little or no distal movement (reflecting poor or no CST integrity) are more likely to benefit from bilateral training,\textsuperscript{32,40} thereby exploiting disinhibition of the ipsilesional hemisphere through interhemispheric interactions, and ipsilateral pathways from the contralesional hemisphere.\textsuperscript{5,22,41}

Distal control is important for most ADLs, such as bathing, dressing, and preparing and cleaning up after meals. However, there is no report of an intervention that showed a consistent pattern of improvement in hand function.\textsuperscript{5} Given the importance of an early return of distal control,\textsuperscript{35-38,42} it is plausible that the
increase of control of wrist and finger extensors in upper limb is emphasized in interventions. To date, however, there have been no trials in which wrist and finger extensors were targeted specifically by unilateral or bilateral training after stroke. Considering the apparent importance of control over wrist and fingers for functional outcome, all studies presented in this thesis address the severity of the upper limb paresis and/or control over the distal part of the upper limb.

**Treatment intensity**

In healthy subjects, studies investigating a dose-response relationship in skill acquisition have shown that the most important determinant that distinguishes between the skills of experts and those of amateurs is time spent on deliberate practice. When regarding upper limb rehabilitation as a process of learning to accomplish complex motor tasks, it is likely that the same principle applies. Hence, the dose or intensity of an intervention (i.e., the amount of time spent on deliberate practice) may play an important role in upper limb rehabilitation after stroke. In fact, previous research suggests that greater treatment intensity (of the same intervention) will lead to better outcomes. Moreover, studies comparing interventions with an equal intensity generally showed equal outcomes. In order to investigate the impact of type of therapy between experimental and control groups in RCTs, the intensity or dose of therapy needs to be controlled in both groups (i.e., dose-matched). Obviously, the intensity of the interventions is also addressed in the studies presented in the present thesis.

**Outline of the thesis**

Despite the brief history of bilateral upper limb training, a growing number of mechanical and robotic devices for this approach have been proposed. Chapter 2 presents an overview in which a large number of these recently developed devices are discussed and a qualitative evaluation of the clinical applicability is provided. Chapter 3 entails a systematic review including a meta-analysis of randomized clinical trials investigating unilateral versus bilateral upper limb exercise therapy. In this analysis, the effects on upper limb function of both types of upper limb training were compared with regard to two key factors: severity of upper limb paresis and time of intervention post-stroke. Chapter 4 describes the design of a single-blinded randomized clinical trial (RCT) recruiting patients from May 2009 till December 2012 at the rehabilitation center Reade in Amsterdam. In this ULTRA-stroke (acronym for Upper Limb TRaining After stroke) program the merits of equally dosed, modified versions of CIMT and BATRAC, both with emphasis placed on the increase of distal control, were compared with each other and with those of
a dose-matched conventional treatment of eighteen sessions in patients from one to six months post-stroke. To this end, the program did not only focus on clinimetric effects, but also on how the observed changes in sensorimotor functioning related to changes in the associated bimanual coupling and brain dynamics. The clinical results of the ULTRA-Stoke trial, pertaining to the three WHO-ICF levels, i.e., (I) body functions and structure, (II) activity, and (III) participation,11 are presented in Chapter 5. Potential changes in bimanual coupling were investigated using a series of tasks to discern intended and unintended coupling effects between the hands. The results of this part of the ULTRA-stroke program are described in Chapter 6. At the time of this writing, the analysis of the brain dynamics data from the ULTRA-stroke trial was still incomplete and therefore not included in this thesis. As an aside with respect to the main theme of the thesis, we also used the data from the ULTRA-stroke trial to investigate the relation between observed and perceived upper limb recovery. In Chapter 7 the (non)matching of objective and subjective improvements in upper limb function after stroke are discussed and related to clinical and demographic characteristics. Finally, in Chapter 8 the main findings of this thesis are summarized, and a critical reflection on the research as described in this thesis as well as a discussion of clinical implications and future considerations are presented.

List of WHO-ICF terminology

**Health condition** is an umbrella term for disease, disorder, injury, or trauma. Stroke will be the health condition to be discussed in this thesis.

**Body structures** are the structural or anatomical parts of the body, such as the upper limb, its components, the brain, and its hemispheres.

**Body functions** are the physiological functions of body systems, such as movements and sensory perception.

**Activity** is the execution of a task or action by an individual, such as manipulating objects and self-care activities.

**Participation** is a person’s involvement in a life situation including the perspective of societal functioning.

**Capacity** is the construct that indicates the highest probable level of functioning that a person may reach on the levels of Activity and Participation.

**Performance** is a construct that describes what individuals do in their current environment, and so introduces a person’s involvement in life situations.