Recovery of arm motor function in the subacute phase after stroke

Aspects of assessment, treatment and neural reorganization

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Dissertation for the degree of philosophiae doctor (PhD)
University of Bergen, Norway
2012

To my father Paul Brunner, in loving memory

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SCIENTIFIC ENVIRONMENT

This thesis was carried out at the Physiotherapy Research Group, Department of Public Health and Primary Health Care, University of Bergen. My supervisors were Professor Liv Inger Strand, University of Bergen, and Professor Jan Sture Skouen, University of Bergen and Haukeland University Hospital.

The studies were carried out with help from the Departments of Physiotherapy and Occupational therapy at Haukeland University Hospital and Haraldsplass Diaconal Hospital. The second study was partly integrated in the Bergen ESD Stroke Study.

The third study was conducted in collaboration with the Bergen fMRI group, mainly represented by associate Professor PhD Renate Grüner, National Resource Center for fMRI.

The Norwegian Fund for Post-Graduate Training in Physiotherapy funded my position as a PhD research fellow. The Grieg Foundation and the Rieber Foundation funded the operating costs for the third study.

ACKNOWLEDGEMENTS

I am very grateful that I was given the opportunity to realize this PhD thesis at the University of Bergen. This work would not have been possible without the help of many other people directly and indirectly involved.

First, I would like to express my deep gratitude to my main supervisor Professor Liv Inger Strand. Neurorehabilitation became one of the focus areas of the Physiotherapy Research Group under her leadership, which gave me the opportunity to follow my research passions. Her guidance during the last four years helped me through difficult phases of the project, and a meeting with her always had a positive effect and made me feel better and more knowledgeable afterwards. She has been a role model as a scientist of integrity, a patient and fair teacher and a supporting and empathetic person.

My co-supervisor Professor Jan Sture Skouen has been a constant support throughout my PhD studies. His profound knowledge in the field of rehabilitation, his foresight, his openness for new ideas and his diplomatic abilities never failed to impress me. Despite his huge workload he managed to improvise and react promptly whenever the need arose.

I greatly appreciate all the help I received from the physiotherapists and occupational therapists at Haukeland University Hospital, the Department of Rehabilitation and Physical Medicine in Nordås and Haraldsplass Diaconal Hospital concerning recruitment of patients and testing. I would like to thank especially the frequent testers Silje Nødtvedt, Trude Holvik and Trine Line Hansen for their help with assessments.

Parts of this work were substantially facilitated by being integrated in the Bergen ESD Stroke Project. I would like to thank the leading researcher Håkon Hofstad for his support and for inviting my participation in the Bergen ESD Stroke Project. In this context I wish to express my gratitude for the smooth teamwork with the ambulatory team and the community team concerning patients involved in my projects. It was a pleasure to work with you all. Also thanks to the staff of the Neurology Section at Haukeland University Hospital who were very helpful when I was looking for potential patients.

Four physiotherapists in private practice, Metter Rokne, Beate Anne Kvamsdal, Inger Beate Birkeland and Aashild Eldøy agreed to treat project patients if they were discharged during the project period, and two of them did in fact get involved. Thank you very much for your willingness and contributions.

Physicist PhD Renate Grüner was a main contributor to the third study. I would like to thank her for helping me approach the exciting field of neuroimaging by providing profound knowledge and steady nerves during a demanding analysis procedure. I would also like to express my gratitude to the radiographers Eva Øksnes, Turid Randa and Roger Barndon who skillfully and empathetically handled the project patients, and patiently answered my questions.

My dear colleagues at the Physiotherapy Research Group were a source of interesting discussions, helpful advice and emotional support. It has been a fantastic place to work during the last four years, characterized by professional expertise, respect and generosity, which deeply impressed me. Alice Kvåle, Målfrid Råheim, Rolf Moe-Nilssen and my fellow PhD students set high professional standards, and it was fun to be there.

I want to thank the Norwegian Fund for Post-graduate Training in Physiotherapy for financing this project. I am very grateful for the financial support for the third study received from the Grieg Foundation and the Rieber Foundation.

My friends, especially my TTP club, who gave me something to look forward to and the opportunity for laughter in times of relative solitude.

And, of course, thanks to my wonderful family, my husband Wolfgang and my children Mona and Malte. Wolfgang not only provided emotional support but also inspired me by asking reasonable and relevant lay questions about my work that I had forgotten to ask because I was diving too deeply into the subject. Mona and Malte always reminded me of what matters in life. Thank you for tolerating a temporarily absent-minded and irritable wife and mother.

Bergen, September 2012

ABBREVIATIONS

AO	Action observation
APBT	Active and passive bilateral training
ARAT	Action research arm test
BATRAC	Bilateral arm training with auditory cueing
BOLD	Blood oxygen level dependent
CNS	Central nervous system
CT	Computed tomography
DTI	Diffusion tensor imaging
EEG	Electroencephalography
GMP	Generalized motor program
ICF	International classification of functioning, disability and handicap
MEG	Magnetoencephalography
fMRI	Functional magnetic resonance imaging
M1	Primary motor cortex
MAL	Motor Activity Log
MIC	Minimally clinically important change
MRI	Magnetic resonance imaging
MI	Motor imagery
MNI	Montreal Neurological Institute
MMSE	Mini mental status examination

NHPT	Nine hole peg test
PET	Positron emission tomography
rCBF	Regional cerebral blood flow
RCT	Randomized controlled trial
TMS	Transcranial magnetic stimulation
UE	Upper extremity

ABSTRACT

Early after stroke, approximately two thirds of all patients experience impaired motor function of an arm impacting personal, social and occupational areas. The objective of this thesis was to examine different aspects of arm motor recovery in the subacute phase after stroke with regard to possible treatment alternatives. This was realized in three different studies: In the first study the recovery of arm motor function and the proportion of patients eligible for Constraint-induced movement therapy (CIMT) were examined in a longitudinal, repeated measurement design. In the second study two different treatment approaches for patients with mild to moderate paresis of an arm were compared in a randomized controlled trial. In the third study functional MRI was applied to study changes in potential mirror neurons after stroke and compared to healthy controls.

The first study revealed that the number of patients regarded eligible for CIMT, according to defined motor criteria, constantly decreased during the first 3 months. Most patients with mild to moderate paresis regained satisfactory arm function, all receiving standard rehabilitation. In conclusion, it was proposed that CIMT should not be offered sooner than 4 weeks post stroke to patients with persisting motor deficits.

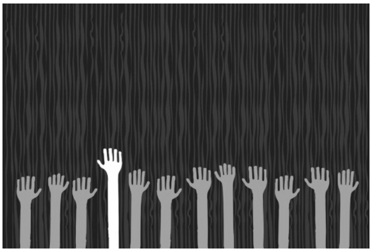
No difference in change between the group receiving modified CIMT and the group receiving bimanual training was found in the second study. The results suggest that bimanual training may be as effective as modified CIMT in improving arm function in the subacute phase after stroke.

In the third study changes over time in potential mirror neurons were found, concomitant with improvement of arm motor function. The activation of mirror neurons early and late after stroke and in healthy control subjects strengthens the notion that treatment approaches targeting those neurons may be a means of restoring arm motor function after stroke.

LIST OF PAPERS

Paper I

Brunner IC, Skouen JS, Strand LI

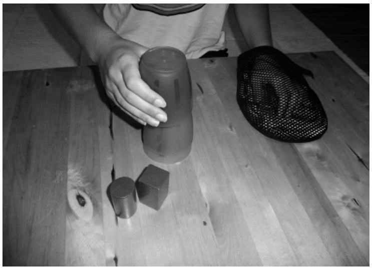


Recovery of upper extremity motor function with regard to eligibility for constraint-induced movement therapy

Top Stroke Rehabil. 2011 May-Jun;18(3):248-57

Paper II

Brunner IC, Skouen JS, Strand LI

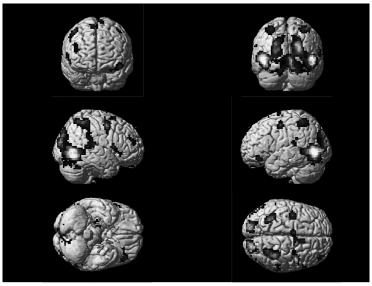


Is modified Constraint-induced movement therapy more effective than Bimanual training in improving arm motor function in the subacute phase post stroke: A randomized controlled trial

Clin Rehabil.2012 May (Epub ahead of print)

Paper III

Brunner IC, Skouen JS, Ersland L,Grüner R.



Plasticity and response to action observation: A longitudinal fMRI study of potential mirror neurons in patients with subacute stroke.

Submitted

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1. INTRODUCTION

1.1 IMPAIRMENTS AND THEIR CONSEQUENCES

Stroke is the leading cause of disability in the western world, with an estimated incidence of 114 to 350 cases per 100 000 persons and a prevalence of 1.5 % to 3 % in different European countries.[1] An exponential increase due to an aging population is expected worldwide.[2, 3] Both acute treatment and rehabilitation of stroke have improved considerably during the last decades. The widespread establishment of specialized stroke units with dedicated interdisciplinary teams has contributed to reducing mortality and long term disability.[4] Early treatment, such as thrombolysis in ischemic stroke within a few hours post onset prevents many patients from experiencing lasting symptoms, but a substantial number of stroke survivors still have to live with long-term impairments. [5] These impairments comprise a broad array of physical, cognitive and emotional difficulties that impact on personal, social and occupational areas and quality of life. [6-9]

1.2 RECOVERY

Recovery is an umbrella term for different structural and functional changes that lead to improvement in performance and self-experience. Lack of consistency in use of this term has been criticized [10] Recovery can be described as regaining or approaching former possible capabilities and the term can be further subdivided into restitution and compensation. [10] Restitution means resumption of a pre-stroke state with the original body structures, which is rare after stroke, but can occur when small infarcts leave enough functionally intact tissue, or when function was only compromised by oedema. [11] Most recovery though, comprises compensation with modified use of the affected body parts, or use of alternative body parts, or alternative strategies to accomplish a task.

Attempts have been made to describe different aspects of recovery according to the ICF classification. Levin et al. (2009) proposed a distinction between recovery and compensation at the neuronal level, the body function level and the activity level. Recovery here always means a restoration of the original state both in the brain and with regard to movement patterns, while the term compensation encompasses alternative strategies and is not sub-classified under recovery. [10] It can be discussed as to how important a distinction between “true” recovery and compensation is for the patient. Compensation strategies may be successful in the short term, but limit performance in the long term. In this context, can using the less affected arm result in an under-stimulation of the more affected arm and corresponding brain areas, thereby aggravating the functional condition after stroke. At the level of cortical reorganization recruitment of the contralesional primary motor cortex can inhibit the ipsilesional primary motor cortex. On the other hand compensation is necessary to accomplish the activities of daily living for many patients. A clarification of the theoretical constructs underlying the term recovery helps clinicians and researchers to choose the right outcome measures for different aspects of recovery.

This thesis focuses on recovery of arm function in the subacute phase post stroke, and comprises the following aspects:

- The course of recovery and eligibility for an intensive training approach

- Intensive treatment approaches for the paretic arm

- Reorganization of specific brain networks with possible implications for treatment

1.3 RECOVERY OF ARM MOTOR FUNCTION AFTER STROKE

Impaired motor function of an arm is among the most common disabilities after stroke, although estimates on incidence vary somewhat. Initial severity of paresis and time after stroke seem to be the most important predictors for regaining arm motor function. In the classic Copenhagen Stroke Study 421 patients were studied with repeated measurements during a 1 year period after admittance to hospital. Of patients with initial mild paresis 79 % reached normal arm motor function after one year, whereas only 18 % of the patients with initial severe paresis achieved the same functionality.[12] Time after stroke was shown to be an important predictor of recovery, most patients reaching a plateau after 9 weeks. According to a study by Kwakkel et al. (2003) on 102 severely impaired patients, upper limb motor function in 30-60 % of the patients tended to be more or less impaired 6 months after stroke. [13] In a subsequent study based on the same patients, it was found that most improvement occurred within the first 4 weeks after stroke. [14] Verheyden et al. (2008) could not find any differences in the time course of recovery of the trunk compared to the arm and leg, and functional ability in daily life activities. [15] This study corroborated the finding that the most notable improvements occurred during the first 3 months, in accordance with the above mentioned and other studies. [16-18]

Clinical evaluation using standardized measurement tools has revealed features that help to predict long term improvement of arm motor function. The presence of active finger extension and shoulder abduction within 72 hours post stroke predicted in 98 % of the patients some dexterity of the arm within 6 months. [19] Strength and 2 point-discrimination at 2 and 4 weeks post stroke were also found to be reliable predictors of dexterity at 6 months post stroke. [20] Kinematic measures, that assess range of motion, smoothness of movement, speed, trajectory and other parameters may also be useful predictors of motor recovery. [21] Motor evoked potentials were suggested as a supplementary tool to predict upper limb recovery, especially for patients with pronounced initial paresis [22, 23] but did not always yield more accurate prognosis than clinical assessment alone. [24] Motor evoked potentials allow inferences about the integrity of the cortico-spinal tract which seems to play a major role in regaining dexterity. Cortico-spinal tract damage can also be examined with the help of neuroimaging techniques such as fMRI. [25]

Although predictors of arm motor recovery doubtlessly can help in rehabilitation planning, they also constitute a risk of that the individual's potential will be overlooked. Stinear (2010) pointed out that a methodological weakness in predictor studies is the lack of description of the type of rehabilitation the patients received in prognostic studies. The frequently used term "standard rehabilitation" can comprise a broad range from no treatment to some treatment to intensive training programmes and thereby constitutes a major confounder. [26] She recommends that dose and intensity of the rehabilitative treatment provided should be included as a variable when predicting and assessing outcome.

Studies on the time course of recovery indicate that there is a critical time-window within the first 3 months when most plasticity can be expected. [12, 14, 15] While plasticity is present throughout life, a brain lesion puts the brain into a receptive, "juvenile" state for a limited time. This is reflected in an up-regulation of proteins that promote remapping and rewiring processes of the brain enhancing synaptic connectivity, as demonstrated in animal studies. [11] The crucial question for all neurorehabilitation professionals is how to exploit this time-window in the most beneficial way for the patient. Some clues derived from research with humans and animals may guide rehabilitation practice. [27] Plasticity is inherent to the brain, but is also use-dependent and can be enhanced by adequate stimuli in terms of an enriched environment and training. [28, 29] Physical and occupational therapy with challenging activities that started soon after stroke was found to be associated with better functional outcomes than later onset and less intense therapy. [30, 31] There are, however, some indications that activities in the first days should not be too forceful in order to avoid an exacerbation of the damage in the penumbra, the area around the infarction, , due to anoxic cell death. [32]

Another factor that may limit intensive training is post stroke fatigue, which affects approximately 30 % to 70 % of all stroke survivors to various degrees. [33] Consequently, although intensive and challenging activities are important stimuli for the reorganizing brain, other factors have to be taken into account. Given a potentially beneficial set of treatment options, the art and challenge of rehabilitation consists of providing the right treatment to the right patient at the right point in time. The fact that impaired arm motor function has a profound effect on several domains of health-related quality of life should be an impetus to provide high-quality rehabilitation services also for upper limb rehabilitation. [8] A prerequisite for targeted rehabilitation is knowledge as to which subgroups may benefit from a certain approach and at which stage after stroke it may be most suitable.

There have been attempts to define the characteristics that may predict treatment success when participating in Constraint-induced movement therapy (CIMT), but these studies mainly included participants in the chronic phase after stroke who already fulfilled some minimal motor criteria. [34-36] Active finger extension, better motor function of the hand and age were found to predict treatment outcome. There is a lack of studies examining the eligibility for different treatment approaches in the acute and subacute phase, when most plasticity can be expected.

1.4 NEWER TREATMENT APPROACHES FOR ARM MOTOR RECOVERY

This chapter focuses on neurorehabilitative treatment approaches that are relevant for this thesis, and is not meant to provide a comprehensive overview. Constraint-induced movement therapy and bilateral approaches were the basis for the randomized controlled trial in paper II, and treatment approaches based on mirror neurons served as a motivation for the fMRI study in paper III. Some other interesting approaches which are not directly related to this thesis are shortly mentioned.

1.4.1 Constraint-induced movement therapy (CIMT)

CIMT was not based on experiences gained from practical work with patients, but was rather a paradigm for translational research, where results from animal studies were applied to humans. [37] Developed by Taub and coworkers in the 1970s CIMT was based on research with monkeys, which underwent surgical severance of the afferent nerves transferring somatic sensation in one forelimb. [38] In the absence of sensory feedback the monkeys did not use the affected forelimb, even though the motor nerves were intact. This was partly explained by diaschisis, a cortical or spinal shock due to a local injury, leading to depressed motor activity. Diaschisis is presumed to last up to 2-6 months in non-human primates and during which time behavioural changes could be observed. This led to the development of the learned non-use model. [39] When the animal tried to move the injured forelimb the movement was clumsy and ineffective. In terms of behavioural psychology the unsuccessful attempt to move the affected limb could be experienced as punishment and thereby as negative reinforcement. Repeated frustrating attempts lead to avoidance and compensation with the intact limb, and this avoidance strategy again results in decreased cortical representation and secondary muscular atrophies of the affected limb. [38] In contrast, when the monkey was forced to use the impaired limb by restraining the intact one, learned non-use could be reversed.

Taub and colleagues observed that the monkeys even after several years of non-use were able to use the affected limb again when forced to do so.

The logical next step was to transfer the knowledge of learned non-use derived from this animal research to patients with stroke and other brain injuries. Some initial studies were mainly based on “forced use”, i.e. restraining the better Upper extremity (UE) and thereby inducing use of the affected UE. [40, 41] From the early 1990s, additional intensive task practice was introduced as a crucial part of the concept. [42] The first studies with patients in the chronic phase post stroke showed promising results [41-43], generating a large body of research during the following years. CIMT is often described as a “therapeutic package” and although restraining the intact UE has attracted much attention, task oriented training and behavioral techniques seem to be of equal importance. [44] Intense repetitive use of the affected UE is a key factor of the concept, or as Taub stated: “The common factor appears to be repeatedly practicing use of the paretic arm. Any technique that induces a patient to use an affected limb many hours a day for a period of consecutive days should be therapeutically efficacious.” [45] Task oriented training was supplemented with techniques from behavioural psychology, such as positive reinforcement and shaping. [46] Positive reinforcement is provided in terms of feedback and encouragement by the therapist supervising the training. The term shaping means dividing a behavioral or motor objective into small steps and gradually approaching the intended motor task. The selected motor tasks should be challenging at the limit of what is currently possible for the patient, thus stimulating effort and motivation but avoiding frustration. [44] The third essential component of CIMT is the so-called “transfer package”, comprising different cognitive strategies to increase compliance and adherence to the training protocol: A formal contract with the participant, and if possible, the caregiver; a home diary where the participant has to write down the time spent on daily training and wearing the restraining mitt; the daily application of the Motor Activity Log (MAL) a structured interview assessing frequency and quality of use of the affected limb and a home skills assignment. [44]

CIMT usually lasts 14 days during which time the participants are expected to wear the mitt 90 % of all waking time and engage in repetitive task oriented training for 6 hours / day on weekdays. CIMT seems to be suitable only for a limited subgroup of patients with stroke, who are cognitively intact, highly motivated and capable of some active extension of the wrist and fingers. Over the last years a large body of research on CIMT has emerged. CIMT appears to be a superior treatment approach compared to standard treatment, which are usually less intensive, but results are incoherent with regard to long-term effects.[47, 48] A recent update of an earlier Cochrane meta-analysis, including 18 RCTs with a total of 674 participants revealed a modest positive effect on arm motor function but no effect on disability. The authors recommend interpreting the results with caution, referring to small-study bias and a lack of equally-dosed training for the control groups in many cases.[49]

Modifications of CIMT

Inspired by the apparent efficacy of CIMT, but deterred by the high demands on resources for such intensive training, several modifications of CIMT (mCIMT) have been developed, referred to as “modified”,[50] “distributed”[51] or “shortened”[52]. One of the most extensively investigated modifications of CIMT was developed by Page et al., in which contact with a therapist was reduced to 3 x 0.5 hours a week, but the training period was extended to 10 weeks. This modification was employed with patients in the acute and chronic phase after stroke and resulted in larger UE motor improvement of the experimental group when compared to a group receiving traditional rehabilitation. [50, 53, 54]

In other studies various combinations were applied, such as 3 hour daily arm and hand training and a restraint for 90 % of waking hours for 2 weeks [52], or 2 hour daily training, restraint for 6 hours per day for 3 weeks [55] , or 4 hour daily training and a shoulder sling for 90 % of waking hours for 10 days [56], or forced use only by wearing a mitt without a special training program. [57] Some of the studies corroborated the superiority of the modification of CIMT used [55, 56], but others did not. [52, 58]

In the early phase after stroke, CIMT of less intensity is usually applied. The results of one study indicate that higher intensity CIMT might even be detrimental in the acute phase.[59] Other attempts to reduce costly therapist contact have resulted in group- and home-based CIMT and the development of AutoCite, which is an automatic work station.[60] Furthermore, combinations of CIMT and botulinum toxin A, or CIMT and mental practice have been tried out, but are still at the experimental stage.[61-63] CIMT is not restricted to UE motor function in adults with stroke. Some of the underlying principles have been transferred to the treatment of patients with aphasia [64], children with congenital hemiparesis [65], and to the lower limb [66].

1.4.2 Bimanual approaches

Bimanual or bilateral arm training is a generic term, which comprises different approaches, from simple repetitive movements to advanced task-related training. McCombe Waller et al. (2008) suggested that training of the hemiplegic arm should include a certain amount of bimanual tasks, since activities of daily living usually involve the coordinated use of both hands.[67]

Mechanisms that are hypothesized to exert a beneficial influence on the recovery of the paretic UE are derived from movement research in healthy persons. Fitts' law implies that there is a relationship between the time needed for a movement, the amplitude of the movement and the width of the target. As the difficulty of a manual task increases, the time required to complete it also increases. This law is attenuated with regard to interlimb coordination as demonstrated in a classic experiment by Kelso and colleagues.[68] Persons, who were asked to strike different targets with the index finger of both hands, synchronized the movement of both hands automatically. When an easy target for one hand was combined with a difficult target for the other hand, the movement time for the easy target increased when both movements were performed simultaneously. Both hands were acting as a single unit and not independently, the so called "symmetry-constraint" A recent replication study confirmed the results of Kelso et al.[69] The susceptibility of both hands to act as a unit was also observed in an asynchronous task, where both hands were moved in opposite directions. The faster the performance, the more difficult it became to avoid synchronous movements.[70]

Three basic models have been proposed as an underlying neurophysiological basis of bimanual coordination. One is the generalized motor programme (GMP), based on the work of Bernstein and Schmidt. A common motor plan for both hands is hypothesized, which can be modified by hand-specific parameters in order to enable different hand movements.[71] The intermanual crosstalk model suggests two different motor plans, which can interact at two or more levels in the central nervous system (CNS), e.g. via intercallosal connections or uncrossed corticospinal fibres. Both of the above models have their shortcomings, as pointed out by Cardoso de Oliveira (2002).[70] Assuming that hand-specific parameters control the movements of each hand derived from a common motor plan, the GMP does not explain the shifting degree of coordination between the two hands, which should be more static when hand-specific parameters are regulated isolated for each hand. Intermanual crosstalk on the other hand, fails to explain the close coupling between the hands, as observed in the transition of a movement from anti-phase to in-phase when frequency increases.[71] Both models share a hierarchical structure and are not mutually exclusive. A non-hierarchical model to explain bimanual coordination is the dynamic systems approach, which assumes different neural networks with mutual influence. In this approach “coordinative structures”, such as muscles can be regulated as a unit, making movements economical by reducing the possible degrees of freedom, but at the same time providing enough flexibility for adaptions to the task and the environment.[70] None of the three models mentioned can fully explain bimanual coordination, but it is obvious that motor actions of one hand influence the other, and that this influence might be exploited therapeutically.

In the case of case of stroke it is not the task or the environment that sets the constraint, but the paresis. Stroke seems to provoke adaptive processes, approximating peak velocities and movement trajectories, bringing speed and path of motion of both hands closer to each other.[72] When comparing unimanual and bimanual tasks, the paretic UE is found to influence the non-paretic UE in bimanual tasks. The movement time of the non-paretic hand is prolonged in bimanual tasks, which gives the impression that the paretic UE inhibits the non-paretic.[73]

Also facilitating effects of the non-paretic on the paretic UE have been observed in a study using bimanual aiming tasks. Here, patients had to strike two different targets with their paretic and non-paretic arm. Increased peak velocity of the paretic UE and a tendency towards synchronization of the movements made both hands reaching the targets simultaneously in many of the trials.[72] It is suggested to analyze wether inter-limb coupling is preserved after stroke in order to integrate facilitating bimanual exercises in the treatment. Lesion-induced asymmetry may be balanced by changing environmental conditions, such as loading the non-paretic arm.[74, 75]

Knowledge about how patients with paresis of an UE may benefit from coupling mechanisms between the two arms is still very limited. Relatively simple movements, such as flexion and extension of the elbow, wrist flexion and extension, pushing and pulling handles, or symmetric aiming tasks are usually investigated in bimanual training protocols.[72, 76-78] Daily life activities mainly consist of complex complementary tasks, where the dominant hand normally manipulates, while the other, usually the non-dominant, stabilizes.[79] While it may be helpful to use principles of intermanual coupling to facilitate simple movements, complex skilled activities are based on overcoming these restraining patterns.[80] The skills of a mechanic or an expert piano player depend on the independent use of each hand. It is possible that exploiting synchronization tendencies based on innate motor programs could be beneficial for severely impaired patients with very limited arm motor abilities. Patients with moderate to mild paresis on the other hand may not benefit from such training in the same way.

Examples of bimanual approaches

Bimanual approaches aim to exploit coupling mechanisms and rebalance interhemispheric inhibition and facilitation. In several small scale studies and one large RCT Bilateral arm training with auditory cueing (BATRAC) was investigated. In this approach the patients use a device with two handles that are pushed and pulled in a transverse plane cued by auditory signals. Six weeks of training with BATRAC was found to improve strength and arm motor function.[77] However, in a subsequent study with 21 participants improvement was only found in some patients who also showed signs of cortical reorganization as assessed by functional magnetic resonance imaging (fMRI).[81] Replication with a condensed protocol could not corroborate an improvement in arm motor function.[82] In an RCT with 111 chronic patients where BATRAC was compared to dose-matched therapeutic exercises similar improvements were found in both groups.[78] An fMRI study with a subgroup of the participants suggested a difference in the reorganization patterns in the BATRAC group.

Another approach, called active and passive bilateral training (APBT), combines active wrist movements of the non-paretic arm with passive wrist movements of the paretic arm with the expectation of activating homologous muscles. A pilot study implied a beneficial effect on affected arm motor function for some patients. Improvement in these patients correlated with a decrease in cortical maps on the contralesional side, as derived from transcranial magnetic stimulation (TMS) evoked potentials, which was interpreted as a restoration of balance between the hemispheres. [76] When APBT was applied to prime the motor system prior to other arm training and compared to a group only receiving arm training, no difference on arm motor function was found immediately after the intervention; however a beneficial long-term effect was shown in patients in the chronic phase post stroke. [83] Studies combining robot-assisted training with bimanual training suggest an improvement in strength and arm motor function, but transfer to activities of daily living could not be demonstrated. [84]

To date the largest comparison study of bilateral and unilateral arm training (n = 106) by Morris et al. (2008) is also one of the few studies where subacute patients (2-4 weeks post onset) trained on function related tasks, such as placing pegs and lifting a glass to the mouth. The patients trained either by using both hands symmetrically or the paretic hand only. The authors found no superiority of bilateral training on arm function as assessed using ARAT, but rather an advantage for unilateral training with regard to dexterity as assessed by the Nine Hole Peg Test (NHPT) and a dexterity subscale of the ARAT. There were no differences with regard to initial severity of paresis either.[85] As the authors themselves state, performing functional tasks in a simultaneous manner by both hands may be somewhat artificial, since those tasks are preferably performed unilaterally or in a bimanual complementary manner.

Impairment-oriented training is not based on bimanual interactions, but does focus on the training of the affected arm without any restraint of the non-affected. It comprises two different approaches according to the severity of paresis. Arm Basis training for patients with severe arm paresis is based on regaining motor control in successive stages, starting with repetitive single joint movements without weight bearing and advancing to multi-joint movements including postural control. The second approach, Arm Ability Training, comprises advanced functional activities and is targeted at patients with mild arm paresis, who lack speed and precision. Similarly to CIMT, repetitive and varied training with different levels of difficulty is a key concept. Studies have demonstrated promising results.[86, 87]

Several systematic reviews on the efficacy of bimanual training have been published during the last years. These have revealed ambiguous results and varying quality of methodology of the studies that were included. A Cochrane review by Coupar et al. (2010) could not confirm any superiority of simultaneous bilateral training compared to other rehabilitation or placebo. The authors note the poor methodological quality, such as lack of proper randomization procedures and lack of control groups.[88] These conclusions are in contrast to other reviews by Cauraugh et al. (2010), and Summers et al. (2006) where the authors found support for bimanual training when compared to different control treatments including standard care.[89, 90] Some evidence for improvement of arm motor function in patients with chronic stroke was found by Latimer et al. (2010), but the studies included were mostly cohort studies without adequate control intervention.[91] The most recent review by van Delden et al. (2012), which only included RCTs, compared unimanual with simultaneous bimanual training and similarly to Coupar et al. found no superiority of bimanual training.[92] Interestingly, the authors looked at subgroups classified by severity of paresis and time post stroke and, in the chronic phase post stroke, found a marginally positive effect for unilateral training CIMT and mCIMT for patients with mild paresis.

All in all, the results of different studies and systematic reviews are inconclusive. Both unimanual and bimanual training seem to improve arm motor function, the challenge is to identify subgroups that may benefit more from one or other of the approaches. Reliable comparisons are only possible when experimental and control groups receive dose-matched training.

1.4.3 Action observation and mental practice

Mirror neurons

In studies with macaques using single neuron recordings it was demonstrated that there are neurons in the premotor cortex area F5 that discharge not only when the monkey executes an action but also when it observes an action. These so-called mirror neurons constitute an overlap of the visual system and the motor system. The term mirror neurons or mirror neuron system does not describe a separate entity, but rather a "mechanism intrinsic to most motor-related cortical areas".[93] Seminal studies by Rizzolatti, Gallesi and others revealed that mirror neurons not only reflect the actions of others, but that they are able to interpret and add missing parts of actions, provided that they are familiar with the observed action or have enough clues to deduce the intention. [94-97]

After the discovery of neurons with mirror properties in macaques it seemed natural to look for similar mechanisms in humans. Evidence for the existence of neurons with mirror properties in humans has derived from electrophysiological studies using magnet encephalography (MEG) and transcranial magnetic stimulation (TMS).[98] Subsequent neuroimaging studies applying functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) allowed a more exact spatial localization of neural circuits responding to both movement execution and observation and even showed a roughly somatotopic organization.[99, 100] According to a recent meta-analysis the following brain regions are consistently found to respond to the observation and execution of movements in humans: The inferior and superior parietal lobe, inferior frontal gyrus and the dorsal and ventral premotor cortex.[101] This network, the parietofrontal mirror system, is involved in the recognition of motor acts, and is assumed to provide the neurobiological basis for imitation learning and action understanding. Other mirror systems are suggested for the recognition of emotions.[102]

Some key features for the activation of neural systems with both visual and motor properties have been identified in studies with healthy participants. Recognizing an action as part of our own motor repertoire makes understanding and interpretation easier and causes a stronger activation of cortical areas than watching unfamiliar actions.[103] Nevertheless the mirror neuron system seems to play an important role in imitation learning of novel movements. Some studies found a stronger activation for unpractised compared to practised movements in early stages of the learning process. [104, 105]

Observing or imagining an action involves creating a mental representation and activating a "vocabulary of acts" as Rizzolatti called it. [98] These mental representations may provide a pathway to the rehabilitation of motor function after stroke when the execution of motor acts is impaired.

Action observation and mental practice as treatment approaches for stroke

Jeannerod's "Simulation hypothesis" claims that movement execution, motor imagery and action observation are all driven by the same basic mechanism. Motor imagery and action observation are conceived as "offline" operations. [106] The last decade has seen much interest in the possible benefit of neurons with mirror properties within neurorehabilitation. Motor imagery (MI), also called mental practice, and action observation (AO) have been suggested as a means of rehabilitation by several authors. [107-109]

In MI, patients are usually prompted to mentally rehearse motor actions, sometimes accompanied by auditory and visual cues. [110] In AO studies, patients watch motor actions, often daily life activities, viewed on a DVD. [107, 111] Both approaches can be applied in motor rehabilitation after stroke as preparation for active exercises for patients with severe paresis, or as an adjunct to conventional therapy for patients who are capable of active movement. According to a meta-analysis of 6 studies with 119 patients some benefit in favour of MI was suggested when combined with physical training [112], while a recent larger RCT failed to corroborate a therapeutic benefit of MI when applied solely. [110] The application of MI in a research context has disadvantages, as there is no control of what patients actually do, and the ability to imagine motor acts could be impaired as a result of the brain damage. [113, 114]

Action observation, where patients watch video clips of different arm movements has been tried out in several small scale studies with patients in the chronic phase, [111, 115, 116] and in a recent large study with patients in the subacute phase post stroke. [107] In the latter study, patients (n = 102) watched video clips of daily life hand actions, and subsequently tried to execute the same activities with the affected arm. The experimental group experienced larger improvement of arm motor function than a control group receiving the same amount of arm training and sham AO. Further research on mirror neurons and on the potential benefit of mirror neuron based treatment for different groups of patients appears worthwhile.

1.4.4 Technology-based arm rehabilitation

Virtual reality and robotics

Several virtual-reality and robot-assisted training systems have been introduced to rehabilitation, promising to improve strength, endurance and motor function, while at the same time maintaining motivation and providing entertainment. Those systems offer advantages such as the possibility of increasing dose and intensity of therapy and enhancing the motivation of patients by adding a playful element. [117] Furthermore, many systems allow stepwise adaptation to increasing motor abilities, thus maintaining the challenging character of the tasks while offering different forms of feedback. Various systems employing virtual reality technology have been developed during the last years, from virtual shopping malls to adapted, commercially-available gaming systems, and virtual reality systems based on activating the mirror neuron system. [118-120] Several studies support the application of virtual reality methods to upper limb rehabilitation, but large-scale clinical evidence is still lacking for the superiority of these methods compared to traditional rehabilitation as reviewed by Laver et al. (2011) and Henderson et al. (2007). [121, 122]

Robot-assisted treatment systems also provide the possibility of enhancing the intensity of training and at the same time provide assistance when the patient is not able, or only partially able, to perform a movement. They are often applied in combination with virtual reality. Several devices have been developed, with various degrees of freedom, some emphasising shoulder and elbow movements, others wrist and finger or whole arm movements. [123-125] Robotic devices can be divided into exoskeleton devices which are placed on the patient's arm and hand, inducing movement directly to the corresponding joints in defined degrees of freedom; and end-effector based robots, e.g. gloves with sensors, which allow the patient to choose a movement strategy, while often offering some support against gravity. [123]

Especially interesting with regard to motor relearning after stroke appear to be interactive systems which can provide support when needed and can interact with the patient's actions. Some systems are limited to simple movements, such as wrist flexion/extension, while others train more complex movements similar to daily life activities. What may benefit the individual patient depends on his/her motor and cognitive function. Other crucial factors are the simplicity of the appliance and the variety of tasks offered, e.g. the degree to which they can be individually tailored. Timmermans et al. (2009) provide some evidence derived from motor learning research that may help both designers and clinicians to gauge the possible benefit of technology-based rehabilitation systems. [125]

Generally speaking the results from different studies applying technology-based arm rehabilitation are promising, but many devices are still to be evaluated in RCTs.

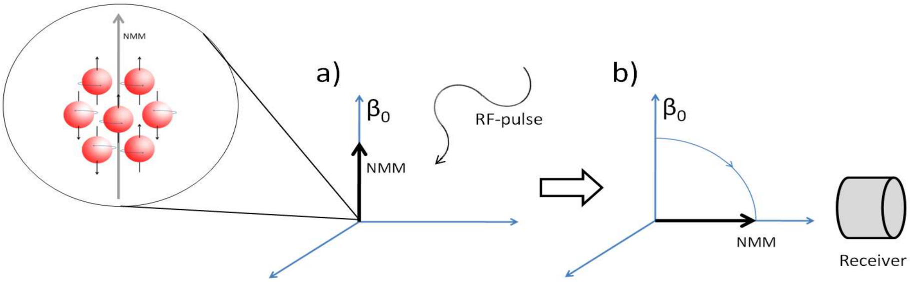
1.5 NEUROIMAGING IN STROKE RECOVERY

1.5.1 Some basics

Neuroimaging techniques have become a widely used method of studying the brain in health and disease and can provide fascinating insights into plasticity. A plethora of studies investigating brain reorganization after stroke has emerged during the last two decades, but it is still not common to transfer results from brain imaging studies into clinical practice. [126, 127] This is partly because the patterns of reorganization vary, and partly because it is difficult to interpret them. There are several non-invasive methods to study plasticity in brain function following stroke, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), electroencephalography (EEG), transcranial magnetic stimulation (TMS), and magnetoencephalography (MEG), to name some of the most important. Each technique has advantages and disadvantages. While fMRI and PET are superior with regard to spatial resolution and allow an exact localization in the range of millimeters, EEG and TMS are superior in terms of temporal resolution, reflecting brain processes in fractions of seconds. [126] The following paragraph concentrates on studies where fMRI was applied, because this method was used in this thesis.

When patients with stroke are admitted to hospital, MRI is a standard diagnostic tool to determine the location and the extent of the infarction. Functional MRI is usually applied in research only to study functional changes. The basic signal origin is the same for all MRI images, namely that it is the magnetic properties of protons in hydrogen atoms attached to water molecules that are probed. Protons are positively charged and have an intrinsic property called spin. When exposed to a strong magnetic field, such as in an MRI bore (typical clinical field strengths of 1.5 or 3 Tesla), the protons align with the field around them due to the spin and set up themselves an internal magnetic field.

A second external magnetic field is then applied for a brief time, hence the name radio frequency pulse, to manipulate (excite) the internal magnetic field that the protons set up. Immediately after the pulse excitation, the protons will relax from this excited energy state back to the original energy state. In doing so, an electric signal can be measured that is caught by a receiver and can be translated into an image. The strength of the measured signal is tissue dependent due to differences in the relaxation process of the protons in various tissues. To describe these differences mathematically, two timing constants T1 and T2 are defined. It is because T1 and T2 differ between tissues, i.e. gray matter versus white matter in the brain, and between healthy tissues various disease conditions, i.e. infarctions, tumors, inflammation, that has allowed MRI to have a tremendous impact on clinical diagnostics and research. Although the T1 and T2 timing constants can be measured for each tissue, it is more common to report on for instance "T1weighted images", i.e. images that emphasize the T1 properties of the tissue. Two additional time constants, the echo time (TE) and the repletion time (TR) are used to determine the degree of T1- or T2 weighting the resulting image will have. This is why TE and TR are reported in imaging studies to describe the experimental setting rather than T1 or T2.



a) Protons are aligned with the external magnetic field (β0), and set up an internal field (NMM)to which a radiofrequency pulse (RF) is applied b) After the application of the radio frequency pulse, an electric signal can be measured by the receiver

Figure 1. Signal generation in MRI. Illustration by M. Ystad, with permission. [128]

Functional MRI is an indirect measure of neural activity. [126] It is based on differences in the magnetic properties of blood in the capillary vessels in the brain, the so- called blood oxygenation level dependent contrast (BOLD), that is imaged. [129] Neuronal activity in the brain requires oxygen which is attached to hemoglobin and transported by red blood cells. Oxygenated and de-oxygenated hemoglobin have different magnetic properties, oxygenated hemoglobin is diamagnetic, i.e. with masked magnetic properties, while de-oxygenated hemoglobin is paramagnetic, i.e. the magnetic properties are emphasized. The firing of neurons in a particular brain region causes an increased level of oxygenated hemoglobin in the draining parts of the capillaries, since more oxygenated blood is supplied than needed. Thus, the BOLD signal is an expression of the balance between the two forms of hemoglobin and echoes the increased consumption of oxygen in certain brain regions. Since BOLD signal differences are very small (1-5%) during behavioural or mental tasks, many repetitions are required. Functional MRI provides valuable insights into the involvement of brain regions and neural networks in neural processes both in healthy persons and persons with neurological disorders.

1.5.2 Functional MRI and motor recovery after stroke

Functional MRI enables researchers to observe neuroplasticity in a much more direct way than would be possible using clinical parameters alone. The term neural plasticity describes the ability of the central nervous system to change and adapt as a response to environmental changes, learning processes or disease throughout life. [130] This ability can be ascribed to diffused networks and redundant connectivity that allow the brain to remap and restructure according to changed conditions, at least to a certain degree. Stroke and other brain injuries induce reorganization processes through which the brain attempts to compensate for loss of function. Reorganization happens spontaneously, but can also be influenced or facilitated by rehabilitative treatment. [130, 131] The degree of function regained can vary greatly, depending on the severity of the initial paresis, time post stroke, lesion location and integrity of the cortico-spinal tract, to name the most important factors. [132, 133] Nevertheless, three principal mechanisms have been identified as described by Johansen-Berg (2010): 1) Changes within primary motor areas, which means a shift to dorsal or ventral within M1 when moving an affected limb, 2) increased recruitment of secondary motor areas, such as the supplementary motor area (SMA), premotor cortex (PMC) and parietal areas, and 3) an increased activation of different areas of the undamaged hemisphere. [126]

Longitudinal fMRI studies provide interesting insights into how task-dependent activation patterns may change over time after stroke. The involvement of the contralesional hemisphere has been a matter of debate, but there is some agreement that better outcome is associated with greater activation in the ipsilesional hemisphere during movement of the paretic UE. [126, 134] The laterality index is an expression for the degree of unilateral or bilateral hemispheric involvement when performing unimanual motor tasks with the affected arm. A higher laterality index reflects less bihemispheric involvement, and a more normal activation. Ward et al. (2003) studied task-related activation in 8 patients without damage to the primary motor area (M1) and 4 control subjects. When performing a motor task, the related activation in relevant motor areas of both hemispheres decreased over time proportional to an improvement of motor function. [135] A cross-sectional study by the same authors that included 20 patients > 3 months post stroke and 26 control subjects revealed an increased task-related recruitment of bilateral brain regions in patients with poor recovery compared to patients with good recovery, who showed a more lateralized, ipsilesional activation. [136] An increased involvement of the ipsilesional M1, but also increased activation in secondary contralesional somatosensory cortex and bilateral somatosensory association areas, was observed in well-recovered patients in a study by Askim et al. (2008). [137] The patients underwent intensive early task-related physical therapy which may have influenced the cortical reorganization process.

There is evidence for treatment-induced changes in neuroplasticity. Boyd et al. 2010 examined whether cortical reorganization is influenced by the rehabilitative training provided. [138] They compared the performance of a targeting task in two groups of patients with chronic stroke. One group received task-specific training and the other group unspecific arm training sessions between the first and the second fMRI exam. Only the task-specific training resulted in an increased laterality index, which led to the conclusion that task-specific training may prevent maladaptive changes. A review encompassing 5 fMRI studies and several other neuroimaging studies corroborated the correlation between motor improvement and plastic changes as a result of targeted treatment interventions, such as Constraint-induced movement therapy. [131]

In most fMRI studies post stroke the patients have performed active motor tasks during the fMRI exam. This implies that the subjects at least to some degree should be able to move the hemiparetic arm and excludes a larger number of patients such as patients with paralysis, or patients unable to follow instructions. Resting state fMRI provides the opportunity to investigate changes in connectivity when the patient is at rest without an imposed task. [139] Both functional connectivity, describing the temporal connection between brain regions, and functional connectivity, describing the influence different brain regions have upon each other, can be assessed.

Interesting findings suggest a correlation between intact functional and effective connectivity and motor performance. In a study by Carter et al. (2010) a significant correlation between impaired arm motor function and a loss of interhemispheric functional connectivity in acute stroke patients was found.[140] In a subsequent study by the same group it was suggested that the extent of cortico-spinal tract damage influences resting state connectivity which again is related to motor performance. [141] A correlation between corticospinal tract damage and resting state connectivity was only observed when the damage was less than 10 %. Wang et al. observed a random mode, less effective connectivity in the motor network of patients with stroke as compared to healthy controls. [142] Patients with significant motor impairments had diminished effective connectivity from fronto-parietal control regions to the motor system during the resting state as demonstrated in a study by Inman et al. (2012). [143] The researchers suggest that the loss of control of high-level control systems may contribute to impaired motor function.

These studies illustrate that a stroke can have widespread effects on several task- dependent and task-negative networks. Potential mirror neuron networks may also be influenced by stroke. Neuroimaging studies in healthy persons revealed that brain areas such as the frontal premotor cortex, the parietal cortex and a temporo-occipital network are frequently activated when executing an action and also when only observing it, [144] but there are no studies examining longitudinal changes of an execution / observation matching system in patients with stroke. This highlights the need for a better understanding of the processes occurring in neurons with mirror properties, especially when considering that promising new treatment approaches are based on the mirror neuron system. [107]

In summary it can be stated that fMRI provides a means to examine the changes stroke imposes on several activity-dependent and resting state networks. Stroke can have a widespread impact on remote brain areas and disturbs the intricate interplay of different networks. With this knowledge in mind it may be easier to understand impairments that cannot be explained by structural damage alone. At the moment it is still difficult to determine the clinical significance of the changing patterns of brain activation, but in the long term it may be possible to target rehabilitative approaches according to observed network changes. [145]

Literature study was completed 18.August 2012.

2. OBJECTIVES

The overall objective of this PhD project was to explore different aspects regarding recovery of arm function in the subacute phase post stroke. This was realized by studying patients with paresis of an arm during the first 3 months after stroke onset and assessing their eligibility for CIMT. In a randomized controlled trial two intensive training alternatives for patients with impaired arm motor function were compared. In the third study longitudinal changes of neurons with mirror properties were assessed with fMRI on the background of new treatment approaches targeting a putative mirror neuron system.

The aims of papers I - III were:

Paper I

To assess the eligibility for Constraint-induced movement therapy (CIMT) and modifications of CIMT for patients with impaired arm function in the subacute phase post stroke.

Paper II

To compare the effect of modified Constraint-induced movement therapy to task-related bimanual training for patients in the subacute phase post stroke.

Paper III

To study changes over time and response to action observation in potential mirror neurons in patients in the subacute phase post stroke.

3. METHODS

3.1 DESIGN

In all three studies a longitudinal repeated measures design was used to assess change over time. In the first and third study the change was examined within one group, in the third study the change was also compared to a non-impaired control group; while in the second study two groups were compared in a randomized controlled trial.

3.2 PARTICIPANTS

Paper I

For the first study all patients with a diagnosis of stroke admitted to Haukeland University Hospital and Haraldsplass Diaconal Hospital in Bergen, Norway between November 2008 and October 2009 were screened for inclusion. If they suffered from impaired arm motor function 1-2 weeks after stroke they were invited to participate in a series of repeated testing of arm motor function. Those patients whose medical and cognitive status did not allow motor testing during their stay at the hospital were only registered as suffering from arm paresis. A sample of 100 patients was registered, of whom 54 patients were not able to participate in the motor assessments mostly due to cognitive impairments. The remaining 46 patients were assessed 3 times during the first three months post stroke.

Paper II

For the second study comparing mCIMT to dose-matched bimanual training all patients with a diagnosis of stroke admitted to Haukeland University Hospital and Haraldsplass Diaconal Hospital in Bergen, Norway between March 2009 and June 2011 were screened for inclusion. They were offered participation in this study 2-16 weeks post stroke if they had experienced impaired arm motor function, and were medically stable and cognitively able to comply with the treatment protocol. Motor criteria applied included the ability to extend the wrist and fingers of the affected arm at least 10 degrees. After receiving written and verbal information, the patients were given at least 24 hours to consider their participation. Of 453 patients screened for inclusion 414 did not meet the inclusion criteria. From the remaining 39 patients 9 declined to participate. The thirty patients who accepted were randomized to one of the two treatment groups. All assessments were completed in 28 patients, two were drop-outs, one in each group.

Paper III

All patients admitted to the two local hospitals between July 2010 and September 2011 were screened and invited to participate in the fMRI study if they had suffered a first time stroke during the previous 15 days, were medically stable, able to give informed consent and continued to experience some degree of impaired arm motor function. Exclusion criteria were severe cognitive deficits, a former stroke (with the exception of clinically silent lacunar infarcts) and special fMRI relevant criteria, such as metal implants and claustrophobia. Of 32 patients approached, 21 consented to participate. An age and sex-matched convenience sample recruited from colleagues and using e-mail advertisements served as a control group.

Table1. Eligibility criteria for inclusion of patients and healthy controls

Paper	N	Eligibility criteria
Paper I: Recovery of upper extremity motor function post stroke with regard to eligibility for Constraint-Induced Movement Therapy	46	1) Diagnosis of stroke 2) Persistent impaired arm motor function 1-2 weeks post stroke 3) No major cognitive problems, Mini Mental State Examination less than 20 4) Medically stable 5) Able and willing to participate in motor testing
Paper II: Is modified Constraint-induced movement therapy more effective than bimanual training in improving upper extremity motor function in the subacute phase post stroke: A randomized controlled trial	30	1) First-time stroke or former stroke with no residual motor impairment 2) Between 2-16 weeks post stroke 3) At least 10 degrees wrist and finger extension, but less than 52 points on the Action Research Arm Test 4) No other orthopedic or neurological conditions that limit participation 5) No severe cognitive problems, defined by less than 24 on Mini Mental State Examination 6) Able and willing to participate
Paper III: Plasticity and response to action observation: A longitudinal fMRI study of potential mirror neurons in subacute stroke patients	18 patients	1) First-time or earlier lacunar infarct without residuals 2) Inclusion within 15 days after stroke onset 3) Impaired arm motor function compared to normative data of adults of same age and sex, assessed by Nine Hole Peg Test 4) Able to transfer with the help of one person 4) No fMRI specific contraindications 5) No major cognitive problems, defined by less than 20 on Mini Mental State Examination
	18 age- and sex-matched healthy controls	1) No history of neurological disease 2) No fMRI specific contraindications

Table 2. Baseline characteristics of the participants included in papers I – III

Paper I	**Recovery of arm motor function and eligibility for CIMT**		
	All patients N=100	Patients tested N=46	Patients not tested N=54
Age (y), mean (SD)	72.2 (13.5)	69.4 (15.4)	78.4 (10.2)
Sex, male / female, n	63 / 37	29 / 17	34 / 20
Side of paresis, right / left, n	58 / 42	28 / 18	30 / 24
Paper II	**Modified CIMT compared to bimanual training**		
	All patients N = 30	mCIMT N= 14	Bimanual training N=16
Age (y), mean (SD)	63.0 (11.6)	61.0 (10.0)	64.8 (12.8)
Sex; male / female, n (%)	19 (63.3) /11 (36.7)	11(78.6) /3(21.4)	8 (50.0) / 8 (50.0)
Side of paresis right / left, n (%)	12 (40.0) / 18 (60.0)	6 (42.9) / 8 (57.1)	6 (37.5) / 10 (62.5)
Type of stroke infarction / haemorrhage, n (%)	25 (83.3)/ 5 (16.7)	13 (92.9)/ 1 (7.1)	12 (75.0)/ 4 (25.0)
Time between stroke and intervention in days, mean (SD)	43.7 (33.8)	48.43 (39.3)	36.9 (25.1)
Paper III	**Response to action observation**		
	Patients N = 18	Healthy participants N = 18	
Age (y), mean (SD)	60.7 (11.6)	60.6 (11.9)	
Sex Male / female, n (%)	12 (67) / 6 (33)	11 (61) / 7 (39)	
Side of paresis Right /left,n, n (%)	6 (33) / 12 (67)		
Type of stroke Subcortical / cortical	14 (78) / 4 (22)		
Time between stroke and 1rst scan in days, mean (SD)	8.9 (4.1)		

3.3 PROCEDURES

3.3.1 Procedures paper I

All patients admitted with a diagnosis of stroke as confirmed by CT or MRI were screened and asked to participate in motor testing if they continued to experience impaired arm motor function 1-2 weeks after stroke. This limit was set to exclude patients with most spontaneous recovery, who would not need further rehabilitation. The first assessment usually took place at the hospital, with a few exceptions when the patient had already been discharged and was followed by an ambulatory team, or had been transferred to a rehabilitation unit. The second and third assessment took place at an outpatient clinic or a rehabilitation unit or the patient's home, depending on the whereabouts of the patient. The test equipment was easily portable. To limit travelling time and costs only patients living in the municipality of Bergen or in surrounding municipalities within 30 km distance were included. The patients were first assessed with the Action Research Arm Test and then with the Nine Hole Peg Test, the same sequence at each test session. The presence or absence of cognitive problems was evaluated with the Mini Mental State Examination; unless more comprehensive neuropsychological testing had already been conducted.

3.3.2 Procedures paper II

Patients 2-16 weeks post stroke and fulfilling the inclusion criteria as described in 3.2 were offered participation. Blinded assessments were conducted pre-treatment, post-treatment and 3 months after treatment by experienced physiotherapists or occupational therapists. After the first assessment the patients were randomized to one of two groups, modified Constraint-induced movement therapy or bimanual training. Randomization was achieved by a computerized random numbers generator. Blocks of 4 were chosen to facilitate an even distribution to the treatment alternatives. Opaque, sealed envelopes were prepared by a person not involved in the study. The treatment started as soon as possible after inclusion, usually on the next working day. This RCT has been registered at ClinicalTrials.gov, identification number NCT 00851123.

Common features of the treatment in both groups

The intervention was intended to provide an intensive training programme that is easily applicable at different levels of the health care system. Therapist contact regarding functional arm training was 4 hours / week. The patients received other necessary rehabilitation according to their individual needs. Key concepts applied to both groups were derived from motor learning and CIMT principles, namely massed practice and shaping.[44, 146] To achieve sufficient intensity, despite the limited therapist contact both treatment groups were supposed to follow an individually tailored self-training programme and use the affected arm at least 2-3 hours a day. The exercises were adapted to the patients' increasing motor abilities at least 3 times during the intervention. When possible, daily life activities were proposed in the exercises, but strength and mobilization exercises were also included. The self-training programme consisted mainly of domestic chores and personal care, since these activities are relevant for everybody. According to the patient's interests and needs office work and leisure activities were also trained, e.g. drilling and screwing. The written exercises usually comprised different difficulty levels according to shaping principles. [44] Difficulty could be increased by e.g. using smaller or heavier objects, placing objects further away or higher up, or increasing speed or number of repetitions. Behavioural enforcements derived from the CIMT concept [147] to increase adherence and compliance were also applied to both groups, and comprised the following elements:

- Contract: A formal contract describing briefly the content of the intervention had to be signed by the patient and the therapist. The patient had to formulate 2-3 specific goals for the training. The contract is intended to increase the patient's awareness of the expected role as an active participant in his/her own rehabilitation. Table 3 shows an English translation of the main points used in both groups, the points only applicable for the mCIMT are indicated in parenthesis.

Contract on intensive bimanual training / modified Constraint-induced movement therapy

What the training comprises

- The training will be offered for a period of 4 weeks. It is important that you do your home exercises for several hours every day during this time.
- You will receive training for your arm with a therapist for 4 hours / week as well as a written self-training programme. The training will be adapted to your motor abilities
- You are asked to exercise 2-3 hours daily on your own, including week-ends.
- You will be given a log book to write down how many hours you spend exercising.
- You will be given a log book to write down how many hours you spend exercising and how many hours you wear the mitt. (mCIMT group)
- You will be tested once before the training starts and once afterwards, and a final time three months after completion of the training.

I,…(name)…., want to participate in the bimanual / mCIMT training. I agree to exercise for 2-3 hours every day. I am aware that adherence to the training schedule is important for the result.

I want to achieve the following goals:

…………………………………………………………………………………………..

………………………   …………………………..   ……………….

Date   Signature patient   Signature therapist

- A log book was used in which the patients had to write down the hours spent exercising, which encompassed the use of the affected arm in daily life activities. The log book could also be used to express positive or negative experiences with the training. It was regularly checked by the therapist to remind the patient of the importance to use his/her affected arm and to discuss possible obstacles.

Special features of the mCIMT training

The main difference between the two groups was restraint of the less affected arm in the mCIMT group. Patients randomized to mCIMT training were expected to wear a mitt on the less affected hand for at least 4 hours a day. The patients could choose when they wore the mitt, but were requested to wear it during periods of activity. The therapist provided suggestions of relevant daily life activities, which were tried out and modified if necessary. The focus was on unimanual exercises with the affected arm, both when training with a therapist or in the self-training programme.

Some examples:

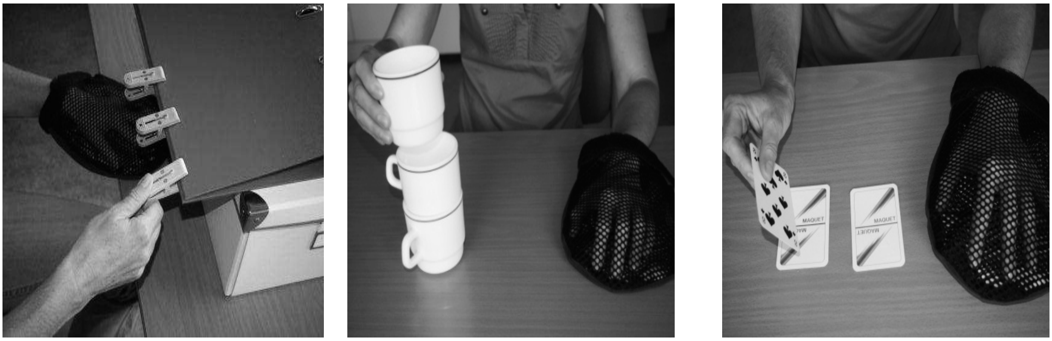


Figure 2. Different tasks used in mCIMT training

Special features of the bimanual training

Training in the bimanual group focused more on exercises where both arms were used in a natural context and no restraining mitt was worn. Because the patients included had moderate to mild arm paresis, simple repetitive bimanual movements did not seem adequate and a task-related approach was chosen. Typical exercises included symmetrical bimanual movements such as catching and pitching a ball, lifting objects, and pushing and pulling. Asymmetrical movements included exercises such as unscrewing a lid, where the non-dominant hand stabilizes the object and the dominant hand manipulates the lid. The patients were especially reminded of the importance of not letting the less-affected arm compensate too much for the weaker arm.

Some examples:

Figure 3. Different tasks used in bimanual training

3.3.3 Procedures paper III

The healthy control participants were invited to a single fMRI exam. The patients were examined twice, the first time within 15 days after stroke onset, and the second time after 3 months when a plateau of motor improvement is expected. [14] They received standard rehabilitation except for one patient, who also participated in the second study with intensive arm training. The participants were familiarized with the fMRI protocol and the objects used during the exam outside the scanner. The same protocol was applied to all patients on both occasions and to the healthy participants once. The patients underwent motor assessment using the Action Research Arm Test and Nine Hole Peg Test. The fMRI paradigm consisted of 3 different motor tasks, a resting state fMRI and an action observation sequence. For the motor and action observation conditions a block design was applied. Each active and rest block lasted for 30 seconds and was repeated 4 times.

The motor tasks comprised the following conditions:
1. Right vs. left: The participants had to squeeze a balloon alternately with the left and the right hand
2. Affected vs. rest for the patients or dominant vs. rest for healthy controls: The balloon had to be squeezed with the affected or dominant side respectively, interleaved with periods of rest
3. Bimanual vs. rest: A cylindrical device had to be twisted, interleaved with periods of rest.

During the action observation condition the patients watched a pair of hands executing the same bimanual task that they had performed earlier. The video-clip showed alternately movement and stills, where the hands were only holding the device. The patients were instructed to watch carefully, but not to move actively, which was ensured by visual inspection. The action observation sequence was embedded in two resting state blocks. The unilateral movement and resting state data are not part of this thesis.

3.4 OUTCOME MEASURES PAPERS I - III

Outcome measures in papers I and II were all related to the assessment of arm motor function, since this was the main and only focus in these studies. In paper III also fMRI was applied.

The Action Research Arm Test (ARAT) is one of the most commonly applied assessment tools internationally for motor function of the whole arm after CNS damage. [148] The ARAT was the main outcome of papers I and II. It was developed by Lyle (1981) based on the Upper Extremity Function Test by Carroll (1965). [149] It consists of 19 items, structured in 4 sub-tests to assess both proximal and distal arm motor function. The items are related to activities of daily living. The hierarchical structure of the ARAT allows skipping of some of the items if a person has quite good or very poor motor function, thus making the test procedure less burdensome for the patient and time-saving for the therapist. Test-retest and inter-rater reliability have been found to be very high for patients in the chronic and subacute phase after stroke, ICC and Spearman's rho > 0.95. [150, 151] Criterion validity and face validity was demonstrated by high correlation with the Fugl-Meyer Motor Assessment and Box and Blocks test, Spearman's rho > 0.92 [151] and Motor assessment scale (MAS) > 0.96 [152]. A minimal clinically important change (MIC) is reported to be 5.7 (10 %) on the 0-57 point scale for patients in the chronic or sub-acute phase post stroke. [153] For patients very early after a stroke (< 2 weeks) a higher MIC has been recommended, since larger changes are expected to happen in this phase. [154]. The ARAT covers a broad range of difficulty levels but has shown some floor and ceiling effects. [151, 155]

The Nine Hole Peg Test (NHPT) is a timed measure where the patient has to place 9 pegs into holes and remove them again. Scores are expressed as pegs / second or pegs / minute. The NHPT is used to assess manual dexterity at a relatively high level and can detect further improvement of manual dexterity in patients who obtained a maximum score on ARAT. Psychometric properties have been reported to be good to satisfactory in a review study by Croarkin et al. (2004). [156] Test-retest reliability for patients in the subacute and chronic phase after stroke was found to be very high, ICC > 0.85. [157] Responsiveness to change has been indicated in a study of stroke patients.

[158] Normative data for different age groups have been established, which makes a comparison between patients and age-matched healthy persons possible. [159]

The Motor Activity Log (MAL) reflects the patient's own experience of the use of the affected arm. This questionnaire is a structured interview where the patient is asked to report his / her impression of the amount of use and the quality of use of the affected arm on a 5 point scale when performing 30 different daily life activities. The psychometric properties have been considered satisfactory with regard to internal consistency, alpha > 0.88, and construct validity when correlated with ARAT, Spearman's rho = 0.63. [160] A revised version omitting two of the 30 items has demonstrated high reliability, r = 0.82 and construct validity, 0.72. The correlation with accelerometry was moderate, r = 0.52. [161]

3.5 STATISTICAL ANALYSES

SPSS 19 (SPSS, Inc, Chicago, Illinois) was used for analysing the data from the clinical assessments in all three papers. Statistical Parametrical Mapping (SPM8) analysis software package (Wellcome Department of Cognitive Neurology) running under MATLAB 7.7 (Mathworks) was used for statistical analysis and preprocessing of the fMRI data in paper III.

3.5.1 Statistical analyses paper I

Descriptive statistics were used to describe baseline characteristics and the status of arm motor function at baseline, after 4 weeks and after 3 months. Baseline characteristics were compared between the patients who were able to participate in motor assessments and the patients who were not, using Chi-square tests for categorical data (sex, side of lesion) and independent samples t-test for ratio data (age). ARAT scores were categorized into three severity subgroups, and the proportion of patients belonging to each subgroup at different points in time was graphically depicted in error bars, showing confidence interval and mean. To illustrate the flow of patients from one subgroup to another during the time course of recovery, frequencies of ARAT scores within the subgroups at each point in time were counted and also graphically depicted. A general assessment of change was performed with paired t-tests for ARAT scores and NHPT scores.

3.5.2 Statistical analyses paper II

Descriptive statistics were used to describe patient characteristics. Differences at baseline between patients randomized to the mCIMT group or bimanual training group were examined by chi-square tests for categorical data and independent samples *t*-tests for continuous data. Normal distribution and homogeneity of variance was explored. Analysis of covariance (ANCOVA) is an extension of t-tests comparing the ratio of within group variability to between group variability and taking into account the influence of covariates. [162] ANCOVA was applied to examine differences between the groups at post treatment and at follow-up assessment after adjusting for the influence of baseline scores on ARAT and NHPT as a covariate. As there were two drop-outs, one in each group, intention to treat analysis was conducted for ARAT and NHPT data: Both drop-outs occurred shortly after inclusion, therefore the mean change at post treatment and follow-up in the respective group was added to the baseline to conduct an intention to treat analysis (ITT). ITT was compared to per protocol analysis (ANCOVA) with actually available data to examine possible differences of p-values.

3.5.3 Statistical analyses paper III

Due to the small sample size, non-parametric statistics were applied for the clinical assessments. Clinical change in ARAT and NHPT scores of the patient group from first to second exam was examined by Wilcoxon signed rank tests. Functional MRI pre-processing included several processes that prepare the raw data from the scanner for statistical analyses. Slice-timing corrections were performed because all slices of a volume were acquired at slightly different time points. Data were normalized to a Montreal Neurological Institute (MNI) template to allow group comparisons. Smoothing to average of data points with their neighbours to improve the signal to noise ratio (SNR) and thereby sensitivity was performed. General linear modelling was applied using a fixed-effect model for individual patients and a random-effect based on individual analyses for group analysis. Voxel-wise t-statistic was used for each individual to determine areas with statistically significant activation. Change within group was assessed using a one-sample t-test with a significance level of $p < 0.001$ and a minimum spatial extent of 30 voxels. Differences between groups were examined with two-sample t-tests with an uncorrected significance level of $p<0.001$.

4. SUMMARY OF RESULTS

4.1 PAPER I

Recovery of upper extremity motor function with regard to eligibility for Constraint-induced movement therapy (CIMT)

Of a total of 100 patients more than half were considered ineligible for CIMT early after stroke, mostly due to cognitive problems. Upper extremity motor function in the 46 patients studied over time improved considerably from the first assessment 1-2 weeks after stroke (T1) to the last assessment 3 months after stroke (T3). Scores for the Action Research Arm Test (ARAT) increased from a mean score of 25.2 (*SD* 21.5) at T1 to 38.0 (*SD* 24.7) at T3, $p < .001$. The number of patients eligible for CIMT, defined as the ability to extend the wrist and 3 fingers at least 10 degrees as a lower limit, and an ARAT of more than 51 as an upper limit, decreased during the course of the first 3 months. While 21 of the 46 patients assessed at T1 would have met the motor criteria, the number decreased to 14 at T2 (4 weeks after stroke) and further to 6 at T3 (3 months after stroke). A top score on ARAT was reached by 18 (45 %) of the patients at T3, and another 6 patients (15 %) reached a score of more than 51, implying reasonable motor function. After 3 months only 6 patients who would have been considered eligible remained. Notably, 3 of these patients who had not met the motor criteria at T2, 4 weeks after stroke, thus regained sufficient arm motor function to participate in CIMT relatively late after stroke. All patients received standard rehabilitation, comprising physical and occupational therapy.

The results suggest that many patients reach satisfactory motor function without special interventions, under the prerequisite that comprehensive standard rehabilitation is provided. CIMT may preferably be offered after the first month if pronounced motor impairments persist. Some patients with initially poor motor function will only at a later stage in recovery acquire sufficient arm motor function to participate in CIMT or other forms of intensive task-related training and many patients have to be excluded due to cognitive problems.

4.2 PAPER II

Is modified constraint-induced movement therapy more effective than bimanual training in improving arm motor function in the subacute phase post stroke?

Thirty patients 2 – 16 weeks post stroke were randomized to 4 weeks of mCIMT or bimanual training. Patients in the mCIMT group had to wear a mitt on the less affected arm for 4 hours a day and focussed on unimanual training, while patients in the bimanual training group were only cognitively stimulated to include their affected arm and focussed on bimanual training. Patients in both groups improved considerably, $p < .001$. However, no difference between the groups could be found at post-treatment or at follow up assessment after three months. The change score on ARAT, which was the main outcome measure, from pre-treatment to follow-up assessment was 17.77 (14.66) in the mCIMT group and 15.47 (13.59) in the bimanual training group, $p = .891$. The difference was not statistically significant, but there was a tendency toward more improvement at post-treatment in the bimanual group, which was evened out at follow-up assessment.

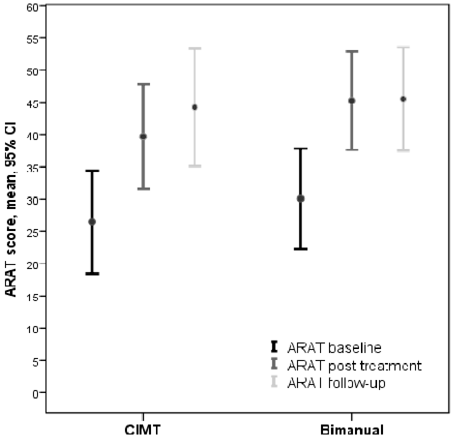


Figure 4. Error bars depicting mean scores and SD on Action Research Arm Test (ARAT) for both groups at pre-, post- and follow-up assessment.

Twelve patients showed clinically significant improvement (> 5.7 on ARAT) in each group, being 92 % of the mCIMT group and 80 % of the bimanual training group. This improvement could be maintained in 10 patients in each group at follow-up assessment, being 77 % of the mCIMT and 67 % of the bimanual group. No differences were found for the NHPT or the MAL.

According to a power calculation, a total of 60 patients had to be included. Due to problems with patient recruitment and a prolonged project period, an interims-analysis was conducted. Because only minor differences between the groups were demonstrated, the study was terminated prematurely. Bimanual training was comparable effective as mCIMT in improving arm motor function in patients in the subacute phase post stroke, although we cannot know how much the patients would have improved without such intensive training.. Wearing a physical restraint does not seem necessary when patients are able to consciously involve the affected arm in exercises and daily life activities.

4.3 PAPER III

Plasticity and response to action observation: A longitudinal fMRI study of potential mirror neurons in patients with subacute stroke

In this study longitudinal changes of potential mirror neurons in 18 patients with impaired arm function in the subacute phase post stroke were assessed twice using fMRI; the first time within two weeks, and the second time 3 months post onset. Arm motor function was evaluated on both occasions with the ARAT and the NHPT. Functional MRI data from patients were compared to data from 18 age- and sex-matched neurologically healthy participants undergoing the same fMRI protocol.

The action observation condition, in which patients watched the same bimanual movement that they had executed earlier, elicited activations in several areas associated with the mirror neuron system. Distinct parietal and frontal clusters, such as BA 6 (premotor cortex), BA 4 (primary motor cortex) and BA 40 (inferior parietal lobe) were involved. The spatial extent of activated clusters was reduced early after stroke compared to 3 months after and to healthy controls. Concomitant with an extension of activated clusters, arm motor function improved.

When looking for regions that were active both when executing and when observing the bilateral movement in the respective group, most overlap for all participants was found for the inferior parietal lobe, regarded as a higher order motor area. The premotor (BA 6) and area M1 (BA 4), superior parietal lobe (BA7), associated with complex sensory integration and movement planning, and insula, associated with body awareness were also involved across conditions.

The results of this study demonstrate that potential mirror neurons are activated early and at a later stage after stroke and that they may provide a means of accessing the motor system via treatment approaches, such as action observation.

5. DISCUSSION

5.1 DISCUSSION PAPER I

5.1.1 Methodological considerations

Design

In this study a longitudinal repeated measures design was applied to study the change of arm motor function over time. This design implies that the patients serve as their own controls, but also allows the researcher to study the group as a whole [163] and, for example, to report the mean or median change for all the patients over time. In a repeated measures design it is crucial to determine meaningful time points of assessment regarding the research question of the study. In this study, the first assessment took place 1-2 weeks after stroke. This was to exclude patients with spontaneous recovery of arm motor function during the first days after onset, as CIMT would not be appropriate for this group. The other two time points, 4 weeks and 3 months after onset, were based on earlier studies on recovery of arm motor function, which demonstrated that most improvement occurs during the first month, and that a plateau is reached after 3 months. [12, 13, 15]

The 3 time points of assessment over 3 months post stroke delineate the main dimensions of recovery. However, it would have been desirable to have another assessment between 4 weeks and 3 months, for instance after 8 weeks, in order to acquire a better estimate of when the patients became eligible for CIMT. In this period the brain is still in a state of increased plasticity and rehabilitative treatments such as CIMT should be offered before the end of the 3-month period if considered appropriate. An additional assessment between 3 and 6 months would also have been interesting with regard to detecting more patients with late recovery. Although most improvement occurs early after stroke, some patients with initial poor motor function can still enhance motor function at a later stage. [21]

All patients admitted during the study period were screened for persisting deficits of arm function 1-2 weeks after stroke. Defining 1-2 weeks after stroke as the time point for the first evaluation took into account practical obstacles caused by hospital routines. It would have been preferable to set a fixed day, since most improvement occurs early after stroke and there may be pronounced functional differences between day 8 and day 13 after stroke onset. Not setting a fixed day has probably influenced the mean score of the first assessment. Unfortunately, many patients would not have been available on a fixed day due to other examinations or treatments, and we might have lost a large number of the potential participants.

Outcome measures

The measures applied, ARAT and NHPT, are reliable and valid tools for evaluating arm motor function [151, 156], and cover a broad spectrum of functional abilities from gross motor function to advanced dexterity. The ARAT has demonstrated high concurrent validity when compared to the Fugl-Meyer Test and Box and Blocks Test, thus supporting the internal validity of the construct measured. [151] Nevertheless, the ARAT comprises both a floor and a ceiling effect [151], making it difficult to differentiate between patients with very little arm motor function and, at the other end of the spectrum, between patients who have already obtained relatively good motor function. Apart from the gross motor subtest most of the subtests require at least some manual dexterity. Many items involve the ability to lift the arm to place objects on a shelf, which can be restricted by orthopaedic problems not related to hemiplegia. The applicability of the ARAT can also be compromised when patients suffer from hemiplegic shoulder pain, a common complaint at some stage after stroke. [164] In these cases a low score may not reflect real functional abilities, but an unwillingness to move the arm caused by pain. Accomplishing a top score on ARAT on the other hand, does not necessarily imply normal manual dexterity as patients can still experience limitations of fine motor skills.

The NHPT as a supplement to the ARAT allows for differentiation at a high level of arm motor function, with the additional advantage that normative data for different age groups have been published earlier. [159] It has a pronounced floor effect, since the completion requires fine motor skills. The movements required are rather stereotype, inserting and removing pegs, but nevertheless demanding for many patients with stroke. One disadvantage of the measures applied is that both reflect activity as only one aspect of the ICF domains. This was, however, considered sufficient for paper I, and will be further elaborated in discussion of the results.

Internal validity

It is possible that the regular assessment of arm motor function made the patients more aware of their affected arm and that this influenced use and motivation. On the other hand, there were only three assessments and long intervals between each, preventing a notable stimulating effect. High test-retest reliability inter-rater reliability of the applied measures in clinically stable patients suggest that we observed real changes of arm motor function based on spontaneous recovery and rehabilitation. Better performance on the tests due to learning effects appears unlikely.

The most obvious methodological weakness of paper I is the limited follow-up of patients considered as cognitively too impaired to participate in CIMT at the first assessment after stroke. Many of the patients, especially elderly patients and those living in nursing homes had been diagnosed with dementia before suffering a stroke and would not have been eligible. A number of the patients, however, may have suffered transient cognitive impairment and younger patients in particular often experience improvement of cognitive abilities. [165] As we did not consider minor cognitive problems to be an obstacle for participating in CIMT, we applied a rather low cut-off on MMSE of 20/30, which allows some cognitive impairment. Due to limited resources a follow-up of patients with cognitive impairments or other medical conditions beyond their stay at the hospital was not possible, thus some patients could have become eligible at a later stage.

External validity

The number of patients was limited with only 46 patients, out of 100 considered, undergoing the motor assessments. Nevertheless, the sample studied encompasses an unselected pool of patients with impaired arm motor function after stroke and, taking into account the limitations mentioned above, the results should be transferable to patients with stroke in general.

5.1.2 Recovery of arm function

Recovery of arm function has been studied extensively earlier [12, 13, 15, 21], but not with regard to the provision of specific treatment. CIMT has proven to be an effective treatment approach for patients in the chronic phase after stroke, but the time point at which to initiate CIMT early after stroke has not been elucidated. As a complementary study to the RCT in paper II, this study focused on eligibility for CIMT at specific points in time in the subacute phase post stroke.

Improvement of arm motor function

Not surprisingly, the results of this study corroborated earlier findings that most improvement of arm motor function occurs during the first 4 weeks after stroke and that some further improvement can be expected in the following weeks. [14, 15] By subdividing the patients into severity subgroups according their ARAT scores we gained further insight into the recovery process starting from different baseline scores.

Also here, as expected, baseline scores were an important predictor for recovery. Of the 17 patients who did not meet the minimal motor criteria early after stroke, almost two thirds (59 %) did not improve, continuing to suffer from paralysis after 3 months. Interestingly, three of the patients with initial severe paresis first obtained sufficient motor function to become eligible at some time between the second and third assessment. Similar observations were made in a study by Mirbagheri et al. (2008) based on 20 patients during a longer follow-up period. Some of the patients with initial pronounced paresis, but not paralysis, continued to improve up to 9 months post stroke. [21] This does not disprove the fact that improvement in most patients happens soon after stroke, but emphasizes the need for closer follow-up over a longer period of time. In particular, younger patients starting at a low level of motor function should be offered rehabilitation beyond the first weeks as functional gains can even be made in the chronic phase. [166] Two of the three patients in our study who became eligible at a later stage were in employment when they suffered a stroke that resulted in comprehensive motor deficits. Arm motor function is an important factor for re-entering the work-force after stroke, which in turn affects the quality of life. (Rachpukdee 2012)

Initial scores can provide some guidance for offering CIMT. We found that none of the patients who obtained the top score on ARAT at 3 months had a score of less than 34 at 4 weeks. The picture was more diverse 1-2 weeks after stroke. Most patients who later regained satisfactory arm function had a score above 20 on ARAT, indicating some dexterity. However, there were two patients who only scored 0 or 1 at this point in time, but nevertheless re-acquired a high level of dexterity at three months, indicating that an early prognosis based on voluntary finger movements may not be appropriate for all patients.

Because much improvement takes place in the first month after stroke it may be reasonable to wait until 4 weeks before initiating CIMT, conditional on the provision of comprehensive standard rehabilitation. In this study the patients usually received 5 – 10 hours physical and occupational therapy a week, and other treatments, such as speech and language therapy according to their needs. This could be regarded as rather comprehensive, although some patients might have benefited from even more intensive rehabilitation. In several studies based on animal experiments the need for early and intensive stimulation to re-acquire lost motor functions has been emphasized. [28, 167, 168] The patients had been admitted to dedicated stroke units with multi-disciplinary teams, and some had been included in an early supported discharge study and followed up by an ambulatory and a community team. Stroke unit care and early supported discharge has proven to be beneficial in terms of independence and quality of life [169, 170], and may also have influenced recovery of arm motor function in our patients.

Criteria for CIMT

The criteria applied for eligibility were based on former CIMT studies, where usually at least some degree of extension of the wrist and fingers is a prerequisite to participate, see for example Taub et al. (2006), Wolf et al. (2006). [166, 171] This seems reasonable since basic flexion and extension is needed for simple grip and release movements. Patients without some voluntary finger movements would be helpless when wearing a restraint on the less affected arm. Furthermore, to avoid unnecessary or unsuitable training an upper limit had to be defined. MAL scores as a reflection of actual use of the affected arm were used as an upper limit in some studies, excluding patients with a substantial arm use defined as > 2.5 on MAL, which reflects rare to occasional use. [171, 172] Patients assessed on an acute ward a short time after stroke onset usually do not have the opportunity to perform the activities mentioned in the MAL and cannot judge the amount and quality of use of the affected arm realistically. We therefore decided to set an ARAT score of 51 as an upper limit, which implies that motor function is still noticeably impaired but at the same time implies the ability to improve according to an earlier proposed clinically important difference of 5.7 points. [150] A slightly higher ARAT score of < 53 is applied by van Delden et al. in an on-going study. [173]

Cognitive impairment

A surprising observation in this study was the fact that a substantial number (33 %) would have been excluded from CIMT due to cognitive problems, at least at the time of the first assessment. Cognitive impairment in patients with stroke is frequent, even if transient for some patients. According to a recent study 10 % of all patients with first-ever stroke had already been diagnosed with dementia. [9] A further 10 % will develop dementia soon after stroke, and after recurrent strokes the probability rises to one third. Cognitive impairment will not only exclude them from CIMT, but also from many other treatment approaches, where compliance, motivation and stamina are a prerequisite. A future challenge is to develop neurorehabilitative treatment approaches, which are suitable for patients with cognitive impairment and which stimulate both motor and cognitive function.

Clinical implications

The results of this study suggest that CIMT should not be initiated earlier than 4 weeks after stroke, because many eligible patients, based on motor criteria, recover with standard rehabilitation. Some patients with poor motor function initially will at a later stage in recovery obtain sufficient arm motor function to participate in CIMT or other forms of intensive task-related training.

5.2 DISCUSSION PAPER II

5.2.1 Methodological considerations

Design

In this study a single-blinded randomized controlled design was applied, which is the preferred scientific design because it secures the random allocation to one of two or more groups. [163] The assessments were performed by blinded raters, but the character of the intervention did not allow a blinding of either the patients or the therapists.

Internal validity

The intended sample size of 60 patients was not reached due to problems with patient recruitment. As was also shown in Paper 1, a small percentage of the stroke patients admitted to the hospital were found to be eligible for CIMT in the sub-acute phase and, furthermore, some of the eligible patients were not motivated for the intensive training due to cognitive or medical problems. Inclusion of too few patients comprises first and foremost the risk of overlooking a difference where there might in fact be one. [162] The interims per protocol analysis revealed no statistically significant difference in change between the groups, neither in ARAT, the primary outcome measure, nor in the secondary outcome measures (HPT, MAL AOU, MAL QUO), Neither was a difference found when conducting an intention to treat (ITT) analysis, that took the missing data into account. A premature termination of the study with regard to limited resources seemed justified, but not reaching the intended number of patients compromises the validity of the study. Difficulty in recruiting a sufficient number of patients is a well-known phenomenon in CIMT studies. [52, 57] A post hoc sample power analysis based on the observed post intervention scores and standard deviations revealed that 94 patients in each group would have been necessary to detect a difference on ARAT of 5.7 at an alpha level of 0.05 and a power of 80 % in favour of the mCIMT group. This number is not realistic to achieve within a reasonable time frame at one site, and the difference would in all probability not be large enough to be meaningful for the patients.

Sample

Most patients (30 of 39) who fulfilled the inclusion criteria gave their consent to participate. Reasons for not participating varied, and were sometimes related to personal physical or mental factors, such as awaiting surgery, or to social factors, such as taking care of a handicapped spouse. Three patients expressed a fear of not having enough stamina to comply with the protocol. The patients who were invited to participate received comprehensive information about the study and were given 24 hours to consider their participation. This may have contributed to the low dropout rate of only two patients, who had to stop the training due to unexpected medical complications soon after inclusion.

Outcome measures

The outcome measures used in this study were limited to the activity domain of the International Classification of Functioning, Disability and Health (ICF). Applying a broader array of outcome measures including the assessment of impairment and participation would have provided a more holistic picture of the patients' recovery of arm function. However, the intervention was primarily expected to influence the ability to perform daily life activities and therefore measures at an activity level seemed most appropriate. Half of the patients were also included in another stroke study focusing on the effect of early supported discharge [174], and this study also included several assessment tools. Hence, the focus on the activity domain was also based on the necessity to reduce the burden for the patients. Assessing improvement at a participation level seemed not relevant with regard to the intervention.

External validity

The results of this study cannot be transferred to patients with stroke in general, as only a very limited subgroup is regarded as eligible. However, with some caution, the results can be generalized to subacute stroke patients with mild to moderate arm paresis. Caution should be exercised due to the small sample size, which comprises the risk of bias. Assessing the results of this study in the light of other small scale studies, nevertheless provides the basis for some generalization, since several of the studies have reached similar conclusions. [52, 57, 59] Furthermore, the participants came from a rather unselected population encompassing most of the stroke patients living in this area.

5.2.2 Comparison of mCIMT and bimanual training

The results in the light of other studies

CIMT is a promising treatment approach for a selected subgroup of patients with stroke. However, the superiority of CIMT has not been demonstrated for patients in the subacute phase post stroke. The aim of this study was to compare the effect of mCIMT to a similar task-related bimanual approach early after stroke. In our study no statistically significant difference was found between the group receiving mCIMT and the group receiving bimanual training. These results are in accordance with several studies concerning patients in the acute or subacute phase post stroke [57, 59, 175, 176] , but also in contradiction to some other studies [177-179]. A recent meta-analysis by Nijland et al. (2011) including 5 RCTs suggests a more favourable outcome of low intensity CIMT, i.e. less than 3 hours training a day and wearing a restraint for less than 90 % of waking hours, compared to more hours of training and restraint, when patients are recruited within the first two weeks after stroke. [180]

When CIMT and mCIMT are compared to other treatment options, both intensity and content of the experimental and the control intervention have to be taken into account. To rule out intensity as a confounding factor, treatment should have equal dosage in both groups, as was the case in our study. When CIMT was compared to standard rehabilitation of less intensity, as in the “Excite trial” which is the largest study to date, a superior effect of CIMT was found for patients between 3 and 9 months post stroke. [171] Wang et al. studied a subacute sample (mean 11.3 weeks post) and found less improvement in one of the three groups receiving less intensive standard rehabilitation. [181]. Some more training intensity may always be achieved when wearing a restraint on the less affected arm, which is why the restraint is an essential part of the CIMT concept.

When a dose-matched control intervention was conducted the results were equivocal. One of the most studied modifications of CIMT by Page et al. implied an extended intervention period of 10 weeks, but only three 0.5 hour sessions a week of training with a therapist also in the subacute phase post stroke. The studies by Page et al. [178, 182] demonstrated a favourable effect of the applied modification of CIMT when compared to a dose-matched control intervention. In these studies the control intervention mainly consisted of proprioceptive neuromuscular facilitation (PNF), which seems rather inadequate since PNF is an obsolete approach lacking evidence of effectiveness in stroke rehabilitation. [31] In one study where mCIMT was compared to equally dosed standard physical and occupational therapy most improvement was found in the experimental mCIMT group [177]. In other studies where the content of the control intervention was similar to that of the CIMT intervention and also based on functional training, no difference was found between the groups [57, 176]

The intervention

The intervention chosen in our study was similar in both groups with respect to the functional, task-related content and the shaping procedures applied. For patients usually eligible for CIMT with mild to moderate arm paresis, task-related training seemed more appropriate and challenging than simple repetitive movements used in Bilateral arm training with rhythmic auditory cueing (BATRAC) or Bilateral arm training (BAT). [183, 184] Exploiting bimanual coupling when performing simultaneous movements may be helpful for patients with severe paresis, but advanced manual dexterity usually comprises complementary movements of both hands, e.g. one hand stabilizing an object and the other hand manipulating. On the other hand, treatment approaches for patients who were only lacking some speed and precision, such as Arm ability training [185] seemed too difficult for many patients in our target group. We proposed exercises close to daily life activities, which provide the possibility to train coordination of both hands in an ecologically valid context.

The self-training programme focused on either unimanual or bimanual exercises for the respective group and, in addition, the therapists were asked to weight the training accordingly. However, there were many hours of the day that the patients did not dedicate to special exercises but were only asked to include the affected arm as much as possible in daily activities. This may have resulted in more similarity than intended between the two groups. However, the relatively satisfactory compliance with the targeted hours of wearing a mitt in the mCIMT group, suggests that at least greater unimanual use of the affected arm was achieved.

Learned non-use

CIMT seems to be more beneficial in the chronic phase than in the acute and subacute phase post stroke. This is not surprising as CIMT is a behavioural approach aiming to reduce or reverse learned non-use. One study applying kinematics found that

CIMT decreased compensatory strategies and thereby improved function, but improvement at an impairment level could not be determined. [186] Learned non-use may not be established to the same degree early after stroke, where reduction of impairment in a narrower sense can still be expected. However, it was surprising how fast learned non-use seemed to be established in individual patients, e.g. one patient shelled an egg with his unimpaired hand only, which looked rather difficult and arduous. Nevertheless, most patients in our study focused on using the affected hand when prompted to do so. Equivalent improvement of arm motor function was also found in a recent study with subacute and chronic patients, all receiving the same amount of massed practice. [187] The patients in one group had to wear a physical restraint, while the other group was only frequently reminded to use the affected arm. This indicates in accordance with our study that conscious attention to using the affected arm can provide sufficient impetus for many patients. A physical restraint may, however, be a helpful reminder for patients who are inclined to only use the unimpaired hand, sometimes due to minor cognitive impairments affecting motivation and body awareness.

The treatment concept

It has to be considered that all modifications of CIMT are a dilution of the original concept. Modifications of CIMT are a compromise with regard to what is desirable and what is achievable in terms of the patients' stamina and the resources available. The physical restraint is only one part of the whole treatment package, and as Taub et al. (1999) emphasized the repetitive practice of the affected arm is the most important factor. [45] In our study patients in both groups were asked to spend several hours a day with a self-training programme to achieve sufficient intensity. Self-training was also implemented because we wanted to provide a treatment option which is implementable at different levels of the health care system. Only 4 hours of therapist guided functional arm training a week may seem sparse. On the other hand, many patients in the acute and subacute phase experience diverse impairments and have to attend other therapies, which limit their capacity for arm training. The training concept applied here seemed viable for most patients in different settings, but a more comprehensive training programme offering more therapist contact might have increased motivation and effectiveness.

Clinical implications

There is research evidence for mechanisms that can stimulate neural plasticity, repetitive practice being one, but also intensity and salience of the experience are important. [146] In CIMT, several of these aspects are integrated, behavioural and cognitive strategies are applied, such as shaping to maintain a challenging character of the training, and contracts to emphasize the active role of the patient. Such strategies can be introduced to different treatment approaches such as bimanual training in this study, under the prerequisite that patients are cognitively capable to comply. If frequent use of the affected arm can be achieved by cognitive means a physical restraint may not be necessary in the subacute phase post stroke.

5.3 DISCUSSION PAPER III

5.3.1 Methodological considerations

Design

A longitudinal repeated measures design was used to study changes over time in patients with stroke, allowing for within subject comparisons at two time points, the subjects acting as their own controls. Two examinations with fMRI and clinical assessments were performed at distinctive points in time after stroke, the first time point early after stroke, and the second time point after 3 months when spontaneous recovery is expected to plateau. [130] Further examinations, including long term follow-up, might have provided more information about reorganization processes, but were not possible due to limited resources. A cross-sectional design was applied to study neural response in age- and sex-matched neurologically unimpaired control subjects.

Internal validity

Brain activation was also studied under two conditions: in healthy persons and in patients with stroke. The neurologically unimpaired persons were examined only once. A limitation with this procedure is that we did not take into account possible variations in the healthy controls, who might have responded somewhat differently if examined two or more times. However, rather consistent activation patterns have been reported across studies in healthy persons under various action observation conditions as reviewed by Molenberghs et al. (2012), suggesting that variations from time to time and from person to person do not conceal a common response in healthy persons. [101]

Blood oxygen level dependent functional MRI (BOLD fMRI) is an indirect measure of neuronal activity and has to be interpreted with caution. The hemodynamic response can be compromised by generalized vascular disease in patients with stroke. [188] Cerebral autoregulation, a mechanism which secures a constant blood flow to the brain, has also been found to be less effective early after stroke (< 4 days post stroke). [189] Nevertheless, numerous studies provide a robust body of evidence regarding the reorganization of the motor system post stroke, for example as reviewed by Rehme et al. (2011). [134] BOLD fMRI can in combination with clinical assessments provide a valuable means of assessing changes of neuronal plasticity.

The paradigm

The paradigm applied in our study was somewhat monotonous, especially for the healthy controls in the action observation condition. Two of the subjects reported that they had fallen asleep for some time while watching the video and their action observation data had to be excluded from the analysis. The monotony of the video clip was attributable to the necessity to compare data from the motor task with the action observation condition. This required a task simple enough that it could be carried out by patients with impaired arm motor function, and a corresponding video clip showing the same task. . However, inclusion of other video clips and embedding a control condition would have improved the paradigm.

External validity

To ensure that the experiment was conducted safely and smoothly quite strict inclusion criteria had to be applied to the patients included in the fMRI study. Besides usual fMRI exclusion criteria, such as metal implants and claustrophobia, the patients had to be able to communicate and follow instructions, and be able to stand and transfer indepently or with only a little help. These criteria excluded many of the patients admitted, leaving a highly selected group of patients which was on average less impaired and younger than the stroke population in general. Due to the protocol we also had to exclude patients with severely impaired arm motor function. However, we did include patients with an age span from 41 to 79 years and with both cortical and subcortical lesions in both hemispheres, thus the group covers a rather broad array of other factors. Considering the restrictions and the limited sample size, the results can only be generalized with caution to a similar patient group with mild to moderate paresis. Even the control group may have been special because health professionals and academics were overrepresented. This was not regarded as a problem as the tasks were not cognitively challenging.

5.3.2 Plasticity and response to action observation

Treatment approaches based on mirror neurons for patients with an arm paresis after stroke, such as action observation and mirror training have shown promising results. [107, 111, 116, 190] However, neuroimaging studies examining potential mirror neurons have mostly included healthy persons and we know little about neurons with mirror properties in patients with stroke. In paper III we explored the response to action observation at two different time points during the subacute phase after stroke and concomitantly assessed the clinical recovery of arm function. Neurologically healthy participants served as control subjects.

Activation patterns compared to other studies

The study revealed an involvement of several motor-related areas such as the inferior parietal lobe and premotor and supplementary motor areas bilaterally. In numerous studies with healthy participants these areas are also identified as being part of a mirror neuron system, as reviewed by Molenberghs et al. (2012) and Caspers et al. (2010). [101, 191] A recent study by Nedelko et al. (2011) examining the influence of age on mirror neurons found activation in the lateral prefrontal gyrus, ventral premotor cortex and inferior parietal lobe to be independent of the age of the group. Considering that most patients with stroke are elderly, these results also provide some support for observation as a treatment approach. In particular, the inferior parietal lobe, premotor and supplementary motor areas seem to play a crucial role as their frequent involvement has been reported in meta-analyses. [101, 191] The inferior parietal lobe is regarded as a higher order part of the motor system, of special importance for motor acts including tool use. [192, 193] Based on experiments with monkeys and humans, the inferior parietal lobe is proposed to play a crucial role in understanding and interpreting observed actions, including prediction of subsequent actions. [194, 195] The tool used in our action observation paradigm, the cylindrical device, may have contributed to the strong response of neurons in the inferior parietal lobe, even if it was a rather abstract tool and the observed action predictable.

The involvement of premotor and supplementary motor areas in our study both early and later after stroke and in healthy subjects also suggests an at least partially intact response to action observation. When activated areas during action observation were masked with those discharging during execution the same activation pattern evolved. The activation of premotor and supplementary motor areas under all conditions in patients and healthy subjects confirms the existence of an observation/ execution matching system.

The Broca area (BA 44,45) and its homologue on the right hemisphere were originally regarded as the human equivalent to mirror neuron area F 5 in macaques. [196]

These areas were also activated in our study, but only in patients 3 months after stroke. Morin and Grèzes (2006) proposed that rather the adjacent premotor cortex (BA 6) shares the visual and motor properties that can be regarded as mirror neurons, which is in accordance with our study. However, peak activation in BA 44 and 45 was frequently reported in other studies as reviewed by Caspers et al. (2010), suggesting that the involvement may vary according to features of the task observed and the mindset of the observer.

Changes from first to second exam

The activation pattern changed during the process of recovery in terms of a larger spatial extent, but also with differences in areas involved. Considerably fewer clusters were activated within two weeks compared to 3 months post stroke. The second exam also revealed an activation of distinct clusters in the inferior frontal gyrus (BA 47) and the thalamus. Since the increased extent of activated areas co-occurred with an improvement in arm motor function it can be interpreted as a trend towards normalization. The inferior prefrontal gyrus is associated with complex cognitive functions and interconnected with most other parts of the brain, such as the thalamus. The pronounced thalamic activation three months after stroke may be explained by its function as a relay station and could be seen as a compensational mechanism. [197]

Action observation and motor imagery have been proposed as treatment approaches to facilitate motor recovery after stroke.[107, 110] It is suggested that both observation and imagery share the same underlying neuronal mechanisms. An internal representation of the observed or imagined action is created to assess the feasibility of a planned action and to prime the motor system for subsequent action. [106] Our data confirm the presence of an execution / observation overlap also in stroke patients, which may provide the basis for enhancing motor function by action observation, sometimes referred to as video-based training.

Interestingly, the spatial extent of activation increased from early after stroke to the second assessment after three months, suggesting that the responsiveness to action observation changes over time. It is difficult to say to what extent fewer activated areas early after stroke limit the receptiveness for action observation as a treatment approach. It may be sufficient to provide additional stimulation for the motor system that some motor areas respond when observing movement. Beneficial effects of action observation in improving arm motor function in patients with subacute stroke support this assumption. [107]

All patients included in our study received rather comprehensive rehabilitation, which, together with spontaneous recovery, influenced the reorganization of the motor system and may also have contributed to the reorganization of potential mirror neurons. Changes in potential mirror neurons may merely reflect the improvement of arm motor function, or may constitute an interaction of mutual influence.

Clinical implications

Our results suggest that action observation may be a means of enhancing motor function in the subacute phase, even if, as demonstrated in our study, a stronger cortical response can be expected at a later stage. Cortical lesions of visual areas and key areas of the mirror neuron system may be a limiting factor for the application of action observation. The same applies to frequent stroke-related symptoms, such as attention deficits, cognitive impairments and fatigue. Nevertheless, the basic notion that similar areas are activated in healthy persons and patients with stroke may encourage clinicians to apply treatment approaches targeting mirror neurons to improve motor function after stroke.

5.4 ETHICAL CONSIDERATIONS FOR ALL STUDIES PAPERS I – III

After stroke, patients can be vulnerable physically and psychologically. We endeavoured to provide comprehensive information about the purpose of the respective study and emphasized that participation was voluntary. Because of the character of the three studies only patients who were able to give informed consent could participate in treatment and assessments.

In papers I and III the participating patients received treatment that was independent of the studies. This involved assessments of arm motor function at three different time points in Paper I. These assessments were of little burden to the patients, since few measures were applied and the patients were visited at their respective places of residence.

In paper III, the patients and healthy control participants were informed about the special conditions of an fMRI examination, such as the noise from the scanner and the necessity to lie still for about 40 minutes, which can be experienced as unpleasant. All patients included were familiar with MRI, since this is a standard examination when admitted to the stroke unit, and therefore had an idea as to what to expect from an fMRI. As MRI does not use X-rays, the participants were not exposed to potentially harmful side-effects. The examination was tolerated well by all participants and no adverse effects occurred.

In paper II, the patients in both groups received treatment of apparently equal quality with equivalent treatment time and therapist contact, so no group appeared to be disadvantaged. Additional training and exercises can be experienced as exhausting. It was therefore part of the intervention that the patients could distribute the self-training throughout the day according to their needs and general condition. Other necessary rehabilitation was not compromised by participation in the study.

All three studies were approved by the Regional Ethical Committee and the studies were conducted according to the Helsinki Declaration.

6. CONCLUSIONS AND FUTURE PERSPECTIVES

No difference in change was found between the group receiving mCIMT and the group receiving bimanual training without the use of a mitt to physically prevent the use of the unimpaired arm. The results suggest that a physical restraint may not be necessary when patients are able to focus on using the affected hand. Cognitive elements from the CIMT approach to increase motivation, compliance and adherence could be implemented in the bimanual training of the present study. Because wearing a mitt may be experienced as a nuisance, a cognitive approach might preferably be applied in patients who are able to control their arm use.

Future research should examine different forms of bimanual training and define the patients who could possibly benefit. It would be interesting to explore in which cases innate bimanual coordination patterns can be used to improve arm motor function.

Potential mirror neurons were shown to be active both early after stroke and after 3 months, although they underwent changes during the course of recovery. The results suggest that mirror neurons are a possible avenue to the motor system early after stroke. The concept of mirror neurons as a means of improving motor function is relatively new. Several treatment approaches targeting mirror neurons, such as action observation, mental practice and mirror therapy have to be studied further. Also virtual reality systems which comprise mirror modalities warrant further research. Such training may be more applicable for patients with cognitive impairment than intensive CIMT and bimanual training, and may represent a supplementary method of training.

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