Reflections on mirror therapy in stroke:

Mechanisms and effectiveness for improving hand function

Marian Michielsen

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REFLECTIONS ON MIRROR THERAPY IN STROKE:
Mechanisms and effectiveness for improving hand function

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Promotor:	Prof.dr. H.J. Stam
Overige leden:	Prof.dr. M.A. Frens
	Prof.dr. P.J. Koudstaal
	Prof.dr. G. Kwakkel
Copromotoren:	Dr. J.B.J. Bussmann
	Dr. R.W. Selles

ABOUT THIS THESIS

The present thesis of Marian Michielsen is not a standard thesis and it did not follow the standard process for a thesis. The reason for this is tragic, as many people know. However, probably not all readers of this thesis are familiar with the circumstances in which this thesis was accomplished. As supervisors of the PhD study of Marian Michielsen, we feel it our duty to explain some of the background.

During her favorite sport mountain climbing, Marian died on Monday the 11th of July 2011 at the age of 28 years. She was in the final stage of her PhD study and the completion of her thesis would take only a few months. Her death was dramatic; for her family, friends, acquaintances, colleagues, and for us, her supervisors. After some time we started to think about the possibility to award Marian a posthumous doctorate's degree. Marian's parents indicated that they would appreciate this. Because of that, we submitted a request for a posthumous graduation of Marian to the Rector of the Erasmus University.

We felt we had good reasons for this request. First, there was the status of the 5 core chapters of Marian's thesis. Three of the 5 manuscripts (Chapters 2, 3 and 4) -all with Marian as first author- had been published in international peer reviewed journals. The fourth manuscript (Chapter 5) was almost ready for submission. The final manuscript (Chapter 6) was finalized up to the results section; only the results of some additional measurements had yet to be analyzed and also the discussion needed attention. Second, the quality of the manuscripts was high: two of the three published manuscripts had been published in a top-10% journal and the third manuscript in a top-25% journal. In the last months, the two remaining manuscripts have been submitted; one of which has already been accepted for publication. Finally, our favorable judgment of Marian's work and the magnificent portfolio, comprising all her activities during her PhD study, were important in our decision to submit the request.

A draft of the general introduction was ready, and also the long list of potential theorems and the names of all people who had to be mentioned in the acknowledgments. The content of the general discussion was indicated by some individual sentences and key words, but had yet to be written. A general summary of the thesis was also not yet written. This was discussed with the Doctorate Board of the Erasmus University and after careful consideration this Board decided to agree with the start of the process of a posthumous graduation.

Both the Board and we, as Marian's supervisors, discussed how to deal with the chapters that were not finished yet. Starting point had always been that it should be and remain Marian's thesis. That is why we, in consultation with the Doctorate Board, have made a clear distinction between Marian's text and our text. The text of the general introduction is based on sentences written by Marian; she certainly would have made further adaptations to it, but we decided to leave the text as original as possible. We based the general summary as much as possible on Marian's words and sentences from the summaries of the separate manuscripts. Also the theorems were mainly written by Marian. We selected them together with some of her closest friends and colleagues from the (long) list made by Marian. The general discussion was more difficult: as said, there were only fragments of text, thoughts and topics, but not appropriate yet to publish. Therefore we decided to write the discussion ourselves and to keep it short. We are convinced that we followed the vision, thoughts and ideas of Marian as much as possible. Finally, all parts had to be combined into this thesis. In this process, Marian's friends and direct colleagues have played an important role.

Hans Bussmann
Ruud Selles
Gerard Ribbers
Henk Stam

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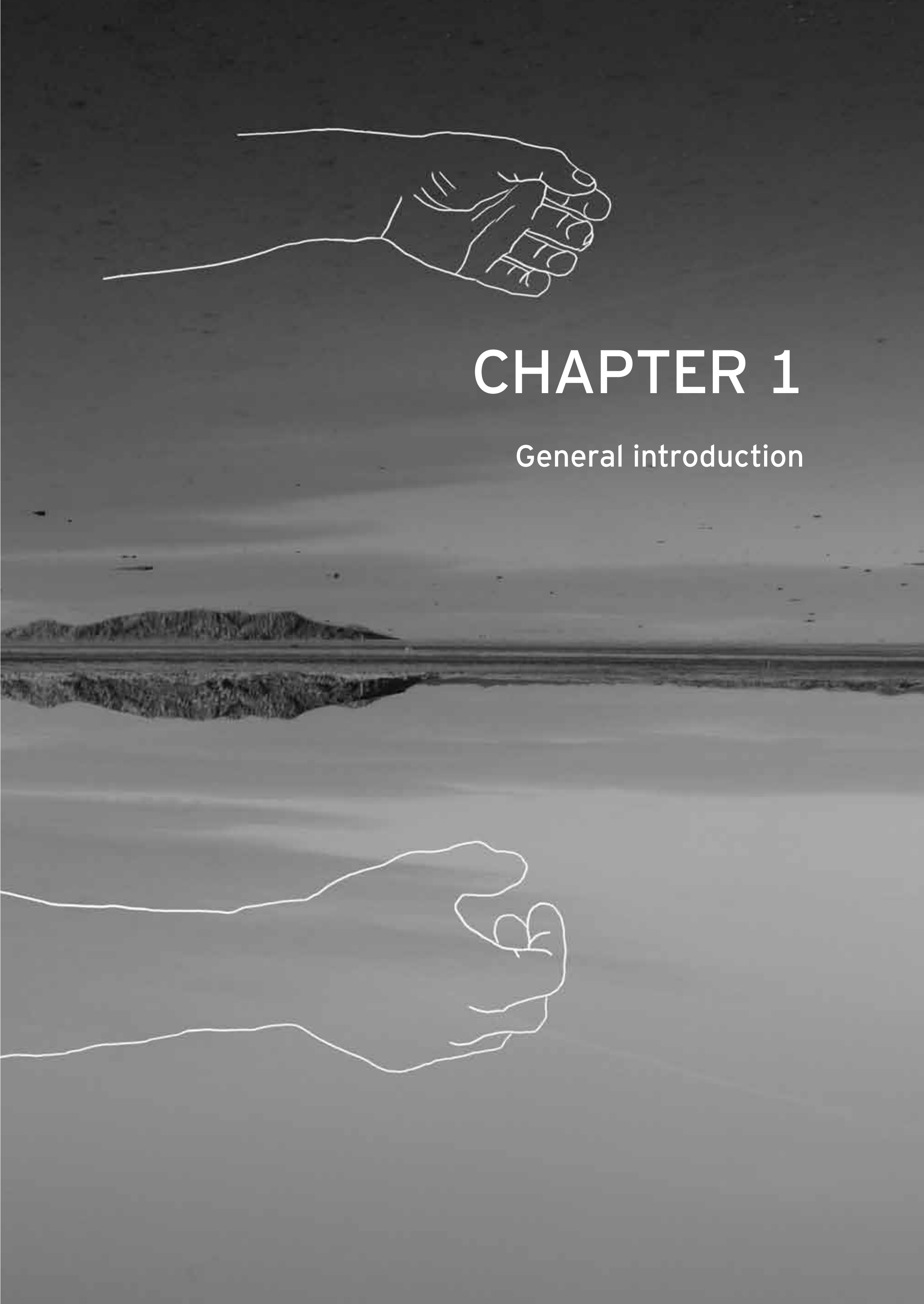

CHAPTER 1

General introduction

GENERAL INTRODUCTION

Stroke is currently the second cause of death in the western world[1]; one year following stroke, half of all patients have died[2]. From the surviving half, a large part remains disabled and 55% to 75% of them have a paretic arm[3]. This makes stroke the main cause of acquired adult disability[4]. Deficits after a stroke consist, amongst other things, of motor problems, sensory problems and spasticity, and can range from complete paralysis of the upper-extremity towards relatively minor coordination deficits. Such impairments affect an individual's ability to complete everyday activities (disability) and affect participation in everyday life situations[5]. As there is no cure for stroke, rehabilitation is the primary means of increasing upper limb functioning[6].

Maximizing upper-extremity function is a key factor in motor rehabilitation following stroke. Pomeroy et al.[7] defined three basic principles to treat paresis; [1] priming techniques that increase the excitability of the motor system and promote plastic reorganization in response to physical activity, [2] augmenting techniques that enhance activation of paretic muscles during physical activity, and [3] task-specific exercises. Mirror therapy is an example of a priming technique. Designed by Ramachandran et al.[8], mirror therapy was originally developed to diminish phantom limb pain in amputees. In 1999, Altschuler et al. introduced mirror therapy for improving motor function of the arm and hand following stroke[9] and showed that motor performance of chronic stroke patients improved. Although several additional studies were small and often not well controlled, recent, high-quality, randomized controlled trials have also reported mirror therapy to improve motor function in patients with subacute[10] and acute stroke[11]. However, despite the encouraging clinical results, little is known about the underlying mechanisms of mirror therapy.

While the influence of mirror therapy at the level of brain organization and plasticity is not well-established, on the other end of the spectrum, i.e. at the level of translation of functional improvement towards daily life improvement, we also still have a lot to learn. It is important to realize that motor recovery following stroke does not stop at the level of motor function, but that improvements have to translate to improved actual use of extremity in daily life in order to be beneficial to the patients.

The International Classification of Functioning, Disability and Health (ICF) provides a framework for classifying improvements following stroke rehabilitation interventions[4]. The ICF distinguishes 3 domains: body function and structures, activity (including a capacity and performance classifier), and participation. The model stresses that translation of improvements between those levels will not automatically take place, and it has been shown that there is no 1-on-1 relationship between motor functional improvements and use of the upper-extremity in daily life[12]. As a result, the emphasis on assessing the outcome of interventions in terms of real-world upper limb use has increased in the last years.

Several studies have included measurement of upper limb use in daily life. So far, this is mostly based on subjective methods (e.g. Taub et al.[13]; Mark et al.[14] and Wolf et al.[15]). Accelerometers and other portable devices allow for the assessment of actual upper limb use over a prolonged period of time and in a home setting, providing the opportunity to gain detailed insight in the exact amount of use of the upper-extremity in daily life, and the relationship between use of the upper-extremity in daily life and motor function[16]. In 2007, De Niet et al.[17] presented the Stroke Upper Limb Activity Monitor (Stroke-ULAM) to objectively measure upper limb usage. The Stroke-ULAM has the added capability to detect body postures and motions, and creates the opportunity to discriminate between independent upper limb movements and upper limb movements caused by whole body movements (e.g. during walking).

AIM & OUTLINE OF THIS THESIS

The thesis consists of two related parts. Part 1 (Chapters 2 & 3) focuses on the objectively measured use of the upper-extremity in daily life, whereas in part 2 (Chapters 4, 5, & 6) the effectiveness and mechanisms of mirror therapy will be examined.

The relationship between actual performance and function, capacity, and self-perceived performance of the paretic upper limb following stroke is the central topic of **Chapter 2**. In order to realize this, outcomes on the Stroke-ULAM will be compared with outcomes on regularly-used measurement tools for function, capacity and self-perceived performance.

In **Chapter 3** we quantify in detail uni- and bimanual upper limb use in chronic stroke patients in daily life as measured with the Stroke-ULAM, and compare this with healthy controls. This study not only includes the consequences of stroke on the paretic side, but also on the activity of the non-paretic arm.

In part 2, we firstly report a study on the effectiveness of mirror therapy, taking in account all ICF levels and including daily life functioning in our therapy assessment. **Chapter 4** describes a randomized controlled trial on the short and long term effects of mirror therapy on all ICF domains as well as the subsequent cortical reorganization. **Chapter 5** describes a functional magnetic resonance imaging study in which we examined the neuronal correlates of mirror therapy in stroke patients using fMRI techniques. Finally, in **Chapter 6**, we examine the relative contribution of a mirror in exercising a reaching task and in the differences in unilateral and bimanual exercises when training such a reaching task with and without a mirror with the goal of improving the application of mirror therapy and enhancing its clinical effectiveness.

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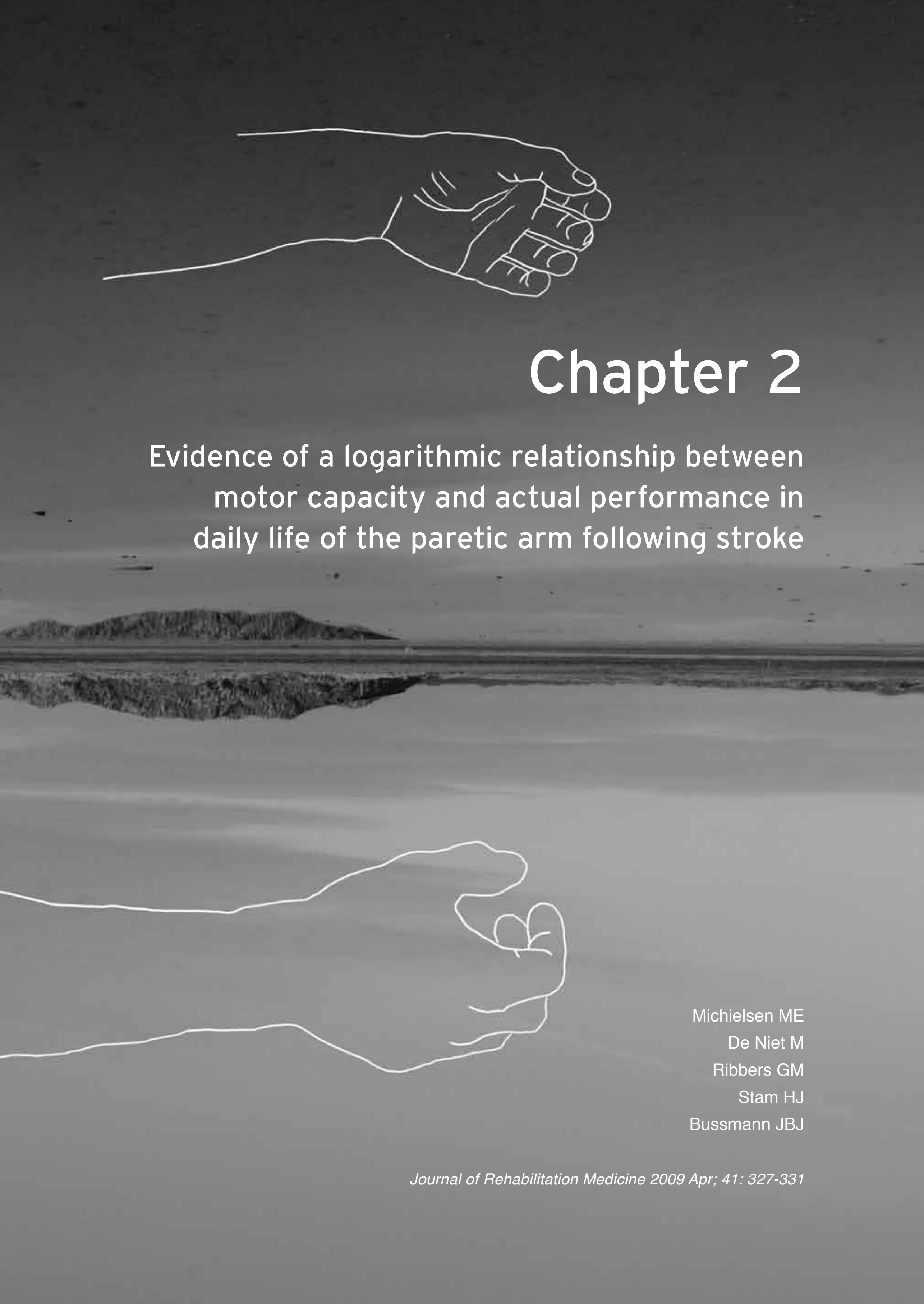

Chapter 2

Evidence of a logarithmic relationship between motor capacity and actual performance in daily life of the paretic arm following stroke

Michielsen ME
De Niet M
Ribbers GM
Stam HJ
Bussmann JBJ

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ABSTRACT

Objective To examine the associations between actual performance in daily life and function, capacity and self-perceived performance of the paretic upper limb following stroke.

Methods Seventeen individuals with stroke were included in this study. Correlation coefficients between actual performance (measured with the Stroke-Upper Limb Activity Monitor), function (Fugl-Meyer Assessment), capacity (Action Research Arm test) and self-perceived performance (ABILHAND questionnaire) were determined.

Results High correlations were found between actual performance and function (r = 0.75; 95% confidence interval (CI): 0.42–0.90), and capacity (r =0.71; 95% CI: 0.35–0.89), whereas a moderate correlation was found between actual performance and self-perceived performance (r = 0.64; 95% CI: 0.21–0.86). For the relationship between actual performance and both function and capacity, logarithmic regression explained more variance than did linear regression.

Conclusion The present study provides first evidence of the existence of a non-linear relationship between actual performance, function and capacity of the paretic upper limb following stroke. The results indicate that function and capacity need to reach a certain threshold-level before actual performance also starts to increase. Because of the small sample size of the present study caution is needed when generalizing these results.

INTRODUCTION

Stroke is the major cause of long-term neurological disability in adults in Western society[1]. In the acute stage of stroke approximately half of all stroke survivors are left with severe loss of function in the hemiparetic upper limb[2]. Rehabilitation of the upper limb can be focused on different aspects of human functioning. The International Classification of Functioning, Disability and Health (ICF) described by the World Health Organization, distinguishes the following 3 levels: body function and structures, activity, and participation[3]. For the activity level, 2 different qualifiers are provided: capacity and performance. Activity capacity describes what someone can do, indicating a person's highest probable level of functioning. It refers to a "standardized" environment to neutralize the varying impact of different environments on the ability of the individual and to allow for international comparisons for all persons in all countries. Activity performance on the other hand, describes what a person actually does in his or her home environment, expressing the individual's involvement in a life situation. In general, rehabilitation interventions for the upper limbs after stroke are focused on improvements in the levels of body function and activity capacity, whereas the ultimate aim is to improve activity performance[4].

Many evaluation tools are used to evaluate the efficacy of rehabilitation interventions, wherein different tools have been developed to measure at the different levels of functioning[5 6]. Whereas the levels of body function and activity capacity can be validly assessed in a laboratory setting, measurement of activity performance should be performed in a ecologically valid setting (e.g. the home setting) in order for environmental factors to be taken into account[7]. When assessing activity performance, a distinction has to be made between self-perceived activity performance and actual activity performance. Self-perceived activity performance provides information about the manner in which someone experiences the difficulties caused by his disability[8], whereas actual activity performance provides objective information about the manner in which a disability affects one's functioning in daily life. Self-perceived activity performance can be regarded as a subjective construct, justifying a subjective (self-reports, questionnaires) assessment. Actual activity performance, on the other hand, is an objective construct and should be assessed accordingly. However, difficulties in objective assessment have so far had the result that actual activity performance is usually also assessed in a subjective manner[9].

In 2000, Uswatte et al.[10] were the first to present an objective measurement tool for upper limb usage. With the placement of accelerometers on both arms, their activity-monitoring device was able to register upper limb usage in a home setting.

Chapter 2

Vega-Gonzales and Granat[11] developed another objective measurement tool, using pressure techniques. Recently, De Niet et al.[4] presented the Stroke Upper Limb Activity Monitor (Stroke-ULAM) to objectively measure upper limb usage. The Stroke-ULAM is based on both accelerometry and electro-goniometry. In comparison with earlier devices, the Stroke-ULAM has the added capability to detect body postures and motions. This is an important feature, as it creates the opportunity to discriminate between independent upper limb movements and upper limb movements caused by whole body movements (e.g. during walking).

The relationship between actual activity performance (from now on referred to as "actual performance") of the paretic upper limb and impairments at the levels of body function (from now on referred to as "function") and activity capacity (from now on referred to as "capacity") has so far received limited attention in scientific literature[12]. It is, however, an important issue, as it can provide insight into whether and how rehabilitation interventions aimed at function or capacity will also lead to improvements in actual performance. The concept of learned non-use provides a good illustration that the former is not always the case, showing that patients often do not use their affected arm to its full ability[13 14]. Additionally, being able to objectively measure actual performance renders the opportunity to assess to what degree self-perceived activity performance (from now on referred to as "self-perceived performance") is related to actual performance, an issue that has also not yet received much attention.

The aim of the present study was to increase understanding of the relationship between actual performance and function, capacity, and self-perceived performance of the paretic upper limb following stroke. In order to realize this, outcomes on the Stroke-ULAM were compared with outcomes on regularly used measurement tools for function, capacity and self-perceived performance[15-17].

METHODS

Subjects

Patients in the chronic phase after stroke (minimum one year post-onset) were recruited through Rijndam Rehabilitation Center. Eighty-eight patients were contacted, of whom 12 agreed to participate. In addition, 5 sub-acute stroke patients (between 1 and 3 months post-onset) were randomly selected from patients who were hospitalized in the rehabilitation center during the measurement period. Inclusion criteria were: knowledge of the Dutch language and the ability to walk indoors. Patients were excluded when they had co-morbidities that influenced upper limb usage. All participants gave written informed consent before participating in the study. The study was approved by the medical ethics committee of the Erasmus MC Rotterdam.

Procedure

The protocol contained both standardized measurements in a laboratory setting and prolonged ambulatory monitoring of upper limb activity using the Stroke-ULAM in the home environment (chronic patients) or in the rehabilitation centre (sub-acute patients). The laboratory measurements were done prior to the home measurements and consisted of 2 tests: the Fugl-Meyer Assessment (FMA) and the Action Research Arm Test (ARAT). During the home measurements, each patient wore the Stroke-ULAM for at least a 12-h period. To prevent fatigue in the patients, the laboratory measurements were executed a day in advance. After the ambulatory monitoring, the ABILHAND questionnaire was used to index self-perceived activity performance.

Instruments: Actual performance

Stroke-ULAM. The Stroke-ULAM measures wrist movement using accelerometers and goniometers. With accelerometers placed on the thigh and the sternum, the Stroke-ULAM also distinguishes body postures and motions from each other (e.g. periods of sitting, standing and walking are detected). As such, independent upper limb movements can be discerned from upper limb movement caused by whole body movement. The Stroke-ULAM has 2 main outcome measures: (i) an absolute measure for each upper limb (level of usage); and (ii) a relative measure indicating the level of usage of the affected upper limb compared with the unaffected upper limb (proportion). These outcome measures can be derived from both electrogoniometric and accelerometric data. The electrogoniometry level of usage (for both affected and unaffected upper limb) is the elbow joint movement of the upper limb per minute (in degrees per minute), whereas the proportion is the level of usage of the affected upper limb divided by the level of usage of the unaffected upper limb. The level of usage for accelerometry is expressed as the intensity per minute (in g/min). The intensity depends on the variability of the raw acceleration signal around the mean value, that is, the higher the variability, the higher the intensity. The accelerometric proportion is calculated in the same way as the electrogoniometric proportion. Previous research already showed that: (i) outcomes derived from goniometers and accelerometers did not differ much; and (ii) defined proportion of the level of usage as the most appropriate outcome measure of upper limb usage in daily living conditions[4 10]. Therefore, in the remaining part of this paper only the proportion derived from accelerometry will be used as outcome measure for actual performance.

Instruments: Function

Fugl Meyer Assessment. The upper-extremity part of the FMA examines the voluntary movement and the ability to execute upper limb movements outside of synergies. It consists of 9 components: reflexes, flexor synergy, extensor synergy, movement combining synergies, movement out of synergy, normal reflex activity, wrist, hand, and co-ordination speed. The FMA assessment scores range from 0 to 66, with higher scores indicating better motor recovery[15].

Instruments: Capacity

Action Research Arm Test. The ARAT evaluates 4 types of movement: grasping, gripping, pinching and gross movement. The test contains 19 items arranged in hierarchical order starting with the most difficult item in each subgroup followed by the easiest item. The score on each item is based on both the completeness of the movement and the duration of the movement. For each item, a time limit has been determined and exceeding the time limit results in a point reduction of the item score. The maximal score for the ARAT is 57[16].

Instruments: Self-perceived performance

ABILHAND. The ABILHAND is a questionnaire that measures the patient's perceived difficulty in performing activities of daily life that require the use of the upper limbs. Participants are asked to estimate their difficulty in performing each activity when done without help, irrespective of the limb(s) used and whatever the strategies used to do the activity. The manual ability is rated on a 3-level response scale. The score, given in logit, is the conversion of the ordinal score into a linear measure of ability located on a unidimensional scale[17].

Statistics

The Mann-Whitney Wilcoxon rank test was used to compare test scores between patients in the sub-acute phase and those in the chronic phase. Subsequently, a correlation analysis was performed to determine the strength of the relationships between Stroke-ULAM and FMA, ARAT and ABILHAND. The strength of the respective relationships was described using Spearman's correlation coefficient (r) and was based on Munro's correlation descriptors[18] (very low = 0.15–0.24, low = 0.25–0.49, moderate = 0.50–0.69, high = 0.70–0.89, and very high = 0.90–1.00). Scatter-plots of the relationships between the measurement tools were visually inspected to determine linearity. Based on this, Stroke-ULAM values were log transformed, and for the relationships between Stroke-ULAM and FMA, ARAT and ABILHAND a logarithmic regression model ($y = a \ln(x) + b$) was compared with a linear regression model (y =

ax + b). The difference between goodness-of-fit in the models was assessed by applying the Wilcoxon rank test on the individual square of the residuals of both models.

RESULTS

Table 1 shows patients characteristics and mean scores on all evaluation tools. No differences were found between test results of patients in the sub-acute phase and those in the chronic phase on any of the evaluation tools (all $p > 0.001$). Therefore, the 2 groups were collapsed for the remaining part of the analysis. In Table 2, correlation coefficients between the scores on Stroke-ULAM, FMA, ARAT and ABILHAND are presented. Correlation coefficients between Stroke-ULAM and both FMA ($r = 0.75$) and ARAT ($r = 0.71$) are high, whereas the correlation coefficient between Stroke-ULAM and ABILHAND is moderate ($r = 0.64$). Figure 1 shows scatter plots of the relationships between respectively Stroke-ULAM and FMA, Stroke-ULAM and ARAT and Stroke-ULAM and ABILHAND.

Table 1. Patient characteristics and mean test scores on the Fugl Meyer Assessment (FMA), Action Research Arm test (ARAT), ABILHAND questionnaire and Stroke Upper-Limb Activity Monitor (Stroke-ULAM).

	Sub-acute, n = 5	Chronic, n = 12
Age, years, mean (SD)	58.6 (16.1)	50.8 (11.7)
Women, n	0	7
Time post-onset, months, mean (SD)	2 (0.91)	46.18 (4.65)
Haemorrhagic stroke, n	2	5
Paresis of right side, n	5	9
Paresis of dominant UL, n	2	5
FMA score, median (IQR)*	55 (12, 58) **2–63**	49 (31.25, 55.5) **5–58**
ARAT score, median (IQR)*	28 (0, 45) **0–55**	38 (19.75, 47) **0–56**
ABILHAND score, logits, mean (SD)*	1 (2.19) **–2.43–2.60**	1 (2.11) **–1.96–5.98**
Stroke-ULAM Proportion, mean (SD)*	36.94 (24.83) **13.07–68.85**	40.20 (20.89) **12.48–89.63**

*The range of the test-scores is shown in bold.

SD: standard deviation; IQR: interquartile range; UL: upper limb.

Table 2 also shows the results of both the logarithmic and the linear regression analysis between Stroke-ULAM and FMA, ARAT and ABILHAND, as well as a comparison between goodness-of-fit of both methods. As can be deduced from Figure 1 and Table 2, logarithmic regression explains more variance compared with linear regression for both the relationship between Stroke-ULAM and FMA ($p < 0.05$) and the relationship between Stroke-ULAM and ARAT ($p < 0.1$).

Table 2. Associations between actual performance and function, capacity and self-perceived performance.

	Spearman's correlation		Linear regression			Logarithmic regression			Linear vs logarithmic	
	R (95% CI)	p	R^2 (95% CI)	R_{ss}	p	R^2 (95% CI)	R_{ss}	p	Z score	p
Stroke ULAM										
FMA	0.75 (0.42–0.90)	<0.001	0.58 (0.31–0.85)	3102	<0.001	0.72 (0.52–0.92)	2078	<0.001	–2.49	<0.05
ARAT	0.71 (0.35–0.89)	<0.001	0.57 (0.30–0.84)	3120	<0.001	0.66 (0.43–0.89)	2494	<0.001	–1.73	<0.1
ABILHAND	0.64 (0.21–0.86)	<0.01	0.30 (–0.02–0.62)	44.73	<0.01	0.33 (0.01–0.65)	42.69	<0.01	–0.05	0.96

R: Spearman's correlation coefficient; CI: confidence interval; R^2: R squared; R_{ss}: Residual Sum of Squares; Stroke ULAM: stroke upper-limb activity monitor; FMA: Fugl-Meyer Assessment; ARAT: Action Research Arm Test.

DISCUSSION

The aim of the present study was to examine the manner in which actual performance is related to function, capacity and self-perceived performance of the paretic upper limb following stroke. The results showed high correlations between actual performance and function and capacity, and a moderate correlation between actual performance and self-perceived performance. It is important to note that these strong correlations might be partly caused by the large data range in the present study, which typically enlarges the correlation coefficient. Furthermore, the small sample size of the present study and the resultant large confidence intervals make it necessary to be cautious when interpreting the values of these correlation coefficients. Still, our findings seem to contradict previous publications, which generally showed considerable differences between what a patient can do with his or her paretic arm and how much he or she actually uses it[19 20]. This discrepancy might be due to the fact that these previous studies all addressed performance subjectively, whereas the present study was the first to assess performance in an objective manner.

However, the most important finding from the present study comes from its explorations regarding the nature of the relationships between actual performance, function and capacity. The results concerning this issue indicate that function and capacity need to reach a certain threshold level before actual performance starts to increase

(Figure 1). Beyond that level function and capacity only increase moderately in respect to actual performance, which itself starts to increase more rapidly. This idea is supported by the fact that the logarithmic regression model explained more variance compared with the linear regression model, indicating a non-linear relationship between actual performance and function and capacity (Table 2). This is most notably so for the relationship between actual performance and function (72% variance explained with the logarithmic model vs 58% with the linear model), and to a lesser extent for the relationship between actual performance and capacity (66% variance explained vs 57%).

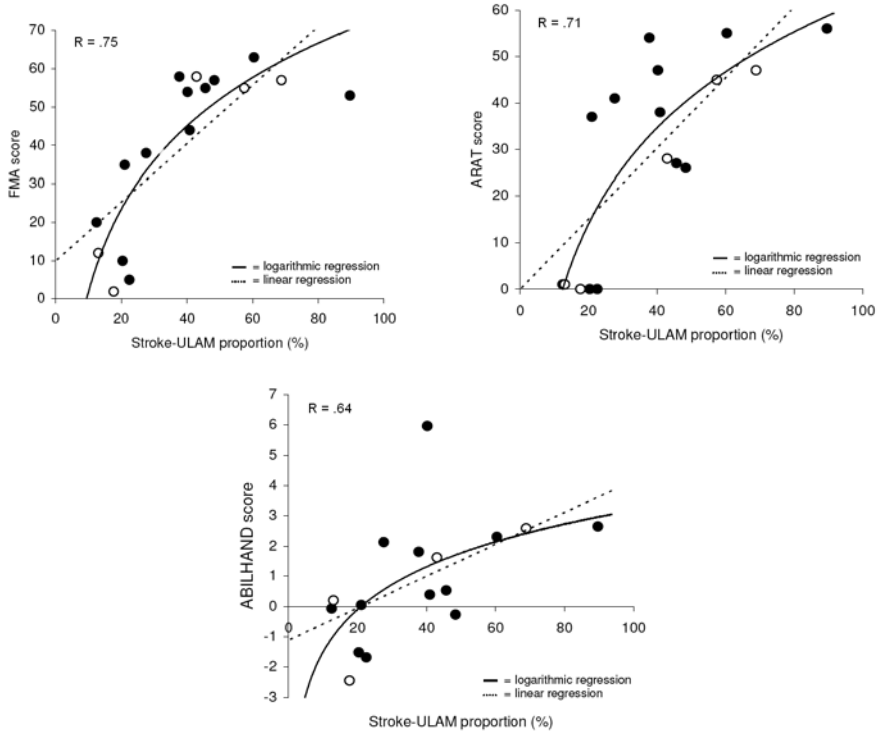

Figure 1. Scatter-plots of the relationships between the Stroke Upper-Limb Activity Monitor (ULAM) and the Fugl Meyer Assessment (FMA) (top left), the Action Research Arm Test (ARAT) (top right) and the ABILHAND questionnaire (bottom). Open dots represent values for sub-acute patients, whereas closed dots represent values for chronic patients.

It must be remembered that the data in this study is cross-sectional. It thus only provides information about different subjects at a given time-point, whereas no conclusions can be drawn from it regarding the course of rehabilitation. However, the observed effect does imply that improvements in function and capacity will not automatically result in an improved actual performance, at least not until they exceed a certain threshold.

Concerning the associations between actual performance and self-perceived performance, the current study revealed a relationship of moderate strength. This is in accordance with findings from previous studies in patients with stroke[21] and CRPS-1[9]. However, as can be deduced from Figure 1, the results of the present study show an outlier with an almost maximal score at the ABILHAND, and a score of only 40% on the Stroke-ULAM. This result is possible because of the subjective nature of the ABILHAND questionnaire, and its allowance for compensation strategies. The size of the correlation coefficient found in the present study between ABILHAND and Stroke-ULAM will of course be influenced by this outlier (even more so given the small sample size). However, this outlier can also be viewed as an extreme example of how large the discrepancies between actual and self-perceived performance actually can be. The former emphasizes how self-reported scores are prone to over- or under-estimation, depending on either motivation and/or cognitive skills[17]. When evaluating a rehabilitation intervention aimed at improving actual performance this is an important issue to take into account, as such "psychosocial factors" are not expected to respond to regular rehabilitation interventions, and might conceal possible improvements in actual performance.

The present study has some potential limitations. First of all, as already mentioned, its sample size was rather small, requiring caution before generalizing results or drawing strong conclusions. Secondly, it is important to note that the aim of the present study was not to validate whether or not the used measurements tools indeed measure in their specific domain of functioning. All used tools have been tested for that previously, but it is still important to keep in mind that the same domain or construct can be validly operationalized in different ways and therefore be measured with different tools. Finally, when measuring actual performance for a longer period of time in daily living situations, the question always remains to what extent the measured period is representative for someone's overall activity pattern. However, in this study the proportion of the level of usage of the affected upper limb in comparison with the level of usage of the unaffected upper limb was used to index actual performance. As this is a measure that is not very susceptible to changes in overall activity (as such changes will affect the activity of both arms equally), it makes the issue of representiveness of the data of less concern.

The main finding of the present study was that even though actual performance and function and capacity of the upper limbs following stroke are strongly related, this relationship appears not to be of a linear nature. This indicates that the size of discrepancies between function, capacity and actual performance can be dependent on the degree of recovery. Furthermore, the present study provided insight into possible differences between actual performance and self-perceived performance. In planning as well as in evaluating the effect of post-acute rehabilitation programs aimed at hand function it is pivotal to understand that there is no one-to-one relationship between function, capacity, self-perceived performance and actual performance, and that improvements on any of those levels might not occur simultaneously. For future research, it would be interesting to examine both the strength and the nature of the relationships between recovery at the different levels of functioning in a longitudinal design.

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CHAPTER 3

Quantifying non-use in chronic stroke patients: a study into paretic, non-paretic and bimanual upper-limb use in daily life

Michielsen ME
Selles RW
Stam HJ
Ribbers GM
Bussmann JBJ

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ABSTRACT

Objective To quantify uni- and bimanual upper limb use in chronic stroke patients in daily life related to healthy controls.

Methods Chronic stroke patients (n=38) and healthy controls (n=18) were included in this cross-sectional observational study. Upper limb use in daily life was measured with the Stroke-ULAM, an accelerometer based measurement device. Unimanual use of the paretic and the non-paretic side as well as bimanual upper limb use were measured for a period of 24 hours. Outcomes were expressed in terms of both duration and intensity.

Results Patients used their unaffected limb much more than their affected limb (5.3 hours vs. 2.4 hours), while controls used both limbs a more equal amount of time (5.4 hours vs. 5.1 hours). Patients used their paretic side less than controls used their non-dominant side and their non-paretic side more than controls their dominant side. The intensity with which patients used their paretic side was lower than in the non-dominant side of controls, while that of the non-paretic side was higher than in the dominant side of controls. Finally, patients used their paretic side almost exclusively in bimanual activities. During bimanual activities, the intensity in which they used their affected side was much lower than that of the non-affected side.

Conclusion Our data show considerable non-use of the paretic side, both in duration and in intensity, and both during unimanual and bimanual activities in chronic stroke patients. Patients do compensate for this with increased use of the non-paretic side.

INTRODUCTION

Fifty to 70% of stroke patients suffer from long-term motor deficits of the upper limb[1] with a decreased use of the paretic upper-extremity in daily life[2]. As this latter may have a great impact on the manner in which a patient is able to participate in daily life activities, maximizing purposeful use of the upper-extremity in daily life is a key factor in motor rehabilitation following stroke.

While it is clear that a decreased motor capacity of the paretic arm influences the use of both extremities, the exact changes in upper limb use following stroke are not yet fully understood. Regarding the paretic upper-extremity, many studies have shown that there is no 1-on-1 relationship between motor impairment and functional use[3 4]. This may be related to the phenomenon of learned non-use[5], which describes how patients will have 'learned' not to use the paretic side to its full capacity[6]. Brain injury causes structural damage to motor pathways as well as depression of neural excitability near the lesion. Decreasing activity of the upper-extremity leads to a further reduction in excitability and as such starts a vicious circle of decreasing excitability and decreasing activity[7].

Even less is known about the consequences of stroke on the non-paretic side. Motor performance of the non-paretic side may be impaired compared to healthy subjects, showing, for instance, decreased speed and consistency of performance[8]. In addition, it has been shown that acute stroke patients have a reduced use in daily life of the non-paretic side compared to healthy subjects[9]. On the other hand, it is generally assumed that post-stroke the non-paretic side will be used more to compensate for decreased use of the paretic side. However, to our knowledge, this has not been investigated in chronic patients.

Overall many questions on techniques to optimize the function of the paretic extremity after stroke still need to be answered. The optimal rehabilitation technique is still not defined, and different approaches in reducing upper-extremity paresis are distinguished[7]. Several therapies have been developed to improve use of the non-paretic arm in daily life. For example, constrained induced movement (CIMT) therapy[10 11]; or Forced Use[12], reported as a beneficial treatment option for motor recovery of the arm[13], prevents the use of the non-paretic upper limb and aims to counterbalance the learned non-use. CIMT is an augmentative technique[7], a high intensity, unimanual training aiming to counterbalance the vicious circle of decreasing excitability and decreasing activity. Further CIMT has aspects of task-specific exercising. Bilateral training programs have also been developed e.g. with rhythmic auditory cueing[14]. To evaluate and understand the effects of upper-extremity training in daily life conditions, detailed insight is needed in unimanual and bimanual function of the arms in daily life conditions. This is the topic of the current paper.

Several studies have included measurement of upper limb use in daily life. For example, Taub et al.[11], Mark et al.[15] and Wolf et al.[5] used the Motor Activity Log (MAL) in their studies. However, although validated against an objective measure[16] the MAL still is a subjective instrument that focuses on how well and how much patients use their most impaired arm in a defined category of activities, and the MAL does not include data on the amount of use of the non-impaired arm and bilateral use. Another method for assessing upper limb use in a home setting is provided by accelerometers and other portable devices providing the opportunity to assess how much stroke patients use their upper limbs in daily life for longer periods[2]. However, so far studies using these devices only assessed upper limb use overall and not in detail. For example, many studies only express actual upper limb use as a ratio between the use of the affected and the use of unaffected side[17], thus omitting information about usage times of the paretic and non-paretic side separately. Secondly, current devices do not differentiate between arm movements resulting from general body movements such as walking, and arm movements during sitting and standing. Thirdly, most measurement devices can not differentiate between the duration of use and the intensity of use, and finally, most devices can or do not differentiate between unilateral and bilateral usage of the arms.

The aim of the present study was to quantify uni- and bimanual upper limb use in chronic stroke patients in daily life, and compare this with healthy controls. Using the Stroke-ULAM[18], we were able to give insight in both duration and intensity of upper limb use, and to discriminate between upper limb movements caused by whole body movements and movements independent of whole body movements, thus providing insight in the amount of functional and purposeful upper limb use in daily life conditions.

METHODS

Participants

Subjects in this study were participating in a randomized controlled trial investigating the effects of mirror therapy on upper limb functioning[19]. Inclusion criteria for the trial were knowledge of the Dutch language, a Brunnstrom score for the upper-extremity between III and V, home dwelling status, and at least 1 year post-stroke. Patients with neglect, co-morbidities that influenced upper-extremity usage, or a history of multiple strokes were excluded. We assessed 182 outpatients (hospitalized between January 1998 and September 2007) for eligibility from Rijndam Rehabilitation Centre in Rotterdam, the Netherlands. A total of 38 patients were enrolled; 79 of the subjects did not meet the inclusion criteria, and 63 were not able or willing to participate in the trial, and data of 2 subjects could not be used for analysis. The data reported in this study are from the subjects' pre-randomization baseline assessment.

In addition to the stroke patients, we recruited 18 healthy control subjects. Control subjects were recruited from several sources (relatives of patients, therapists, researchers). They were age-matched with the 18 first included stroke patients, and had no known neurological or orthopedical pathologies affecting their upper limb function. They were not matched nor selected on any other characteristic, such as setting, marital status, activity level, work etc. The study was approved by the Medical Ethical Committee of the Erasmus University Medical Center.

Apparatus

The Stroke-ULAM (TEMEC instruments, Kerkrade, the Netherlands) consists of 5 piezoresistive acceleration sensors (4 uniaxial, 1 biaxial; size, 1.0x1.0x0.5cm), placed on the lateral side of the left and right thigh (the sensitive axis in sagittal plane while standing), on the sternum (sensitive axes in sagittal and longitudinal plane while standing), and on the upper limbs, just proximal to the wrist joint (sensitive axis perpendicular to the upper limb in sagittal direction in anatomic position). By combining these five sensors, the Stroke-ULAM quantifies upper limb activity of both upper limbs in relation to body postures and motions such as sitting, standing and walking. All sensors were fixed on Rolian Kushionflex using double-sided tape and subsequently attached to the skin. Raw signals of the accelerometers were stored on a Vitaport II digital recorder that was carried in a bag around the waist, with a sample frequency of 128 Hz. After the measurements the raw data were downloaded onto a personal computer.

Procedure

Both patients and controls wore the Stroke-ULAM for a period of at least 24 hours. Subjects were instructed to continue their ordinary life, although swimming and taking a bath or shower were prohibited during the monitoring period. The research questions were not revealed to the subjects prior to the monitoring period to prevent adaptations of daily activity patterns.

Data analysis

Based on feature signals derived from the measured accelerometer signals of the legs and trunk, and by using activity specific settings in the analysis software and a minimal distance-based detection method, the ULAM automatically classifies each second the body posture or motion (lying, sitting, standing, walking, cycling, general non-cyclic motions [e.g. conducting a transfer])[20]. For simplicity we collapsed all body motions (walking, cycling, general non-cyclic motions) in one category.

To analyze upper limb use, from each accelerometer signal of the upper limb the intensity was calculated by calculating the root mean square of the signal after band-pass filtering (finite impulse response, 0.3-16Hz) and down scaling the sample frequency to 1Hz. To determine whether an upper limb was used or not, for each second an algorithm automatically determined whether the intensity of an upper limb sensor exceeded a preset threshold that would depend on the specific body posture or motion (e.g., standing, sitting) that was performed during that second[21]. These thresholds were relatively low, such that even very slow or small movements with the paretic side would be detected. Each second the intensity values exceeded the threshold, the ULAM signal for the upper limb forearm was positive, indicating upper limb use. Bimanual upper limb use was defined as simultaneous activity (i.e. intensity above the threshold) of both upper limbs. In addition, the mean intensity (in g/min) of the sensors during both uni- and bimanual upper limb use was calculated, as well as upper limb use as a percentage of the time spent sitting or standing.

Outcome measures & statistics

Differences between the duration of the mobility related activities between patients and controls were assessed with the use of an independent t-test.
Upper limb use was expressed in absolute values (hours during the 24-h period), as a percentage of the total time a participant spent either sitting or standing, and as mean intensity of the period of uni- or bimanual use. To test for differences in these three outcome measures between non-dominant and dominant arm use in controls and unaffected and affected arm use in patients we performed a repeated measures ANOVA with Group (controls vs. stroke patients) as a between-subjects factor and Side (dominant vs. non-dominant for controls and affected vs. non-affected for patients) as a within-subjects factor. This ANOVA was conducted separately for sitting, standing, and sitting & standing together. For significant main and interaction effects, we used post-hoc t-tests to assess the nature of the differences. The level of significance was set at $P < 0.05$. Statistical analyses were performed with SPSS (SPSS Inc, Chicago, IL, USA) 16.0 for Windows.

Throughout the Results and Discussion section, we will compare the amount of use of the affected upper limb in stroke patients with the non-dominant (i.e. less used) upper limb in controls, and the non-affected upper limb in patients with the dominant upper limb in controls.

RESULTS

Table 1 shows the characteristics of the stroke patients and the healthy controls. It can be seen that the participating stroke patients were relatively long post onset (average 4.5 years) and that in the majority of patients the non-dominant limb was affected. Age of the stroke patients was not significantly different from the controls (p=.39). There was no effect on the data of dominant or non-dominant side affected.

When comparing the duration of the different body postures and motions as a percentage of a 24-hour period (Figure 1), we found that patients performed less body motions than controls (1.6 hours vs. 2.5 hours, p <.01) and were standing less during the day (2.1 hours vs. 3.6 hours, p<.01). In contrast, the duration of sitting was similar in both groups (9.4 hours vs. 9.1 hours, p=.61) while the patients were lying longer than controls (10.8 vs. 8.9 hours, p<.01).

Expressed in total hours, we found that for standing and sitting combined, patients used their unaffected limb much more than their affected limb (5.3 hours vs. 2.4 hours, p<0.01), while for controls the difference between the use of both limbs was much smaller (5.4 hours vs. 5.1 hours, p=.04) (Figure 2). More specifically, this had the result that during sitting patients used their affected side less than controls used

Table 1. Participants characteristics.

Characteristic	Stroke	Healthy
No. of patients	38	18
Age (years)	56.6 ± 12.6	48.1 ± 10.9
Sex (male/female)	20/18	8/10
Time since stroke (years)	4.5 ± 3.2	NA
Affected side (dominant/non dominant)	11/27	NA
Handedness (right/left)	NA	14/4
FM score	35.5 (25.0-52.2)	NA

NOTE. Values expressed as mean±SD, median (interquartile range), or n.
Abbreviations: FM, Fugl Meyer; NA, not applicable.

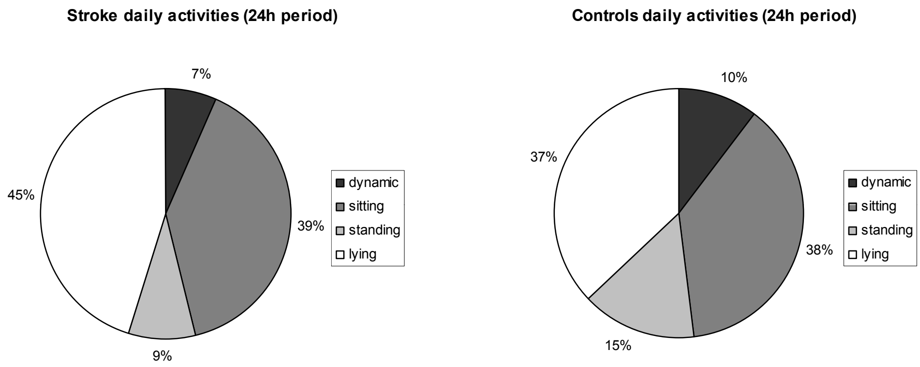

Figure 1. Activity patterns.

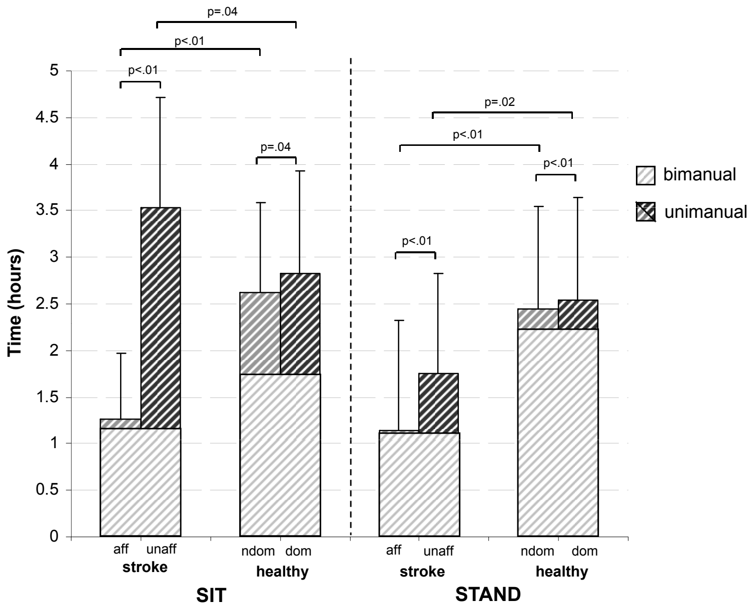

Figure 2. Duration of upper-limb use (24 hour period).

their non-dominant side (1.3 vs. 2.6 hours, p<.01) but their unaffected side more than controls used their dominant side (3.5 hours vs. 2.8 hours, p=.04). During standing however, patients used both limbs significantly less than controls (1.1 & 1.8 hours vs. 2.4 & 2.5 hours, p<.01 & p=.02, respectively).

Because the total amount of standing was lower in patients than controls (Figure 1), we also expressed upper limb use as a percentage of time spent sitting or standing (Figure 3). This showed that percentagewise during standing and sitting patients used their unaffected side more than controls used their dominant side, while they used their affected side less than controls used their non-dominant side.

Figures 2 and 3 also show to what extend the upper limb use is unilateral or bilateral in nature. In both figures, it can be seen that almost all activity of the paretic arm in

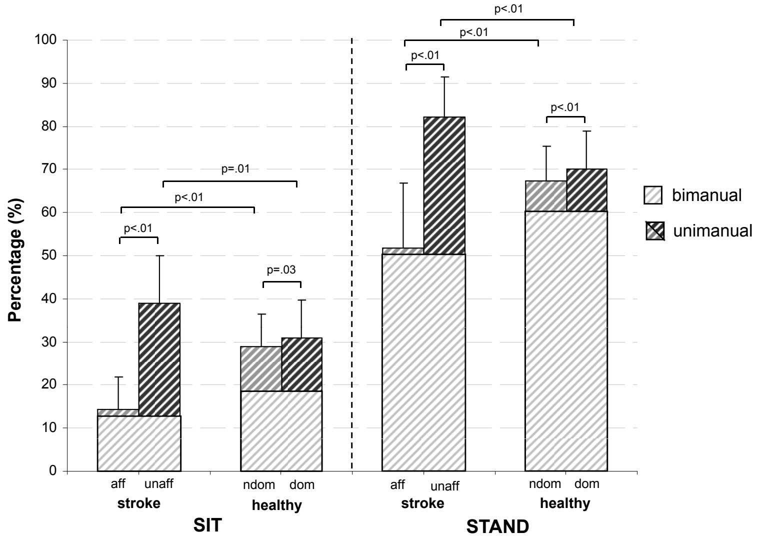

Figure 3. Upper-limb use as a percentage of total time spent sitting or standing.

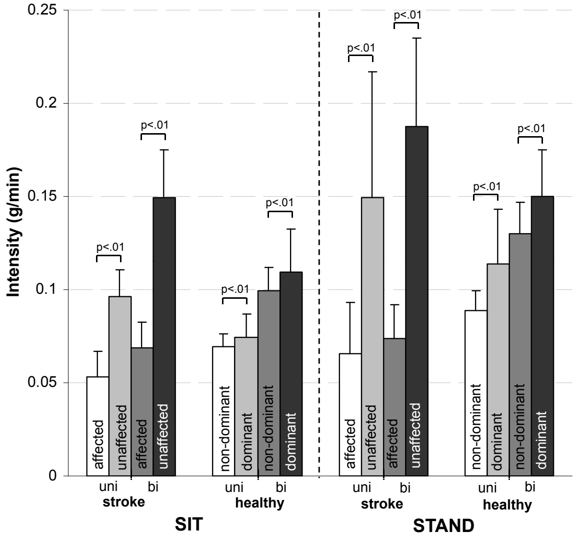

Figure 4. Intensity of upper-limb use during the periods of uni- and bimanual use.

stroke patients is bimanual; unimanual use of the paretic upper limb is nearly absent. In contrast, controls display a considerable amount of unimanual upper limb use with both their dominant and their non-dominant limb.

When focusing not on the duration of usage but on the intensity of upper-extremity usage (Figure 4), we found that intensity of upper limb use is highest during bimanual activities, both for patients and controls. In patients, intensity of the affected upper limb during bimanual use is much lower than that of the unaffected upper limb during both sitting and standing, while in controls, the intensity of the dominant and non-dominant side during bimanual use is more equal.

Finally, we assessed the influence of whole body movements on the measured amount of upper limb activity. In order to do so, we re-analyzed our data as if we would have only had placed accelerometers on both upper limbs. We thereto calculated the mean intensity of both upper limbs over the 24h measurement period, not differentiating between upper limb use during different body postures and motions. This analysis showed a lower intensity of the affected limb of stroke patients compared to controls (0.02 g/min versus 0.04 g/min), but an equal intensity of the non-affected upper limb of stroke patients and of control subjects (0.04 g/min versus 0.04 g/min).

DISCUSSION

In this study, we quantified non-use of the paretic side of chronic stroke patients in a 24 hours daily life setting by comparing the activity of the paretic side with the non-paretic side and with that of control subjects. Our main finding is that patients use their paretic side much less than controls use the non-dominant extremity. The patients compensate for this with the non-paretic side, which is used more intensive that the dominant side of the controls. As a result, the total amount of use of both upper limbs together is not much decreased in patients compared to controls, but the distribution of usage over the two limbs is highly different. Furthermore, our data show that stroke patients hardly use their paretic side unimanually, and that even during bimanual activities, the intensity of the paretic side movement is much lower than that of the non-paretic side. In summary, our data clearly show considerable non-use of the paretic side, both in duration and in intensity, and both during unimanual and bimanual activities.

Our results differ from a study of Lang et al.[9], who compared the amount of real-world upper limbs use of acute stroke patients with that of healthy controls. Their results showed that stroke patients had a reduced activity of the paretic side compared to the control group, but, contrary to their expectations, they found that patients also used their non-paretic side less than controls. This difference may be explained by the rehabilitation setting of their participants, where people do not engage in their regular activities. However, it is also possible that in the first weeks following stroke patients have not yet learned to compensate for deficits in their paretic side with their healthy side. Also, in contrast to our study, Lang et al. did not calculate upper limb use separately for the different overall activities of patients, such as lying, sitting, standing and walking. As controls are more dynamically active during the day than patients, the amount of upper limb use caused by such whole body movements will also be much higher, thereby 'artificially' increasing the difference between usage levels in patients and controls. With other words, the more active a person is, the larger the effect on the measured upper limb use when not corrected for body motion. Because chronic patients have shown to be more active than acute patients[22], it can be concluded that without correction for body motion the post-stroke stage will influence the level and ratio of upper limb use.

In the present study, we prevented this problem by measuring upper limb use with the Stroke-ULAM, which allowed us to break down upper limb use into usage during different body postures and motions, thus allowing us to discern functional upper limb use from upper limb use caused by whole body movements. To assess the influence of excluding this 'non-functional' upper limb use on the outcome of our study, we re-analyzed our data as if we would have only had placed accelerometers on both upper limbs. The results of this showed a lower intensity of the affected upper limb in stroke patients compared to controls, but no differences between the intensity of the use of the unaffected upper limb in patients and that in controls. In this set-up, we thus would not have been able to detect the compensational usage of the unaffected side, which supports the added value of the distinction between body postures and motions.

The above illustrates the large influence that whole-body-movements can have on activity results of the upper-extremity, especially when comparing upper-extremity use in groups in which levels of ambulation also differ. Often, researchers deal with this problem by presenting results as a ratio between the affected and the unaffected upper limb, which is less influenced by overall differences in ambulation levels[23]. However, our study also indicates that care should be taken when limiting the assessment of results to this ratio, as changes in the amount of use of the paretic side become impossible to discern from changes in the amount of use of the non-paretic side.

Study limitations

We acknowledge a number of limitations. First, the inconvenience of wearing the ULAM might have affected the behavior of our participants, causing a slight underestimation in the amount of use of both upper limbs in both groups. Secondly, our patients were not randomly chosen from a stroke population, but were patients participating in a clinical trial. For this trial, we excluded patients with either no voluntarily arm function, or in whom arm-hand function had been restored to almost normal levels. As such, all patients participating in the present study had a mild to moderate hemiparesis. Since this is a population that is targeted by most studies on upper-extremity rehabilitation, we feel that they do give a picture of an important part of the stroke population. Another limitation is related to the control group employed. The control subjects were matched on age and gender, but not on their home environment, marital status etc. The background of not matching on other characteristics is dual. First of all, there are many potential confounders of which the effect on daily activities have not been extensively studied, making matching almost impossible. Secondly, differences in many characteristics (such as home environment) can considered to be, at least partly, the result of the disorder, and therefore we feel that matching on such characteristics is not appropriate.

In conclusion, we showed that stroke patients have a large degree of non-use of the paretic side, but compensate for this with increased use of the non-paretic side. In addition, we showed that patients hardly use their affected side for unimanual activities, and when they use their paretic side during bimanual activities, they do so with a much lowered intensity. Although we did not directly measure this, our findings might indicate that during daily activities the paretic side is mainly used in a supporting or a fixating role during bimanual activities. Ultimately, whatever rehabilitation technique is used, any treatment should be aimed at optimizing upper-extremity function in daily life conditions. Although some techniques have more evidence than others[13], still much is uncertain about the effectiveness of rehabilitation interventions[24]. This stresses the importance of further research. We feel that detailed insight in the degree of upper limb use of both the paretic and non-paretic side contributes to designing and evaluating more optimal therapeutic interventions.

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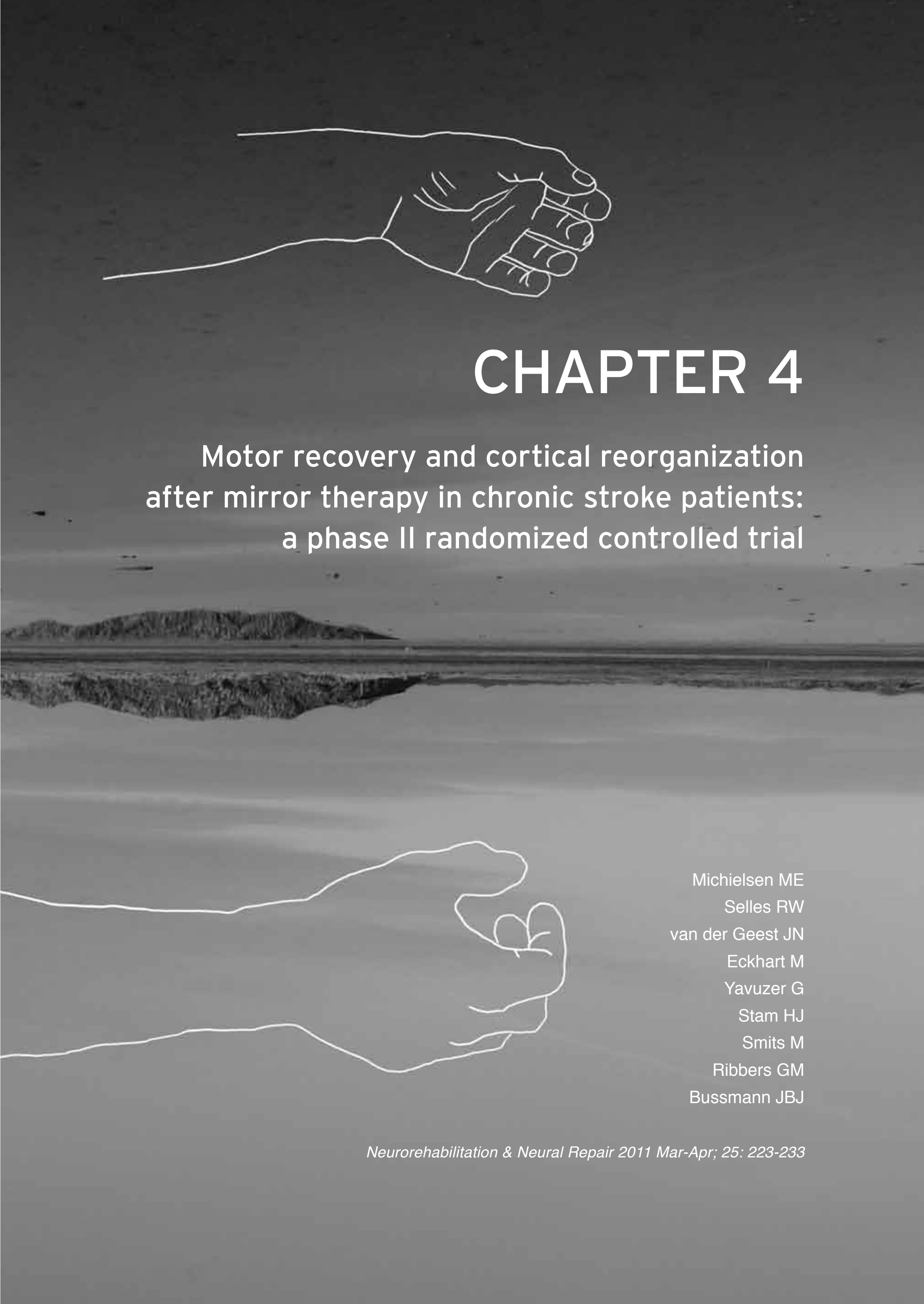

CHAPTER 4

Motor recovery and cortical reorganization after mirror therapy in chronic stroke patients: a phase II randomized controlled trial

Michielsen ME
Selles RW
van der Geest JN
Eckhart M
Yavuzer G
Stam HJ
Smits M
Ribbers GM
Bussmann JBJ

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ABSTRACT

Objective To evaluate for any clinical effects of home-based mirror therapy and subsequent cortical reorganization in patients with chronic stroke with moderate upper-extremity paresis.

Methods A total of 40 chronic stroke patients (mean time post onset, 3.9 years) were randomly assigned to the mirror group (n = 20) or the control group (n = 20) and then joined a 6-week training program. Both groups trained once a week under supervision of a physiotherapist at the rehabilitation center and practiced at home 1 hour daily, 5 times a week. The primary outcome measure was the Fugl-Meyer motor assessment (FMA). The grip force, spasticity, pain, dexterity, hand-use in daily life, and quality of life at baseline-posttreatment and at 6 months-were all measured by a blinded assessor. Changes in neural activation patterns were assessed with functional magnetic resonance imaging (fMRI) at baseline and posttreatment in an available subgroup (mirror, 12; control, 9).

Results Posttreatment, the FMA improved more in the mirror than in the control group (3.6 ± 1.5, $P < .05$), but this improvement did not persist at follow-up. No changes were found on the other outcome measures (all Ps >.05). fMRI results showed a shift in activation balance within the primary motor cortex toward the affected hemisphere in the mirror group only (weighted laterality index difference 0.40 ± 0.39, $P < .05$).

Conclusion This phase II trial showed some effectiveness for mirror therapy in chronic stroke patients and is the first to associate mirror therapy with cortical reorganization. Future research has to determine the optimum practice intensity and duration for improvements to persist and generalize to other functional domains.

INTRODUCTION

From 55% to 75% of stroke survivors have a paretic arm[1] that may improve primarily within 6 months[2]. Further intensive training can lead to improved motor function and associated cortical reorganization[3]. Yet these training programs often make use of expensive apparatus[4] or require an intensive one-on-one interaction with a therapist[5], which hinders implementation on a large scale. Mirror therapy may be a suitable alternative. Designed by Ramachandran et al[6], mirror therapy was originally developed to diminish phantom limb pain in amputees. The reflection of the unimpaired arm in a mirror gave patients the sensation of having 2 moving arms, which led to a reduction in pain. In 1999, Altschuler et al[7] introduced mirror therapy for recovery of hemiparesis following stroke. In a crossover design, they showed that motor performance of chronic stroke patients improved. Although several additional studies were small and often not well controlled[8-10], 2 recent, high-quality, randomized controlled trials have also reported mirror therapy to improve motor function in patients with subacute[11] and acute[12] stroke.

Despite the encouraging clinical results, little is known about the underlying mechanisms of mirror therapy. Ramachandran et al[6] referred to a "learned paralysis" in the brain, which could possibly be "unlearned" as a result of the mirror illusion[13]. Other studies have attributed the positive effects of mirror therapy in stroke to motor imagery[8] or the mirror neuron system[11]. The prevailing idea is that observing mirrored movements causes additional neural activity in motor areas located in the affected hemisphere, which should eventually result in cortical reorganization and improved function. Research in healthy subjects has provided some evidence of such mechanisms, with the use of either transcranial magnetic stimulation[14 15] or functional magnetic resonance imaging (fMRI)[16]. However, results of these studies are not conclusive, do not give insight into long-term neuronal changes, and do not necessarily apply to stroke patients.

The aim of this phase II study was 2-fold. First, we evaluated the effect of mirror therapy on upper-extremity function in a group of chronic stroke patients. As the intervention had to be both effective and efficient, an unsupervised training program to be performed at home was developed and carried out with supervised weekly sessions. Our primary focus was on improvements in motor function, but to get a detailed insight in any effects of mirror therapy, outcomes were also measured at the other International Classification of Functioning, Disability and Health (ICF)[17] domains. Second, we used fMRI to examine whether mirror therapy could induce cortical reorganization.

MATERIALS AND METHODS

Participants

After contacting 182 outpatients (hospitalized between January 1998 and September 2007) from the Rijndam Rehabilitation Centre in Rotterdam, the Netherlands, we enrolled 40 patients. Inclusion criteria were knowledge of the Dutch language, a Brunnström score for the upper-extremity between III and V[18] (the 6 stages of the Brunnström score range from [I] flaccidity toward [VI] full-range voluntary extension and individual finger movements present but less accurate than on the opposite side), home dwelling status, and at least 1 year poststroke. Patients with neglect, comorbidities that influenced upper-extremity usage, or a history of multiple strokes were excluded. For patients to participate in the fMRI experiment the following additional inclusion criteria applied: ability to perform a hand squeezing movement, no metal implants, no claustrophobia, and no severe obesity. The study was approved by the Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam, and all patients gave written, informed consent before participating.

Sample Size

To calculate the necessary number of patients, we performed a power analysis on data from the literature. Assuming a clinical relevance of 10% on the Fugl-Meyer motor assessment[19] (FMA) score, a standard deviation of 3.2[20], and a loss of patients at follow-up of 10%, we calculated that 20 patients in each group would be sufficient to have an 80% chance of detecting a statistically significant difference in improvements between the 2 groups.

Study Design

All participants were randomly assigned to either the experimental group receiving mirror therapy (mirror group) or the control group. One of the authors otherwise not involved in the intervention used a computer random number generator to create the randomization sequence and constructed sealed envelopes containing the assignments. Patients received their group allocation assignments after baseline measurements were performed, just before the first training session.

Measurements of upper-extremity function were performed before intervention (baseline), right after intervention (posttreatment), and 6 months after intervention (follow-up). All assessments were made by the same investigator, who was blinded to group allocation. Blinding of the patients or the physiotherapist was not possible because of the nature of the therapy. Examinations with fMRI were done in scanning sessions at baseline and posttreatment. Posttreatment clinical measurements and fMRI examinations were performed within a week after the last treatment session.

Intervention

All patients participated in a 6-week training program. Both mirror and control groups performed bimanual exercises, with the difficulty of the exercises depending on the patients' individual levels of functioning. Exercises were not only based on the Brunnström phases of motor recovery but also consisted of functional exercises such as moving objects. The control group had a direct view of both hands, whereas the mirror group practiced with the affected hand positioned behind the mirror while they looked at the reflection of the unaffected hand in the mirror. To ensure that patients focused at the mirror reflection of their unaffected hand instead of their moving unaffected hand itself, a cover was placed over their unaffected hand (Figure 1). Patients practiced at the rehabilitation center once a week under the supervision of a physiotherapist and were instructed to practice 5 times a week, 1 hour per day, at home. Home practice materials consisted of an instruction booklet with photographs and a digital video disk with film fragments of the exercises to be performed. Regular telephone calls were made by the physiotherapist to assure that patients complied with their exercise regimens. Furthermore, patients were instructed to keep detailed accounts of their practice schedules and experiences. These diaries were inspected by the physiotherapist during each training session in the rehabilitation center.

Figure 1. Setup for mirror therapy.

Outcome Measures

As mirror therapy consists of exercises mainly on the level of body function, we chose as primary endpoint the difference in improvement between both treatment groups in motor function as measured with the upper-extremity part of the FMA (including arm, wrist, and hand function measurements). Additionally, in the body function ICF domain, we measured grip force with a Jamar handheld dynamometer (Sammons Preston, Bolingbrook, IL), spasticity with the Tardieu scale[21], and pain with a visual analog scale ranging from 0 to 100 mm. In the activity domain, we measured motor capacity with the Action Research Arm Test[22], self-perceived performance with the ABILHAND questionnaire[23], and actual performance in daily life during 24 hours with the Stroke-ULAM[24]. The Stroke-ULAM consists of accelerometers placed on both arms and has been described in detail and tested for its validity in an earlier study. Because of the inconvenience of wearing the ULAM, measurements were not performed at 6-month follow-up. The ratio between the amount of use of the unaffected and the affected arms was used as outcome. In the participation domain, we measured quality of life with the EQ-5D[25]. To evaluate the effects of mirror therapy at cortical levels, we calculated the difference between groups in the change in activation balance between affected and unaffected hemispheres as measured with fMRI (see the following).

fMRI Experiment

In all, 12 patients from the mirror group and 9 patients from the control group were eligible to participate in this part of the study. During the scanning sessions, patients lay on their backs in the scanner with their upper arms comfortably resting on the scanner table alongside their torsos, with their elbows flexed so that their hands were 20 cm apart above their waists. By means of 2 mirrors attached to the head coil above each patient's head, patients were able to look in the direction of their feet and view both hands.

The experimental task consisted of 10 alternating 30-second periods of 5 rest and 5 active conditions (block design). In the active periods, patients had to open and close the affected hand; in the rest periods patients had to hold the hand still. Patients were instructed to pace the opening of their hand to a metronome with a rhythm of 0.5 Hz. The onsets of the rest and active conditions were indicated verbally by using simple words (start, rest) generated by a computer program (Matlab version 7.1; Mathworks, Sherborn, MA). Auditory stimuli were presented to the patients through MRI-compatible headphones. The hand movement was practiced before the scan session started.

Imaging was performed on a 3T MR system (HD platform, GE Healthcare, Milwaukee, WI). For anatomical reference, a high-resolution, 3-dimensional, inversion recovery, fast spoiled gradient echo, T1-weighted image was acquired (TR/TE/TI 10.7/2.2/300 ms, 18° flip angle, matrix 416 × 256, and field of view 250 × 175 mm^2). For functional imaging, a single-shot, T2*-weighted, gradient echo echo-planar imaging (EPI) sequence was used (TR/TE 3000/30ms, 75° flip angle, matrix 64 × 96, field of view 220 × 220mm^2). The imaging volume covered the entire brain, including the cerebellum.

Statistical Analyses

Clinical outcome

To test the study hypothesis, we used a generalized estimating equations approach. Under the assumption that missing data are random and not due to group allocation or treatment effect, this model estimates missing data values, thereby allowing the use of data from all participants, irrespective of whether they were measured at all time points. Each outcome measure was used as a separate response variable, and group (mirror vs control) and time (baseline vs posttreatment vs follow-up) were inserted in the model as predictors. The interaction of group × time was used to determine the efficacy of the intervention. Significance was set at .05.

fMRI data

The imaging data were analyzed using statistical parametric mapping software (SPM5; Wellcome Department of Cognitive Neurology, University College London, UK), implemented in Matlab version 7.1 (MathWorks, Natick, MA).

All functional images for each participant were realigned to the first scan of each session and then coregistered to the T1-weighted anatomical scan. Subsequently, images were transformed to standard Montreal Neurologic Institute space. To prevent warping around the lesions, we used a segmentation-based normalization approach[26]. Finally, normalized images were spatially smoothed by using a Gaussian filter of 8-mm full width at half maximum.

Preliminary analyses showed that the realignment parameters estimated during spatial preprocessing were sometimes correlated with task design. Therefore, we decided not to model the realignment parameters in the design matrix as regressors of no interest, as this would have resulted in canceling out task-related activation. Instead, we used the ArtRepair Toolbox[27 28], which evaluates all volumes and detects the ones most affected by movement. Those volumes are repaired by interpolation to avoid side effects in the high-pass filter and then deweighted in the general linear model estimation to maintain unbiased estimates. The experimental block design was convolved with the canonical hemodynamic response function, and the resulting model was estimated using a high-pass filter at 128 seconds to remove low-frequency artifacts.

In the first-level analysis, contrast maps were calculated for the active periods versus rest for each patient and each session separately. In addition, contrasts were calculated for the pretreatment versus posttreatment sessions for each patient. Contrast images from patients with left-sided lesions were flipped about the mid-sagittal plane, so that the affected hemisphere corresponded to the right side of the brain for all patients.

Second-level analyses

We merged both groups and performed a random effect analysis on the baseline contrasts of task versus rest to show the typical activation patterns. To assess the differences between groups following therapy, we concentrated on effects within certain regions of interest (ROIs). Using the Anatomy Toolbox[29] and the Anatomical Automatic Labeling Atlas (AAL)[30], we defined ROIs for each hemisphere separately for the following areas: primary motor cortex (M1), dorsal premotor cortex (PMd), primary sensory cortex (S1), supplementary motor area (SMA), and cerebellum. M1 was constructed of Brodmann areas 4a and 4p; PMd of Brodmann area 6 excluding SMA and the ventral premotor cortex (area below z = +51); S1 of Brodmann areas 1, 2, and 3. SMA and the cerebellum were integrally derived from the AAL atlas.

These ROIs were used to calculate weighted laterality indexes (wLI), which measure the relative amount of activation between the 2 hemispheres[31 32]. We chose this measure because previous research showed that it correlates with residual clinical deficit and is sensitive to detecting subtle therapy-associated changes in cortical activation[33]. Using this method, we first normalized for intersubject variations in global fMRI signal to reduce the chances of floor or ceiling values. For each condition, a threshold was defined as half the average value of the 5% highest t-values within a certain ROI. Subsequently, within that ROI, the sum of the t-values of all voxels above this threshold (sum-t) was computed. The wLI was then calculated as

$$\mathrm{wLI} = \left(\sum t_{\mathrm{ipsi}} - \sum t_{\mathrm{CONTRA}}\right) / \left(\sum t_{\mathrm{IPSI}} + \sum t_{\mathrm{contra}}\right),$$

where the subscripts contra and ipsi, respectively, refer to contralateral and ipsilateral with respect to the side of the lesion. wLI values can range between –1 and 1, with higher values indicating a larger contribution of the affected hemisphere.

Changes in wLI within each ROI for the 2 groups separately were assessed using the Wilcoxon rank sum test. Differences in the amount of change in the wLI between groups before and after treatment were assessed with the Mann-Whitney U test. We chose to use nonparametric statistics because of the risk of ceiling or floor effects (in spite of our use of the wLI instead of LI). Significance was set at .05.

Finally, a correlation analysis (Spearman's correlation coefficient) was performed to assess the relationship between changes in wLI and changes in FMA scores.

RESULTS

Table 1 presents demographic and clinical characteristics of the 2 treatment groups, showing no differences. Figure 2 shows the flow chart of the study. None of the reported dropouts were because of group allocation or treatment effect. Figures 3 and 4 show the structural brain images of the participants of the fMRI subgroup.

Clinical Measures

All patients attended all 6 training sessions in the rehabilitation center, and the home-kept diaries showed no differences in total home-based practice time between the groups. All patients kept to their regimens, which resulted in an average home training time of 30 hours.

Analyses followed the intention-to-treat principle. Table 2 shows the estimated marginal means and standard deviations for all measurement tools at baseline, posttreatment, and follow-up as well as the between-group comparisons of the change scores from baseline to posttreatment and from baseline to follow-up. Posttreatment, the mirror group had improved significantly more on the FMA than the control group ($P = .04$), but this difference was not present at follow-up ($P = .53$). No other significant effects were found between or within groups.

Cortical Reorganization

In all, 3 patients who were scanned at baseline did not complete the training program and were not scanned posttreatment. Two other patients were discarded from further analysis because their data sets contained scanner artifacts. The remaining analyses were therefore conducted on data from 9 patients in the mirror group and 7 patients in the control group. Figure 5 shows the activation maps as calculated in the random effects analysis of the task condition versus the rest condition. In general, in all sessions, activation patterns were in accordance with the expected activation for a hand motor task. Activity was observed bilaterally in the precentral and postcentral gyri

Table 1. Patient characteristics.

Characteristic	All patients		Patients with fMRI	
	Mirror group	**Control group**	**Mirror group**	**Control group**
No. of patients	20	20	9	7
Age (years)	55.3 ± 12.0	58.7 ±13.5	51.9 ± 9.3	59.0 ±10.4
Time since stroke (years)	4.7 ± 3.6	4.5 ± 2.6	6.2 ± 4.4	5.2 ± 2.5
Sex (male/female)	7/13	13/7	2/7	5/2
Affected side (dom/ndom)	6/14	6/14	2/6	3/4
Type of stroke (infarct/hemorrhage)	14/6	14/6	7/2	6/1
FMA score baseline	39.7 ± 14.1	36.4 ± 14.7	43.7 ± 12.5	36.9 ± 9.1
FMA score posttreatment	43.5 ± 14.0	36.6 ± 14.2	48.2 ± 11.2	37.6 ± 8.5
Location of stroke lesion				
Cortical (with or without subcortical)	8	5	6	2
Subcortical	7	5	3	3
Brainstem[a]	1	3	-	2
Unknown	4	7	-	-
Bamford Classification				
LACS	8	8	3	1
PACS	8	7	5	3
TACS	3	2	1	1
POCS	1	3	-	2

Abbreviations: fMRI, functional magnetic resonance imaging; dom, dominant; ndom, nondominant; LACS, lacunar stroke; PACS, partial anterior circulation stroke; TACS, total anterior circulation stroke; POCS, posterior circulation stroke.
[a]Brainstem lesions are located above the corticospinal tract.

(M1 and S1), the medial superior frontal gyrus (SMA), at the junction of the superior frontal sulcus and the precentral sulcus (PMC), and in the cerebellum.

Table 3 presents the wLI for each of the ROIs. Within M1, a difference in wLI change between the mirror group and control group was found. The activation in the mirror group shifted toward the affected hemisphere, whereas a small shift in activation toward the unaffected hemisphere was observed in the control group. In the other regions no differences in the wLI were observed between the 2 groups. No significant correlations were observed between pretreatment and posttreatment changes in wLI and FMA scores.

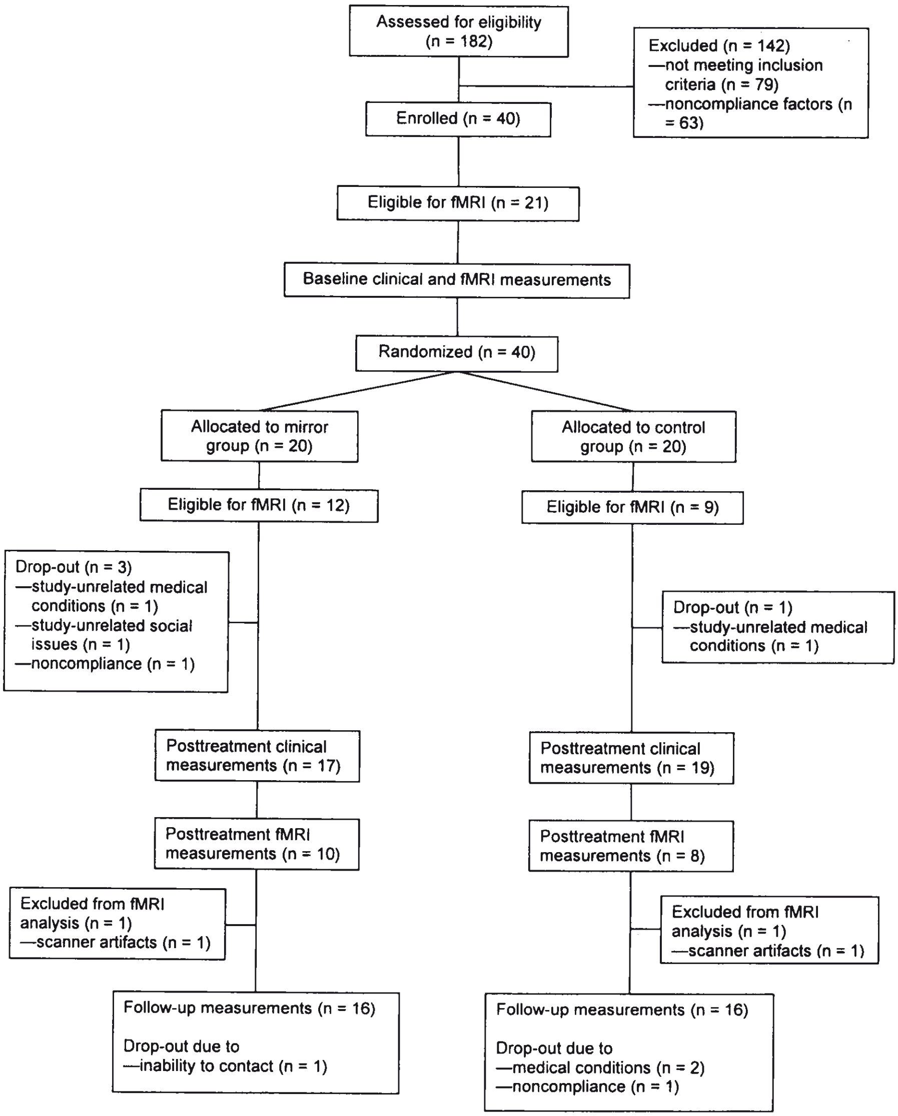

Figure 2. Flow chart.

Chapter 4

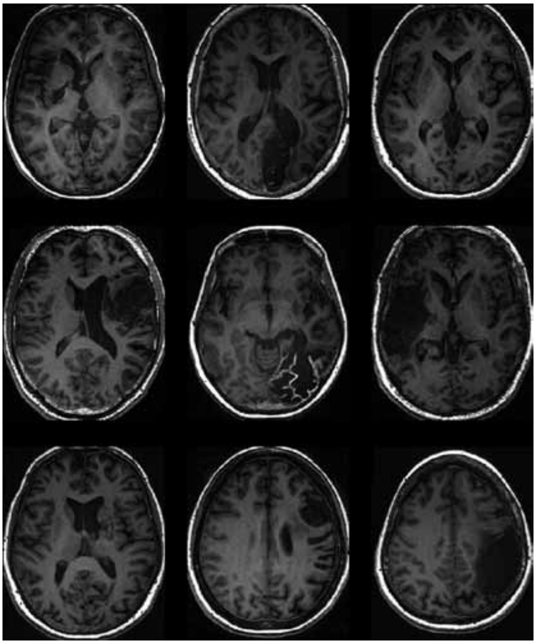

Figure 3. TI-weighted magnetic resonance imaging scans at the level of maximum infarct volume for each patient of the mirror group.

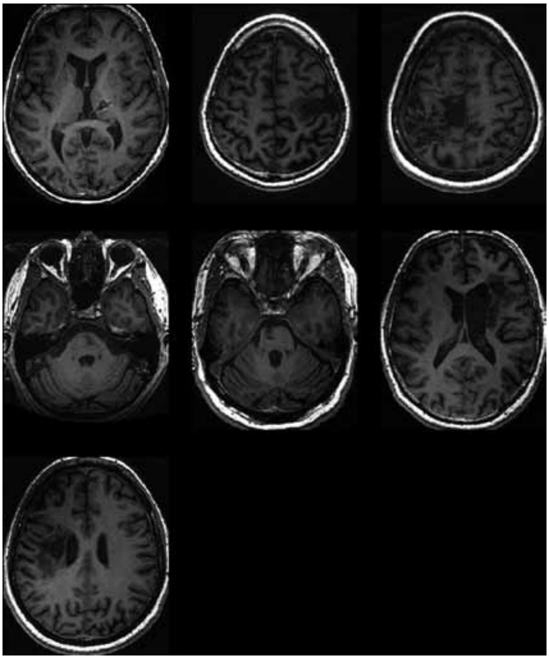

Figure 4. TI-weighted magnetic resonance imaging scans at the level of maximum infarct volume for each patient of the control group.

Table 2. Mean scores on the clinical outcome measures and their changes over time.

		Baseline[a]	Posttreatment[a]	Follow-up[a]	Δ Posttreatment (95% CI)[b,d]	*P* value	Δ Follow-up (95% CI)[c,d]	*P* value
FMA	Mirror	39.7 ± 14.1	43.5 ± 14.0	41.1 ± 14.9	3.6 ± 1.8 (0.2–7.1)	.04	1.5 ± 2.5 (-3.4–6.5)	.53
	Control	36.4 ± 14.7	36.6 ± 14.2	36.3 ± 16.2				
Grip force (kg)	Mirror	11.2 ± 7.8	12.3 ± 9.9	11.6 ± 5.7	1.2 ± 1.6 (-2.0–4.4)	.47	0.4 ± 2.4 (-4.2–5.1)	.86
	Control	15.4 ± 9.7	15.2 ± 8.5	15.3 ± 8.4				
Tardieu elbow	Mirror	61.0 ± 41.3	70.2 ± 34.8	72.3 ± 37.3	13.1 ± 9.5 (-5.5–31.7)	.17	12.4 ± 12.0 (-11.1–35.9)	.30
	Control	78.7 ± 14.3	74.7 ± 30.3	77.9 ± 31.3				
Tardieu wrist	Mirror	20.0 ± 27.0	23.6 ± 25.3	21.4 ± 21.5	-1.8 ± 6.3 (-10.9–19.8)	.79	4.5 ± 7.8 (-10.9–19.9)	.57
	Control	30.1 ± 33.0	35.5 ± 28.2	26.9 ± 25.9				
Pain (VAS [mm])	Mirror	9.3 ± 19.0	8.8 ± 10.8	8.0 ± 12.8	2.6 ± 6.8 (-9.9–15.1)	.68	-4.0 ± 8.4 (-20.4–12.5)	.63
	Control	12.3 ± 21.6	9.2 ± 14.1	14.9 ± 25.3				
ARAT	Mirror	23.8 ± 15.8	25.5 ± 17.4	24.6 ± 18.7	1.1 ± 2.0 (-2.9–5.1)	.58	0.4 ± 2.8 (-5.0–5.8)	.89
	Control	20.6 ± 17.0	21.1 ± 16.8	20.9 ± 17.6				
ABILHAND	Mirror	0.97 ± 0.90	1.35 ± 1.23	1.17 ± 1.03	0.35 ± .15 (-.13–.83)	.15	-0.04 ± .28 (-.59–.51)	.89
	Control	1.10 ± 1.32	1.13 ± 1.42	1.34 ± 1.69				
Accelerometric proportion[e]	Mirror	0.30 ± 0.14	0.29 ± 0.09		-0.01 ± .02 (-.05–.03)	.59		
	Control	0.28 ± 0.09	0.28 ± 0.13					
EQ-5D	Mirror	0.75 ± 0.11	0.76 ± 0.13	0.76 ± 0.20	-0.05 ± .05 (-.15–.06)	.38	-0.03 ± .06 (-.16–.09)	.63
	Control	0.75 ± 0.18	0.81 ± 0.12	0.79 ± 0.14				

Abbrevations: Δ indicates change; CI, confidence interval; FMA, Fugl-Meyer assessment; VAS, visual analog scale; ARAT, action research arm test; EQ-5D, EuroQol.

[a]Values are mean ± standard deviation.

[b]Between groups difference of mean change at posttreatment from baseline .

[c]Between groups difference of mean change at follow-up from baseline.

[d]Values are mean ± standard error of the mean.

[e]Accelerometric proportion was measured only at baseline and posttreatment.

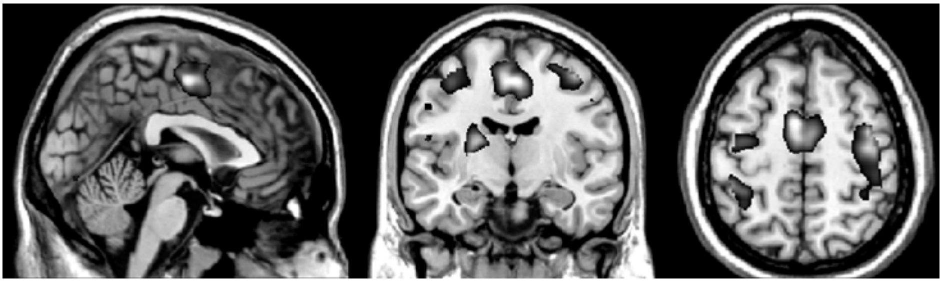

Figure 5. Activation map of the 2 experimental groups combined at baseline of the task condition versus rest (P<.0001).

Table 3. Voxel count in affected and unaffected hemisphere and Weighted Laterality Indices (wLI) for the baseline and the posttreatment fMRI examinations and the corresponding changes for each of the 5 ROIs (*P* values are estimated using the Wilcoxon (P_{within}) and the Mann-Whitney U (P_{within}) tests)[a,b].

Area		Unaffected	Affected	Unaffected	Affected	Unaffected			Affected		
		Baseline		Posttreatment		Change (95% CI)	P_{within}	$P_{between}$	Change (95% CI)	P_{within}	$P_{between}$
M1	Mirror	6268 ± 4052	8010 ± 4250	3743 ± 4321	5353 ± 2810	2525 ± 2849 (335–3715)	.04	.05	2658 ± 3554 (-74–5390)	.07	.03
	Control	4551 ± 4237	6408 ± 3952	5342 ± 3227	5419 ± 2066	-791 ± 3258 (-3804–2222)	.61		990 ± 3473 (-2223–4302)	.50	
PMd	Mirror	8182 ± 4157	12081 ± 4132	4061 ± 3859	7178 ± 4105	4121 ± 4433 (713–7529)	.05	.15	4903 ± 5354 (788–9019)	.04	.43
	Control	6339 ± 5240	9070 ± 6994	5653 ± 3265	7830 ± 6702	686 ± 5231 (-4152–5523)	.87		1240 ± 5528 (-3872–6353)	.50	
SMA	Mirror	7009 ± 4694	10534 ± 4083	3757 ± 2861	6780 ± 4097	3252 ± 3606 (480–6024)	.03	.19	3754 ± 5382 (-383–7891)	.11	.96
	Control	7183 ± 3676	8835 ± 6473	6585 ± 3413	7938 ± 5085	598 ± 4039 (-3183–4334)	.87		897 ± 7159 (-5723–7518)	.74	
S1	Mirror	10895 ± 8048	16688 ± 9845	6022 ± 5680	9620 ± 5712	4874 ± 6854 (-394–10139)	.11	.26	7068 ± 7890 (1003–13133)	.04	.49
	Control	8121 ± 5949	13339 ± 8334	7988 ± 6118	11623 ± 5593	133 ± 8167 (-7421–7687)	.74		1716 ± 6113 (-3937–7369)	.40	
CB	Mirror	5904 ± 4848	6045 ± 7228	8065 ± 10457	4905 ± 5458	-2161 ± 7862 (-8204–3882)	.86	.87	1140 ± 6734 (-4036–6316)	.52	.96
	Control	8331 ± 7215	10473 ± 8905	8828 ± 7513	6965 ± 7159	-497 ± 5497 (-5581–4587)	.90		5307 ± 9090 (-4899–11915)	.31	

Area		Baseline	Posttreatment	Change (95% CI)	P_{within}	P_{within}
M1	Mirror	0.11 ± 0.21	0.44 ± 0.50	.33 ± .39 (.03–.63)	.05	.03
	Control	0.17 ± 0.31	0.10 ± 0.38	-.07 ± .28 (-.33–.19)	.40	

PMd	Mirror	0.21 ± 0.17	0.41 ± 0.38	.20 ± .30 (-.03–.43)	.11	.43
	Control	0.05 ± 0.50	0.07 ± 0.44	.02 ± .30 (-.26–.30)	.50	
SMA	Mirror	0.24 ± 0.29	0.33 ± 0.30	.09 ± .21 (-.07–.25)	.17	.96
	Control	0.00 ± 0.30	0.11 ± 0.19	.11 ± .23 (-.10–.32)	.31	
S1	Mirror	0.12 ± 0.47	0.34 ± 0.51	.22 ± .34 (-.04–.48)	.07	.49
	Control	0.18 ± 0.40	0.19 ± 0.49	.01 ± .33 (-.30–.32	.99	
CB	Mirror	0.16 ± 0.59	0.33 ± 0.53	.17 ± .49 (-.21–.54)	.52	.96
	Control	-0.05 ± 0.48	0.13 ± 0.64	.18 ± .53 (-.31–.66)	.31	

Abbreviations: M1, primary motor cortex; PMd, dorsal premotor cortex; SMA, supplementary motor area; S1, primary sensory cortex; CB, cerebellum.
[a]P values are estimated using the wilcoxon (P_{within}) and the Mann-Withney U ($P_{between}$) Tests.
[b]All values are mean ± standard deviation.

DISCUSSION

Our study has 2 important findings. We showed that in patients with chronic stroke, practicing with a mirror resulted in modest, but statistically significant, improvements in upper-extremity motor function. This effect disappeared in the follow-up measurements and did not transfer to the ICF domains activity and participation. In addition, we demonstrated that mirror therapy caused a shift in activation balance M1 toward the lesioned hemisphere, suggesting neural reorganization. As we did not measure cortical activation at the 6-month follow-up, we do not know whether this change persisted.

The results on our clinical outcome measures are in agreement with previous studies on patients with subacute[11] and acute[12] stroke. The size of the FMA change in the present study is not very different from that in a study of patients with more acute stroke. Mirror therapy may thus be beneficial at all stages after stroke. The fact that the current study was based on unsupervised, home-based treatment is in this respect promising.

The effects we observed on motor function did not persist at the 6-month follow-up and did not transfer to any other ICF domains. This is in disagreement with the study of Yavuzer et al[11], who reported improved motor function as well as improved activities of daily living also at 6-months' follow-up. This discrepancy might be because of the more sensitive activities of daily living (ADL) measurement tool used by Yavuzer et al, as well as the difference in time post-onset. Whereas the subacute stroke patients in the study by Yavuzer et al were still in the rehabilitation center, the chronic stroke patients in our study were home based with daily living routines that were already well adjusted to their disabilities. Improvements in motor function may therefore cause less change in these routines. This lack of transfer to the activity and participation domain may also explain the lack of persistence of improvements in motor function: as patients do not involve the affected arm more in a home setting, therapeutic improvements will deteriorate more rapidly, following the "use it or lose it" principle[34].

The improvements we found in motor function did not reach the generally accepted clinically relevant level of 10%[35]. However, other training studies in chronic stroke patients have reported similarly small improvements, often using more complicated therapeutic strategies[4 36]. Although one could argue that the improvements we found are small and would not have survived a correction for the multiple comparisons (eg, a Bonferroni correction), from a clinical point of view, any improvements in this group are promising, especially considering that this was a short, easily implemented and nonintensive home training program.

A novel aspect of this study was that we evaluated the effect of mirror therapy on cortical organization. Our results suggest that after a period of mirror therapy the hemispheric activation balance shifts toward the affected hemisphere. This is in agreement with previous research showing a similar shift during the recovery following stroke[37] and after arm-tracking training[38]. At least several adaptation mechanisms occur following stroke, amongst them increased recruitment of the undamaged hemisphere[39]. Whether this increased recruitment is beneficial or detrimental remains controversial[40]. However, several studies have shown that increased activation in contralesional motor areas is associated with worse motor function[31 41], whereas a more normal distribution of hemispheric activation is usually found in better recovered patients[42]. In our study, the mirror illusion seems to bring the disturbed activation balance within the hemispheres more toward normality. Our data show that this shift in hemispheric balance was mainly caused by a decrease in contralesional M1 activation, which is also in line with previous research[31].

We found no correlation between functional gains and changes in hemispheric balance. This may be because of our small sample size and the small changes we found on both measures. Although several studies have reported correlations between recovery of motor function and changes in brain activation patterns[31 37 42], such relationships are not always found[43 44], illustrating that the relationship between measures of brain reorganization and behavioral improvement remains complex[45 46].

The question that remains is which mechanism is responsible for the functional improvements and neural changes following mirror therapy. As mirror therapy resulted in larger improvements than the control intervention, the mirror does seem to have an additional effect beyond repetitive task-orientated training[47]. It is possible that by providing an image of a normal moving hand, the mirror illusion enriches the training environment and increases somatosensory input, thereby inducing excitability of the motor cortex[40]. Research in healthy subjects using transcranial magnetic stimulation has provided some proof of such a mechanism, although these results are not conclusive[14 48]. Alternatively, the mirror illusion might increase attention to the motor task, which is known to increase cortical activity[49] and is of importance during motor recovery following stroke[42]. In literature, mirror therapy is often linked with the mirror neuron system or motor imagery. One imaging study in healthy participants provided some proof for the activation of the mirror neuron system by the mirror illusion, but again these results were not conclusive[16]. Definite evidence for the contribution of specific neural areas to the effects of mirror therapy has to come from patient studies investigating neural activation patterns directly associated with mirror viewing.

The results of the present study should be interpreted with some caution. First, our treatment groups were of only moderate size, and the findings on neural activation changes are based on only a small number of participants. Because of the latter, we were unable to perform a random effects fMRI analysis to make population based interferences. Furthermore, our sample included patients with large lesions, including partial M1 damage. Previous fMRI studies have shown, however, that partial infarction of M1 still allows for functional recovery, accompanied by adaptive functional reorganization within spared M1[44]. In addition, some of the differences in activation patterns following treatment could be because of adaptation to the scanner or task. Although the overall decrease in activation observed in both hemispheres (Table 3) indicates that some adaptation occurred, it is not likely that changes in wLI are caused by such adaptation.

The generalizability of our results has limitations. First, our sample consisted mainly of nondominant hemisphere stroke. Second, although lesion size and motor deficits of our participants were considerable compared with patients in most fMRI research, we did exclude patients with complete hemiplegia. Whereas small lesions and modest motor deficits are preferable for making strong fMRI inferences, therapies such as mirror therapy may be especially relevant for patients with large motor deficits for whom virtually no treatment is available[50].

In conclusion, our phase II trial shows that mirror therapy improves motor function in chronic stroke patients more than a control intervention and leads to changes in cortical organization. However, the clinical improvements we found were small, did not persist 6 months after therapy, and were not reflected in ICF domains of activity and participation. A key question in future research is how to augment the effect of mirror therapy. The focus herein should be on identifying the optimal treatment regimens and subpopulations for the effects of mirror therapy to persist and translate to improvements in performance of daily activities and participation.

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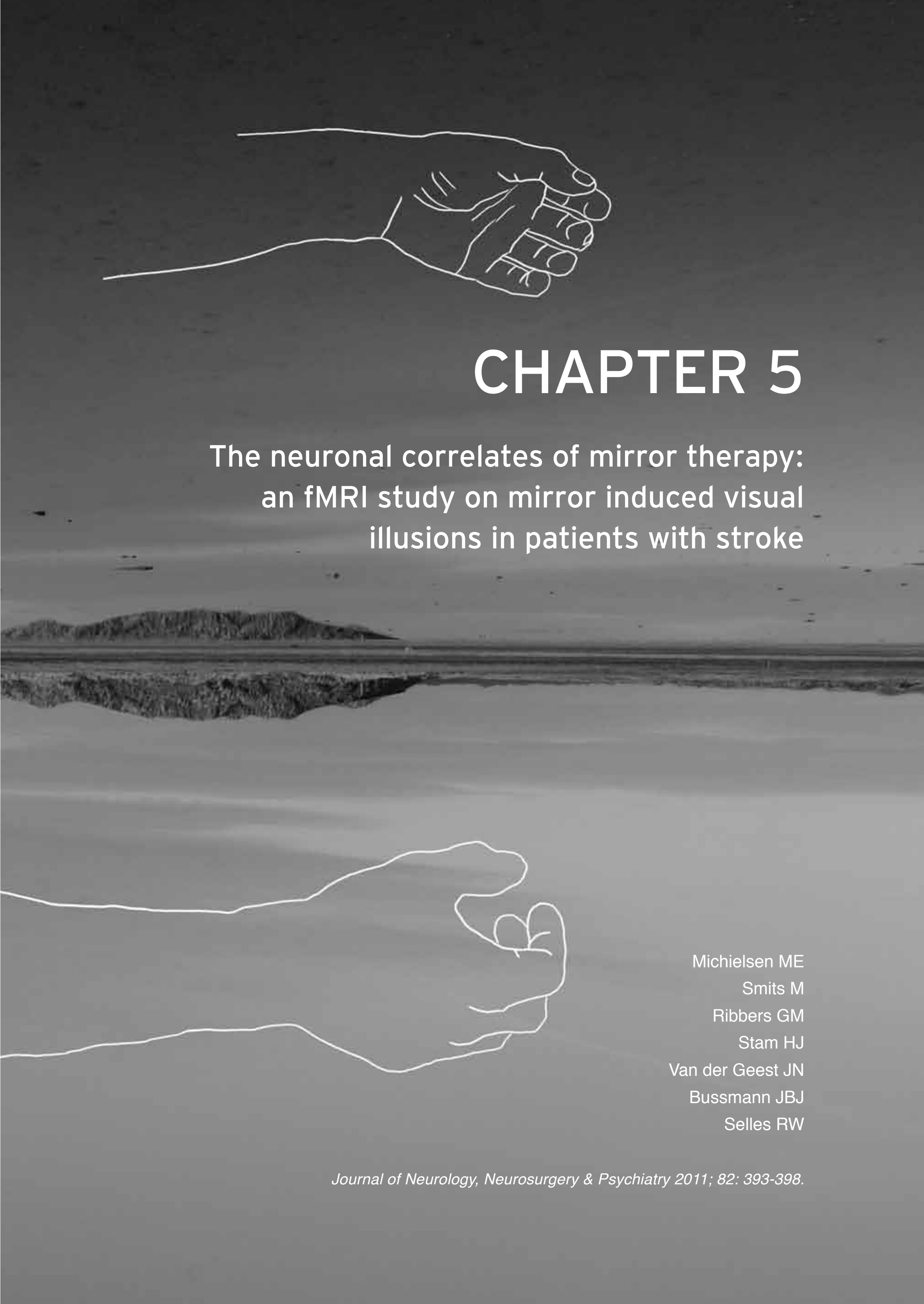

CHAPTER 5

The neuronal correlates of mirror therapy: an fMRI study on mirror induced visual illusions in patients with stroke

Michielsen ME
Smits M
Ribbers GM
Stam HJ
Van der Geest JN
Bussmann JBJ
Selles RW

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ABSTRACT

Objective To investigate the neuronal basis for the effects of mirror therapy in patients with stroke.

Methods Twenty-two stroke patients participated in this study. The authors used functional MRI to investigate neuronal activation patterns in two experiments. In the unimanual experiment, patients moved their unaffected hand, either while observing it directly (no-mirror condition), or while observing its mirror reflection (mirror condition). In the bimanual experiment, patients moved both hands, either while observing the affected hand directly (no-mirror condition) or while observing the mirror reflection of the unaffected hand in place of the affected hand (mirror condition). A two-factorial analysis with movement (activity vs rest) and mirror (mirror vs no mirror) as main factors was performed to asses neuronal activity resultant of the mirror illusion.

Results Data of 18 participants were suitable for analysis. Results showed a significant interaction effect of movement x mirror during the bimanual experiment. Activated regions were the precuneus and the posterior cingulate cortex ($p<0.05$ false discovery rate).

Conclusion In this first study on the neuronal correlates of the mirror illusion in patients with stroke, the authors showed that during bimanual movement, the mirror illusion increases activity in the precuneus and the posterior cingulate cortex, areas associated with awareness of the self and spatial attention. By increasing awareness of the affected limb, the mirror illusion might reduce learned non-use. The fact that the authors did not observe mirror-related activity in areas of the motor or mirror neuron system questions popular theories that attribute the clinical effects of mirror therapy to these systems.

INTRODUCTION

Mirror therapy was first introduced by Ramachandran and coworkers to alleviate phantom limb pain in amputees[1]. By showing patients the reflection of their unimpaired arm in a mirror, they retrieved the sensation of their amputated arm without pain. Since then, the paradigm of mirror therapy has also been studied in other pain-related syndromes (especially chronic regional pain syndrome)[2] and motor-related syndromes (stroke, hand surgery)[3 4]. The focus of these studies has been on potential clinical effects; reduction in pain and improvement of motor function. Relatively little research has focused on the mechanisms that underlie the effects of mirror therapy.

Presumably, different working mechanisms are behind the effects of mirror therapy on pain and motor symptoms. For the latter category, the focus of the current study, a number of mechanisms have been proposed. Ramachandran originally hypothesized that paralysis following stroke might have a 'learnt' component, which could possibly be 'unlearnt' by means of the mirror illusion[5]. Others suggested that mirror therapy might be a form of visually guided motor imagery[6]. Motor imagery itself has proven to be effective in the rehabilitation of patients with hemiparesis[7] and the mirror-induced visual feedback of the imagined movement might further facilitate this. In addition, it has been hypothesized that the observation of the mirror illusion might trigger the mirror neuron system (MNS)[3]. Mirror neurons were initially discovered by Di Pelligrino and coworkers in monkeys[8] and are a particular type of neurons that discharge both with performance of a motor action and with observation of another individual performing similar motor actions[9]. As single cell studies are not normally performed in the human brain, there is as yet no direct evidence for the existence of a MNS in humans. However, brain imaging data do suggest the existence of a similar system[10 11]. Previous research has indicated the potential of the MNS in motor recovery by showing that the observation of movements performed by others improves motor performance in patients with stroke[12]. It is conceivable that observing one's own mirrored movement promotes recovery in a similar way.

A number of studies have evaluated the neuronal correlates of mirror therapy by examining the observation of the mirror reflection of a moving hand in healthy subjects. These studies were based on the hypothesis that the mirror illusion would increase excitability or activity in primary motor areas in the hemisphere ipsilateral to the moving hand. Using transcranial magnetic stimulation[13-15], magnetoencephalography[16], electroencephalography[17] and functional MRI (fMRI)[18] the authors compared neuronal activity or excitability ipsilateral to the moving hand with or without observing its mirror reflection. The magnetoencephalography study reported the mirror illusion to

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suppress 20 Hz activity, indicating increased activation of the primary motor cortex[16], while the electroencephalography study reported that the mirror illusion of movement induced lateralized readiness potentials, indicating cortical motor preparation for the non-moving hand[17]. On the other hand, the transcranial magnetic stimulation studies either found no effect of the mirror illusion on motor cortex excitability[14 15] or indicated that the mirror illusion needs to be combined with motor imagery in order to increase motor cortex excitability[13]. Finally, an fMRI study from our research group[18] found no increased activity in sensorimotor areas as a result of the mirror illusion, but did find an increase in activity in the superior temporal sulcus (STS), presumed to be due to involvement of the MNS[19].

So far, no studies on the neuronal correlates of the mirror illusion have been performed in patient groups. It seems obvious that caution has to be taken when generalizing results from mirror studies in healthy participants to patients with stroke. Patients have a damaged hemisphere, and alteration of activity within that hemisphere might not be as easily achieved as in healthy participants. Furthermore, patients with stroke performing mirror therapy are generally instructed to practice bimanually, moving affected and unaffected limbs together[3 20 21]. As patients with stroke move asymmetrically, placing a mirror between their hands will give them a sudden illusion of normal movement of the involved hand, creating an incongruence between task performance and visual feedback. This situation cannot be created similarly in healthy controls, and is conceptually different from the experiments in which healthy controls move only one hand.

In summary, while clinical trials have presented promising results of mirror therapy in several patients groups, the working mechanisms have not yet been investigated in patients. Additionally, results of the studies on the working mechanisms in healthy participants have not been conclusive, and effects that have been found in these studies cannot be generalized to patients with stroke. In the present study we therefore investigated the neuronal correlates of the mirror illusion in patients with stroke. We used fMRI to compare two different sets of conditions: 1) moving the unaffected hand while observing it directly versus moving the unaffected hand while observing its mirror reflection and 2) moving both hands while observing the affected hand directly versus moving both hands while observing the mirror reflection of the unaffected hand in place of the affected hand. We hypothesized that observing the mirror reflection would increase neuronal activity in the affected hemisphere.

MATERIALS & METHODS

Participants

Patients who took part in this experiment were selected participants of a randomized controlled trial investigating the effects of a rehabilitation program of mirror therapy (http://www.trialregister.nl NTR1052). In this trial, 40 patients with stroke were included and randomly assigned to either an experimental (mirror) group or a control group. Patients from the trial that were eligible to be scanned in an MRI scanner were asked to take part in the present study. This study took place ahead of the start of the clinical trial, before patients had been allocated to a treatment group. Inclusion criteria for the randomized controlled trial were knowledge of the Dutch language, a Brunnström Score for the upper-extremity between III and V, home dwelling status and at least 1 year poststroke. Patients with neglect, comorbidities that influenced upper-extremity usage or those who had suffered multiple strokes were excluded from participation. For patients to be able to take part in the present study, the following additional inclusion criteria applied: a Brunnström score of IV or V and standard MRI exclusion criteria. Application of these criteria resulted in a total of 22 eligible patients. The study was approved by the Medical Ethics Committee of the Erasmus MC Rotterdam and all patients gave written informed consent before participating in the study. Before the fMRI experiment started the Fugl Meyer[22] assessment of upper-extremity function was administered to all participants for descriptive purposes.

FMRI experiment

The fMRI paradigm we used was based on one previously designed in our laboratory[23]. We performed two separate experiments each involving two conditions within a single scanning session. In the first experiment patients were instructed to move only their unaffected hand (unimanual), either while looking directly at it (no mirror condition) or while observing its reflection in a mirror (mirror condition). In the second experiment patients were instructed to move both their hands (bimanual) either while looking directly at their affected hand (no mirror condition) or while observing the mirror reflection of their unaffected hand in place of their affected hand (mirror condition) (see Figure 1). In all four conditions, patients could see two hands. In the no mirror conditions of both experiments, patients had a direct view of both their affected hand and their unaffected hand. In the mirror conditions, patients had a direct view of their unaffected hand and saw the reflection of their unaffected hand in place of their affected hand, also leading to visual feedback of two hands.

During scanning, patients lay on their back in the scanner with their upper arms comfortably resting on the scanner table alongside their torso and their elbows flexed in such a way that their hands were 20 cm apart above their waists. By means of two

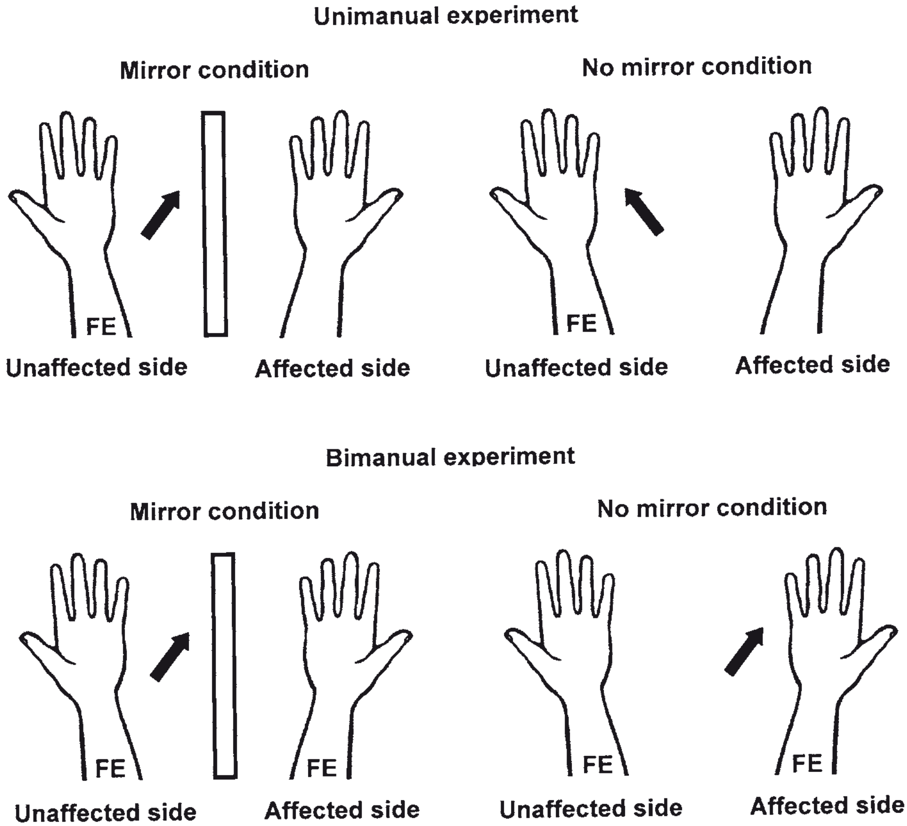

Figure 1. Schematic representation of the four conditions. FE indicates which hands perform the flexion-extension movements, and the arrow is used to indicate the direction of gaze in each condition.

mirrors attached to the head coil above the head, patients were able to look in the direction of their feet and thus could view both their hands.

All four conditions were performed using a block design, consisting of 10 alternating 30 s periods of five rest blocks and five active blocks. In the active blocks patients had to open and close either their unaffected hand or both hands, in the rest blocks patients had to hold their hands still. Patients were instructed to pace the opening of their hands to a metronome with a rhythm of 0.5 Hz. The onsets of the rest and active conditions were indicated verbally using simple words (start, rest) generated by a computer program (Matlab 7.1; Mathworks, Sherborn, Massachusetts). Auditory stimuli were presented to the patients through MRI-compatible headphones. The hand movement was practiced before the scan session started.

The four conditions were presented to the patients in random order. During the mirror conditions, a large mirror was placed between the subjects' hands in such a way that the mirror image of the unaffected hand was superimposed on the position of the affected hand. The large mirror was made of MRI-compatible material (plexiglass) and was shaped in such a way that it fitted inside the scanner bore and fully obstructed the view of the hand behind the mirror (see Figure 2). In this way, a visual illusion of two normal hands was created. Before the scanning session, patients practised outside the scanner with a regular mirror as used during mirror therapy in order to make sure they experienced the visual illusion. While it is hard to objectively quantify the presence or strength of the illusion, all subjects reported that the illusion of seeing the affected hand moving in an unimpaired fashion was similar to their experience during the mirror exercises outside the MRI scanner. Imaging was performed on a 3T MR system (HD platform, GE Healthcare, Milwaukee, Wisconsin). For anatomical reference, a high-resolution, three-dimensional, inversion recovery, fast spoiled gradient echo, T1-weighted image was acquired (TR/TE/TI 10.7/2.2/300ms, 18° flip angle, matrix 416×256, and field of view 250×175 mm^2). For functional imaging, a single-shot, T2*-weighted, gradient echo echo-planar imaging sequence was used

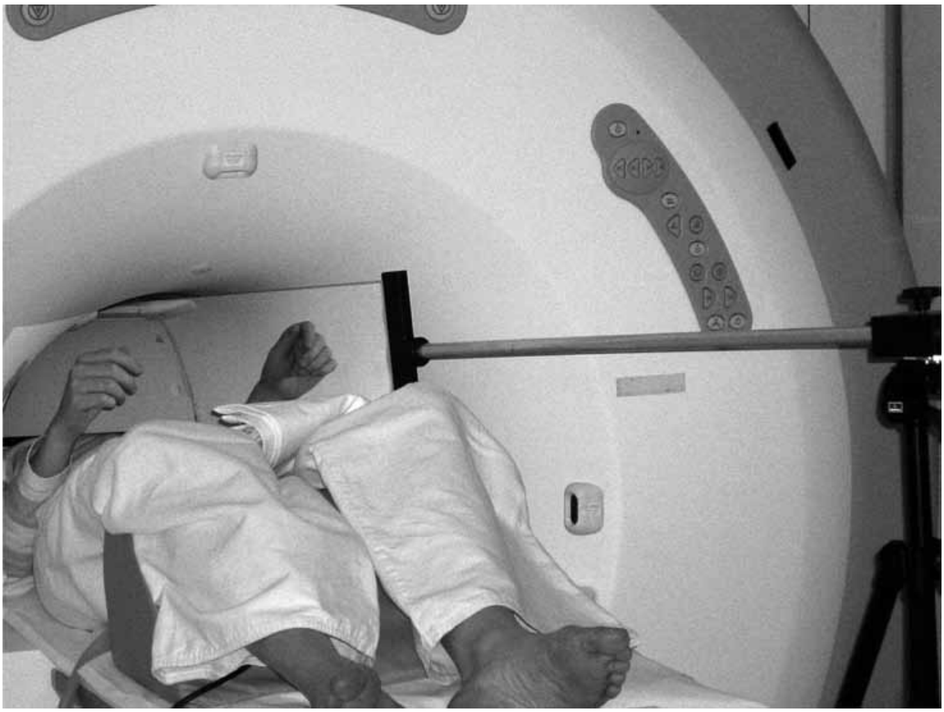

Figure 2. Participant lying in the scanner during the mirror condition. The unaffected hand is not visible, as it is positioned in front of the mirror.

(TR/TE 3000/30ms, 75° flip angle, matrix 64×96, field of view 220×220 mm^2). An fMRI acquisition lasted for 5 min 15s, including 15 s of dummy scans that were discarded. For each of the four conditions 100 volumes were collected. The imaging volume covered the entire brain including the cerebellum.

Statistical analyses

The imaging data were analyzed using statistical parametric mapping software (SPM5, Wellcome Department of Cognitive Neurology, University College London, London) implemented in MATLAB version 7.1 (Mathworks).

All functional images for each participant were realigned to the first scan of each condition and then coregistered to the T1-weighted anatomical scan. Subsequently, images were transformed to standard Montreal Neurologic Institute space. To prevent warping around the lesions, we used a segmentation-based normalization approach[23]. Finally, normalized images were spatially smoothed by using a Gaussian filter of 8 mm FWHM.

Preliminary analyses showed that the realignment parameters estimated during spatial preprocessing were sometimes correlated with the task design. Therefore, we decided not to model the realignment parameters in the design matrix as regressors of no interest, as this would have resulted in cancelling out task-related activation. Instead, we used the ArtRepair Toolbox[24], which evaluates all volumes, detects those most affected by movement, and deweights these in the general linear model estimation. The experimental block design was convolved with the canonical haemodynamic response function, and the resulting model was estimated using a high-pass filter at 128 s in order to remove low-frequency artefacts.

In the first-level analysis, statistical maps were calculated for each of the four task blocks (i.e., movement with mirror, movement without mirror, rest with mirror, rest without mirror) for each patient and each experiment (bimanual and unimanual) separately. Statistical maps of patients with left-sided lesions were flipped about the midsagittal plane, so that the affected hemisphere corresponded to the right side of the brain for all patients. The statistical maps were used for second-level analyses.

Second level analysis

We performed a two-factorial analysis with movement (activity vs rest) and mirror (mirror vs no mirror) as main factors for both the unimanual and bimanual experiments separately. Main effects of movement and mirror as well as the interaction between movement and mirror were investigated. Significance was set at $p<0.05$ (false discovery rate corrected) with a minimum cluster size of 20.

RESULTS

Four patients were discarded from further analysis, one due to scanner failure and three due to scanner artefacts in their data sets. The remaining analyses were thus conducted using data sets of 18 patients. The characteristics of these patients are presented in Table 1.

In a two-factorial design, we examined main effects of movement (task condition vs rest), mirror (mirror condition vs no mirror condition) and the interaction effect between movement and mirror for both experiments. Observed activation patterns for the main effect of movement were in accordance with the expected activation for uni- and bimanual hand motor tasks. Activity was observed in the pre- and postcentral gyrus (primary motor and sensory cortex), in the medial superior frontal gyrus (SMA), at the junction of the superior frontal sulcus and the precentral sulcus (premotor cortex) and in the cerebellum (Table 2).

Analysis of the main effect of mirror (mirror vs no mirror) showed no significant areas of activation in either of the two experiments. The interaction of mirror * movement showed no significant activation for the unimanual experiment, but it did show significant activation in the bimanual experiment, in the precuneus and the posterior cingulate cortex. Post hoc analysis revealed that this was caused by increased activity in the movement with mirror condition versus the movement without mirror

Table 1. Patient characteristics of the study participants .

Characteristic	Total*
No. of patients	18
Age (years)	54.7 ± 9.9
Time since stroke (years)	5.2 ± 3.6
Sex (male/female)	10/8
Affected side dominant/nondominant)	6/12
Type of stroke (infarct/haemorrhage)	16/2
Location of stroke lesion	
- Cortical (with or without subcortical)	13
- Subcortical	3
- Brainstem†	2
FM score	41.9 ± 11.3

*Values are mean ± SD.
†Brainstem lesions are located in the pons, above the crossing of the cortico-spinal tract.
FM, Fugl-Meyer.

Table 2. Areas of activation (main effect of movement).

Areas of activation (unimanual experiment: main effect of movement)

Anatomical location	**Side**	**Cluster size**	**Z-score**	**Montreal Neurological Institute**		
				X	**Y**	**Z**
Pre- and postcentral Gyrus	Unaffected	2103	7.57	-34	-26	54
Cerebellum	Unaffected	1287	7.28	16	-56	-20
Middle occipital/temporal gyrus	Affected	612	6.18	42	-64	4
Medial frontal gyrus, superior frontal gyrus, cingulate gyrus	Affected, unaffected	448	6.17	-6	-6	56
Middle occipital/temporal gyrus	Unaffected	491	5.98	-48	-70	-2
Precentral gyrus	Unaffected	36	5.72	-52	0	8

Areas of activation (bimanual experiment: main effect of movement)

Anatomical location	**Side**	**Cluster size**	**Z-score**	**Montreal Neurological Institute**		
				X	**Y**	**Z**
Pre- and postcentral gyrus	Unaffected	853	7.11	-42	-20	52
Medial frontal gyrus, superior frontal gyrus, cingulate gyrus	Unaffected	331	6.43	-6	-4	58
Pre- and postcentral gyrus, medial and superior frontal gyrus, cingulate gyrus	Affected	665	6.36	36	-16	56
Middle occipital gyrus, inferior temporal gyrus	Affected	33	5.63	44	-72	0
Middle occipital/temporal gyrus, inferior temporal gyrus	Unaffected	55	5.35	-46	-68	0

Areas are tresholded at $p<0.05$ (false discovery rate-corrected) with a minimum cluster size of 20 voxels.

Table 3. Areas of activation (bimanual experiment: interaction movement * mirror).

Anatomical location	**Side**	**Cluster size**	**Z-score**	**Montreal Neurological Institute**		
				X	**Y**	**Z**
Precuneus	Affected, unaffected, central	78	5.28	2	-58	58
Posterior cingulate cortex	Unaffected	117	4.68	-6	-36	8

Areas are tresholded at $p < .05$ (false discovery rate-corrected) with a minimum cluster size of 20 voxels.

condition. Table 3 and Figure 3 show the activated clusters for the interaction effect of movement * mirror in the bimanual experiment.

DISCUSSION

In an attempt to unravel the working mechanism of mirror therapy, this study investigated the neuronal correlates of the mirror-induced visual illusion in patients with stroke. In this first study, to our knowledge, in which patients with stroke participated instead of healthy volunteers, we showed increased activity as a result of the mirror illusion during bimanual movement in two areas: the precuneus and the posterior cingulate cortex. We found no differential effect on neuronal activity of the mirror illusion during unimanual movement; nor did we find any evidence for the mirror illusion to increase activity in motor areas or the MNS.
A network including both the precuneus and posterior cingulate cortex is reported to be associated with mental representation of the self[25]. More specifically, research showed that the precuneus is activated when actions are being interpreted as being controlled by the self as well as during self-centred mental imagery strategies[26] whereas the cingulate cortex becomes activated during spatial navigation[27] and has been found to process information about the spatial positions of the limbs in monkeys[28]. The mirror illusion of a normal moving affected hand thus seems to increase

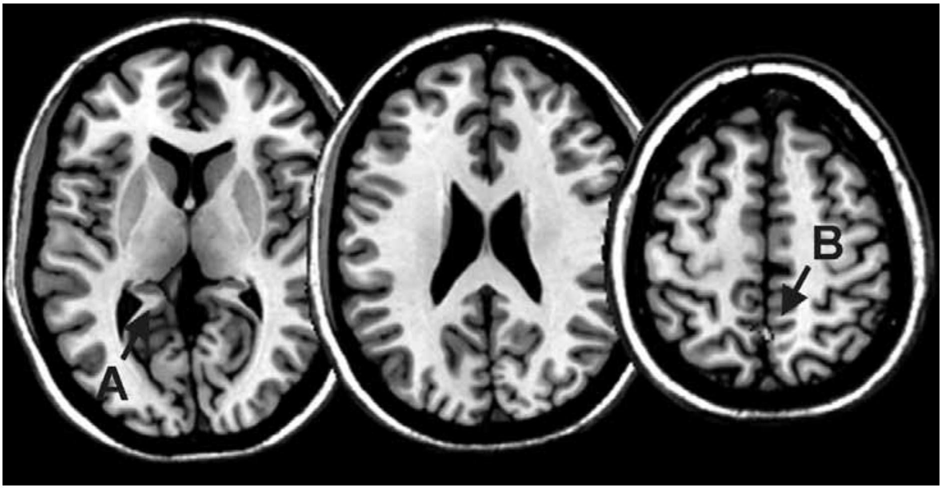

Figure 3. Activation map of the interaction effect of movement x mirror for the bimanual experiment (p<.05, FDR corrected, minimum cluster size 20). Label A: posterior cingulate cortex; Label B: precuneus.

alertness and spatial attention towards this hand. The fact that we did not find this activation during the unimanual condition, suggests that it is not so much the illusion of a virtual moving hand that causes this activation, but the mismatch between the movement one performs and the movement that is observed. Research showing that the cingulate cortex becomes activated during conflict monitoring, specifically during action conflicts, supports this[29].

Two previous studies in healthy participants have reported increased neuronal activity in similar areas as a result of an incongruence between movement observation and action[30-32]. Dohle et al.[30] found that such incongruence increased activation in occipital and posterior parietal areas, amongst them the precuneus, which they suggest to play a decisive role during mirror therapy[21]. In an earlier experiment Fink et al.[31] also reported on the neural correlates of a conflict between visual and proprioceptive information. Using positron emission tomography, they investigated the effect of the mirror illusion during either in-phase movements or out-of-phase movements that are perceived as in-phase movements due to the mirror. Their results showed an effect of the mirror in the dorsolateral prefrontal cortex (DLPCF) and in the superior posterior parietal cortex (Brodmann's area (BA) 7). BA 7 is a point of convergence between vision and proprioception and plays a role in visuo-motor coordination. The precuneus, which in our study became activated during the bimanual mirror condition, is part of BA 7[26] but is located more medial than the area of activation reported by Fink et al. The main difference between our study and Fink et al.'s is that in the latter, participants actively had to create the motor-sensory conflict (by moving out of phase), while in our patient group this resulted from the involved arm not being able to perform similar movements as the non-involved arm. The situation created by Fink et al. likely induces a larger cognitive burden for the participants, which may explain increased DLPCF activation, while the main effect of the mirror they observed in BA 7 is in line with our findings of precuneus activation in the presence of a motor-sensory conflict, albeit under different experimental settings.

The question is how the involvement of the areas we found activated by the mirror illusion relates to the reported improvements in motor function following mirror therapy[3 21]. Possibly, by increasing the spatial attention towards the affected limb, the mirror illusion might help in overcoming the learnt non-use phenomenon[21 33], and as a result of the ensuing increased use of the limb improve motor performance. An alternative hypothesis, supported by the fact that we only observed increased cortical activation during the bimanual experiment, might be that the effects of the mirror lie in an enhancement of spatial coupling between limbs. It is well known that when two arms move simultaneously, movements become more temporally and spatially stable[34]. In stroke rehabilitation, this phenomenon has been exploited in the form of bimanual training programs. Several studies have shown that bimanual training strategies have a favorable effect over unimanual training[35], demonstrating that spatial coupling can cause the affected limb to take on the properties of the non-affected limb, thereby improving motor performance. The hypothesis that the mirror illusion enhances this spatial coupling is supported by studies on healthy volunteers, showing that the mirror illusion increased the tendency of one limb to take on the spatial properties of the other limb[36 37].

So far, several reviews and clinical studies have attributed the effects of mirror therapy to activation of motor areas or the MNS[3 38-40]. As mentioned, in the present study we did not observe activation resulting from the mirror illusion in these areas (eg. M1, PMC, SMA, Broca area), neither in the unimanual experiment or in the bimanual experiment. Research performed in healthy subjects has also been unable so far to provide convincing evidence for the activation of these areas by the mirror illusion; only the fMRI study by Matthys et al. showed some evidence for MNS activation by reporting increased activation within STS[18]. However, although STS is reported to be related to the MNS[19], this area has been associated with many different behaviors, and its exact function remains poorly understood[41]. Matthys et al. also reported activation in the superior occipital gyrus, an area connected with the PPC trough the dorsal stream. Activation of this area may reflect increased attentional demands for the integration of vision and proprioception induced by the mirror, which is in line with our present results. It should be noted that the analysis strategy of Matthys et al. differed from the strategy employed in the present paper. Contrary to our approach, Matthys et al. did not apply an ANOVA design and thus did not examine the effect of the mirror, the hand motor performance and its interaction separately. As a final note on the proposed activation of the MNS or motor system by the mirror illusion, a previous study showed that whereas observation of actions attributed to another individual activated the motor system, observation of identical actions linked to the self did not[42]. The MNS thus seems to distinguish between observing actions linked to the self and actions linked to others. This finding further undermines the notion that the mirror illusion of self-performed movements might trigger the motor or MNS.

We acknowledge that our study has some limitations. In general, detecting study-related effects in fMRI experiments in patients with stroke is difficult, as the neuronal circuitry may be distorted and heterogeneous between subjects. Some authors try to get around this issue by including only patients with minor lesions, which is a major source of selection bias. In the current study, in order to enlarge the contrast between mirror and no mirror conditions in the bimanual experiment, we explicitly enrolled patients with larger motor deficits. Consequently, the within-group variability was considerable, which may have decreased the power to detect differences between conditions. Another issue, related to the severity of their motor deficit, is that some patients had problems keeping their head still during the experimental task. As these movements were task-related, we could not simply regress head motion-related activation as this would have cancelled out task-related activation as well. However, we used an alternative, sensitive method to deal with this issue (see Methods), and the activation patterns we observed are in accordance with the expected activation for uni- and bimanual hand motor tasks, implicating the validity of our analysis. A general limitation of this and similar studies is that it is difficult to objectify the strength of the illusion patients experience when inside the scanner. To maximize the mirror illusion during scanning, all patients practiced with a standard mirror used for mirror therapy outside the scanner, and they all reported similar illusion strength during the measurements inside the scanner as outside.

In conclusion, the present study showed that during bimanual movement, the mirror illusion alters neuronal activation in the precuneus and posterior cingulate cortex, areas related to alertness and spatial awareness. We did not find any differential effect on neuronal activity of the mirror illusion during unimanual movements; nor did we find evidence for the mirror illusion to increase activity in motor areas. By increasing awareness of the affected limb, possibly due the mismatch between action and observation, the mirror illusion might reduce learnt non-use. The fact that we did not observe any activation in areas belonging to the motor or MNS questions popular theories that contribute the clinical effects of mirror therapy to these systems. As research into the working mechanism of mirror therapy has so far mainly focused on these systems, we suggest that future research should adopt a broader perspective, among other things taking the ideas as proposed in this paper into account. Since a better understanding of why and how mirror therapy works may lead to a more effective application and might help in selecting patients for which mirror therapy will be most effective, it is important that efforts to unravel the neuronal correlates of mirror therapy continue.

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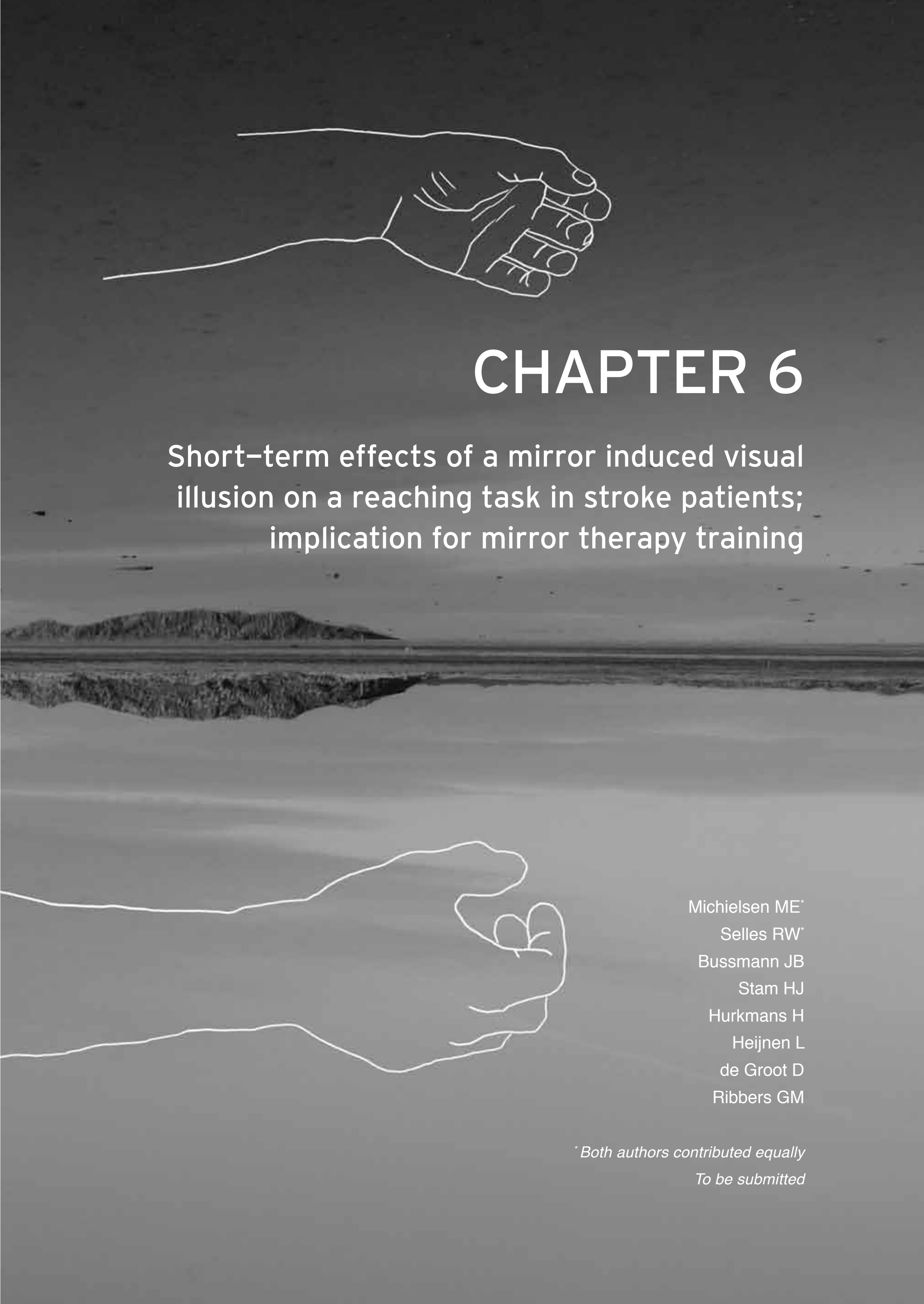

CHAPTER 6

Short–term effects of a mirror induced visual illusion on a reaching task in stroke patients; implication for mirror therapy training

Michielsen ME*
Selles RW*
Bussmann JB
Stam HJ
Hurkmans H
Heijnen L
de Groot D
Ribbers GM

** Both authors contributed equally*

To be submitted

ABSTRACT

Objective to gain insight in the relative contribution of a mirror in training a reaching task and in the differences in unilateral and bimanual training paradigms with and without the use of a mirror.

Methods We included 93 stroke patients who were at least 6 months post stroke. Participants were instructed to perform a reaching task as fast and as fluently as possible. After six baseline trials with the paretic arm side and with direct visual control, patients were randomly allocated to one of the five experimental groups: 1) task performance with the paretic arm with direct view (Paretic-No Mirror condition), 2) task performance with the non-paretic arm with direct view (Non-paretic-No Mirror condition), 3) task performance with the non-paretic arm with mirror reflection (Non-paretic Mirror condition), 4) task performance with both sides and with a non-transparent screen preventing visual control of paretic side (Bilateral-Screen condition), 5) task performance with both sides with mirror reflection of the non-paretic arm (Bilateral-Mirror condition). Patients practiced the task 70 times under the allocated experimental condition. As follow-up measurement, patients again performed 6 trials using only their paretic side and with direct visual control. Kinematic data from the arm and trunk were recorded and primary outcome measure was the movement time of the reaching task.

Results We found the largest intervention effect in the Paretic-No Mirror condition. However, the Non-paretic-Mirror condition was not significantly different from the Paretic-No Mirror condition, while the Unaffected-No Mirror condition had significantly less improvement than the Paretic-No Mirror condition. In addition, movement time improved significantly less in the bimanual conditions and there was no difference between both bimanual conditions.

Conclusion The present study confirms that using a mirror reflection can facilitate motor learning. In contrast to some previous literature, our data indicate that bimanual movement using mirror training may be less effective than unilateral training, at least for learning this relatively simple reaching task.

INTRODUCTION

It has been reported that 55% to 75% of stroke survivors suffer from a paretic arm[1]. Intensive, task-specific training programs has been shown to improve motor function, even in patients in the chronic phase of stroke[2], but are generally time consuming and expensive. Mirror therapy, originally designed by Ramachandran and co-workers to alleviate phantom limb pain[3], is a cheap and promising intervention to improve upper limb function in acute[4], sub-acute[5] and chronic stroke patients[6].

While most studies on mirror therapy indicate improved motor performance in stroke patients, the reported size of improvements has been relatively small[4 6]. In addition, there are differences between studies in how mirror therapy is performed. Amongst others, differences exist in whether the patient is instructed to move the paretic hand behind the mirror as much as possible together with the uninvolved hand in front of the mirror or whether to practice unimanually, only with the non-paretic arm. Moving both the paretic and non-paretic arm together provides a direct motor training paradigm related to bimanual training programs[7]. The surplus value of the mirror reflection is that the mirror replaces feedback on movement of the affected side with a form of 'virtual feedback' that creates the illusion that the paretic side moves with a normal movement pattern. However, from the relatively small number of trials and the lack of a direct comparison of different types of mirror training, the most optimal training is presently unclear.

While from a motor learning perspective it may be most effective to instruct patients to move the paretic side behind the mirror as much as possible, it could be argued that the strength of the mirror illusion decreases as a result of paretic side movement, as it causes an incongruence between task performance and visual feedback. In addition, movement of the paretic arm behind the mirror may increase proprioceptive feedback of the arm behind the mirror, which then may partly disrupt the visual illusion. This would suggest that movement of the arm behind the mirror may not be beneficial and may even be detrimental. Currently, there are insufficient empirical data or theoretical support to support either bilateral or unilateral treatment paradigms.

The aim of the present study was to gain insight in the relative contribution of a mirror in training a reaching task and in the differences in unilateral and bimanual training paradigms with and without the use of a mirror. We used a short-term motor learning task, which allowed us to compare several conditions in an effective, controlled manner. The aim was not to create a clinically meaningfully change in arm function, but to study the effects of the different learning conditions.

METHODS

Participants

Patients were recruited from Rijndam Rehabilitation Centre Rotterdam, Rehabilitation Centre Blixembosch Eindhoven and Rehabilitation Center Leijpark Tilburg, all located in the Netherlands. After contacting 252 outpatients (hospitalized between January 1998 and August 2010), 93 patients were enrolled who were at least 6 months post stroke. Inclusion criteria were knowledge of the Dutch language, home dwelling status, and a Brunnström score for the upper-extremity between III and VI[8]. The 6 stages of the Brunnström score range from [I] flaccidity to [VI] full-range voluntary extension and individual finger movements although less accurate than on the opposite side. Patients with neglect, comorbidity that influenced upper-extremity usage, or a history of multiple strokes were excluded from participation.

Sample size

The sample size was calculated on data from a study of Cirstea and Levin[9], on which our experimental paradigm was based. Assuming a standard deviation of .20s, we calculated that 12 patients in each group would be sufficient to have an 80% chance of detecting a statistically significant difference in improvements of .25s between any 2 groups. To increase the power, we aimed for a total of 20 patients in each groups.

Clinical assessment

Before the start of the experiment, motor ability of the participants was evaluated with the Fugl-Meyer Assessment[10 11]. The upper-extremity part of the FMA examines voluntary movements and the ability to execute upper limb movements outside of synergies. It consists of 9 components: reflexes, flexor synergy, extensor synergy, movement-combining synergies, out of synergy movement, normal reflex activity, wrist, hand, and coordination speed. The FMA scores range from 0 to 66, with higher scores indicating better motor recovery.

Experimental procedure

Our experimental paradigm was based on a study of Cirstea and Levin[9]. Participants had to perform a simple motor task consisting of a pointing movement with the index finger. Participants had to move their index finger from a target located next to their chair towards a target located in front of them (Figure 1). The distance and height of the end target was adjusted according to the length and ability to extend the arm for each subject. The target was placed such that, at the end of the pointing movement, the finger just did not make contact with the target. A computer-generated sound indicated the start of the trial, and patients were instructed to maintain their finger

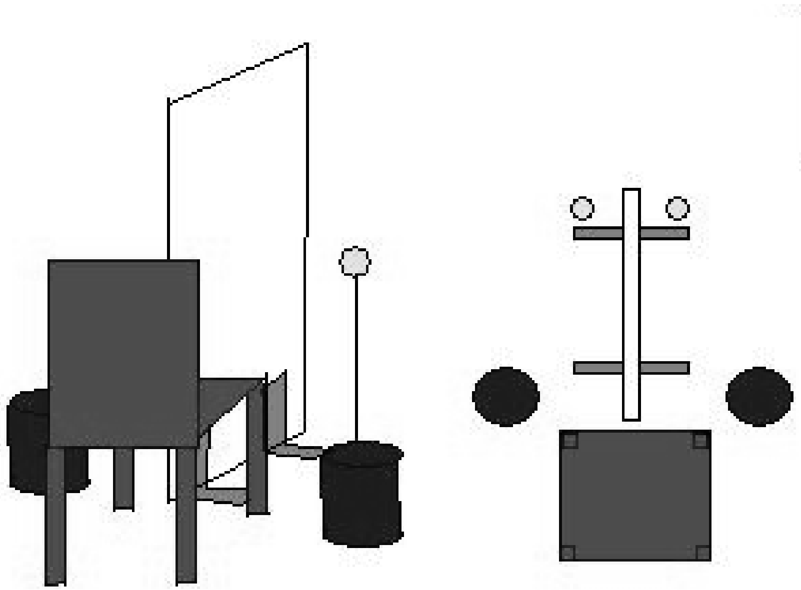

Figure 1. Side view and top view representation of the measurement setup. The participants had to move their index finger from a target located next to their chair towards a target located in front of them. The distance and height of the end target was adjusted according to the length and ability to extend the arm for each subject. The target was placed such that, at the end of the pointing movement, the finger just did not make contact with the target. During the measurements of baseline and follow-up performance, subjects moved only the involved hand. Based on the experimental condition, a mirror could be placed between both hands.

at the final position until a second sound indicated the end of the trial. Patients were instructed to move as fast and as fluently as possible towards the target.

All participants began with performing the reaching task with their paretic side and with direct visual control. A total of six trials served as baseline measurements. After these first six trials, patients were allocated to one of the five experimental groups (see below), and practiced the task 70 times under the allocated experimental condition. After the practice period, they again performed 6 trials using only their affected side with direct vision, which served as follow-up measurement.

Experimental conditions

Participants were randomly assigned to one of the five experimental conditions. To minimize possible confounding effects of motor ability and age, we stratified participants into groups based on age (older or younger than 55 years of age) and motor function (Fugl Meyer score smaller or larger than 50). In this way we created four strata, which were all randomized separately into the experimental groups.

The experimental conditions were as follows: 1) task performance with the paretic arm with direct view (Paretic-No Mirror condition), 2) task performance with the non-paretic arm with direct view (Non-paretic-No Mirror condition), 3) task performance with the non-paretic arm with mirror reflection (Non-paretic-Mirror condition), 4) task performance with both sides and with a non-transparent screen preventing visual control of paretic side (Bilateral-Screen condition), 5) task performance with both sides with mirror reflection of the non-paretic arm (Bilateral-Mirror condition).

Data acquisition and analysis

Kinematic data from the arm and trunk were recorded with a three-dimensional optical tracking system (Qualisys, Sweden). Reflecting markers were placed on the tip of the index finger, on the middle of the third metacarpal bone, on the wrist at the head of the ulna, on the elbow at the lateral epicondyle, on the shoulders at ipsilateral and contralateral acromion processes and on the trunk at the top of the sternum. Movements were recorded for 3–5s at 420Hz. Based on the recordings, 3D position profiles were created with Qualisys Track Manager (1.5.1.x).

Outcome measures

Based on the study of Cirstea and Levin[9], we defined the movement time of the reaching task as the primary outcome measure of the present study. As secondary outcome measures, we determined reaction time, peak movement velocity, and the precision of reaching the target. In addition, the number of peaks in the velocity profile were calculated as a measure of the smoothness of the trajectory.
To calculate the outcome measures, first, raw X-Y-Z position data were pre-processed using a smoothing filter with a cutoff frequency of 8 Hz. The velocity of the index finger was then obtained by differentiating x, y and z marker positions. To determine the beginning and the end of the movement, we used a two step-approach, wherein we first low-pass filtered the signal at a very low frequency (2 Hz) to obtain a global estimate of the end-point in the signal. To estimate the exact end point, we used a model of Schot et al.[12], wherein multiple sources of information are combined. For the present study, we combined the distance from the target, the velocity in forward (y) direction and the time since movement in the model to predict the exact end of the movement.

Movement time was defined as the time between start and end of the movement. Reaction time was defined as the time between the start signal and the start of the movement. Peak velocity was defined as the highest value in the velocity scalar, as calculated from the filtered x-y-z velocities. Movement precision was defined as the smallest difference between the tip of the index and the target position en smoothness was defined as the number of peaks in the filtered velocity signal.

Statistical analysis

For each task and parameter, individual mean values and coefficients of variation for the 5 baseline and follow-up trials were calculated and used for group analysis. We omitted the first trial of the 6 baseline and follow-up trials. A linear mixed-model analysis was used to test for differences in the intervention effect (the differences between baseline and follow-up) between the different conditions. In this mixed model approach, we included a random effect for the slope (change in measure between baseline and follow-up) and for the baseline value per patients.

The condition, time (difference baseline and follow-up) and the interaction between condition and time were used as fixed effects. The linear mixed-model compared condition 1 (Paretic-No Mirror condition) with each of the other four conditions. In addition, we compared condition 2 (Non-paretic-No Mirror) with condition 3 (Non-paretic-Mirror) and we compared condition 4 (Bilateral-Screen) with condition 5 (Bilateral-Mirror) since these pairs comprised of similar conditions except for the mirror effect. Furthermore, we compared the two mirror conditions (Non-paretic-Mirror plus Bilateral-Mirror) with the two no-mirror conditions (Non-paretic-No Mirror and Bilateral-Screen). All statistical analyses were performed using SAS and a $p<.05$ was considered statistically significant.

RESULTS

Ninety-three patients participated in this study. Table 1 shows the patient characteristics of all five experimental groups. While we found relatively large differences in the time since stroke between groups, we did not find a significant correlation ($r=.151$, $p=.155$) between this variable and the primary outcome measure (the change in movement time between baseline and follow-up). Therefore, we did not further correct for the time since stroke between groups.

Figure 2 shows the results of the primary outcome measure (movement time) before and after the 70 training trials in each of the 5 different conditions. We found an overall time effect between the baseline and follow-up measurements ($p<.0001$), indicating that the groups significantly improved following the reaching exercises. The largest improvements in movement time were seen in Paretic-No Mirror condition and the Non-paretic-Mirror condition, which were not significantly different from

Table 1. Patients characteristics. Values are mean (SD).

	Affected-Only	**Unaffected-No Mirror**	**Unaffected-Mirror**	**Bimanual-No Mirror**	**Bimanual-Mirror**
No. of patients	17	21	20	18	17
Age (years)	57 (11)	60 (9)	58 (12)	58 (11)	57 (11)
Time since stroke (month)	36 (31)	41 (39)	35 (35)	24 (18)	22 (15)
Sex (male: female)	10:7	13:8	13:7	7:11	12:5
Affected side (dominant : non-dominant)	8:9	11:10	9:11	12:6	10:7
FM score	50.5 (10.9)	45.6 (13.4)	45.7 (16.0)	47.3 (13.6)	50.0 (10.2)
Baseline recordings					
Movement time (sec)	1.44 (.33)	1.36 (.43)	1.36 (.39)	1.20 (.29)	1.30 (.38)
Reaction time	.42 (.16)	.43 (.18)	.45 (.18)	.39 (.18)	.42 (.19)
Peak velocity (m/s)	1.20 (.40)	1.25 (.42)	1.26 (.48)	1.29 (.35)	1.43 (.43)
Number of peaks (n)	3.5 (2.1)	2.9 (2.1)	2.9 (1.9)	2.4 (1.5)	2.9 (1.9)
Precision (cm)	.12 (.11)	.13 (.08)	.14 (.10)	.17 (.11)	.12 (.08)

FM: Fugl-Meyer.

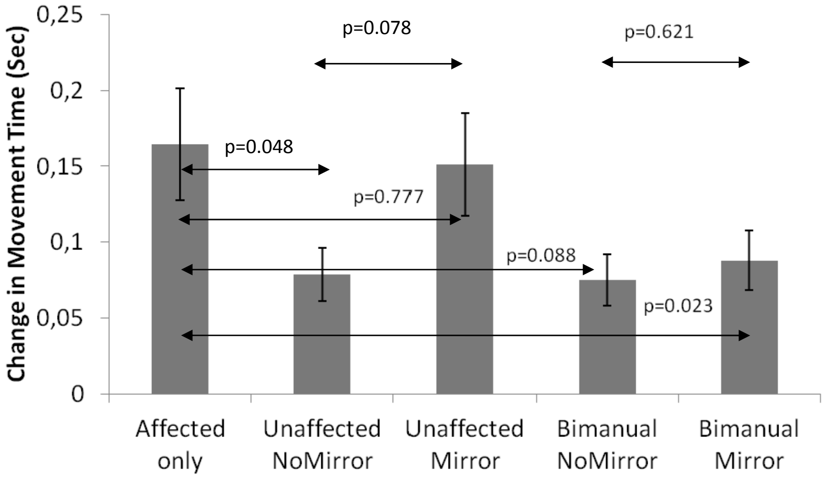

Figure 2. Mean (SEM) change scores in movement time during the five different conditions. The p-values indicate the difference in change scores between the Affected-Only condition with each of the other four conditions. In addition, p-values are shown between both Unaffected-conditions and both Bimanual conditions.

each other. In constrast, the improvements in the Non-paretic-No Mirror condition and the Bilateral-Mirror condition were significantly smaller than the Paretic-No Mirror condition, and the Bilateral-Screen condition approached statistical significance. When comparing the Mirror conditions with the No Mirror conditions, we found a trend towards a larger improvement in the Non-paretic-Mirror condition versus the Non-paretic-No Mirror conditions (p=.078) while both Bimanual conditions showed no significant difference (p=.621). Finally, the comparison of the combined Mirror conditions (Non-paretic-Mirror plus Bimanual-Mirror) versus the combined No Mirror conditions (Non-paretic-No Mirror plus Bimanual-Screen) was not significantly different (p=.102).

The changes between baseline and follow-up measurements for the secondary outcome measures are shown in Table 2. We found no time-effects between the baseline and follow-up measurements for the reaction time and the movement precision, while we did find significant time effects for the peak velocity and the number of peaks. When comparing the change scores of the Paretic-No Mirror condition with the other four conditions, we generally found no significant differences. Only for the peak velocity, both bimanual conditions (Bilateral-Screen and Bilateral-Mirror) improved significantly less than the Paretic-No Mirror condition.

Table 2. Mean (SD) of the outcome of the changes between baseline and follow-up for the secondary outcome measures. The reported p-values correspond to the differences in the change between baseline en follow-up for that specific condition compared to the change between baseline and follow-up in the first condition (AFF).

		Affected-Only	**Unaffected-No mirror**		**Unaffected-Mirror**		**Bimanual-No mirror**		**Bimanual mirror**	
	p-value for overall intervention effect	Change	Change	p-value	Change	p-value	Change	p-value	Change	p-value
Reaction time (sec)	.19	.023 (.091)	-.001 (.083)	.47	-.018 (.111)	.21	.006 (.085)	.61	-.019 (.067)	.17
Peak velocity (m/s)	<.01	,153 (,318)	,058 (,178)	.18	,088 (,203)	.35	-,016 (,184)	.03	-,010 (,313)	.04
Number of peaks (n)	<.01	-.747 (1.622)	-.328 (.908)	.22	-.566 (1.214)	.59	-.329 (.628)	.51	-.188 (1.094)	.13
Movement Precision (cm)	.06	,021 (,051)	,006 (,008)	.20	,003 (,024)	.15	,013 (,023)	.98	,019 (,028)	.71

DISCUSSION

The aim of the present study was to gain insight in the surplus value of a mirror in exercising a reaching task and in the differences in unilateral and bilateral training paradigms with and without a mirror in patients in the chronic stage after stroke. We found a significant overall intervention effect on movement time, indicating a learning effect after 70 training movements. When comparing the conditions, we found the largest intervention effect in the Paretic-No Mirror condition in which only the paretic hand was trained and in the Non-paretic-Mirror condition. The Non-paretic-No Mirror condition showed significantly less improvement than the Paretic-No Mirror condition. In addition, improvement in movement time was significantly smaller in the Bimanual-Mirror condition, while there was a trend that the improvement in the Bimanual-No Mirror condition also was significantly smaller that the Paretic-No Mirror condition.

To our knowledge, this is the first study to compare a larger number of mirror and no-mirror training paradigms in stroke patients. Previous studies on mirror therapy in stroke were mainly case series (e.g.,[13 14]) or randomized controlled trials (e.g.,[4-6]) on the effects of several weeks of mirror training using functional measures such as the Fugl Meyer score and the FIM scores as outcomes. In these trials, heterogeneous treatment paradigms are used both in the mirror training and the control groups. In the first mirror therapy study on stroke patients, Altschuler et al.[15] compared mirror training with the same training but using a non-transparent screen between both hands. Training was bimanual in the sense that patients were instructed to also move the involved hand. Similar instructions were given in the trials by Michielsen et al.[6] and Dohle et al.[4], both comparing a mirror group with a control group who performed similar exercises without a mirror or screen. Yavuzer et al.[5] also used bimanual movements. However, in this study, the control group used a non-transparent screen between both arms. In healthy controls, Hamzei et al[16]. compared 4 days of 20 minutes training between a mirror group and a control group. In both groups, the contralateral arm was inactive. Finally, Sütbeyaz et al.[17] also used a non-transparent screen between both arms in the control group but instructed patients to only move the unaffected arm.

Our findings indicate that training with a mirror increases motor learning, which is in line with earlier clinical studies as well as with two recent studies on healthy participants that also used short training programs and relatively simple motor tasks (Hamzei et al.[16] and Nojima et al.[18]). Most of the clinical studies used bimanual training in both groups and since all of these studies report small but significantly better results in the mirror group compared to the control group, it may be surprising that in the present study the training effects of the bimanual training were relatively small and that there was no significant difference between the Bilateral-Screen and the Bilateral-Mirror conditions. Our findings suggest therefore that this specific training is more effective when moving only the non-paretic arm. Possible, as suggested in the introduction, this may be caused by a bimanual movement creating more proprioceptive feedback from the movements of the hand behind the mirror, thereby decreasing the strength of the visual illusion.

Overall, we found smaller learning effects in the bimanual conditions compared to the Paretic-No Mirror conditions. A reason why the training effects in the bimanual conditions were relatively small might be that these conditions were more tiresome for the affected arm of the patients than both Non-Paretic-No Mirror conditions. In the two Non-Paretic-No Mirror conditions (Non-paretic-Mirror and Non-paretic-No Mirror), subjects performed only affected arm movements during the baseline and follow-up measurements, while in the bimanual conditions subjects performed 70 bilateral movements. However, it may also be related to the fact that the mirror and the transparent screen prevent visual feedback about the task performance during the training.

The aim of this study was to compare different training schemes within a single study using a simple reaching task in a short training session. This approach is in line with the recent study of Hamzei et al.[16] who randomized 26 healthy controls to a mirror group and a control group. In this study, significantly more improvement in a motor task of moving pegs and marbles was found in the mirror groups compared to the control group after only 4 days of 20 minutes of training. Similarly, Nojima et al.[18] trained a rotation movement of a ball in 10 sessions of 30 seconds in healthy subjects and found a significantly larger increase in the number of rotations in a mirror group compared to a control group. The similar outcomes of these two studies and our study indicate that simple motor tasks such as these can be used to study differences in motor learning in an efficient way. While outcomes of such studies should be further tested in randomized controlled clinical trials, short training sessions of simple motor tasks may be effective paradigms to develop training schemes.

The present study has a number of limitations. One limitation, as already mentioned earlier, was that fatigue of the involved hand may have been different between conditions. While this indeed may have influenced some of the conditions, it did not influence the direct comparison between the mirror and no-mirror conditions. A second limitation is that the number of patients per group is relatively small. The power analyses of our study was based on findings by Cirstea and Levin[9] who showed a .25s improvement in the Paretic-No Mirror condition, which was comparable with the present study (.19s improvement). We did find a significant difference in the primary outcome measure, indicating sufficient power for these comparisons.

In summary, the present study confirms that using a mirror reflection can facilitate motor learning as confirmed by the relatively large effect of the mirror when moving only the non-paretic arm. In contrast to some previous literature, our data indicate that bimanual training with a mirror may not be more effective than unilateral training, at least not for learning a simple reaching task. The present data do not suggest that mirror training alone is more effective than directly training the involved hand. Taken together, this suggests that mirror therapy may be effective in specific situations, such as where the patients is not yet able to move the paretic arm or where the paretic arm is easily fatigued. For patients with a less severe paresis and higher FIM-scores, it may be more effective to combine mirror training with other training paradigms such as constrained induced movement therapy than to use it as a stand-alone treatment.

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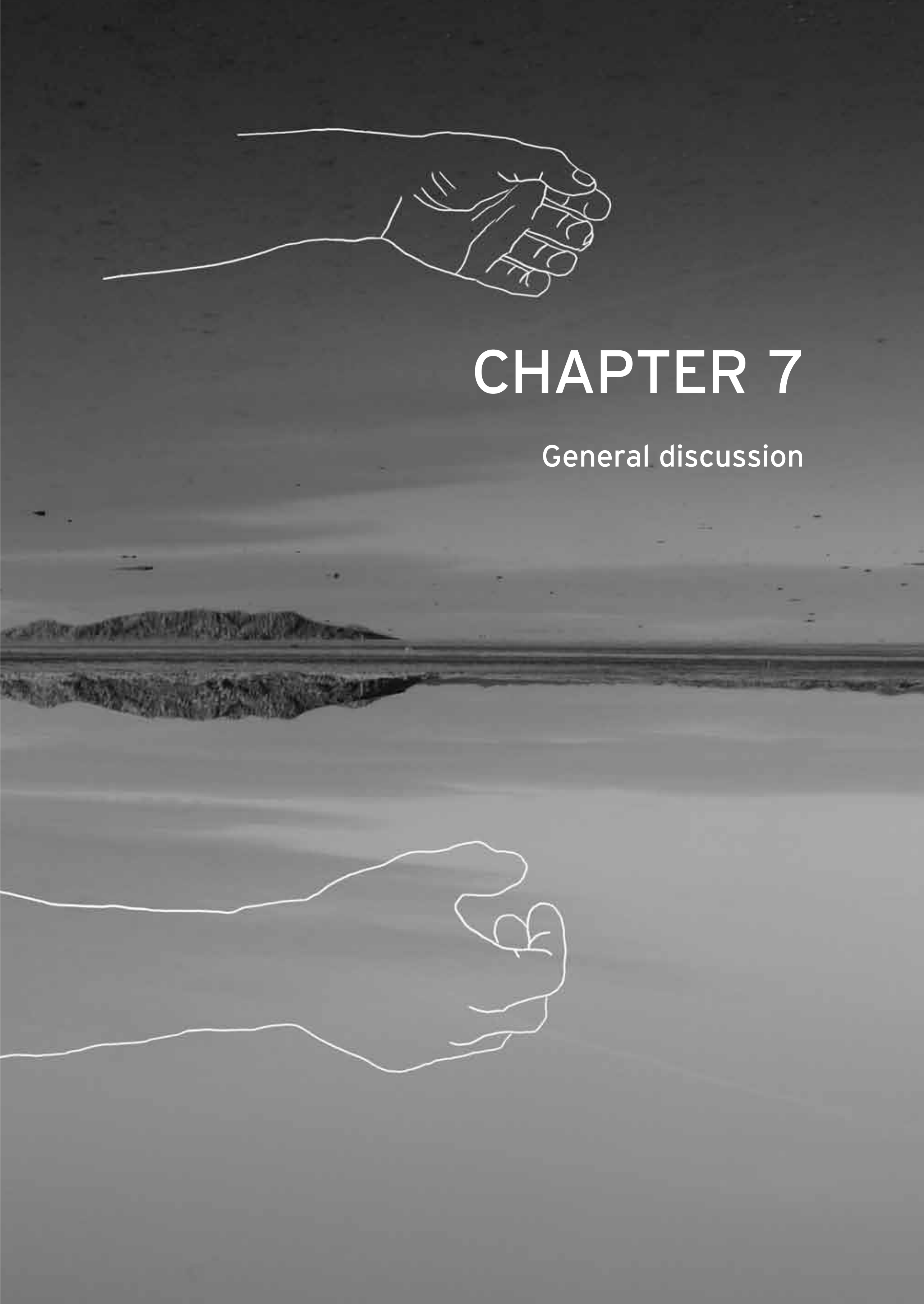

CHAPTER 7

General discussion

GENERAL DISCUSSION

Ever since the second half of the 20th century, the field of neurorehabilitation has been expanding. An increasing number of patients survive an acute insult of the brain, with stroke as a leading cause of long-term disability. Stroke is an age-related disorder, and with the increasing age of the general population, the demand of effective and efficient neurorehabilitation programs is likely to expand[1]. In the early days, neurorehabilitation was based on pragmatism rather than on science. In the past decades, however, research has shown that the brain is not a static organ but retains the ability to modify anatomical and functional connections even after injury, generally referred to as brain plasticity. Nowadays, many studies address the question whether this intrinsic capacity of the brain can be stimulated therapeutically to improve motor control, and cognitive and linguistic functions after brain injury.

This thesis focuses on paresis of the upper-extremity after stroke. A paresis is a problem of motor execution with a reduced ability to voluntarily activate the spinal motoneurons, due to damaged cortical motoneurons or white matter fibres that project to the spinal cord. It is a syndrome with muscle weakness, spasticity, a decreased ability to fractionate movements, and higher-order planning deficits as key problems[2]. Fifty to 70% of stroke patients suffer from a paretic upper limb[3]. As the latter has a great impact on the ability of a patient to participate in daily life activities, maximizing upper-extremity function is a key factor in motor rehabilitation following stroke. Pomeroy et al.[4] defined three basic principles to treat paresis: [1] priming techniques that increase the excitability of the motor system and promote plastic reorganization in response to physical activity (e.g. mirror therapy, repetitive transcranial magnetic stimulation, transcranial direct current stimulation); [2] augmenting techniques that enhance activation of paretic muscles during physical activity (e.g. robot-assisted therapy, constrained-induced movement therapy); and [3] task-specific exercises, which are the core of most motor rehabilitation programs. However, the surplus value of most of these therapies beyond spontaneous recovery is unclear.

Mirror therapy is the central theme of this thesis. Does it work, how does it work, and does the treatment paradigm determine the magnitude of the effect of mirror therapy? The International Classification of Functioning, Disability and Health (ICF) provides a framework to study the effect of any rehabilitation intervention, distinguishing 3 domains of functioning: [1] body function and structures, [2] activity, and [3] participation[5]. For the domain of activity, 2 qualifiers are identified: *capacity* and *performance*. Capacity describes what someone can do, indicating a potential level of functioning. Performance describes what a person actually does, indicating the actual level of functioning in a daily life situation. An important characteristic of the studies of this thesis is that different domains of functioning were covered, with innovative outcome measures. For example, the set of measures included brain activity outcomes derived from fMRI measurements, but also the level of arm-hand usage measured objectively in daily life (with the stroke Upper Limb Activity Monitor; stroke ULAM). This approach resulted in detailed insight in the effects of mirror therapy, but also in the mutual relationships between domains.

The relationships between different ICF domains is a frequent research topic in rehabilitation medicine. In Chapter 2 we related the innovative Stroke-ULAM data with a function and capacity measure in chronic stroke patients. We found a logarithmic relationship between capacity and performance that was not previously reported, indicating that improvements in capacity, measured with the Action Research Arm test (ARAT), do not to automatically result in improved performance, at least not until capacity reaches a certain threshold. This indicates that the size of discrepancies between function, capacity and actual performance depends on the degree of recovery. Since this was a cross-sectional study, however, this finding will have to be confirmed by future longitudinal studies.

A second study [Chapter 3] showed a significant amount of non-use of the paretic arm, which was compensated by increased use of the unaffected arm, even to an extend that surmounts the use of the dominant arm in healthy controls. It is evident that a stroke leads to impaired function of the arm and hand and a decreased capacity to perform activities. This may lead to less usage of the impaired hand and arm in daily life activities. This impaired function, capacity and usage may be related to the severity of the paresis, but may further be reinforced by learned non-use. In learned non-use the paretic arm is used below its potential capacity by compensation of the non-affected extremity. We found that the paretic arm appears to be used almost exclusively in bimanual activities; patients choose to perform unimanual activities almost always with the non-affected arm. While this may be an efficient compensation strategy to perform daily life activities, it can be an undesirable strategy that eventually hinders functional recovery.

In several studies of this thesis, the Stroke-ULAM was used. The Stroke-ULAM detects body postures and motions, and allows to discriminate between independent upper limb movements and upper limb movements caused by whole body movements (e.g. during walking). The stroke-ULAM provides detailed information on movement behaviour (body postures and movements, transitions) and upper limb activity in daily life situations. Although the device is innovative and validated[6], it is not without any limitations. A shortcoming is that functional activities which are not associated with sufficient accelerations, are not in any circumstances detected as upper limb activity. Although low detection thresholds are set in the analysis software, activities as holding a book, fixating objects (e.g. a steering wheel), and small movements needed high levels of dexterity (e.g. clipping nails) may not always be measured as upper limb usage. In the future, additional signals (e.g. EMG) might contribute to a more reliable detection of arm-hand usage.

Another drawback of the stroke-ULAM is that it is relatively obtrusive. The accelerometers themselves were small, but they were connected to a relatively heavy data recorder by cables that may have been experienced as uncomfortable. However, technological developments are on-going, and at this moment the stroke-ULAM has been replaced by a wireless system (VitaMove). While this new device is already a considerable improvement, future improvement and miniaturization of sensors, batteries and other parts of the hardware will further increase the feasibility and applicability of ambulatory devices.

The second part of this study focused on mirror therapy, focusing not only at studying the effects of mirror therapy (Chapter 4), but also into the mechanisms of mirror therapy (Chapter 5 & 6). From that perspective, we feel that this thesis can be considered as a good example of “translational research”.

As already stated, mirror therapy is considered a priming technique that improves paretic arm function after stroke. Ramachandran originally hypothesized that paralysis following stroke might have a ‘learned’ component, which could possibly be ‘unlearned’ by means of the mirror illusion[7]. Others suggested that mirror therapy might be a form of visually guided motor imagery[8]. Motor imagery itself has proven to be effective in the rehabilitation of patients with hemiparesis[9] and the mirror-induced visual feedback of the imagined movement might further facilitate this. In addition, it has been hypothesized that the observation of the mirror illusion might trigger the mirror neuron system (MNS), which are neurons that discharge both with performance of a motor action and with observation of another individual performing similar motor actions[10]. Previous research has indicated the potential of the MNS in motor recovery by showing that the observation of movements performed by others, improves motor performance in patients with stroke[11]. It is conceivable that observing one’s own mirrored movement promotes recovery in a similar way.

Does mirror therapy indeed improve function of the paretic arm? In our randomized controlled trials with patients in the chronic stage after stroke (Chapter 5), we found a small but significantly improved Fugl-Meyer motor assessment score compared to the control group. However, this effect disappeared after six months and no effects were found on grip force, spasticity, pain, dexterity, hand-use in daily life, and quality of life. Our results of small but positive effects of mirror therapy in stroke are in line with other trials reported in the literature[12-14].

Further, using fMRI analysis, we demonstrated that neural activity during movements of the involved hand before and after the intervention showed a shift in activation balance towards the lesioned hemisphere (Chapter 5). Our study was the first to show that in stroke patients mirror therapy increases activity in the ipsilesional precuneus and the posterior cingulate cortex, a network reported to be associated with the mental representation of the self[15]. Instead of activating undamaged motor networks, the mirror illusion of a normal moving hand may increase alertness and spatial attention towards the paretic hand. This effect only occurred during bimanual movements. No differential effect on neuronal activity of the mirror illusion during unimanual movement was found. Apparently not so much the illusion of a virtual moving hand, but the mismatch between the performed and observed movement seems to cause the activation patterns during the mirror illusion.

There are important differences in the treatment paradigm between mirror therapy studies. Amongst others, differences exist in whether or not the paretic hand behind the mirror is instructed to move as much as possible with the uninvolved hand that is in front of the mirror. Therefore, we performed a separate study with the aim to gain insight in the relative contribution of a mirror in exercising a reaching task and in the differences in unilateral and bimanual exercises when training such a reaching task with and without a mirror. We found again a significant positive effect of introducing a mirror on the task performance of the involved hand, specifically when comparing unilateral training of the unaffected hand with and without a mirror. However, in contrast to some previous literature, our data indicate that bimanual movement using mirror training may be less effective than unilateral training, at least for learning a relatively simple reaching task.

CONCLUSION

We as supervisors of Marian Michielsen know that Marian was struggling with a future final paragraph of her thesis in which she felt that she would have to give an overall conclusion on the role of mirror therapy in stroke. We discussed this topic with her on many occasions. On the one hand, it is clear that mirror therapy consistently improves hand function in different studies. This finding was confirmed in the RCT and the reaching task study presented in this thesis. Additionally, effects of mirror therapy were found even in chronic patients and after a training period of only moderate length and intensity. These findings contributed to the positive part of the balance. At the other part, however, while the results are consistent, they are also small and do not translate to the activity and performance measures of hand function. Furthermore, the positive effects did not sustain on the long term.

We frequently discussed whether these small effects should be regarded as positive or as too small to be clinically relevant, without reaching a final conclusion. As supervisors, we feel that the effects of mirror therapy are at least similar to those of other, sometimes more intensive, expensive or high-tech interventions in stroke rehabilitation (e.g., some robotic applications or some forms of neurostimulation). Nowadays, with an increasing number of studies focusing on the neural correlates of mirror therapy, findings seem inconsistent and do not support a single hypothesis on the neuronal basis of mirror therapy. Overall, we feel that this thesis supports to the notion that mirror therapy can play and important role in the range of therapeutic interventions aimed at improving motor function in stroke. It is proven-effective, low-tech, allows for home use and many patients report the exercises as motivating and helpful. More than as a stand-alone treatment, however, we feel that it should be part of a range of different interventions that include conventional arm training interventions as well as more recent techniques such as arm robotics and transcranial stimulation.

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SUMMARY

According to the World Health Organization stroke is the main cause of acquired adult disability. Deficits encompass both motor and sensory problems and the expression can range from complete paralysis towards relatively minor coordination impairments. The consequences of stroke often affect the ability to complete everyday activities and impair participation in everyday life situations. However, the exact consequences of decreased motor capacity on the amount of use of both the paretic and non-paretic upper-extremity in daily life are unknown.
Recovery takes place both spontaneous and through training. Spontaneous recovery typically plateaus after three months. Training induced recovery has no absolute time window, but the largest improvements occur within the first year. In both spontaneous and training induced recovery neural plasticity plays a key role. Recent functional post-stroke interventions have focused on promoting this brain plasticity. An interesting intervention in this respect is mirror therapy. The effects of mirror therapy are attributed to the simulation hypothesis: a neural network is activated not only during overt motor execution, but also during observation or imagery of the same motor action. Although there is growing evidence that mirror therapy improves motor function still little is known about its underlying mechanisms and whether the regained function leads to improved actual use of an extremity in daily life.

In **Chapter 2**, we examined the associations between actual performance in daily life, function, capacity and self-perceived performance of the paretic upper limb in 17 stroke patients. Actual performance was measured with the Stroke-Upper Limb Activity Monitor, an accelerometer-based measurement device. We found strong logarithmic correlations between actual performance and function (Fugl-Meyer Assessment) and capacity (Action Research Arm test). Moderate correlations were found between actual performance and self-perceived performance (ABILHAND questionnaire). The non-linear relationships indicate that function and capacity need to reach a certain threshold-level for actual performance to increase.

In **Chapter 3**, usage of the upper limbs of stroke patients was studied and compared to healthy controls. Upper limb use of 38 stroke patients and 18 healthy controls in daily life was measured for 24 hours with the Stroke-Upper Limb Activity Monitor. We found that patients use their non-paretic arm 2.2 times more then their paretic arm, whereas controls show a more equal use of both arms. Patients use their paretic arm less than controls use their non-dominant arm, and their non-paretic arm more than controls their dominant arm. The intensity of movement of the paretic arm in patients was lower than that for the non-dominant arm of controls. Furthermore, movement intensity of the non-paretic arm in patients was higher than that of the dominant arm of controls. Patients used their paretic arm almost exclusively in bimanual activities. The movement intensity of their paretic arm during such tasks was much lower than that of their non-paretic arm. Taken together, our data show considerable non-use of the paretic arm in chronic stroke patients, both in duration and in intensity and both during unimanual and bimanual tasks, indicating that patients compensate for their paretic arm non-use by increasing the use of their non-paretic arm.

Chapter 4 describes the results of a randomized clinical trial on the effects of home-based mirror therapy and subsequent cortical reorganization in patients with chronic stroke with moderate upper-extremity paresis. Forty chronic stroke patients followed a 6-week training program of either mirror therapy or comparable therapy without a mirror. Both groups trained once a week under supervision of a physiotherapist at a rehabilitation center and were asked to practice at home 1 hour daily, 5 times a week. Measurement of upper-extremity function was performed before intervention, directly after intervention (post-treatment), and 6 months after intervention (follow-up). Our results showed that only at post-treatment, motor function (Fugl-Meyer motor assessment) had improved more (9.5%) in the mirror group than in the control group. No difference in change was found for grip force, spasticity, pain, dexterity, hand-use in daily life, and quality of life. fMRI results demonstrated a shift in activation balance within the primary motor cortex towards the affected hemisphere in the mirror group only. From these findings, it can be concluded that there is a small but significantly greater effectiveness of mirror therapy in chronic stroke patients compared to control treatment. Future research may be needed to determine the optimum practice intensity and duration for improvements to persist and whether effects can be extended to other functional domains.

In **Chapter 5**, the neuronal basis for the effects of mirror therapy in patients with stroke was investigated using fMRI. Neuronal activation patterns were determined in 18 stroke patients while performing unimanual and bimanual tasks, with and without a mirror. During the unimanual task, patients moved their unaffected hand, either while observing it directly (no-mirror condition) or while observing its mirror reflection (mirror condition). For the bimanual task, patients moved both hands, either while observing the paretic arm directly (no-mirror condition) or while observing the mirror reflection of the unaffected hand in place of the paretic arm (mirror condition). We found a significant interaction effect of movement x mirror for the bimanual task, indicating an increased neuronal activity as a result of the mirror illusion during bimanual movement. Activated regions were the precuneus and the posterior cingulate cortex. Our study is the first to report on neuronal correlates of the mirror illusion in patients with stroke. We showed that during bimanual movement, mirror illusion increases activity in the precuneus and the posterior cingulate cortex. These areas are associated with awareness and spatial attention. By improving awareness of the affected limb, the mirror illusion might reduce learnt non-use. No mirror-related activity was observed in areas associated with the motor or mirror neuron system. This questions popular theories that attribute the clinical effects of mirror therapy to these systems.

The aim of **Chapter 6** was to gain insight in the contribution of mirror reflection and unimanual and bimanual movement in practicing a reaching task with the index finger. Patients (n=93; >6 months post stroke) were instructed to move their index finger as fast and as fluently as possible towards the target. Six trials with the affected side with direct vision served as baseline measurements. Patients were then randomly allocated to one of the following practice conditions: 1) affected hand only, without mirror, 2) unaffected hand only, without mirror, 3) unaffected hand only, with mirror reflection of the unaffected hand, 4) bimanual movement with a screen between the arms to prevent visual control of the affected hand, 5) bimanual movement with mirror reflection of the unaffected hand. After practicing the allocated task 70 times patients again performed 6 trials with only their affected hand with direct vision (follow-up trials). We found a significant overall intervention effect on movement time (primary outcome), indicating a learning effect from the practice session. Largest intervention effects were found for affected hand only, without mirror and for unaffected hand only, with mirror reflection of the unaffected hand. Less effect was found for the bimanual conditions. The results confirm that mirror reflection can facilitate motor learning. At the same time, the present data do not suggest that mirror training alone is more effective than directly training the involved hand.

Chapter 7 reflects on the main findings of this thesis and attempts to give an overall conclusion of the present role of mirror therapy in stroke.

SAMENVATTING

Volgens de Wereldgezondheidsorganisatie is een beroerte de meest voorkomende oorzaak van een verworven handicap op volwassen leeftijd. Restverschijnselen zijn van zowel motorische als sensorische aard en de gevolgen kunnen variëren van volledige verlamming tot relatief geringe coördinatie stoornissen. De gevolgen van een beroerte beperken vaak het kunnen uitvoeren van dagelijkse activiteiten en het participeren in het dagelijks leven. Het is echter onduidelijk wat de exacte gevolgen zijn van de verminderde motorische capaciteit op het gebruik van zowel de aangedane als niet-aangedane zijde in het dagelijks leven.
Herstel vindt plaats zowel spontaan als door middel van training. Spontaan herstel vindt voornamelijk plaats in de eerste drie maanden na de beroerte. Herstel door training is niet begrensd in tijd, maar naar verwachting treedt het grootste effect op in het eerste jaar. In zowel spontaan als training geïnduceerd herstel speelt neurale plasticiteit een belangrijke rol. Recente functionele interventies na een beroerte richten zich op het bevorderen van de plasticiteit van de hersenen. Een interessante interventie in dit opzicht is spiegeltherapie. De effecten van spiegeltherapie worden toegeschreven aan de simulatie hypothese: een neuraal netwerk kan worden geactiveerd, niet alleen tijdens de expliciete uitvoering van motorische taken, maar ook tijdens het observeren of zich verbeelden van dezelfde motorische taak. Hoewel er steeds meer aanwijzingen zijn dat spiegeltherapie motorische functies verbetert, is er nog steeds weinig bekend over de onderliggende mechanismen en of de herwonnen functie leidt tot een verbetering van het daadwerkelijke gebruik van een extremiteit in het dagelijks leven.

In **Hoofdstuk 2** hebben we gekeken naar de verbanden tussen feitelijke activiteit in het dagelijks leven en functie, capaciteit en subjectief ervaren prestaties van de aangedane arm bij 17 patiënten met een beroerte. De feitelijke activiteit werd gemeten met de Stroke-Upper Limb Activiteiten Monitor, een meetinstrument gebaseerd op versnellingsopnemers. We vonden sterke logaritmische correlaties tussen feitelijke activiteit en functie (Fugl-Meyer Assessment) en capaciteit (Action Research Arm test). Matige correlaties werden gevonden tussen feitelijke activiteit en subjectief ervaren prestaties (ABILHAND vragenlijst). De niet-lineaire verbanden geven aan dat functie en capaciteit moeten verbeteren tot boven een bepaalde drempel voordat er een toename van feitelijke activiteit plaatsvindt.

In **Hoofdstuk 3** werd het arm-hand gebruik van patiënten met een beroerte gemeten en vergeleken met dat van gezonde controles. Arm-hand gebruik van 38 patiënten met een beroerte en 18 gezonde controles werd gedurende 24 uur in het dagelijks leven gemeten met de Stroke-Upper Limb Activiteiten Monitor. We vonden dat patiënten hun niet-aangedane arm 2.2 keer meer gebruikten dan hun aangedane arm, terwijl de controles hun armen meer gelijkmatig gebruikten. Patiënten gebruikten hun aangedane arm minder dan de controles hun niet dominante arm, en hun niet-aangedane arm meer dan controles hun dominante arm. De intensiteit van bewegen van de aangedane arm van patiënten was lager dan die van de niet dominante arm van controles. Bewegingsintensiteit van de niet-aangedane arm van patiënten was hoger dan bij controles. Patiënten gebruikten hun aangedane arm vrijwel uitsluitend voor tweehandige taken. De bewegingsintensiteit van hun aangedane arm was tijdens deze taken veel lager dan die van hun niet-aangedane arm. Uit onze gegevens blijkt een aanzienlijk verminderd gebruik van de aangedane arm bij chronische patiënten met een beroerte, zowel in duur als in intensiteit en zowel tijdens één- en tweehandige taken. Patiënten compenseren het verminderde gebruik van hun aangedane arm door hun niet-aangedane arm meer te gebruiken.

Hoofdstuk 4 beschrijft de resultaten van een gerandomiseerde klinische trial naar de effecten van spiegeltherapie en de daaropvolgende corticale reorganisatie bij patienten met een chronische CVA met een matige parese van de bovenste extremiteit. Veertig chronische patiënten met een beroerte volgden een trainingsprogramma van 6-weken spiegeltherapie of een vergelijkbare therapie zonder spiegel. Beide groepen trainden één keer per week onder begeleiding van een fysiotherapeut in een revalidatiecentrum en werd gevraagd om elke dag 1 uur thuis te oefenen, 5 keer per week. Functie van de armen werd gemeten vóór de interventie, direct na de interventie, en 6 maanden na de interventie. Onze resultaten lieten zien dat motorische functie (Fugl-Meyer Motor Assessment) alleen direct na de interventie meer was verbeterd (9,5%) in de spiegeltherapiegroep dan in de controlegroep. Geen verschil in verandering werd gevonden voor grijpkracht, spasticiteit, pijn, behendigheid, arm-hand gebruik in het dagelijks leven, en kwaliteit van leven. fMRI resultaten lieten een verschuiving zien in de activatie balans binnen de primaire motorische cortex richting de aangedane hemisfeer in de spiegeltherapiegroep. Uit deze bevindingen kan worden geconcludeerd dat er een klein effect is van spiegeltherapie bij chronische patiënten met een beroerte maar dat het effect significant groter is dan dat van de controle behandeling. Toekomstig onderzoek is nodig om de optimale oefenintensiteit en -duur vast te stellen en om uit te zoeken of er ook effecten plaatsvinden binnen andere functionele domeinen.

In **Hoofdstuk 5** werd de neurogene basis voor de effecten van spiegeltherapie bij patienten met een beroerte onderzocht met behulp van fMRI. Neurale activatie patronen werden bepaald bij 18 patiënten met een beroerte tijdens het uitvoeren van één- en tweehandige taken, met en zonder spiegel. Tijdens de éénhandige taak bewogen patiënten hun niet-aangedane hand, of met normale visuele controle (niet-spiegel conditie) of door te kijken naar de reflectie van de hand in een spiegel (spiegel conditie). Voor de tweehandige taak bewogen patiënten beide handen tegelijk, of met normale visuele controle van de aangedane hand (niet-spiegel conditie) of door te kijken naar de reflectie van de niet-aangedane hand in de spiegel (spiegel conditie). We vonden een significant interactie-effect van beweging x spiegel voor de tweehandige taak wat wijst op een verhoogde neurale activiteit als gevolg van de spiegel illusie. Actieve regio's waren de precuneus en de posterior cingulate cortex. Onze studie is de eerste die rapporteert over de neurale gevolgen van spiegel illusie bij patiënten met een beroerte. Tijdens tweehandige beweging was als gevolg van spiegel illusie verhoogde activiteit waarneembaar in de precuneus en de posterior cingulate cortex. Deze gebieden worden geassocieerd met bewustzijn en ruimtelijke oriëntatie. Door het verbeteren van het besef van de aangedane ledemaat kan spiegel illusie aangeleerd niet-gebruik verminderen. Er werd tijdens de spiegel condities geen verhoogde activiteit gevonden in de motorische cortex of in gebieden met spiegelneuronen. Dit roept vragen op over de juistheid van populaire theorieën die de klinische effecten van spiegeltherapie toeschrijven aan activiteit in deze gebieden.

Het doel van **Hoofdstuk 6** was om inzicht te krijgen in de bijdrage van illusie door spiegel reflectie en één- en tweehandige bewegingen aan het uitvoeren van een reiktaak met de wijsvinger. Patiënten (n=93; >6 maanden na beroerte) kregen de opdracht om hun wijsvinger zo snel en zo vloeiend mogelijk naar een doel te bewegen. Zes herhalingen met de aangedane zijde met normale visuele controle dienden als nulmeting. De patiënten werden vervolgens willekeurig toegewezen aan één van de volgende condities: 1) reiken met alleen de aangedane hand, zonder spiegel, 2) reiken met alleen de niet-aangedane hand, zonder spiegel, 3) reiken met alleen de niet-aangedane hand, met spiegel reflectie van de niet-aangedane hand, 4) reiken met 2 handen met een scherm tussen de armen om visuele controle van de aangedane hand te voorkomen, 5) reiken met 2 handen met spiegel reflectie van de niet-aangedane hand. Nadat de reiktaak met de toegewezen conditie 70 keer was geoefend werden opnieuw 6 herhalingen gedaan met alleen de aangedane hand met normale visuele controle (follow-up). We vonden een significant effect van interventie in het algemeen op bewegingstijd (primaire uitkomstmaat), wat wijst op een leereffect van de oefensessie. De grootste interventie-effecten werden gevonden voor de condities reiken met alleen de aangedane hand, zonder spiegel en reiken met alleen de niet-aangedane hand, met spiegel reflectie van de niet-aangedane hand. Minder effect werd gevonden voor de tweehandige condities. De resultaten bevestigen dat illusie door spiegel reflectie motorisch leren kan stimuleren. Tegelijkertijd blijkt uit de data niet dat spiegeltherapie op zichzelf effectiever is dan het direct trainen van de aangedane arm.

Hoofdstuk 7 gaat in op de belangrijkste bevindingen van dit proefschrift en poogt een alomvattende conclusie te geven over de huidige effectiviteit van spiegeltherapie bij een beroerte.

DANKWOORD

Marian was uiteraard alle patiënten dankbaar voor hun medewerking aan het onderzoek. Daarnaast wilde ze de medewerkers van de diverse revalidatieafdelingen en –centra die meegeholpen hebben aan haar studie bedanken. Tenslotte wilde ze alle medewerkers van de afdeling Revalidatiegeneeskunde van het Erasmus MC bedanken voor de gezellige sfeer. Aan een persoonlijk bericht is zij niet meer toegekomen, maar de volgende mensen wilde zij persoonlijk bedanken:

CURRICULUM VITAE

Marian Michielsen was born near the seaside in The Hague on the 28th of May 1983. After finishing her athenaeum at the Dalton Lyceum in The Hague, she spent a year travelling Mexico and Guatemala. In 2002 she moved to Amsterdam to start studying Human Movement Sciences at the Vrije Universiteit. With her research internship focusing on the influence of expertise and focus of attention on postural control under supervision of dr. J. Stins, she graduated cum laude in 2007 as Master of Science.

Subsequently she began her PhD training at the department of Rehabilitation Medicine, Erasmus Medical Center in Rotterdam. The main subject of her thesis was mirror therapy in stroke patients, with a focus on the effectiveness as well as on the working mechanism. This work resulted in mirror therapy workshops for physical and occupational therapists, which she organized regularly.

Marian took great interest in traveling. During her PhD she travelled half a year through South America. In the summer of 2010 she went to the Wakhan Valley at the border between Tajikistan and Afghanistan to embark on an expedition with three friends to climb previously unclimbed peaks. For this last effort they received the Herman Plugge Award in 2011, a prize for the most outstanding Dutch expedition of the year.

Marian was invited to work as a post doc at the institute of Neuroscience from the Newcastle University to further study the neural control of movement, under supervision of Prof. S. Baker, starting October 2011. Sadly enough she did not make it to this next adventure. July 11th 2011 she died in a climbing accident on the Dreieckhorn, Switzerland.

LIST OF PUBLICATIONS

Michielsen ME, Bussmann JB, Stam HJ, Hurkmans H, Heijnen L, de Groot D, Ribbers GM, Selles RW. Short-term effects of a mirror induced visual illusion on a reaching task in stroke patients; implication for mirror therapy training. *Submitted*.

Michielsen ME, Selles RW, Stam HJ, Ribbers GM, Bussmann JB. Quantifying non-use in chronic stroke patients: a study into paretic, non-paretic and bimanual upper limb use in daily life. *Accepted for publication in Archives of Physical Medicine and Rehabilitation*.

Michielsen ME, Smits M, Ribbers GM, Stam HJ, van der Geest JN, Bussmann JB, Selles RW. The neuronal correlates of mirror therapy: an fMRI study on mirror induced visual illusions in patients with stroke. *Journal of Neurology, Neurosurgery, & Psychiatry 2011 Apr; 82: 393-398.*

Michielsen ME, Selles RW, van der Geest JN, Eckhardt M, Yavuzer G, Stam HJ, Smits M, Ribbers GM, Bussmann JB. Motor recovery and cortical reorganization after mirror therapy in chronic stroke patients: a phase II randomized controlled trial. *Neurorehabilitation & Neural Repair 2011 Mar-Apr; 25: 223-233.*

Stins JF, Michielsen ME, Roerdink M, Beek PJ. Sway regularity reflects attentional involvement in postural control: effects of expertise, vision and cognition. *Gait & Posture 2009 Jul; 30: 106-109.*

Michielsen ME, de Niet M, Ribbers GM, Stam HJ, Bussmann JB. Evidence of a logarithmic relationship between motor capacity and actual performance in daily life of the paretic arm following stroke. *Journal of Rehabilitation Medicine 2009 Apr; 41: 327-331*.

PHD PORTFOLIO SUMMARY

SUMMARY OF PHD TRAINING AND TEACHING ACTIVITIES

Name PhD student:	Marian Michielsen
PhD period:	2007 - 2012
Erasmus MC Department:	Rehabilitation Medicine & Physical Therapy
Promotor(s):	Prof. H.J. Stam
Research School:	None
Supervisors:	Dr. JB Bussmann, Dr. GM Ribbers, Dr. RW Selles

1. PhD training

	Year	Workload (Hours/ECTS)
General academic skills		
- Biomedical English Writing and Communication	2008/2009	3 ECTS
- Research Integrity	2009	2 ECTS
Research skills		
- Biostatistics for clinicians	2009	1.2 ECTS
- BROK	2010	1 ECTS
In-depth courses		
- SPM fMRI course	2007	30 hours
- Winterschool Neuroscience models	2011	40 hours
Presentations		
- fMRI research meeting	2007	4 hours
- Neuroreferaat Rijndam revalidatiecentrum	2007	4 hours
- Brain Awareness Week	2008	4 hours
- Regionaal refereren Zuid-West Nederland	2008	6 hours
- Workshop 'Rotterdam Activity Monitor', ICAMPAM	2008	8 hours
- Trappenberg lezing	2008	16 hours
- Lezing vakgroepmiddag fysiotherapie Sophia Delft	2008	16 hours
- Presentatie Spiegeltherapie symposium Rotterdam	2009	8 hours
- Lezing patientendag Rijndam revalidatiecentrum	2009	4 hours
- Regionaal refereren Zuid-West Nederland	2010	8 hours
- Hersenletsel congres	2010	8 hours
- Libragroep refereeravond	2010	8 hours
- Sensorimotor group talk Newcastle	2011	4 hours
- Transmuraal network Midden-Nederland	2011	4 hours
- Libragroep wetenschapscafe	2011	4 hours
International conferences		
- ICAMPAM	2008	20 hours
- ECPRM Brugge	2008	16 hours
- WCNR Vienna	2010	50 hours
Seminars and workshops		
- VRA najaarscongres	2008	8 hours
- Minicursus 'Methodologie van Patiëntgebonden Onderzoek en Voorbereiding van Subsidieaanvragen'	2009	8 hours
- Leren van Motorische Vaardigheden in de Revalidatie: Huidige inzichten vanuit bewegingswetenschappelijk onderzoek	2009	4 hours
- Symposium spiegeltherapie Rotterdam	2009	8 hours

Didactic skills		
-		
Other		
- Member organization committee ICAMPAM	2008	30 hours
- Organization of workshop: Spiegeltherapie in de praktijk	2010/2011	50 hours
- Research meetings department of Rehabilitation Medicine	2007-2011	150 hours

2. Teaching activities

	Year	Workload (Hours/ ECTS)
Lecturing		
- Lecture on fMRI, part of education for radiologists	2008	10 hours
- Lecture on mirror therapy, NPI	2009	10 hours
- Lecture on mirror therapy, NPI	2010	5 hours
- Lecture on mirror therapy, workshop spiegeltherapie	2010/2011	10 hours
Supervising practicals and excursions		
-		
Supervising Master's theses		
- Maaike de Goffou, Medicine	2008	40 hours
Other		
- Supervision 2nd year education medicine students, literature review	2008/2009	20 hours
- Supervision 'Bachelor research project' of David Warmerdam and Daphne Heemskerk, students Human Movement Sciences	2008	60 hours