# ABSTRACT

## THE EFFICACY OF MIRROR THERAPY IN ADDITION TO CONVENTIONAL THERAPY VERSUS CT ALONE IN THE ACUTE AND CHRONIC STAGES OF STROKE BASED ON THE ACTION RESEARCH AND ARM TEST: A META-ANALYSIS

**Background:** Stroke is one of the leading causes of long term disability for adults and costs the healthcare system 34 billion dollars annually.[1-3] Directly after a stroke up to 85% of survivors have an impairment of the upper extremity.[4] Previous research has shown mirror therapy (MT) is beneficial for improving function in the upper extremity.[5-16] **Objective:** The objective of this meta-analysis was to determine the efficacy of MT in addition to conventional therapy (CT) versus CT alone in the different stages of stroke rehabilitation including the acute and chronic.[5,7-17] **Methods:** A literature review was conducted in the fall of 2018 and consisted of the following databases: Pubmed, Medline, and CINAHL. The studies were assessed and reviewed on the specified inclusion/exclusion criteria. A fixed effect size model of 2 groups was used for the included studies to generate the Q-value, P-value, effect size, and confidence interval. **Results:** The results favored MT in addition to CT as compared to CT alone in all stages of stroke rehabilitation. MT in addition to CT used in the acute stage of stroke rehabilitation was favored over MT in addition to CT used in the chronic stage of stroke rehabilitation. **Conclusion:** This meta-analysis supports current literature that MT in addition to CT is more effective in improving upper extremity function than CT alone in all stages of stroke rehabilitation. The minimal to moderate effect found in the acute stage of stroke rehabilitation suggests that MT in addition to CT is more beneficial in the acute stage of stroke rehabilitation as compared to use in the chronic stage of stroke rehabilitation. The evidence should, however, be interpreted with caution until further studies are included.



Aaron Larson
May 2019

# THE EFFICACY OF MIRROR THERAPY IN ADDITION TO CONVENTIONAL THERAPY VERSUS CT ALONE IN THE ACUTE AND CHRONIC STAGES OF STROKE BASED ON THE ACTION RESEARCH AND ARM TEST: A META-ANALYSIS

by

Aaron Larson

A project
submitted in partial
fulfillment of the requirements for the degree of
Doctor of Physical Therapy
in the Department of Physical Therapy
College of Health and Human Services
California State University, Fresno
May 2019

APPROVED

For the Department of Physical Therapy:

We, the undersigned, certify that the project of the following student meets the required standards of scholarship, format, and style of the university and the student's graduate degree program for the awarding of the doctoral degree.

Aaron Larson
Project Author

Jennifer Adame-Walker (Chair) Physical Therapy

Jeremy Fagundes Physical Therapy

For the University Graduate Committee:

Dean, Division of Graduate Studies

AUTHORIZATION FOR REPRODUCTION

OF DOCTORAL PROJECT

____X______ I grant permission for the reproduction of this project in part or in its entirety without further authorization from me, on the condition that the person or agency requesting reproduction absorbs the cost and provides proper acknowledgment of authorship.

___________ Permission to reproduce this project in part or in its entirety must be obtained from me.

Signature of project author:_______________________________________

## ACKNOWLEDGMENTS

I would first like to thank Dr. Adame-Walker for giving me guidance and endlessly helping me to perfect my doctoral paper and presentation. I would like to thank my father Norman and my aunt Rita for giving me support, love, and motivation through this long and tortuous journey known as school. Thank you two for being there for me during the hardest of times, as well as seeing my successes. My lovely fiancée Corina has been a huge supporter and I am grateful to have you in my life. Everyone in my family has supported me through this process and I couldn’t be happier than where I am right now.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Page

# BACKGROUND

Stroke is one of the leading causes of long term disability for adults and costs the healthcare system $34 billion annually.[1-3] The National Stroke Association classifies stroke as the fifth-leading cause of death in the United States.[17] Its classification was recently upgraded with improved outcomes due to advancement in healthcare treatment of survivors.[17,18] The American Heart Association estimates an annual occurrence of stroke in 795,000 Americans, 185,000 of whom will experience a recurrence.[1,2] On a global scale, 15 million people experience a stroke annually, and 1 out of every 6 individuals will suffer a stroke in their lifetime.[19]

Many neurologic structures are affected after a stroke including the most common, the middle cerebral artery (MCA), which accounts for two-thirds of all cerebral infarcts.[2,20] The MCA supplies the frontal, temporal, and parietal lobes as well as subcortical structures, and an infarct in this area results in many different types of neurological deficits.[2,20] The primary motor cortex, internal capsule, Broca's cortical area, and Wernicke's cortical area may be involved in a MCA stroke.[2] It is important to note that the upper extremity is reported to be more involved than the lower extremity, thus making regaining upper extremity movement a priority in rehabilitation.[2]

## Hemiparesis

Due to the distribution of the MCA, motor deficit is common in patients following a stroke.[2] It has been reported that 80-90% of individuals have motor deficit signs and symptoms after a stroke, and other data indicate about 80% of total individuals experience an impairment of the contralateral limb, also known as hemiparesis.[4,21,22] Hemiparesis is one of the most common disabling conditions after a stroke.[23] This is from pyramidal tract disruption or damage, and the accompanying cortico-reticulospinal fibers, which usually result in what is known as upper motor neuron syndrome (UMNS).[21] Cerebrovascular accidents such as stroke are often noted to lead to UMNS.[24] Classic characteristics of this are weakness, loss of dexterity, spasticity, abnormal synergistic movement, and exaggeration of reflexes.[24] A 2017 study reported that of 8,360 patients who experienced an acute ischemic stroke, 8,346 of these subjects had hemiparesis of the contralateral side.[25] This demonstrates that a large majority of individuals present with weakness of the upper and/or lower extremity contralateral to the side of the brain that experienced the ischemia.[25]

Directly after a stroke around 85% of survivors have an impairment of the upper extremity.[4] Within 3 to 6 months post stroke, 55-75% of these individuals will continue to experience a limitation in their upper extremity function and this may lead to a reduction in quality of life.[4,26] The upper limb allows for many activities of daily living (ADLs) and impairments may compromise the means of completing these tasks.[27] Fractionated movement, defined as the ability to move 1 segment independent of other segments, is considered a normal movement pattern, and damage to the corticospinal system results in non-fractionated movement.[28] A reduction in fractionated movement, also known as synergistic movement, occurs across all segments of the upper extremity for individuals post-stroke[28]

## Motor System Reorganization Post Stroke

While physical effects of a stroke can be widespread and significant, there is potential to recover. Strokes cause cellular degeneration which initiates a neural reorganization process.[29] This process occurs when the neurons, axons, and associated synapses die in the affected region, and the regenerative response occurs.[29] There is a high potential for reorganization to occur, and for new neural connections to arise from this response.[29] Degeneration of axons promotes a process known as axonal sprouting, and this may occur in conjunction with dendritic remodeling and synaptogenesis.[29] Reorganization influences changes to the somatosensory and motor maps, peri-infarct cortex synaptogenesis, corticospinal sprouting, and intracortical sprouting.[29]

Neural connections are influenced by our behavioral experiences, which can create growth and maturation, and this influence is a major component of stroke neurorehabilitation.[29] Studies show that earlier behavior interventions may be more beneficial than later interventions because of the effect on the processes of remodeling and reorganization after a stroke.[29] However, interventions that are performed too early may worsen impairments.[29] Research indicates that the most effective timeframe for implementation of stroke rehabilitation treatment is unknown.[29]

## Current Treatments for Stroke

Current interventions for stroke rehabilitation include proprioceptive neuromuscular facilitation (PNF), Mirror Therapy (MT), flexibility training with early mobilization/range of motion (ROM)/positioning strategies, progressive resistance training, task specific exercises, constraint-induced movement therapy, robot-assisted therapy, bed mobility, gait re-training, balance activities, functional electrical stimulation, orthotics and assistive devices, and aerobic capacity and endurance training.[2] The intervention is prescribed in response to a thorough examination of the individual's specific activity limitations, impairments, and goals.[2] Motor control strategies and motor learning principles are a significant component of rehabilitation to promote resumption of functional activities.[2] These techniques facilitate re-organization, adaptation, and require feedback and a large amount of practice.[2]

## Mirror Therapy

Mirror therapy is a rehabilitative approach where a mirror is placed in the midsagittal plane of the patient.[6,30] The patient has direct view of the unaffected arm and the affected arm is shielded behind the mirror.[6,30] The unaffected hand is moved and the individual views the unaffected arm in the mirror as if it was the affected arm, creating a visual illusion.[6,30] MT was originally used in the 1990's as a treatment for phantom limb pain and studies reported reorganization in the brain via re-mapping of neural connections.[31,32] This was demonstrated in adult brains through changes in magnetoencephalography following mirror therapy.[31] MT applied to individuals with stroke 6 months after the incident was found to be beneficial in reversing disuse of the hemiparetic arm.[23] Current research shows MT is beneficial for improving function in the upper extremity.[5-16] A most recent meta-analysis demonstrated that MT may also improve motor function and ability to perform ADL's.[33] A systematic review showed moderate evidence of MT efficacy in the stroke population.[34] Lastly, a Cochrane database systematic review provided further evidence of MT efficacy in upper extremity motor function improvement, and the associated functional improvements.[35]

## Mirror Neuron System and Its Role in Motor Retraining

The hypothesis for MT effectiveness is the activation of mirror neurons.[36] The concept of mirror therapy is that by observing movements of the non-paretic hand or arm, re-wiring of the brain can occur that creates greater neural activity in the affected cerebral hemisphere.[16,36] This will cause cortical reorganization and improve function in the affected side.[16,36] Mirror neurons were first observed when electrodes were placed on the ventral premotor cortex of monkeys observing researchers eating fruit. The monkeys' brains demonstrated a "mirror effect," meaning an increase in local brain activity.[36] Researchers suggest that there is a mirror neuron system, where observing an action activates cortical areas in the brain of the observer.[36] Furthermore, experiments with electroencephalography have shown mirror neurons to be activated in humans when observing movement.[36] Functional magnetic resonance imaging studies have shown that during imitation tasks, activation of neuron cells occur in various cortical areas of the brain including the inferior frontal lobe, inferior parietal, premotor cortex, and occipital cortex.[36]

Motor imagery, action observation, and imitation are 3 pillars of motor training in the mirror neuron system.[37] Motor imagery is defined as the internal reproduction of a certain motor task, and may occur from solely the intention to move a segment.[36] The motor cortex of the brain stimulates mirror neurons in response to the observation of action, and increases corticospinal facilitation to the muscles used in order to perform the observed actions.[37] Mirror neurons are said to be active in both observation and movement executions. Using these 2 techniques to activate mirror neurons through mirror therapy training is one of the desired goals of the therapy.[37]

The neural activation from action observation includes the visual system: occipital, temporal, and parietal cortices, and the core mirror neuron system: the inferior parietal lobule, ventral premotor cortex, and the inferior frontal gyrus.[37] Observation with intent to imitate is important because it underlies the success of using mirror therapy in stroke rehabilitation.[37] With practice it helps recover lost function in individuals after a stroke and activates the parietal and frontal lobes, middle frontal gyrus, and cerebellum.[37] Functional recovery following a stroke translates to motor learning with a damaged brain system, and practice helps to re-learn motor skills using the above stated components of the mirror neuron system.[37] Rehabilitation after stroke with mirror therapy utilizes the theoretical knowledge of the mirror neuron system.[36-38]

## Purpose

The purpose of this meta-analysis was to determine the efficacy of MT in addition to conventional therapy (CT) versus CT alone in the different stages of stroke rehabilitation including the acute and chronic. Currently, there is not a comparison of the above-mentioned interventions that measures upper extremity function nor the change in this outcome measure in specific stages of stroke rehabilitation. Indicating the effectiveness could help clinicians and researchers alike determine in what stage it is most beneficial. The null hypothesis is that MT in addition to CT is just as effective in all stages based on the Action Research and Arm Test (ARAT). The alternative hypothesis is that there will be a greater improvement in upper extremity function when MT in addition to CT is initiated during the acute stage of stroke as compared to initiation in the chronic stage.

# METHODS

## Search Criteria

The search protocol and study design were developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guidelines (PRISMA). A literature review was conducted in the fall of 2018. The literature search consisted of the following databases: Pubmed, Medline, and CINAHL. The databases were accessed with the Fresno State Henry Madden Library. The search was performed to look further into the effects of MT in addition to CT versus CT alone for individuals who suffered a stroke. The articles were published from 2008-present day 2018 and included the following characteristics: English language, non-animal only human studies, and lastly, were peer-reviewed. The search terms included the following: “Upper Extremity” AND “Mirror Therapy” AND “Stroke” (see Table 1 for the study selection process).

## Eligibility Criteria

The studies were assessed and reviewed on the specified inclusion/ exclusion criteria. Inclusion criteria in this meta-analysis consisted of age range between 18-90, both men and women, unilateral stroke resulting in unilateral hemiparesis, Action Research and Arm Test (ARAT) outcome measure, and MT in addition to CT as treatment. The exclusion criteria in this meta-analysis consisted of severe impairments disabling patients from following instructions, previous strokes, and additional comorbidities or musculoskeletal impairments that did not allow patients to participate in therapy. Filters included English language, from 2008 until 2018, including abstracts, randomized controlled trials, and human subjects.

## Study Selection

Assessment for eligible studies was performed by 1 reviewer. The titles were first reviewed and assessed to ensure relevant topics and aspects of the studies fit the criteria for the meta-analysis. The studies needed to be compliant with the exclusion and inclusion criteria. Studies were initially assessed and filtered out if the abstracts and/or titles did not match the criteria to be included. The selected studies were examined and evaluated in further detail to extract relevant data and content to be used in this meta-analysis (see Figure 1).

## Action Research and Arm Test Outcome Measure (ARAT)

One of the most common outcome measures for upper limb paresis for patients with stroke is the ARAT (see Figure 2).[39-41] It is used to assess functional limitations for stroke survivors in the upper limb. The test has high intra/interrater reliability with an interrater reliability of .98 and test-retest score of .99.[40,42] The ARAT validity has an r range of .91-.94 and is a responsive and valid outcome measure for upper extremity function.[40] The test scores 19 items; 0 means no movement and 3 signifies normal movement.[40] The 4 subscale scores are gross motor with 9 points maximum, grasp with 18 points maximum, grip with 12 points maximum, and pinch with 18 points maximum.[40] The maximum score of 57 would indicate normal function of the upper extremity.[40]

## Data Collection Process

Data regarding the ARAT were taken from the results section of included articles. Aspects of the data from the mirror therapy group and conventional therapy (CT) group extracted were pre/post-test mean, standard deviation, and sample size. These were utilized for the statistical analysis of this meta-analysis.

## Quality Assessment

The articles used in this meta-analysis were assessed using the PEDro scale (see Table 1 for PEDro scale). The PEDro scale has a total of 11 questions but does not score the first one, therefore scoring a total of 10 items as either present or absent. One point is given if the criteria are present and 0 points are given if an item is not present.[43] This scale looks at internal validity of studies and the statistical information to determine how the validity of research can be interpreted.[44] Quality of studies are interpreted with the following: poor quality: ≤3, fair quality: 4 to 5, and high quality 6 to 10.[45] The PEDro score has been accepted as a reliable tool to assess physical therapy randomized controlled clinical trials and the methodological quality within the trials.[43,46]

## Conventional Therapy and Acute/Chronic Stroke Defined

Conventional therapy can encompass a variety of interventions and applications. The research authors of the articles included in this meta-analysis included manual therapy, several treatment modalities, and therapeutic exercise. Invernizzi et al. defined conventional stroke rehabilitation as neurorehabilitative techniques, electrical stimulation, and occupational therapy (OT).[9] Dohle et al. stated that standard therapy was designed to require the execution of arm, hand, and finger postures in response to verbal instructions that included ADL training, OT, and physical therapy (PT).[6] Michielsen et al. reported that all patients participated in a training program consisting of bimanual exercises with the level of difficulty specific to the patient.[16] Thieme et al. defined regular therapy as single and group physical therapy, OT, training for ADLs, and according to specific individual impairments, sports therapy, speech and language therapy, and/or neuropsychological therapy.[35] For purposes of this meta-analysis, conventional or standard therapy was defined as any therapy interventions other than MT used by the stated authors. Acute stroke was defined as the time period from 0 to 3 months and chronic stroke was defined as the time period 6 months or greater post stroke.

## Statistical Analysis

The number of participants, post-test standard deviations, and post-test means of the ARAT were inputted into an Excel spreadsheet to determine the confidence intervals and effect size of MT in addition to CT as compared to CT alone in the acute and chronic stages of stroke rehabilitation. Additionally, to determine the pre to post mean change for MT in addition to CT in the acute and chronic stages of stroke rehabilitation, the number of participants for the MT group, average of pre/post-test standard deviations, and the pre/post-test difference of the ARAT were inputted into an Excel spreadsheet to determine the confidence intervals and effect size. A fixed effect size of 2 groups model analysis was used for the data to determine the Q-value, P-value, effect size, and confidence interval. Forest plots were created to determine the total effect size between the studies (see Figures 3-5 for forest plots). The homogeneity and heterogeneity between studies were determined using the Q-value and P-value statistics. A P-value below .05 signifies that the results are interpreted as statistically significant, as well as a Q-value that is less than the degrees of freedom. The effect size is determined to be minimal if it is below 0.3, moderate if it lies between 0.3-0.8, and large if above 0.8. The outcome measure used was the ARAT. A positive number signifies MT in addition to CT is more beneficial, whereas a negative number signifies that CT alone is superior.

# RESULTS

The electronic database search (PubMed, Cinahl, and Medline) yielded a total of 313 articles. The keywords “mirror therapy,” “upper extremity,” and “stroke” were inputted into the databases to produce the article search. Two hundred-forty-seven articles were then excluded for a remaining 66 due to the following criteria: older than 10 years, non-human subjects, non-peer reviewed, not a randomized controlled trial, non-English language, and duplicates. The remaining 66 titles, abstracts, and articles were read and 62 were excluded because they did not answer the PICO question, match inclusion/exclusion criteria, or have the appropriate outcome measure (see Table 1 for study selection process). Four articles were fully read, analyzed, and included in this meta-analysis.

## Risk of Bias

The criteria qualifications for the included 4 studies were determined by 1 reviewer. Quality assessment scores revealed a range from 5/10 to 8/10 on the PEDro scale. The studies by Michielsen et al. and Thieme et al. had the highest scores included in this meta-analysis (both scored an 8/10 on the PEDro scale). These 2 studies were not rated with a higher score due to the lack of subject/therapist blinding. The study by Dohle et al. scored a 6/10 on the PEDro scale because of the following: lack of patient/therapist blinding, the large dropout rate did not allow outcome measure collection from 85% of subjects, and intention to treat was not mentioned in their study.  Invernizzi et al., which scored a 5/10, was the lowest of all 4 articles, and did not receive a higher score because of: lack of subject, assessor, and therapist blinding, allocation was not concealed, and data from at least 1 key outcome was not stated to be analyzed with intention to treat.

## Description of Studies

The 4 studies utilized in this meta-analysis incorporated MT in addition to CT in comparison to CT alone. The ARAT was used to assess upper extremity motor function across all studies, and pre/post measures were taken from the therapy timeframes described in each study. All participants in MT groups of each study underwent a CT program as well. In each study, both groups received either MT or sham MT. Michielsen et al. had 8 subjects drop out from the MT group due to study-unrelated medical conditions, study-unrelated social issues, noncompliance, and inability to contact.[16] Thieme et al. had 5 subjects drop out due to discharge prior to study, withdrawal of consent, and study-unrelated death.[35] Invernizzi et al. had 1 subject drop out due to discontinued treatment from a new stroke episode.[9] Dohle et al. had 12 subjects drop out due to the following: transfers to acute hospital, medical worsening, lack of cost approval by the health insurance, and withdrawal of patient's consent (see Table 2 for study characteristics).[6]

## Description of Individual Studies

Michielsen et al. included subjects in the chronic stage of stroke rehabilitation (MT group: average of 4.7 years since onset of stroke with SD of 3.6 years; and CT group: average of 4.5 years since onset of stroke with a SD of 2.6 years since the initial onset of stroke) with a total n=40. Patients were randomly assigned to the MT or CT group, and the outcome measurements were assessed by a blinded investigator.[16] Their intervention was a 6-week training program, 1 day a week with a physical therapist at a rehabilitation center and an additional 5 days a week for 1-hour sessions at home. The CT intervention consisted of bilateral and functional exercises in which both groups participated. The MT group performed MT by viewing the unaffected arm in the mirror while the affected arm was covered. The CT group had sham MT with direct view of both hands.[16] Home rehabilitation included a book with videos and photos of exercises to be carried out.[16] Michielsen et al. stated that regular phone calls were made to the participants to ensure compliance, and patients kept diaries of their rehabilitation schedules and experiences which were inspected by the physical therapist once a week.[16] This study suggested neuronal organization occurs with MT that was assessed with functional magnetic resonance imaging.[16]

Thieme et al. included subjects in the acute stage of stroke rehabilitation (MT group: average of 47.6 days since onset of stroke with SD of 25.8 days; and CT group: average of 36.2 days since onset of stroke with a SD of 21.1 days). They examined 3 groups of subjects post stroke including: individual mirror therapy, group mirror therapy, and control therapy.[35] Only individual MT and CT (total n=39) were included in this meta-analysis to keep results consistent with other selected studies.[35] All subjects had CT, which included single/group physical therapy (PT), occupational therapy (OT), and ADL training. CT also included individualized therapies tailored to certain patients as described in the study which included: neuropsychological therapy, sports therapy, speech therapy, and language therapy.[35] The individual MT group was defined as 1 therapist treating 1 patient.[35] The patient viewed the unaffected arm in the mirror, and the affected arm was covered behind the mirror.[35] The patient was then told to move both arms while looking at the mirror as much as possible.[35] The CT group had sham MT that consisted of a group intervention with a piece of wood instead of a mirror to block the affected arm, and the patient was asked to move both arms while viewing the unaffected arm.[35] The MT and CT groups had mirror therapy or sham mirror therapy for 30 minutes, respectively.[35] The intervention was 3 to 5 times a week, performed by a physical therapist or physical therapy student in their last year of physical therapy school.[35] The outcome measures were videotaped and then rated by 1 of the 2 observers who were blinded. The ARAT score increased significantly for all participants in this study.[35]

Invernizzi et al. included subjects in the acute stage of stroke rehabilitation (MT group: average of 23 days since onset of stroke with SD of 3 days; and CT group: average of 24 days since onset of stroke with a SD of 2 days).[9] Both groups received 1-hour CT sessions, 5 days a week, for 4 weeks that focused on the upper limb.[9] The CT group consisted of OT, electrical stimulation, and neurological rehabilitation.[9] Both groups received 30 minutes per session of either MT or sham MT for the first 2 weeks, and 1-hour sessions for the last 2 weeks. MT consisted of viewing their unaffected arm in the mirror, and sham MT occurred while viewing their unaffected arm with a piece of paper over the mirror (no view to affected arm); they performed flexion/extension of the wrists, elbow, shoulder, and pronation/supination of the forearm. This study showed that 4 weeks of treatment demonstrated a substantial effect on the ARAT.[9]

Dohle et al. included subjects in the acute stage of stroke rehabilitation (MT group: average of 26.2 days since onset of stroke with SD of 8.3 days; and CT group: average of 27.8 days since onset of stroke with a SD of 12.1 days).[6] Patients had 6 weeks of MT or sham MT for 30 minutes, 5 days a week.[6] CT included ADL training, OT, and PT, and consisted of finger, hand, and arm movement with verbal instructions. Conventional therapy was over an average duration of 47 days for the CT group, and 45.8 days for the MT group.[6] The CT group had 12.3 hours of OT, 23.8 hours of PT, and 8.55 hours of ADL training. The MT group had 14.7 hours of OT, 24.7 hours of PT, and 4.4 hours of ADL training. MT consisted of the patient being able to view their unaffected arm in the mirror while the affected arm was behind the mirror, and CT or sham MT subjects had a view of both arms.[6] MT was favored and reported to produce significant therapy effects.[6]

## Synthesis of Results

The null hypothesis is that MT in addition to CT is just as effective at increasing UE function in all stages of stroke rehabilitation based on the ARAT. The alternative hypothesis is that there will be a greater improvement in upper extremity function when MT in addition to CT is initiated during the acute stage of stroke as compared to initiation in the chronic stage. The data from the 4 studies were compared and analyzed between groups based on the ARAT to measure upper extremity motor function. MT in addition to CT versus CT alone was favored in both stages of stroke rehabilitation. Initiation of MT in addition to CT in the acute stage of stroke rehabilitation was minimally to moderately favored over initiation of MT in addition to CT in the chronic stage of stroke.

### Primary Analysis: Effect Size of Pre to Post Mean Change for Acute Versus Chronic Stroke Rehabilitation for MT in addition to CT Including Invernizzi et al., Dohle et al., Thieme et al., and Michielsen et al.

The confidence intervals, individual effect sizes, Q-value, P-value, and combined effect size of all ARAT data are shown in Table 3. Confidence intervals were based on a 95% interval. The data were pooled by including 4 studies used in this meta-analysis to assess MT in addition to CT in the acute and chronic stages of stroke. Each acute stroke rehabilitation was paired with the single chronic stroke rehabilitation study included in this meta-analysis. The data yielded a moderate combined effect size of 0.35, Q-value of 4.43, and 2 degrees of freedom. The P-value was 0.11 at a 95% confidence interval, and the upper and lower confidence intervals were 0.74 and -.03, respectively. The P-value did not demonstrate statistical significance, and the studies were heterogeneous due to above stated values.

## Primary Sub-Analysis: Effect Size of Pre to Post Mean Change for Acute Versus Chronic Stroke Rehabilitation for MT in Addition to CT Including Dohle et al., Thieme et al., and Michielsen et al.

The confidence intervals, individual effect sizes, Q-value, P-value, and combined effect size of all ARAT data are shown in in Table 4. Confidence intervals were based on a 95% interval. The data were pooled by including 3 studies used in this meta-analysis to assess MT in addition to CT in the acute and chronic stages of stroke. Each acute stroke rehabilitation was paired with the single chronic stroke rehabilitation study included in this meta-analysis. The data yielded a small combined effect size of 0.11, Q-value of 0.003, and 1 degree of freedom. The P-value was 0.96 at a 95% confidence interval, and the upper and lower confidence intervals were 0.56 and -0.34, respectively. The P-value did not demonstrate statistical significance, and the studies were homogeneous due to above stated values.

## Secondary Analysis: Effect of MT in addition to CT as Compared to CT Alone in the Acute and Chronic Stages Based on the ARAT

The confidence intervals, individual effect sizes, Q-value, P-value, and combined effect size of all ARAT data are shown in Table 5. Confidence intervals were based on a 95% interval. The data were pooled by including all studies used in this meta-analysis to assess MT in addition to CT versus CT alone in the acute and chronic stages of stroke. The data yielded a small combined effect size of

0.28, Q-value of 1.85, and 3 degrees of freedom. The P-value was 0.60 at a 95% confidence interval, and the upper and lower confidence intervals were 0.61 and -.06, respectively. The P-value did not demonstrate statistical significance, and the studies were homogenous due to above stated values.

# DISCUSSION

The purpose of this meta-analysis was to determine the effects of MT in addition to CT versus CT alone in the acute and chronic stages of stroke rehabilitation. All studies within this meta-analysis showed that MT in addition to CT versus CT alone resulted in a better outcome on the ARAT. A small to moderate effect size demonstrated that acute stroke rehabilitation was favored for MT in addition to CT when initiated in the acute stage of stroke rehabilitation as compared to initiation in the chronic stage of stroke rehabilitation. The null hypothesis was rejected, with the evidence demonstrating a difference with MT in addition to CT in the acute and chronic stages of stroke rehabilitation. The alternative hypothesis was accepted due to a minimal to moderate improvement in the acute stage of stroke rehabilitation as compared to the chronic stage. The discussion provides explanations and delves deeper into the results of the analyses. Additionally, the discussion will review current literature, meta-analysis results, reasons for heterogeneity of the primary analysis, dosage of interventions, length of time since stroke, conventional therapy methods, severity of stroke, limitations, future research suggestions, clinical applications, and a conclusion for this meta-analysis.

## Review of Meta-Analysis Results

MT in addition to CT has been shown by multiple authors to be more effective than CT alone.[5-16,33] The current literature reports that implementing MT with other therapeutic treatments results in an improved outcome.[33] Studies from this meta-analysis all buttress the conclusion that MT in addition to CT is more effective than CT alone. The results from the primary analysis included all 4 studies by Michielsen et al., Dohle et al., Invernizzi et al., and Thieme et al.[6,9,16,30]

These studies demonstrated a moderate effect size (ES=.35), indicating that MT in addition to CT was more favorable initiated in the acute stage of stroke rehabilitation based on the ARAT. The primary analysis resulted in a Q-value measured as 4.43 at 2 degrees of freedom and a P-value of 0.10, indicating that these studies were heterogeneous in nature. A high degree of heterogeneity indicates that the studies have dissimilarities which will be explored further.

The primary sub-analysis included studies by Dohle et al., Michielsen et al., and Thieme et al., and compared the effects of MT in addition to CT in the acute and chronic stages. Invernizzi et al. was excluded within this sub-analysis because it appeared as an outlier compared to the other included studies. More information is described in the heterogeneity of the primary analysis and homogeneity of the primary sub-analysis section below. The results from the secondary analysis demonstrated a minimal effect size (ES=.11), indicating that MT in addition to CT within the acute stages of stroke rehabilitation minimally improved the ARAT outcome measure score. The secondary analysis resulted in a Q-value measured as 0.003 at 1 degree of freedom, and a P-value of 0.95, indicating that the 3 studies were homogenous in nature.

The secondary analysis included studies by Dohle et al., Invernizzi et al., Thieme et al., and Michielsen et al. that compared MT in addition to CT versus CT alone in the acute and chronic stages of stroke. The results from the primary sub-analysis demonstrated a minimal effect size (ES=.28), indicating that MT in addition to CT versus CT alone was favored in both the acute and chronic stages of stroke rehabilitation. The primary sub-analysis resulted in a Q-value measured as 1.85 at 3 degrees of freedom, and a P-value of 0.60, indicating that these 4 included studies were homogeneous.

## Reasons for Acceptance of Alternative Hypothesis: Healing and Brain Re-wiring After Stroke

Initiation of MT in addition to CT in the acute stage of stroke rehabilitation appears to demonstrate minimal to moderate improved outcomes in upper extremity function as compared to initiation in the chronic stage of stroke rehabilitation based on the ARAT. This may be in part due to the recovery and repair process of the brain that occurs post-stroke. There is a high degree of neurotransmission recovery in the surviving tissue at the stroke location as well as surrounding areas of tissues that were affected.[47] Recovery on a molecular and cellular level has been shown to occur most in the first 3 months post-stroke.[48] A study by Nakayama et al. demonstrated that within 3 weeks of stroke onset 80% of individuals attained the most upper extremity function, and within 9 weeks 95% of individuals reached the best possible upper extremity function.[48,49] These pieces of information may help interpret why implementing mirror therapy in the acute stage of stroke may be more beneficial than in the chronic stage. After a stroke occurs, the contralateral side of the brain region that was affected is activated more, also known as increased cortical activity at distant sites. MT likely provides more cortical activation during the acute stage to the ipsilateral or affected side of the brain which improves upper extremity motor function.[5,29,33,48] The evidence demonstrates that there is a high rate of healing and re-wiring that occur post-stroke, and for this reason MT in addition to CT likely has a better window of opportunity for functional improvement in the acute stage of stroke rehabilitation of the upper extremity as compared to the chronic stage of stroke rehabilitation.[29,47,48]

## Heterogeneity in the Primary Analysis

The Q-value was larger than the degrees of freedom and the P-value was greater than 0.05. This indicated that there was a degree of heterogeneity within this analysis. The reason for this lies within the study by Invernizzi et al. This study had the most change from baseline to follow-up on the ARAT score, the subjects had the least amount of severity, and it had the least number of subjects drop out. They reported that limitations of the subjects included were less severe as compared to the study by Dohle et al., and this could have led to improved scores on the ARAT.[6,9] Additionally, they were the only study in this meta-analysis to use electrical stimulation (ES). ES has been shown in a recent 2017 systematic review to improve upper extremity function for individuals post stroke in the acute stage of rehabilitation, especially within the first 2 months of recovery.[50] Invernizzi et al. also had only 13 subjects in the MT group, which was the lowest number compared to the other studies. This heterogeneity led to performing a secondary analysis excluding the study by Invernizzi et al., in which the studies demonstrated homogeneity.

## Homogeneity in the Primary Sub-Analysis

The secondary analysis without Invernizzi et al. is more likely a representation of the effects of MT in addition to CT for severely impaired individuals post stroke in the acute and chronic stages of stroke rehabilitation. The MT group from Michielsen et al. included 20 participants, Thieme et al. included 18 participants, and Dohle et al. included 18 participants. The impairment severities between these studies were more similar as compared to the primary analysis. The Q and P-values demonstrated a high degree of homogeneity between the studies indicating similarity. The limitation of all the studies will now be discussed.

Dosage of Interventions

The studies included in this meta-analysis had variable treatment timespans (MT group versus CT group). Minutes of treatment ranged from 30 to 90 per session, days per week ranged from 4 to 5, and weeks of treatment ranged from 4 to 6. Thieme et al. stated that the patients had a maximum of 30 minutes of treatment for MT or CT, indicating that the exact amount of time was not documented.[30] Twenty treatment sessions were provided to patients over 5 weeks, indicating that the total maximal treatment time for each group was 20 hours.[30] They also reported that an additional 10 hours of treatment was given to attain a difference between groups.[30] The author stated treatment time included: transferring, preparation time, and rest breaks.[30] Limitations with this study are lack of known hours, which could lead to unequal intervention duration between groups, and the 10 hours of additional interventions that were not clearly described.[30]

Invernizzi et al. provided patients CT 1 hour each day, 5 days a week, for 4 weeks.[9] The MT and CT group both received 30 minutes of MT (the reflective side of the mirror was turned down for the CT group) for the first 2 weeks and 1 hour for the last 2 weeks.[9] This adds up to 35 hours of therapy. Dosage was the same for both groups.[9] Dohle et al. provided MT or sham MT for 30 minutes 5 days weekly for 6 weeks, totaling 15 hours.[6] CT included ADL training, OT, and PT, and consisted of upper extremity movements with verbal instructions. CT was over an average duration of 47 days for the CT group, and 45.8 days for the MT group.[6] The CT group had 12.3 hours of OT, 23.8 hours of PT, and 8.55 hours of ADL training totaling 44.65 hours. The MT group had 14.7 hours of OT, 24.7 hours of PT, and 4.4 hours of ADL training totaling 43.8 hours. This study did not clarify total hours of individual CT, MT, and sham MT, but rather added the total amount of time for each day, equaling 30 minutes.[6]

Michielsen et al. included 6 weeks of treatment, 1 day a week in the clinic for 1 hour, and 5 days a week for 1 hour at home independently, totaling 30 hours.[16] A Physical Therapist was assigned to make regular phone calls to the patient to ensure the patient was participating in therapy, and that the patients kept detailed logs of their schedules which were inspected once a week in clinic.[16] This study contains a limitation due to the independent nature of therapy for 5 days per week at home. Current evidence demonstrates that a higher dosage of interventions for stroke rehabilitation will improve and enhance motor recovery.[51] Overall, the studies ranged from 20 to 59.65 hours of total intervention time. This large difference in intervention strategies, each having a different number of hours for treatment, makes the intervention dosage not uniform throughout.

## Length of Time Since Stroke

The focus of this meta-analysis was to illustrate the different results produced utilizing MT in the acute and chronic stages of stroke, and to determine when MT in addition to CT has the most benefit for clinical use. To classify the acute or chronic stage of stroke rehabilitation, studies were acute in nature when the time lapse since stroke was less than 3 months and chronic when the time lapse since stroke was greater than 6 months. Invernizzi et al., Dohle et al., and Thieme et al. had both groups (MT and CT) start treatment post stroke within an average of 2 days, 1.6 days, and 3.8 days, respectively. The MT group in the study by Michielsen et al. started interventions 73 days later than the CT group, however this was not seen to be a major limitation because the average start of interventions post stroke was 1,679 days.[16] Overall, both groups (CT and MT versus CT) in all 4 studies were close in time elapsed from onset of stroke to start of treatment. This therefore was not seen to be a major limitation for this meta-analysis.

Time course plays an important role in regaining function after stroke. One study by Jørgensen et al. looked at 1,197 individuals who experienced a stroke and followed them from the time of acute admission to the end of their stroke rehabilitation.[52] They saw that in mild, moderate, severe, and very severe strokes functional recovery was reached in 8.5 weeks, 13 weeks, 17 weeks, and 20 weeks, respectively.[52] In 95% of all patients functional recovery was reached within 12.5 weeks after onset.[52] They reported that after these timespans of functional recovery were completed no significant changes occurred, stating that a prognosis can be made within 12 weeks after stroke onset.[52] The conclusion of Jørgensen et al. was that additional functional and neurological recovery is minimal after 5 months post stroke.[52]

## Conventional Therapy

Each study had similarities and differences in their CT interventions leading to possible limitations in this meta-analysis. Invernizzi et al. used neurorehabilitation techniques, electrical stimulation, and OT, although did not detail specific treatment. This does not give a clear and concise understanding of the exact therapy that was performed since these are umbrella terms that could entail many different types of treatment methods. Dohle et al. used exercises that required execution of the arm and hand, finger postures, ADL training, OT, PT, and defined this as the standard, or conventional therapy.[6] The reader is unclear as to the exact treatment used, and since treatment was directed towards the upper extremity, the use of one treatment over another could give patients an advantage leading to a higher ARAT score.

Thieme et al. defined CT as regular therapy that included OT, training of ADL's, sports therapy, speech and language therapy, neuropsychological therapy, and therapy according to individual impairments.[30] This study provides the most eclectic approach for conventional therapy as compared to other studies which may give these patients an advantage over other studies. Michielsen et al. defined CT as a training program consisting of bimanual and functional exercises.[16] This study is similar to Dohle et al. in that they both focused CT on upper extremity functionality and movement, although the exact treatment approach is vague to the reader. Overall, all 4 studies do not conform to the same conventional therapy, which impacts the outcomes and any comparison between them within this meta-analysis.

## Severity of Symptoms

The severity of hemiparesis at the start of treatment varied in the 4 included studies. Invernizzi et al. described in their research that they included subjects in the acute stroke stage resulting in moderate to severe hemiparesis in the same stage of stroke as those subjects included by Dohle et al. However, Invernizzi et al. likely had better outcomes with motor function per the ARAT because their patients had less severe hemiparesis to start with.[9] Subjects in the study by Dohle et al. started with severe hemiparesis which differed from Invernizzi et al.[30] Theime et al. included patients with severe arm paresis, and Michielsen et al. included patients with moderate upper extremity paresis.[16,30] It has been shown that the amount of functional recovery after stroke in the acute stage correlates highly with initial severity.[48,52,53] This may be the reason why Invernizzi et al. had the largest improvement in the ARAT.

## Limitations

Intervention duration for the included studies ranged from 20-59.65 hours, which could be a limitation to this meta-analysis in that the amount of treatment may affect the outcome. Thieme et al. stated in their research that a maximum of 30 minutes of treatment was given, and within these 30 minutes preparation time was included. This may limit the findings when comparing studies because the exact time of intervention was not identified. Michielsen et al. had the patients work with a Physical Therapist 1 day a week in person, and for 5 days patients were on their own at home. Although the patients kept a journal of their home activities, this is a limitation due to questionable compliance. In the other 3 included studies, the patients were treated in person by therapists, ensuring their completion of activity. Sample size was the lowest for Invernizzi et al. (CT=12 and MT=13) possibly skewing the results in favor of a large effect size.[9] The sample sizes from Dohle et al., Thieme et al., and Michielsen et al. ranged from 16-21 for the CT group, and 16-21 for the MT group. All studies had a relatively low sample size although Invernizzi et al. had the largest effect size and lowest sample size for both groups (MT and CT versus CT), which is a possible limitation.

Each study defined conventional therapy differently and included different forms of treatment. For example, Invernizzi et al. included electrical stimulation, while none of the other studies provided this modality. Thieme et al. and Invernizzi et al. both provided occupational therapy and Dohle et al. focused the conventional therapy on the upper extremity. The trend here is that there is no standard to conventional therapy. It is defined as anything besides MT, and it varied greatly from study to study. The literature provided 3 acute stroke rehabilitation studies and 1 chronic study that were compared against each other.

This was a major limitation and limits the amount of external validity that can be applied. However, this meta-analysis does provide results that may be interpreted with caution.

## Future Research

Suggestions for future research should be implemented and would assist in standardizing research approaches; thus, comparisons would be more accurate. Examining the long-term effects of MT would be useful in determining which stage of stroke benefits the most, and how long the effects of MT last. All 4 studies included in this meta-analysis used the ARAT during the treatment time and only Michielsen et al. looked at effects 6 months post treatment. Michielsen et al. reported an improved ARAT score from baseline for both groups 6 months after interventions ended, and the MT group had a higher score than the CT group.[16] It would be a better comparison if more studies repeated measurements at the 6-month mark to determine if upper extremity function was retained. One study by Meyer et al. stated that clinicians need to improve the techniques used for individuals with stroke to attain long-term retention of function.[54] The same study also found that at 5 years post-stroke, individuals revealed the same functional and motor outcome that was observed at 2 months post stroke.[54] This indicates that it is important to find techniques that will produce long-lasting effects, and that researchers should document long-term effects to determine if function is retained.

Secondly, having the same dosing across future studies would eliminate limitations in this area. Thirdly, having a universal classification system of symptom severity used by all studies would prove to be useful in determining which patients to be included. This would eliminate severely impaired individuals who suffered from a stroke from being included in the same study as slight to moderately affected individuals, and it would be a standardized objective measure. Limiting the inclusion and exclusion criteria by age and other characteristics would be beneficial for future research. Classifying patients based on age would allow clinicians to better develop a prognosis with MT. For example, Dohle et al. included patients that were 25 to 80 years of age, and this is a large age range. Narrowing down the age range and categorizing patients would allow a likely upper extremity functional prognosis based on age. Lastly, designing a study examining the effects of a combination of MT in addition to CT in the acute, sub-acute, and chronic stages of stroke rehabilitation with a large sample size (n=at least 100) would be useful in extrapolating the data.

## Clinical Applications

MT is a cost-effective treatment for individuals post stroke. Necessary equipment can be purchased over the counter for as little as $10.[5,55,56] It is an attractive form of neurological rehabilitation because treatment is simple to administer.[33,57] Additionally, it can be performed in all settings of rehabilitation including: hospital, outpatient, and the home setting.[33] The study by Michielsen et al. demonstrated that if patients are in the chronic stage of rehabilitation and independent, they may administer MT at home independently, making it's utilization very appealing to clinicians.[16] Current literature indicates that MT will benefit patients regardless of whether they are in the acute or chronic stages.[6,9,16,30,33] This meta-analysis supports the utilization of MT in addition to CT for the acute and chronic stages of stroke, providing evidence that clinicians should incorporate these strategies regardless of the stage the patient is in. Although it is inconclusive without more support from future research to extrapolate the information in this meta-analysis as to when to best implement

MT, these techniques do improve upper extremity function, have no adverse effects, no known risks, and therefore therapists should apply MT in their practice.

## Conclusion

The current literature presented in this meta-analysis demonstrated that MT in addition to CT was more effective in improving upper extremity function than CT alone in all stages of stroke rehabilitation. There is a minimal to moderate effective size depending on severity which suggests that MT in addition to CT is more beneficial when initiated in the acute stage of stroke rehabilitation as compared to the chronic. The evidence should, however, be interpreted with caution and not be extrapolated because more studies would need to be performed. In conclusion, mirror therapy is a cost-effective way to improve motor function for individuals' post-stroke.

REFERENCES

REFERENCES


1. Centers for Disease Control and Prevention. Stroke Statistics 2017. https://www.cdc.gov/stroke/facts.htm. Accessed October 13, 2018.

2. O'Sullivan SB. Stroke. In: O'Sullivan SB, Schmitz TJ, Fulk GD, eds. *Physical rehabilitation, 6e.* New York, NY: McGraw-Hill Education; 2014.

3. Spieler J-F, Lanoë J-L, Amarenco P. *Costs of stroke care according to handicap levels and stroke subtypes.* Vol 172004. Doi: 10.1159/000075782.

4. Aprile I, Rabuffetti M, Padua L, Di Sipio E, Simbolotti C, Ferrarin M. Kinematic analysis of the upper limb motor strategies in stroke patients as a tool towards advanced neurorehabilitation strategies: A preliminary study. *BioMed Research International.* 2014; 2014:636123doi; DOI

5. Deconinck FJA, Smorenburg ARP, Benham A, Ledebt A, Feltham MG, Savelsbergh GJP. Reflections on mirror therapy: A systematic review of the effect of mirror visual feedback on the brain. *Neurorehabil Neural Repair.* 2015;29(4):349-361doi; DOI

6. Dohle C, Püllen J, Nakaten A, Küst J, Rietz C, Karbe H. Mirror therapy promotes recovery from severe hemiparesis: A randomized controlled trial. *Neurorehabil Neural Repair.* 2009;23(3):209-217doi; DOI

7. Cacchio A, De Blasis E, De Blasis V, Santilli V, Spacca G. Mirror therapy in complex regional pain syndrome type 1 of the upper limb in stroke patients. *Neurorehabil Neural Repair.* 2009;23(8):792-799doi; DOI

8. Gurbuz N, Afsar SI, Ayaş S, Cosar SNS. Effect of mirror therapy on upper extremity motor function in stroke patients: A randomized controlled trial. *Journal of Physical Therapy Science.* 2016;28(9):2501-2506doi; DOI

9. Invernizzi M, Negrini S, Carda S, L L, Cisari C, Baricich A. The value of adding mirror therapy for upper limb motor recovery of subacute stroke patients: A randomized controlled trial. Vol 482013.

10. Lee MM, Cho H, Song C. The mirror therapy program enhances upper-limb motor recovery and motor function in acute stroke patients. *Am J Phys Med Rehabil.* 2012;91(8):689-696doi; DOI

11. Lim K-B, Lee H-J, Yoo J, Yun H-J, Hwang H-J. Efficacy of mirror therapy containing functional tasks in poststroke patients. *Annals of Rehabilitation Medicine.* 2016;40(4):629-636doi; DOI

12. Park Y, Chang M, Kim K, An D. The effects of mirror therapy with tasks on upper extremity function and self-care in stroke patients. *J Phys Ther Sci.* 2015;27(5):1499-1501doi; DOI

13. Samuelkamaleshkumar S, Reethajanetsureka S, Pauljebaraj P, Benshamir B, Padankatti SM, David JA. Mirror therapy enhances motor performance in the paretic upper limb after stroke: A pilot randomized controlled trial. *Arch Phys Med Rehabil.* 2014;95(11):2000-2005doi; DOI

14. Yavuzer G, Selles R, Sezer N, et al. Mirror therapy improves hand function in subacute stroke: A randomized controlled trial. *Arch Phys Med Rehabil.* 2008;89(3):393-398doi; DOI

15. Arya KN, Pandian S, Kumar D, Puri V. Task-based mirror therapy augmenting motor recovery in poststroke hemiparesis: A randomized controlled trial. *J Stroke Cerebrovasc Dis.* 2015;24(8):1738-1748doi; DOI

16. Michielsen ME, Selles RW, van Der Geest JN, et al. Motor recovery and cortical reorganization after mirror therapy in chronic stroke patients: A phase ii randomized controlled trial. *Neurorehabil Neural Repair.* 2011;25(3):223-233doi; DOI

17. American Stroke Association. Stroke treatment. http://www.strokeassociation.org/STROKEORG/AboutStroke/Treatment/Stroke-Treatment_UCM_492017_SubHomePage.jsp. Accessed October 13, 2018.

18. Pervane Vural S, Nakipoglu Yuzer GF, Sezgin Ozcan D, Demir Ozbudak S, Ozgirgin N. Effects of mirror therapy in stroke patients with complex regional pain syndrome type 1: A randomized controlled study. *Arch Phys Med Rehabil.* 2016;97(4):575-581doi; DOI

19. World Stroke Organization. Facts and figures about stroke. https://www.world-stroke.org/component/content/article/16-forpatients/84-facts-and-figures-about-stroke. Accessed October 13, 2018.

20. Jang SH, Chang MC. Motor outcomes of patients with a complete middle cerebral artery territory infarct. *Neural Regeneration Research.* 2013;8(20):1892-1897doi; DOI

21. Sommerfeld D, Eek E, Svensson A, Holmqvist L, Von Arbin M. Spasticity after stroke - its occurrence and association with motor impairments and activity limitations. *Stroke.* 2004;35(1):134-139doi; DOI

22. Caplan LR. *Stroke syndromes.* Third edition. ed. New York: Cambridge. 2012.

23. Altschuler EL, Wisdom SB, Stone L, et al. Rehabilitation of hemiparesis after stroke with a mirror. *The Lancet.* 1999;353(9169):2035-2036doi; DOI

24. Chen C-L, Wong M-K, Chen H-C, Cheng P-T, Tang F-T. Correlation of polyelectromyographic patterns and clinical upper motor neuron syndrome in hemiplegic stroke patients. *Arch Phys Med Rehabil.* 2000;81(7):869-875doi; DOI

25. Inatomi Y, Nakajima M, Yonehara T, Ando Y. Ipsilateral hemiparesis in ischemic stroke patients. *J Neurol Sci.* 2017;381(sS):522doi; DOI

26. Dobkin BH. Strategies for stroke rehabilitation. *The Lancet Neurology.* 2004;3(9):528-536doi; DOI

27. Harris JE, Eng JJ. Paretic upper-limb strength best explains arm activity in people with stroke. *Phys Ther.* 2007;87(1):88-97doi; DOI

28. Lang CE, Bland MD, Bailey RR, Schaefer SY, Birkenmeier RL. Assessment of upper extremity impairment, function, and activity following stroke: Foundations for clinical decision making. *Journal of hand therapy: official journal of the American Society of Hand Therapists.* 2013;26(2):104-115doi; DOI

29. Jones TA, Adkins DL. Motor system reorganization after stroke: Stimulating and training toward perfection. *Physiology (Bethesda).* 2015;30(5):358-370doi; DOI

30. Thieme H, Bayn M, Wurg M, Zange C, Pohl M, Behrens J. Mirror therapy for patients with severe arm paresis after stroke – a randomized controlled trial. *Clin Rehabil.* 2012;27(4):314-324doi; DOI

31. Ramachandran VS, Rogers-Ramachandran D. Synaesthesia in phantom limbs induced with mirrors. *Proceedings of the Royal Society B: Biological Sciences.* 1996;263(1369):377-386doi; DOI

32. Ramachandran VS, Rogers-Ramachandran D, Cobb S. Touching the phantom limb. *Nature.* 1995;377(6549):489doi; DOI

33. Yang Y, Zhao Q, Zhang Y, Wu Q, Jiang X, Cheng G. Effect of mirror therapy on recovery of stroke survivors: A systematic review and network meta-analysis. *Neuroscience.* 2018; 390:318-336doi; DOI

34. Mei Toh SF, Fong KNK. Systematic review on the effectiveness of mirror therapy in training upper limb hemiparesis after stroke. *Hong Kong Journal of Occupational Therapy.* 2012;22(2):84-95doi; DOI

35. Thieme H, Mehrholz J, Pohl M, Behrens J, Dohle C. Mirror therapy for improving motor function after stroke. *Stroke.* 2013;44(1):E1-E2doi;DOI

36. Carvalho D, Teixeira S, Lucas M, et al. The mirror neuron system in post-stroke rehabilitation. *Int Arch Med.* 2013; 6:41-41doi; DOI

37. Garrison KA, Winstein CJ, Aziz-Zadeh L. The mirror neuron system: A neural substrate for methods in stroke rehabilitation. 2010.

38. de Vries S, Mulder T. Motor imagery and stroke rehabilitation: A critical discussion. Vol 392007.

39. Platz T, Pinkowski C, van Wijck F, Kim I-H, di Bella P, Johnson G. Reliability and validity of arm function assessment with standardized guidelines for the fugl-meyer test, action research arm test and box and block test: A multicentre study. *Clin Rehabil.* 2005;19(4):404-411doi; DOI

40. Lang CE, Wagner JM, Dromerick AW, Edwards DF. Measurement of upper-extremity function early after stroke: Properties of the action research arm test. *Arch Phys Med Rehabil.* 2006;87(12):1605-1610doi; DOI

41. Yozbatiran N, Der-Yeghiaian L, Cramer SC. A standardized approach to performing the action research arm test. *Neurorehabil Neural Repair.* 2008;22(1):78-90doi; DOI

42. Van Der Lee JH, de Groot V, Beckerman H, Wagenaar RC, Lankhorst GJ, Bouter LM. The intra- and interrater reliability of the action research arm test: A practical test of upper extremity function in patients with stroke. *Arch Phys Med Rehabil.* 2001;82(1):14-19doi; DOI

43. De Morton NA. The pedro scale is a valid measure of the methodological quality of clinical trials: A demographic study. *Aust J Physiother.* 2009;55(2):129-133doi; DOI

44. Pedro physiotherapy evidence database. https://www.pedro.org.au/english/faq/. Accessed October 14, 2018.

45. Pedro score. https://www.strokengine.ca/en/glossary/pedro-score/. Accessed October 14, 2018.

46. Maher C, Sherrington C, Herbert R, Moseley A, Elkins M. Reliability of the pedro scale for rating quality of randomized controlled trials. *Phys Ther.* 2003;83(8):713-721doi; DOI

47. Dobkin BH. Clinical practice. Rehabilitation after stroke. *The New England journal of medicine.* 2005;352(16):1677-1684doi; DOI

48. Cramer SC. Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. *Ann Neurol.* 2008;63(3):272-287doi; DOI

49. Parker ME, Snyder-Shall M. Recovery of upper extremity function in stroke patients: The copenhagen stroke study. *Neurology Report.* 1995;19(1):46-47doi; DOI

50. Eraifej J, Clark W, France B, Desando S, Moore D. Effectiveness of upper limb functional electrical stimulation after stroke for the improvement of activities of daily living and motor function: A systematic review and meta-analysis. *Systematic reviews.* 2017;6(1):40-40doi; DOI

51. Cooke EV, Mares K, Clark A, Tallis RC, Pomeroy VM. The effects of increased dose of exercise-based therapies to enhance motor recovery after stroke: A systematic review and meta-analysis. *BMC Med.* 2010; 8:60-60doi; DOI

52. Jørgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Støier M, Olsen TS. Outcome and time course of recovery in stroke. Part ii: Time course of recovery. The copenhagen stroke study. *Arch Phys Med Rehabil.* 1995;76(5):406-412doi; DOI

53. Hendricks HT, van Limbeek J, Geurts AC, Zwarts MJ. Motor recovery after stroke: A systematic review of the literature. *Arch Phys Med Rehabil.* 2002;83(11):1629-1637doi; DOI

54. Meyer S, Verheyden G, Brinkmann N, et al. Functional and motor outcome 5 years after stroke is equivalent to outcome at 2 months follow-up of the collaborative evaluation of rehabilitation in stroke across europe. *Stroke.* 2015;46(6):1613-+doi;DOI

55. Gurbuz N, Afsar S, Ayas S. Effect of mirror therapy on upper extremity motor function in stroke patients: A randomized controlled trial. *Journal of Physical Therapy Science.* 2016;28(9):2501-2506doi; DOI

56. Wittkopf PG, Johnson MI. Mirror therapy: A potential intervention for pain management. *Rev Assoc Med Bras.* 2017; 63:1000-1005doi; DOI

57. Wu C-Y, Huang P-C, Chen Y-T, Lin K-C, Yang H-W. Effects of mirror therapy on motor and sensory recovery in chronic stroke: A randomized controlled trial. *Arch Phys Med Rehabil.* 2013;94(6):1023-1030doi; DOI

# TABLES

## Table 1. PEDro Scale

| Study | Random Allocation | Concealed Allocation | Baseline Comparability | Blind Subjects | Blind Therapist | Blind Assessor | One Outcome Obtained from More Than 85% of the Subjects | Intention -to- Treat- Analysis | Between Group Comparison | Point Estimate Value | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dohle et al. 2008 | ✓ | ✓ | ✓ | | | ✓ | | | ✓ | ✓ | 6/10 |
| Invernizzi et al. 2013 | ✓ | | ✓ | | | | ✓ | | ✓ | ✓ | 5/10 |
| Michielsen et al. 2011 | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ | ✓ | ✓ | 8/10 |
| Thieme et al. 2013 | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ | ✓ | ✓ | 8/10 |

## Table 2. Summary of Study Characteristics

| Study | Level of Evidence/Study Design | Sample Size | Intervention Frequency | Intervention Type |
|---|---|---|---|---|
| Invernizzi et al. | Level 1; A randomized controlled trial | (N=26)<br>Mean age:<br>MT group: 62 y.o.<br>CT group: 71.1 y.o. | Both groups: 1-hour CT, 5 days a week, for 4 weeks<br><br>CT group: 30 minutes of MT for the first 2 weeks and 1 hour for the last 2 weeks (5days/wk)<br><br>MT group: 30 minutes of sham MT for the first 2 weeks and 1 hour for the last 2 weeks (5days/wk) | CT that is patient specific and consisted of neurorehabilitative techniques, ES, and OT, MT for MT group, and sham MT for CT group |
| Dohle et al. | Level 1; A randomized controlled trial | (N=36)<br>Mean age:<br>MT group: 54.9 y.o.<br>CT group: 58 y.o. | CT group CT: OT=12.3 hrs, PT=23.8 hrs, ADL=8.55 hrs<br><br>CT group sham MT: 30 minutes 5 days/wk for 6 wks of CT<br><br>MT group CT: OT=14.7 hrs, PT=4.4 hrs, ADL=5.9 hrs<br><br>MT group MT: 30 minutes 5 days/wk for 6 wks of CT | CT (arm, hand, and finger postures), ADL training/OT/PT for both groups MT for MT group, and sham MT for CT group |
| Thieme et al. | Level 1; A randomized controlled trial | (N=39)<br>Mean age:<br>MT group: 63.8 y.o.<br>CT group: 68.3 y.o. | Both groups: 20 sessions over 5 weeks for a maximum of 30 minutes/session<br>-Author stated an additional 10 hours of treatment was given to attain a difference between groups | CT (single/group PT, OT, and training of ADL's), MT for MT group, and sham MT for CT group |
| Michielsen et al. | Level 1; A Phase II randomized controlled trial | (N=40)<br>Mean age:<br>MT group: 55.3 y.o.<br>CT group: 58.7 y.o. | Both groups: 6 wk CT (included MT or sham MT) 1d/wk in clinic and 5 days at home<br><br>(5 days/wk) | Bimanual and functional exercises for both groups. MT for MT group, and sham MT for CT group |

**Table 3. Results for: Effect Size of Pre to Post Mean Change for Acute Versus Chronic Stroke Rehabilitation for MT in Addition to CT Including Invernizzi et al., Dohle et al., Thieme et al., and Michielsen et al.**

| Study | Effect Size | CI Lower | CI Upper |
|---|---|---|---|
| Dohle et al. 2008/Michielsen et al. 2011 | 0.13 | -0.51 | 0.76 |
| Invernizzi et al. 2013/Michielsen et al. 2011 | 1.06 | 0.30 | 1.82 |
| Thieme et al. 2013/Michielsen et al. 2011 | 0.09 | -0.55 | 0.73 |
| Total | 0.35 | -0.03 | 0.74 |
| Q-value | 4.43 | | |

**Table 4. Results for: Effect Size of Pre to Post Mean Change for Acute Versus Chronic Stroke Rehabilitation for MT in Addition to CT Including Dohle et al., Thieme et al., and Michielsen et al.**

| Study | Effect Size | CI Lower | CI Upper |
|---|---|---|---|
| Dohle et al. 2008/Michielsen et al. 2011 | 0.09 | -0.51 | 0.76 |
| Thieme et al. 2013/Michielsen et al. 2011 | 0.09 | -0.55 | 0.73 |
| Total | 0.11 | -0.34 | 0.56 |
| Q-value | .003 | | |
| P-value | .96 | | |

**Table 5. Results for: Effect of MT in addition to CT as Compared to CT Alone in the Acute and Chronic Stages Based on the ARAT.**

| Study | Effect Size | CI Lower | CI Upper |
|---|---|---|---|
| Dohle et al. 2008 | 0.08 | -0.58 | 0.73 |
| Invernizzi et al. 2013 | 0.77 | -0.04 | 1.59 |
| Michielsen et al. 2011 | 0.23 | -0.39 | 0.86 |
| Thieme et al. 2013 | 0.21 | -0.42 | 0.85 |
| Total | 0.28 | -0.06 | 0.61 |
| Q-value | 1.85 | | |
| P-value | 0.60 | | |

FIGURES

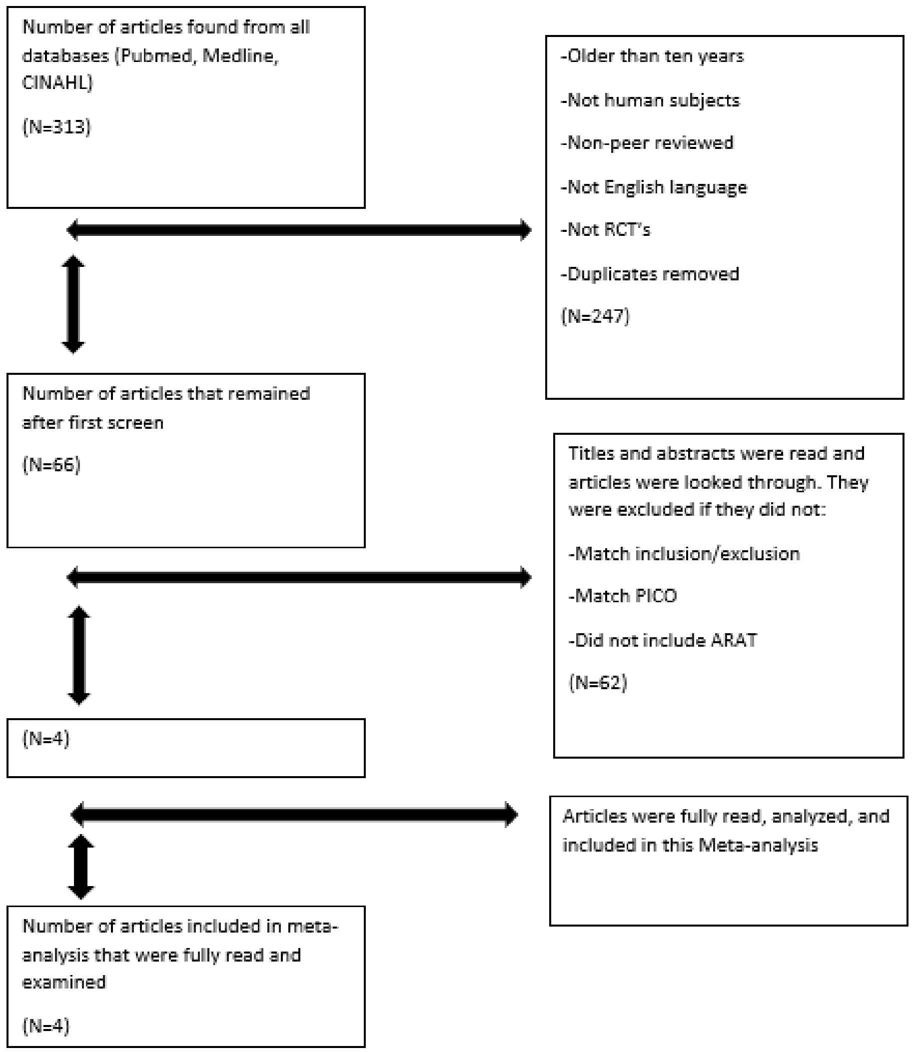


**Figure 1. Study selection process**

**ACTION RESEARCH ARM TEST**

**Patient Name:** ______________________

**Rater Name:** ______________________

**Date:** ______________________

**Instructions**

There are four subtests: Grasp, Grip, Pinch, Gross Movement. Items in each are ordered so that:

- if the subject passes the first, no more need to be administered and he scores top marks for that subtest;
- if the subject fails the first *and* fails the second, he scores zero, and again no more tests need to be performed in that subtest;
- otherwise he needs to complete all tasks within the subtest

| Activity | Score |
|---|---|
| **Grasp** | |
| 1. Block, wood, 10 cm cube (If score = 3, total = 18 and to Grip)<br>Pick up a 10 cm block | ______ |
| 2. Block, wood, 2.5 cm cube (If score = 0, total = 0 and go to Grip)<br>Pick up 2.5 cm block | ______ |
| 3. Block, wood, 5 cm cube | ______ |
| 4. Block, wood, 7.5 cm cube | ______ |
| 5. Ball (Cricket), 7.5 cm diameter | ______ |
| 6. Stone 10 x 2.5 x 1 cm | ______ |
| Coefficient of reproducibility = 0.98 | |
| Coefficient of scalability = 0.94 | |
| **Grip** | |
| 1. Pour water from glass to glass (If score = 3, total = 12, and go to Pinch) | ______ |
| 2. Tube 2.25 cm (If score = 0, total = 0 and go to Pinch) | ______ |
| 3. Tube 1 x 16 cm | ______ |
| 4. Washer (3.5 cm diameter) over bolt | ______ |
| Coefficient of reproducibility = 0.99 | |
| Coefficient of scalability = 0.98 | |
| **Pinch** | |
| 1. Ball bearing, 6 mm, 3rd finger and thumb (If score = 3, total = 18 and go to Grossmt) | ______ |
| 2. Marble, 1.5 cm, index finger and thumb (If score = 0, total = 0 and go to Grossmt) | ______ |
| 3. Ball bearing 2nd finger and thumb | ______ |
| 4. Ball bearing 1st finger and thumb | ______ |
| 5. Marble 3rd finger and thumb | ______ |
| 6. Marble 2nd finger and thumb | ______ |
| Coefficient of reproducibility = 0.99 | |
| Coefficient of scalability = 0.98 | |

*Provided by the Internet Stroke Center — www.strokecenter.org*

| | |
|---|---|
| **Grossmt (Gross Movement)** | |
| 1. Place hand behind head (If score = 3, total = 9 and finish) | ______ |
| 2. (If score = 0, total = 0 and finish | ______ |
| 3. Place hand on top of head | ______ |
| 4. Hand to mouth | ______ |
| Coefficient of reproducibility = 0.98 | |
| Coefficient of scalability = 0.97 | |

**Figure 2. Action research and ARM test**

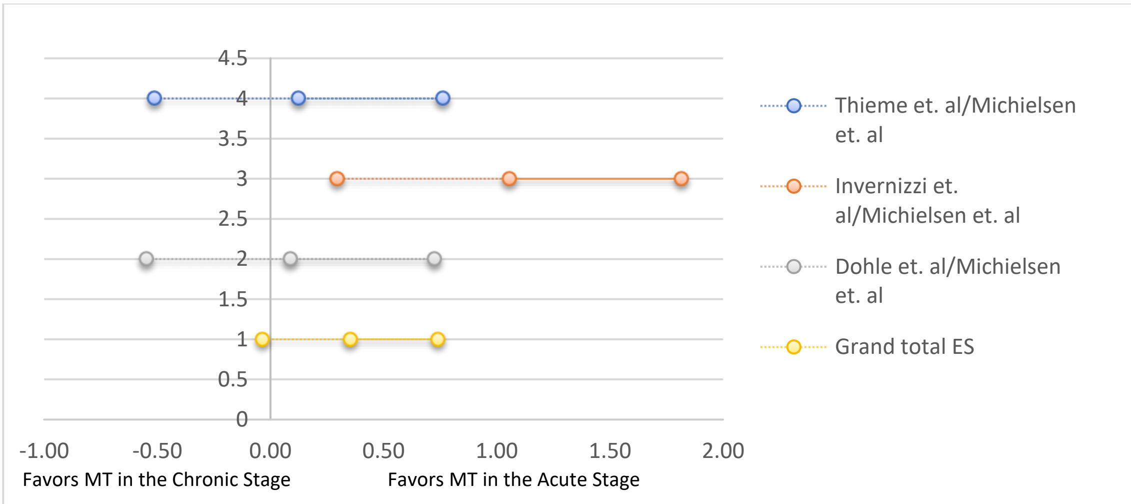


**Figure 3. Effect size of pre to post mean change for acute versus chronic stroke rehabilitation for MT in addition to CT including Invernizzi et al., Dohle et al., Thieme et al., and Michielsen et al.**

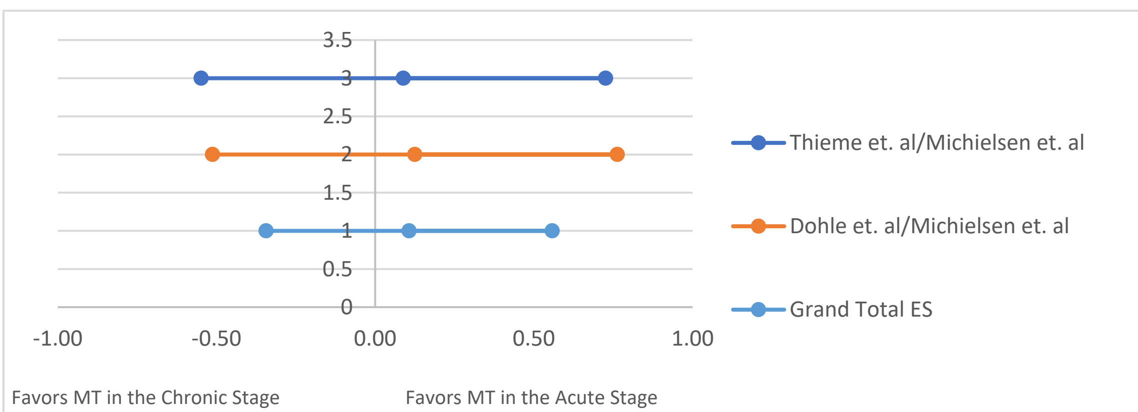


**Figure 4. Effect size of pre to post mean change for acute versus chronic stroke rehabilitation for MT in addition to CT including Dohle et al., Thieme et al., and Michielsen et al.**

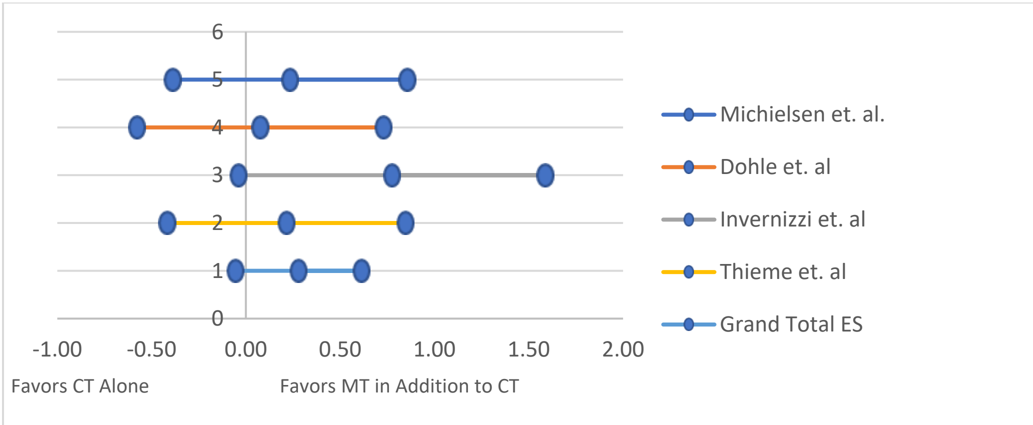


**Figure 5. Effect of MT in addition to CT as compared to CT alone in the acute and chronic stages based on the ARAT**