Mirror Therapy in Unilateral Neglect After Stroke (MUST trial)

A randomized controlled trial

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ABSTRACT

Objective: We explored the effectiveness of mirror therapy (MT) in the treatment of unilateral neglect in stroke patients.

Methods: This is an open, blinded endpoint, randomized controlled trial carried out from January 2011 to August 2013. We included stroke patients with thalamic and parietal lobe lesions with unilateral neglect 48 hours after stroke. Patients were randomized to the MT group or the control group (sham MT), and both the groups received limb activation. Patients received treatment for 1–2 hours a day 5 days a week for 4 weeks. The primary outcome was unilateral neglect assessed by a blinded assessor using the star cancellation test, the line bisection test, and a picture identification task at 1, 3, and 6 months. This study was registered at <http://clinicaltrials.gov> (NCT 01735877).

Results: Forty-eight patients were randomized to MT ($n = 27$) or the control group ($n = 21$). Improvement in scores on the star cancellation test over 6 months was greater in the MT group (mean difference 23, 95% confidence interval [CI] 19–28; $p < 0.0001$). Similarly, improvement in the MT group was observed in the scores on the picture identification task (mean difference 3.2, 95% CI 2.4–4.0; $p < 0.0001$) and line bisection test (mean difference 8.6, 95% CI 2.7–14.6; $p = 0.006$).

Conclusions: In patients with stroke, MT is a simple treatment that improves unilateral neglect.

Classification of evidence: This study provides Class I evidence that for patients with neglect from thalamic and parietal lobe strokes, MT improves neglect. *Neurology*® 2014;83:1012–1017

GLOSSARY

CI = confidence interval; CMC = Christian Medical College; FIM = functional independence measure; LBT = line bisection test; mRS = modified Rankin scale; MT = mirror therapy; PIT = picture identification task; RCT = randomized controlled trial; SCT = star cancellation test; SMD = standardized mean difference.

About 30%–50% of stroke patients are left with considerable residual deficits.¹ Hemispatial neglect can be a major source of functional limitation after stroke.^{2–4} Hemineglect occurs mostly in right hemispheric strokes but can also be seen in left hemisphere strokes. In an observational study, neglect was found in 70% of right and 49% of left hemispheric strokes.⁵ Neglect occurs most frequently and dramatically in left hemisphere in association with lesions of the right hemisphere.⁶ Lesions involving the inferior parietal lobe and superior temporal cortex have been associated with neglect.⁴

Various techniques, such as scanning, visual cueing approaches, limb activation strategies, visual imagery, prisms, and sustained attention training, are being used to treat unilateral neglect.⁷ Mirror therapy (MT) enables patients to control their movements by themselves and is known to be effective in improving upper limb motor recovery and motor function after stroke.⁸ In studies involving a small number of patients, MT has been found to improve hand function and unilateral neglect.⁹ Researchers have used MT in the chronic phase of stroke and have also tested different modalities in the same patient to treat neglect.¹⁰ Hence, we carried out

Supplemental data
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Figure 1 Mirror therapy and sham mirror therapy

(A) Patient performing mirror therapy of affected left upper extremity. (B) Patient performing sham mirror therapy using nonreflecting side of mirror.

this study to explore the effectiveness of MT in the treatment of unilateral neglect in stroke patients.

METHODS **Participants.** This was an interventional, prospective, open, blinded endpoint (PROBE design), randomized controlled trial (RCT) conducted in the Stroke Unit of Christian Medical College (CMC) and Hospital, Ludhiana, India and the College of Physiotherapy, CMC Ludhiana, India from January 2011 to August 2013. All stroke patients with thalamic and parietal lobe lesions within 48 hours of stroke onset who had upper

limb weakness and provided informed consent were included. Patients with a Glasgow Coma Scale score of less than 7 or who were uncooperative were excluded.

Randomization. All eligible participants were randomized to the MT group or the control group (sham MT). A random allocation sequence was made using random digits generated by RALOC (random allocation) software and was conveyed to the investigators by sealed numbered envelope.

Intervention. During the MT, patients sat near a table on which a mirror box (35 × 35 cm) was placed vertically (figure 1A). The affected hand was hidden behind the mirror and the unaffected

Figure 2 Recruitment of stroke patients in the study

Table 1 Demography, stroke clinical characteristics, and outcome measures at baseline

Variables	Treatment group (n = 27)	Control group (n = 21)
Age, y, mean ± SD	63 ± 11	64 ± 12
Women	13 (52)	7 (33)
Type of stroke		
Ischemic stroke	15 (56)	11 (52)
Intracerebral hemorrhage	12 (44)	10 (48)
Risk factors		
Hypertension	22 (82)	19 (91)
Diabetes mellitus	11 (41)	8 (38)
Dyslipidemia	1 (4)	1 (5)
Atrial fibrillation	3 (11)	1 (5)
Coronary artery disease	2 (7)	2 (10)
Carotid stenosis	1 (4)	0 (0)
Previous TIA	0 (0)	4 (19)
Alcohol intake	6 (22)	6 (29)
Smoking	3 (11)	2 (10)
Obesity	3 (11)	3 (14)
NIHSS, median (IQR)	5 (4–10)	5 (4.5–10)
Oxfordshire stroke classification		
TACS	9 (33)	2 (10)
PACS	14 (52)	17 (80)
LACS	4 (15)	2 (10)
Hemisphere		
Right	21 (78)	16 (76)
Left	6 (22)	5 (24)
Location		
Thalamic	13 (49)	9 (43)
Parietal	13 (49)	11 (54)
Primary outcome measures, mean ± SD		
Star cancellation test	18 ± 5	18 ± 6
Line bisection test	1.9 ± 10.6	0.4 ± 11.3
Picture identification task	5 ± 0.4	4 ± 1

Abbreviations: IQR = interquartile range; LACS = lacunar stroke; NIHSS = NIH Stroke Scale; PACS = partial anterior circulation stroke; TACS = total anterior circulation stroke. Data are n (%), unless otherwise indicated.

hand was placed in front of the mirror. Patients were asked to see only the unaffected hand in the mirror. Patients were instructed to perform flexion and extension movements of the nonparetic wrist and fingers while looking into the mirror. Thus, they were seeing the reflection of the unaffected hand as the movement of the affected hand in the mirror. During the session, while they were moving the nonparetic hand, they were asked to do the same movements in the paretic hand. Patients received treatment for 1–2 hours (MT and limb activation) a day 5 days a week for 4 weeks. If they were discharged before 4 weeks, a physiotherapist gave the therapy at home for the rest of the treatment period. The patients in each group were given a home program and it was monitored during the home visit.

All the patients did MT for 1 hour and the next hour was spent on limb activation. Patients were asked to move the paretic upper and lower limbs. If the patients were not able to do this, the treating therapist helped them in the movement. The limb activation movements included tapping the affected hand or fingers on the table or a plain surface. Patients spent about 15–30 minutes doing this voluntary activity. In addition, patients were also taught to do functional and goal-oriented activities such as combing, tying turban (for men), wearing garments, picking up objects and placing them on the table, and pouring and drinking from a cup. Patients spent an average of 30 minutes performing these activities.⁸

Control. The control group carried out similar exercises for the same time period but they used the nonreflecting side of the mirror. The paretic hand was hidden from their sight (figure 1B). The control therapy was given by the same physiotherapist. Both the treatment and the control group received limb activation.

Outcome measures. The primary outcomes were unilateral neglect measured using the star cancellation test (SCT),¹¹ line bisection test (LBT),¹² and picture identification task (PIT).¹³ Secondary outcomes were assessed by functional independence measure (FIM)¹⁴ and modified Rankin Scale (mRS) (good outcome: mRS ≤2).¹⁵ A physiotherapist who was unaware of the group assignments assessed the outcome at 1, 3, and 6 months.

SCT: In the SCT, there are 52 large stars interspersed within 52 small stars, 10 short words, and 13 letters. The stroke patients were asked to cross out all the small stars on the page. The cutoff score of unilateral visual neglect is 51 or fewer stars cancelled by the patient.¹¹

LBT: There are three 20-cm horizontal black lines in the LBT. One line is on the right of the page, one line is in the center, and one is on the left. The patients were instructed to mark the center of each line. Errors were measured in centimeters from the true midline. Leftward errors were indicated with negative numbers and rightward errors were indicated with positive numbers. The cutoff score for unilateral visual neglect was an error of more than 1.4 cm left or right.¹²

PIT: The PIT consisted of 10 pictures on A4 size paper. Patients were asked to identify pictures. The more pictures they were able to identify indicated absence of unilateral visual neglect.¹³

FIM: There are 13 motor and 5 social-cognitive items in the FIM. Functional impairment is classified by a 7-level scale: 1 and 2 = total dependence; 3 to 5 = modified dependence; 6 and 7 = no help required (independence).¹⁴ For the purpose of analysis we divided the FIM into 2 categories: ≤5 dependent, ≥6 independent.

Standard protocol approvals, registrations, and patient consents. All the subjects gave written informed consent. The institutional ethics committee approved this trial. This study was registered at <http://clinicaltrials.gov> (NCT01735877).

Classification of evidence. The primary research question was whether MT is effective in the treatment of unilateral neglect in stroke patients. This study provides Class I evidence that for patients with neglect from thalamic and parietal lobe strokes, MT improves neglect.

Statistical analysis. The sample size calculation was based on effect size 0.5 of the neglect score (Behavioral Inattention test), 80% power, level of significance 0.05, and assuming a dropout rate of 10% using OpenEpi version 3.01. Effect size 0.5 was calculated from the previous study.¹⁶ The required sample size was 40 (20 in each group).

The comparison of primary outcome measures (SCT, LBT, PIT) between the treatment and the control group at baseline to 1, 3, and 6 months was assessed by an analysis of covariance. The comparison between the treatment and the control group during an overall period of 6 months was assessed by a linear mixed

Figure 3 Mean changes in star cancellation test

Comparison of mean changes in the treatment group and the control group on the star cancellation test. The mean change with 95% confidence interval is given, and the *p* value shows the difference between the treatment and control groups.

model. The comparison of secondary outcome measures was performed using a χ^2 test. We used modified intention-to-treat principle for the statistical analysis. Missing values on outcomes were imputed using last observation carried forward method. Statistical analysis was done with SPSS version 21 (IBM Corp., Armonk, NY) and the significance level was set at *p* < 0.05.

RESULTS A total of 402 patients were eligible and 48 were randomized (354 patients were excluded because they did not meet inclusion criteria or did not give

consent). In the final analysis 47 were included. The detailed recruitment algorithm is shown in figure 2.

Demography, stroke clinical characteristics, and outcome measures at baseline. Baseline characteristics were similar in both groups (table 1). At baseline, measures of unilateral neglect (SCT, LBT and PIT) were also similar between randomized groups (table 1).

Mean change of primary outcome measures during follow-up compared to baseline. Improvement was seen in the primary outcome measures during follow-up in patients who received MT compared to the control group. The overall differences were also seen in the SCT, LBT, and PIT in the treatment group (figures 3 and figure 4, A and B).

Comparison of secondary outcome measures (FIM and mRS) between the 2 groups at baseline and follow-up. Based on the FIM, the patients in the treatment group were more likely to be independent during follow-up. Good outcome was seen in more patients in the treatment group at 6 months (table e-1 on the *Neurology*® Web site at Neurology.org).

There were no adverse events seen in either group.

Meta-analysis results. We performed a meta-analysis using the following criteria: RCTs of MT in the treatment of hemineglect and stroke, use of standardized tools to document neglect, clearly defined intervention including duration of treatment, and blinded outcome assessment. We used the following databases: Cochrane Library, PubMed/Medline, PeDRO, Cinahl, and EIRA. For the key words cerebrovascular accident (MeSH) and rehabilitation, there were 15,034

Figure 4 Mean changes in line bisection test and picture identification task

(A) Comparison of mean changes in the treatment group and the control group on the line bisection test. The mean change with 95% confidence interval (CI) is given, and the *p* value shows the difference between the treatment and control groups. (B) Comparison of mean changes in the treatment group and the control group on the picture identification task. The mean change with 95% CI is given, and the *p* value shows the difference between the treatment and control groups.

hits from 1990 to 2013. We also used key words hemispatial neglect and rehabilitation; hemi-inattention, and there were 1,578 hits. Finally, for hemispatial neglect and rehabilitation after stroke 2 RCTs were found.

Including our study, there were 3 trials, which used different screening tools and outcome measures. Star cancellation score was the common outcome measure used in 2 RCTs (including the present study)¹⁷; in the third study¹⁶ they used self-defined neglect score. In the analysis, we included 2 studies that used the same outcome measures. The main characteristics of these 2 trials are given in table e-2. There was a total of 55 patients. Using change in the star cancellation score from baseline, we found that MT had an effect on improving neglect (standardized mean difference [SMD] 2.6, 95% confidence interval [CI] 1.8–3.3; $p < 0.0001$) (figure e-1). A single trial with a 6-month follow-up showed positive effect: SMD 3.6, 95% CI 2.7–4.6; $p < 0.0001$.

DISCUSSION Our results can be explained by the following mechanisms. The visual illusion of the affected hand movement recruits the premotor cortex through its connections with visual areas.¹⁸ MT related to motor imagery creates the visual feedback of the imagined action in the affected limb.¹⁹ Another mechanism is that the mirror neurons are activated when the brain attempts to observe, imagine, and execute an action, and they are known to participate in the new motor skills through observations.^{20,21} Our results are consistent with another study⁷ that compared bilateral MT with sham MT. Meta-analysis of 2 RCTs also showed similar results.

The strengths of the study are that we explored the effectiveness of MT in the treatment of unilateral neglect during the acute phase of stroke. The treatment was monitored at home by a physiotherapist. Outcome was assessed by a physiotherapist who was blinded to randomized treatment and clinical details.

Our study has limitations. There was some imbalance in stroke lesions, manual dexterity, and stage of motor recovery between randomized groups. Since the patients were included from the acute stage with upper limb motor weakness, their activities of daily living were highly limited. Manual dexterity could have been improved by performing activities that require repetition, focus, and hand-eye coordination. Second, the neglect can improve spontaneously with compensatory strategies. The neglect improved in a very small proportion of patients in the control group; however, it was not significant. We found that MT is a simple therapy that can be widely used in the improvement of neglect in stroke patients.

AUTHOR CONTRIBUTIONS

Jeyaraj D. Pandian: literature search, study design, data collection, data interpretation, and writing. Rajni Arora: literature search, study design,

data collection, data interpretation, and writing. Paramdeep Kaur: data analysis, data interpretation, and writing. Deepika Sharma: literature search, study design, data collection, data interpretation, and writing. Dheeraj K. Vishwambaran: literature search, study design, data collection, data interpretation, and writing. Hisatomi Arima: data analysis and writing.

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DISCLOSURE

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Mirror Therapy in Unilateral Neglect after Stroke (MUST trial): A randomized controlled trial (See p. 1012)

This podcast begins and closes with Dr. Ted Burns, Section Editor Podcasts, briefly discussing highlighted articles from the September 9, 2014, issue of *Neurology*. In the second segment, Dr. Andy Southerland talks with Dr. Jeyaraj Pandian about his paper on mirror therapy in unilateral neglect after stroke (the MUST trial). Dr. James Addington then reads the e-Pearl of the week about basilar-type migraine. In the next part of the podcast, Dr. Stephen Donahue focuses his interview with Dr. Michael

Jaffee on the acute diagnosis and management of concussion.

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