의학박사 학위논문

A 2-Axis Robotic Mirror Therapy System to Enhance Proprioception and Functional Recovery of Hemiplegic Arms in Patients with Stroke

뇌졸중 환자에서 고유감각 및 편마비측 상지 기능 회복 촉진을 위한 2축 거울상 로봇 치료 시스템

2016년 8월

서울대학교 대학원

의학과 의공학 전공

범 재 원

A thesis of the Degree of Doctor of Philosophy

뇌졸중 환자에서 고유감각 및 편마비측 상지 기능 회복 촉진을 위한 2 축 거울상 로봇 치료 시스템

A 2-Axis Robotic Mirror Therapy System to Enhance Proprioception and Functional Recovery of Hemiplegic Arms in Patients with Stroke

August 2016

The Department of Medicine,

Seoul National University

College of Medicine

Jaewon Beom

ABSTRACT

Introduction: Mirror therapy has been performed as an effective occupational therapy in a clinical setting for functional recovery of a hemiplegic arm after stroke. It is conducted by eliciting a visual illusion through the use of a mirror as if the hemiplegic arm is moving in real-time while moving the healthy arm. It can facilitate brain neuroplasticity through activation of the sensorimotor cortex. However, conventional mirror therapy has a critical limitation in that the hemiplegic arm is not actually moving.

Methods: We developed a real-time 2-axis mirror robot system as a simple add-on module for conventional mirror therapy using a closed feedback mechanism, which allows for real-time movement of the hemiplegic arm. This is the first attempt that combined a robot with a real mirror for facilitation of proprioception followed by motor recovery. We used three attitude and heading reference system sensors, two brushless DC motors for elbow and wrist joints, and exoskeletal frames.

Results: Motion synchronicity between the motors in the hemiplegic arm and the AHRS sensors in the healthy arm was validated. A study with six healthy subjects showed that robotic mirror therapy was safe and feasible. We further selected useful tasks for activities of daily living training through feedback from six rehabilitation doctors. Two chronic stroke patients showed improvement in the Fugl-Meyer assessment scale and elbow flexor spasticity, proprioception and hemispatial neglect after a 2-week application of the mirror robot system. The enhancement of proprioceptive input can be explained by the functional MRI results. The results revealed that both the lower part of the superior parietal lobule and the premotor cortex (PMC) were activated during the passive range of motion (ROM) exercise, whereas the PMC was mainly activated during the active ROM exercise.

Conclusions: Robotic mirror therapy could enhance proprioceptive stimulus to the sensory cortex, which is considered to be very important in neuroplasticity and functional recovery of hemiplegic arms. The mirror robot system presented in this study can be easily developed and utilized effectively to advance occupational therapy.

Keywords: Mirror therapy, proprioception, rehabilitation robot, stroke, hemiplegia, sensor

Student Number: 2012-30553

CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

ADLs Activities of daily living

AHRS Attitude and heading reference system

BA Brodmann area

BOLD Blood-oxygen-level dependent

fMRI Functional magnetic resonance imaging

MNI Montreal Neurological Institute

PMC Premotor cortex

ROM Range of motion

TFT Thumb finding test

INTRODUCTION

For patients with stroke, dysfunction of a hemiplegic arm exerts a debilitating effect. The ability to perform bimanual activities is essential for daily life, but functional deficit of a hemiplegic arm following a stroke often remains, even a few years after stroke onset. Among various training programs in the hospital, exercises to increase the range of motion or passive repetition of simple tasks have little effect on functional recovery of a hemiplegic arm. For this reason, training for meaningful tasks related to activities of daily living (ADLs) has been incorporated into occupational therapy in hospitals.

Meanwhile, the effects of mirror therapy as well as those of action observation and motor imagery were proven by previous studies in neurorehabilitation (1-4). Mirror therapy is conducted by eliciting a visual illusion through use of a mirror as if the hemiplegic arm is moving in real-time while moving the healthy arm. It can facilitate brain neuroplasticity by activation of the sensorimotor cortex (1). Thus, mirror therapy is effective for improving upper extremity motor function and ADLs (2). As for a comparison with a well-known non-invasive brain stimulation technique, repetitive transcranial magnetic stimulation was not found to have a significant effect on motor function or the Barthel index score (5).

However, conventional mirror therapy has a critical limitation in that the hemiplegic arm is not actually moving. If the hemiplegic arm also moves in real-time, it will facilitate proprioception that refers to joint position sense or kinesthetic sense. Proprioception is provided in skeletal muscle spindles, the Golgi tendon organ, and the fibrous capsules in joints. Then, it is conveyed to the peripheral nerve, the dorsal column-medial lemniscus pathway of the spinal cord, and finally to the sensory cortex of brain. However, the effect of mirror therapy on proprioception has not been established.

We planned to develop a real-time, 2-axis mirror robot system as a simple add-on module to conventional mirror therapy, using a closed feedback mechanism. The hypothesis is that robotic mirror therapy can convey proprioceptive stimulus to the sensory cortex, which is considered important in neuroplasticity and functional recovery of a hemiplegic arm (Fig. 1) (6-8). We had the idea that movements of the healthy arm could be projected to the exoskeletal frame attached to the hemiplegic arm in real-time through inputs from attitude and heading reference system (AHRS) sensors (Fig. 2).

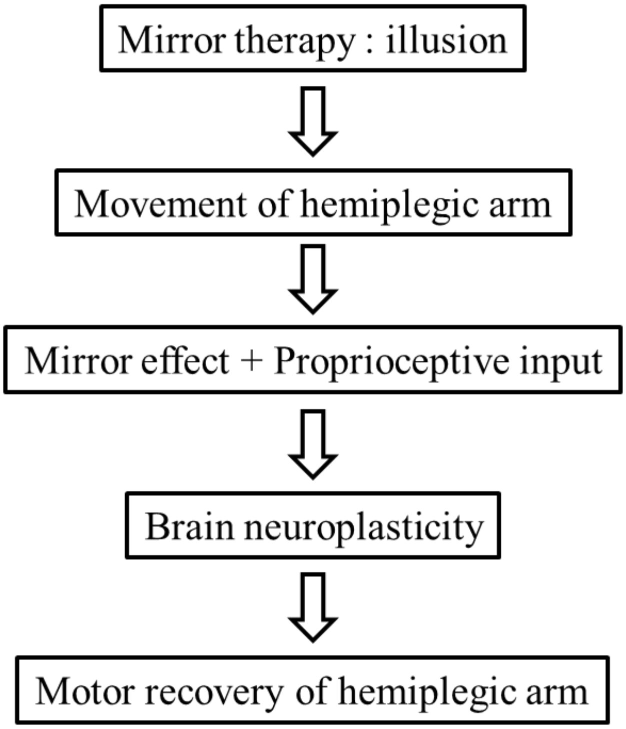


Figure 1. Conceptual flow for the robotic mirror therapy to facilitate proprioceptive stimulus. The experiment is designed in accordance with the conceptual flow for the robotic mirror therapy.

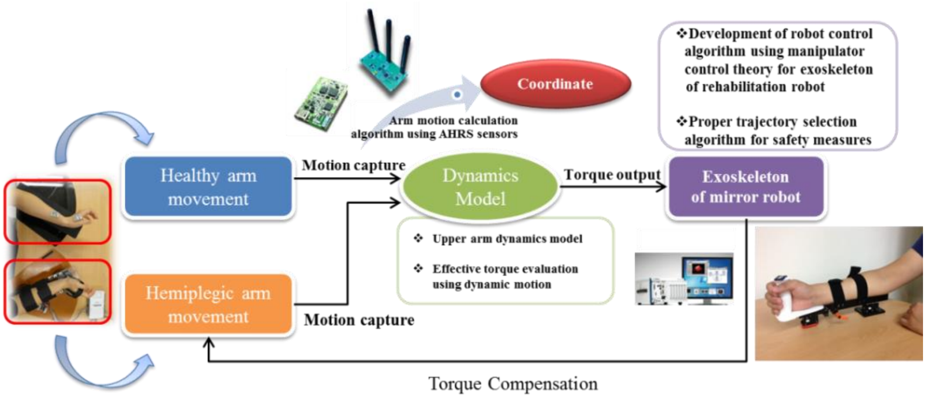


Figure 2. Diagram of the mirror robot system. Movements of the healthy arm are projected to the exoskeleton attached to the hemiplegic arm by a software algorithm through input from three AHRS sensors.

MATERIALS AND METHODS

All of the procedures were reviewed and approved by the Institutional Review Board of Seoul National University Hospital.

1. Mirror therapy tasks

A. Examples of 2-dimensional mirror therapy tasks (Fig. 3)

1) Moving the healthy arm freely while looking in the mirror for about five min for a warm-up exercise. One may utilize a metronome so that the patient can exercise the motion of the healthy arm in a rhythmic manner.
2) Dribbling and placing a small ball into the chosen hole, similar to billiards, on the healthy side for about five min (“Ball in holes” task).
3) Dribbling and placing a small ball into a goal, similar to soccer, for about five min (“Soccer game” task).
4) Moving the handle on the healthy side in numerical order and return in the reverse direction using numbered stickers placed on a table for about five min (“Dots tracing” task).
5) Pushing an object to a chosen place using any object in daily life, such as a cup, using the handle on the healthy side for about five min

(“Moving a cup” task).

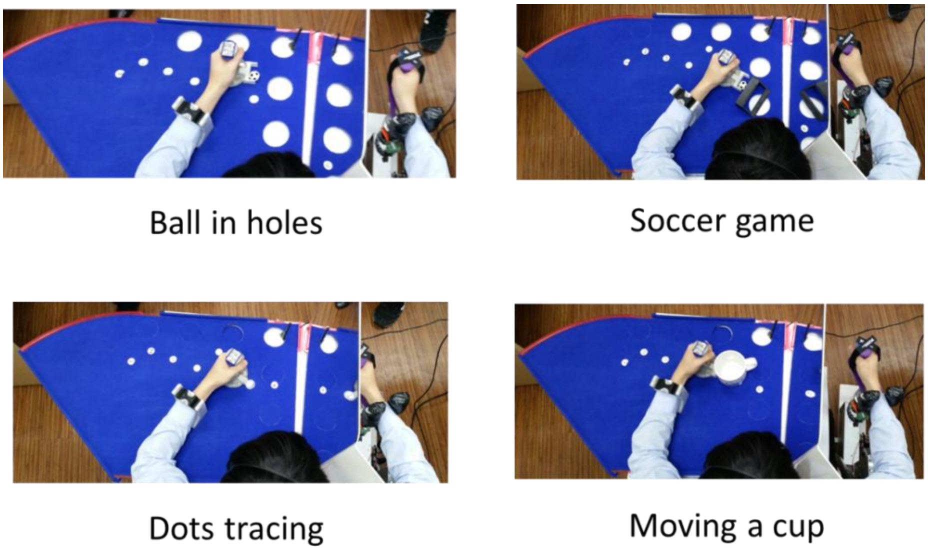


Figure 3. Various tasks using the mirror robot system. The users can be trained for 2-dimensional tasks: ball in holes, soccer game, dots tracing, and moving a cup.

2. Components of the mirror robot system

A. AHRS sensor settings

The mirror robot system consists of three commercially available AHRS sensors. The AHRS sensors consist of a magneto sensor, an accelerometer, and gyro sensors (a total of nine axes). First, the AHRS sensor must be connected to a PC with a USB connector. HyperTerminal, or other communication software, can be used to configure general sensor settings. Once the communication has been established, the next step is to set the channel and assign IDs for each sensor. Some sensors may require calibration of the accelerometer, gyroscope, and magnetometer before use. The output format should be set as quaternions, and sensors should be set to display battery reserve. Quaternions are used to speed up computing as well as to eliminate gimbal lock singularities.

B. Brushless DC motor settings

The mirror robot system uses two high-performance brushless DC motors and controllers. For each controller, connect the power cable to a power supply. Further, connect the motor cable, Hall sensor cable, and encoder cable to the motor. Connect the CAN-CAN cable to another controller. CANopen is used for communication between devices. Set the node ID for each controller to distinguish between devices. Connect the USB cable to the PC for general configuration. Switch on the power supply to power up the controllers and motors. Use the motor manufacturer-provided system configuration software to configure and tune the motor, Hall sensor, and encoder. Angle limits and home position must be configured for safe operation.

C. Assembly of frame and motors

For the elbow joint motor, we put one of the coupling bodies with a keyway on the motor shaft and secured it using an M5 hex socket set screw (Fig. 4). Secure “Elbow coupling hollow cylinder cover” to the elbow motor using 4x M5 socket head screws (10 mm) and place the buffer part of the couplings (middle slider part) on the top of the coupling body that was attached (Assembly A) (Fig. 4). Plug the ball bearing into “Elbow rooftop frame” and secure it with 4x M4 socket head screws (8 mm) (Assembly B, Fig. 5). Plug “Elbow motor force dispersion shaft” into “Lower elbow support” and secure it with 4x M3 socket head screws (6 mm). Then, place “Upper elbow support” on top of the “Lower elbow support” and secure it using 8x M3 socket head screws (12 mm) (Assembly C, Fig. 6). Place the assembly C on top and the assembly B in the middle, and the last part of the coupling body at the bottom. Join the two assemblies and the last part of the coupling body together and secure the coupling body with M5 hex socket set screws (10 mm) (Assembly D, Fig. 7). Secure assembly A and D using 4x M5 socket head screws (15 mm)

(Fig. 7). Rotate the assembly A to secure it at all four points. Secure “Lower wrist coupling hollow cylinder cover” with the wrist motor using 4x M4 socket head screws (10 mm).

Then, one needs to place one of the coupling bodies with a keyway on the motor shaft and secure it using M4 hex socket set screws. Next, place the buffer part of the couplings on top of the coupling body (Assembly E, Fig. 8). Attach “Friction reduction ring” on top of “Wrist rooftop frame” with double-sided tape or any type of adhesive (Assembly F, Fig. 9). Plug “Wrist motor force dispersion shaft” into “Handle” and secure it using 4x M2.5 socket head screws (4 mm) (Assembly G, Fig. 10). Place the assembly G on top, assembly F in the middle, and the last part of the coupling body at the bottom. Join the two assemblies and the last part of the coupling body together and secure the coupling body with M4 hex socket set screws (10 mm) (Assembly H, Fig. 10). Secure “Upper wrist coupling hollow cylinder cover” with the assembly using 4x M3 socket head screws (Assembly I, Fig. 11). Secure assembly E and I using 4x M3 socket head screws (15 mm) (Fig. 11). Secure two “Joint movement limiters” and two shaft collars using 4x M4 socket head screws (15 mm) (Fig. 12A). Use shaft collars to secure shafts and the “Wrist rooftop frame” using 8x M3 socket head screws (8 mm) (Fig. 12B). Slide shaft collars into the shafts and secure additional shaft collars with the “Lower elbow support” using 4x M4 socket head screws (15 mm). Then, join the two parts and secure with a lever (Assembly J, Fig. 13A). Secure the “Support wall” to the assembly J using 6x M4 socket head screws (15 mm) (Assembly K, Fig. 13B). Secure the table stand and assembly K using 6x M6 socket head screws (15 mm) (Fig. 13C).

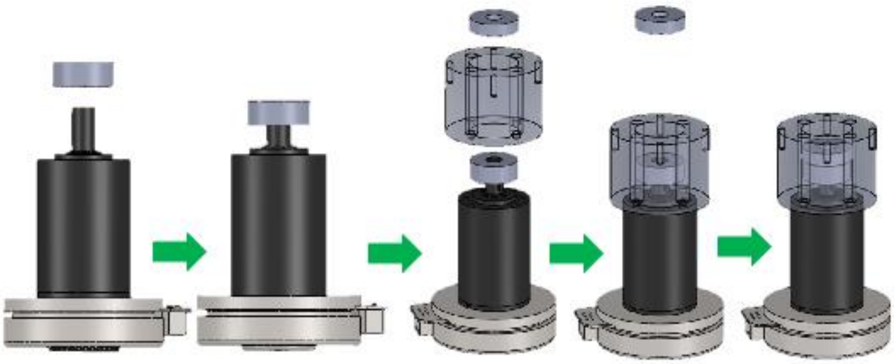


Figure 4. Elbow motor assembly. Assembly steps for elbow joint motor, couplings, and elbow coupling hollow cylinder cover.

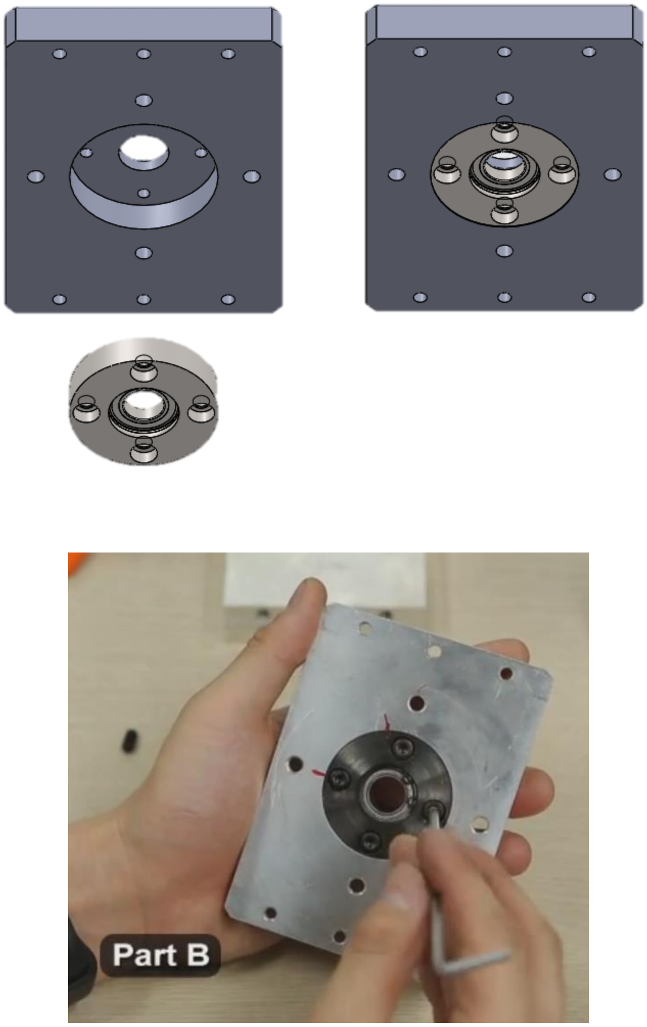


Figure 5. Bearing & elbow rooftop frame assembly. Assembly between bearing and the elbow rooftop frame assembly.

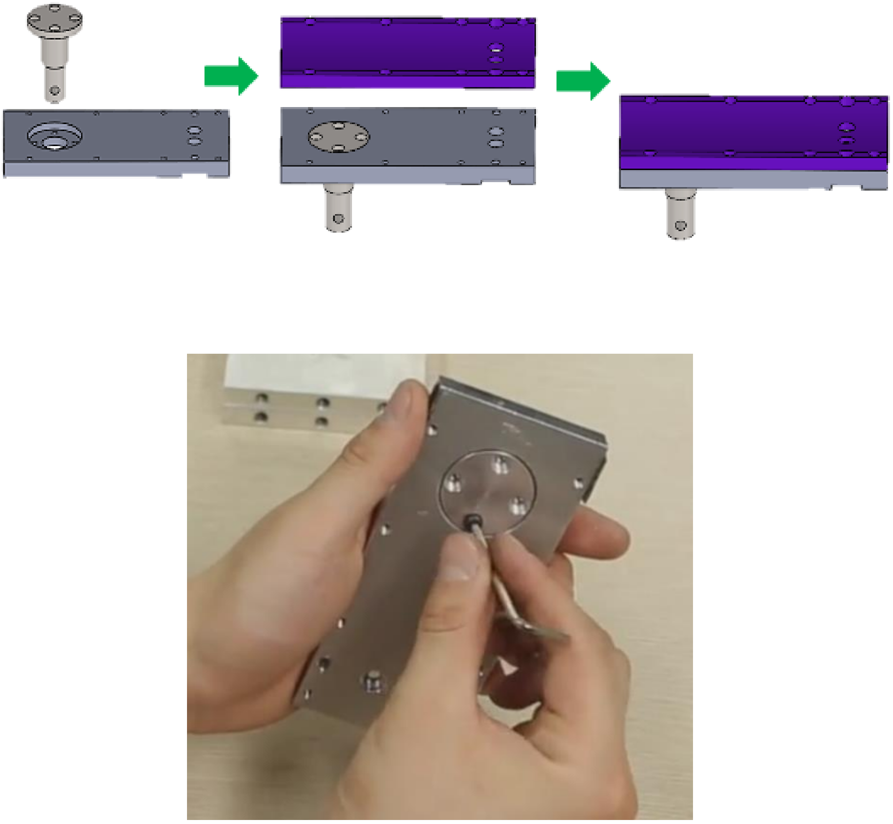


Figure 6. Elbow support assembly. Assembly steps for elbow motor force dispersion shaft, upper elbow support, and lower elbow support.

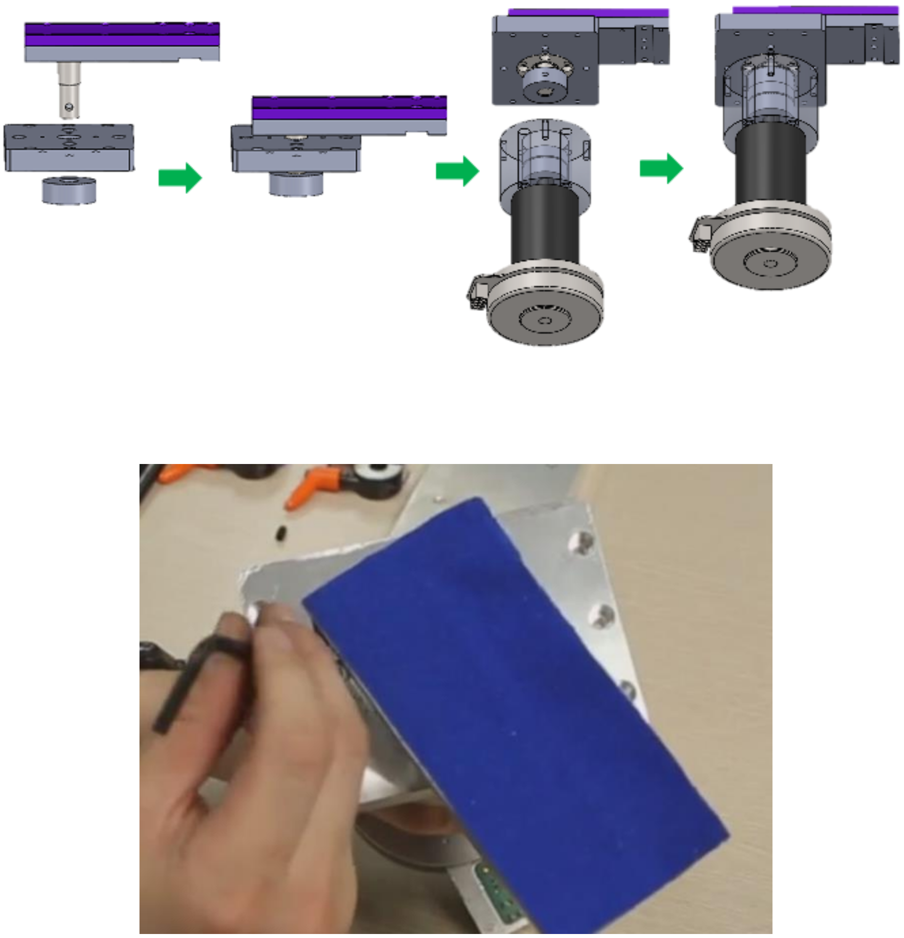


Figure 7. Elbow support and elbow motor assembly. Assembly steps for the elbow support and the elbow motor.

Figure 8. Wrist motor assembly. Assembly steps for wrist joint motor, couplings, and lower wrist coupling hollow cylinder cover.

Figure 9. Friction reduction ring attachment. Attachment of the friction reduction ring to the wrist rooftop frame.

Figure 10. Handle assembly. Assembly steps for the 3D printed handle, coupling, and the wrist motor force dispersion shaft.

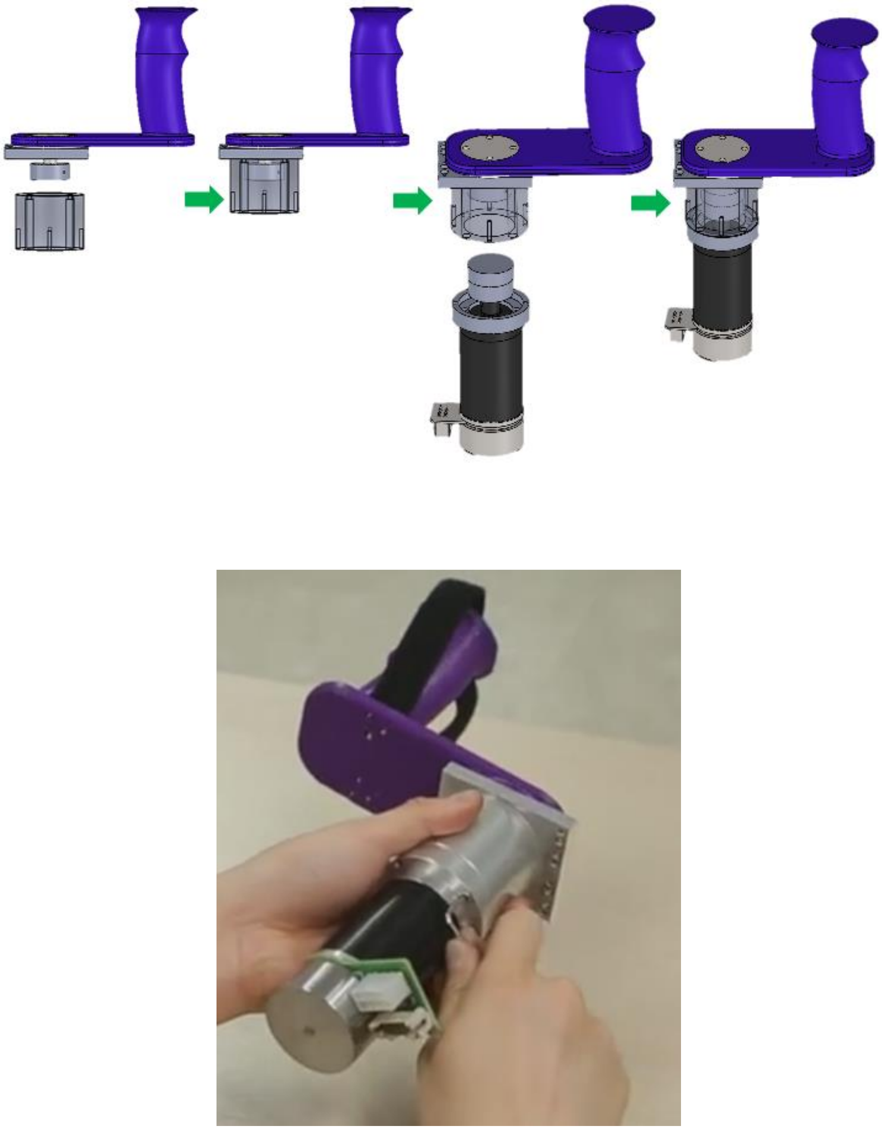


Figure 11. Handle and wrist motor assembly. Assembly steps for the wrist motor and the handle.

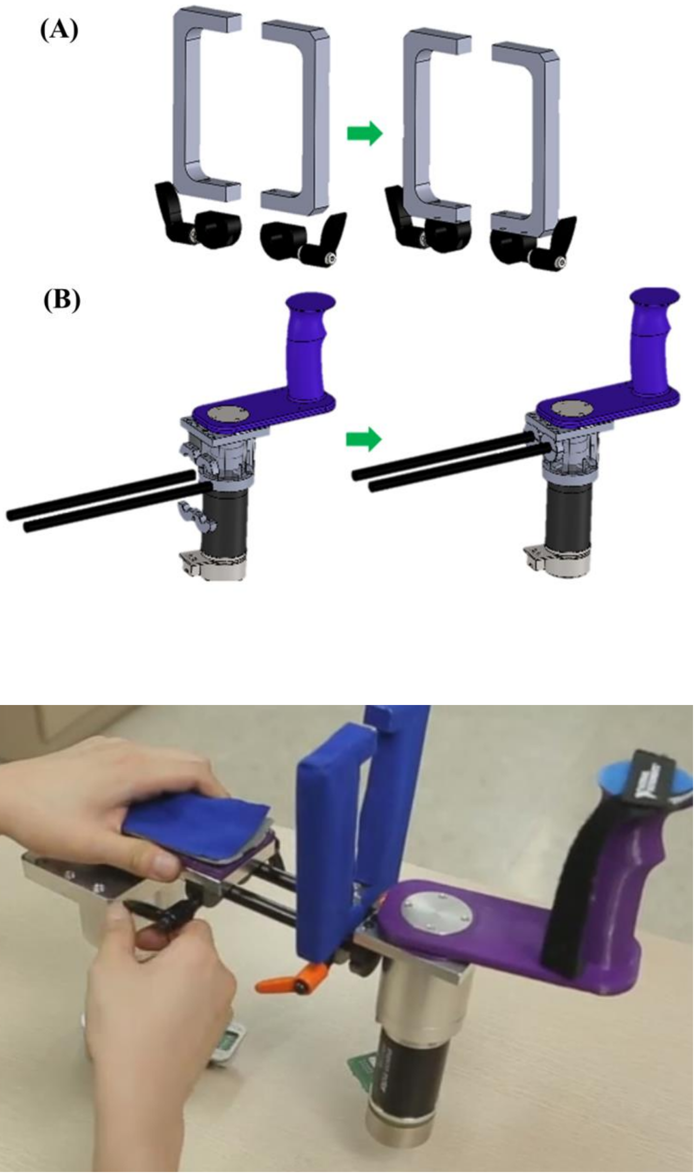


Figure 12. Joint movement limiter assembly. Assembly steps for the (A) joint movement limiter, (B) length adjustment shaft, and the assembled handle.

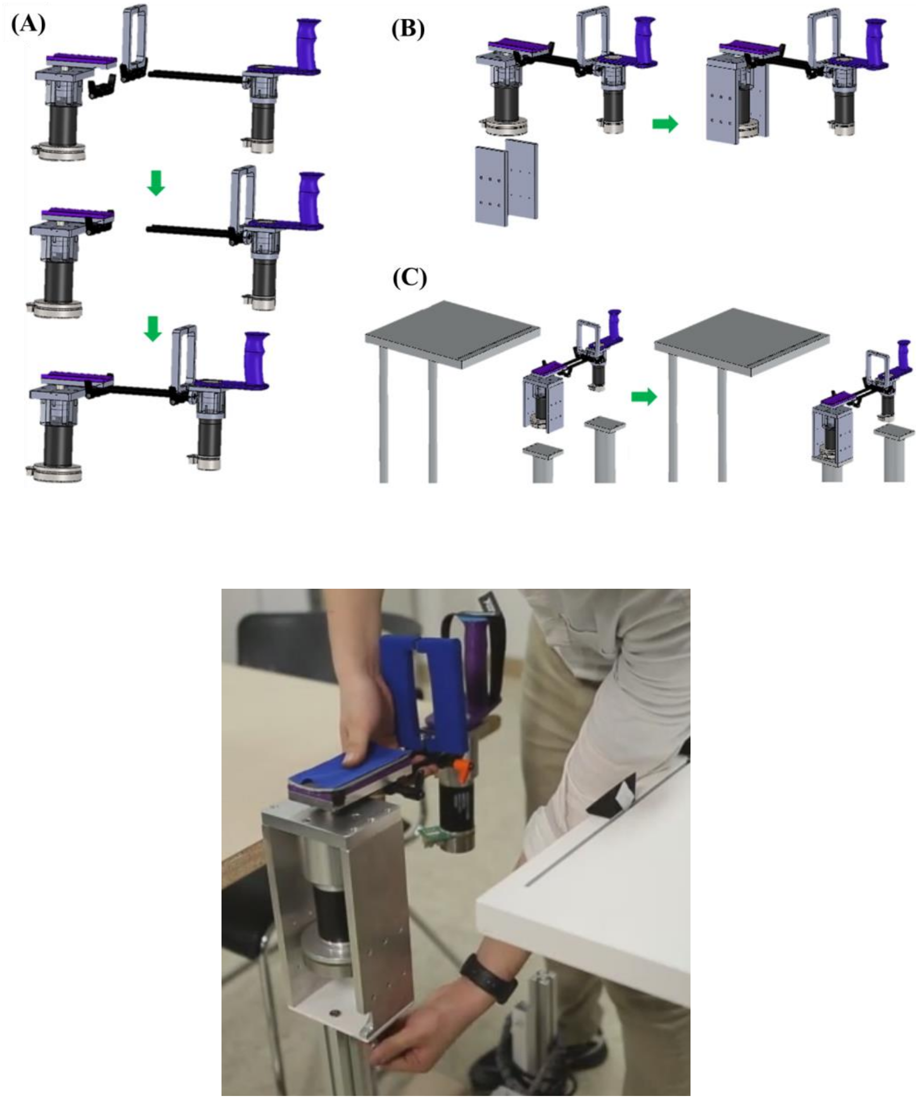


Figure 13. Final assembly. Assembly steps for the (A) assembled elbow motor part with the assembled wrist motor part using shaft collars and shaft, (B) assembled robot with the support walls, and (C) assembled robot with the task table.

3. Clinical application of the mirror robot system

A. Conducting robotic mirror therapy

One needs to adjust the height and width of the task table in accordance with the patient’s condition. Set up a mirror at the midline between both arms and set it on a table or platform. Place the AHRS sensors on the handle, wrist frame, and the edge of the platform on the healthy side aligning in parallel with the robot’s orientation. The sensor’s internal yaw axis should be pointing up. Execute the therapy software in a computer. Set the maximum joint angle limits in accordance with the patient’s joint condition. For safe operation, use an elbow flexion limit less than 50°, elbow extension limit more than -70°, wrist flexion limit less than 80°, and wrist extension limit more than -60°. Plus and minus signs are automatically corrected, and limits are also corrected if out of bounds in software level. Set maximum velocity, acceleration, and deceleration. For these values, use velocity value between 0 and 22.5 RPM for the elbow motor, and use a velocity value between 0 and 33 RPM for the wrist motor. For conventional mirror therapy, set all values to zero to immobilize the robot. One needs to fill out the patient information. Turn on all AHRS sensors before running the software program. While the robot and the healthy arm are at the initial position (both hands away from the body and parallel to each other), press the calibration button to initialize sensor values to zero for the initial position. This setup process takes only about three minutes for healthy subjects (Fig. 14) and probably 4-5 minutes for stroke patients.

For the robotic mirror therapy, a biomedical engineer should act as the main coordinator, and the occupational therapist needs to assist the patient. The instruction (“Do not move your hemiplegic arm on your own.”) is given to the patients.

Figure 14. Setup process for robotic mirror therapy. It takes only about three minutes for healthy subjects.

B. Study protocol for stroke patients

We conducted a case study for stroke patients with a two-dimensional mirror robot for 30 min per day for two weeks (10 sessions). Subjects needed to meet the following inclusion criteria: 1) over 18 years old; 2) supratentorial stroke diagnosed between 4 months and 6 years ago; and 3) upper-limb hemiplegia with Medical Research Council grade 2 or less. Main exclusion criteria were as follows: 1) severe spasticity with modified Ashworth scale of grade 3 or more; 2) mini-mental state examination score less than 12; and 3) global or sensory aphasia.

For the conventional mirror therapy group, we prepared the tasks for fine motor training (Supplementary Fig. 1). These tasks included more complicated tasks so that the participants would be interested in the tasks without the robot system.

Before and after 10 sessions of the therapy, we conducted functional evaluations: the Fugl-Meyer assessment scale of the upper extremity (FMA-UE) (Supplementary table 1) (9), the modified Ashworth scale (Supplementary table 2) (10), the modified Barthel index of upper extremity (MBI-UE: personal hygiene, bathing, feeding, and dressing) (Supplementary table 3) (11, 12), and the Jebsen hand function test, hand power measurement, and hemispatial neglect test (line bisection test and Albert's test) with the same occupational therapist. The motor evoked potential was measured for the patients without the history of brain surgery or seizure.

We selected a thumb finding test (TFT) among various tools for assessing proprioception, because TFT is widely used and reliable (Supplementary table 4) (13, 14). The TFT can be assessed, after confirming normal proprioception in the unaffected arm, by the patient touching the nose with their eyes closed while the examiner lifts the affected arm to eye level. The patient is then asked to grasp the thumb of the affected hand with the unaffected hand, and this is repeated. The examiner then places a hand over the patient's eyes and raises the patient's affected hand to well above the patient's head. The patient is then asked to grasp the thumb as before (14).

4. Functional magnetic resonance imaging analysis

A. Setup for functional magnetic resonance imaging (fMRI) tasks

The functional imaging consisted of two tasks. The first task was to execute the repeated passive range of motion (ROM) exercise on the hemiplegic wrist joint, and the second task was to execute an active ROM exercise on the same joint. An fMRI block design was used in both tasks where two rest blocks (each 20 s) were interleaved by one active block (each 20 s). In both tasks, a pair consisting of one rest block and one active block was repeated eight times.

For the active wrist ROM exercise, the participants were thoroughly instructed before entering the scanner. The "start" and "stop" signs were indicated, and compliance with the instructions was ensured by visual inspection throughout the exam. For the passive wrist ROM exercise, the hemiplegic wrist was manually moved by the researcher's hand during fMRI acquisition.

B. fMRI acquisition

The fMRI scans were conducted with a Siemens MAGNETOM TrioTim syngo scanner using echoplanar imaging (EPI, TE = 30 ms, TR = 3,000 ms; 9 slices of 3.5 mm thickness, voxel size 1.9 × 1.9 × 3.5 mm^3) angulated in parallel to the anterior and posterior commissure line. Whole-brain scans including eight blocks of executed movements consisting of eight EPI, each alternating with seven blocks of rest, were recorded per condition. For anatomical reference, an anatomical data set was obtained using a T1-weighted magnetization prepared rapid gradient (MP-RAGE) (slice thickness 1 mm, TR = 1,670 ms, TE = 1.89 ms, flip angle = 9°) in the same session.

C. fMRI data analysis (15-18)

The fMRI data were preprocessed using Statistical Parametric Mapping 12 (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK; www.fil.ion.ucl.ac.uk/spm/) implemented in MATLAB 2014b (Mathworks Inc., Natick, MA). The preprocessing included slice timing, realignment, co-registration, and spatial smoothing (Gaussian kernel of full-width-half-maximum 6 mm).

1) Analysis protocol for a healthy subject

The images were then realigned and co-registered to the individual anatomical scan, segmented, spatially normalized to the Montreal Neurological Institute (MNI) template and smoothed with an 8 mm Gaussian kernel (full width at half-maximum).

2) Analysis protocol for a stroke patient

The participant's own MRI scan was used to determine the region of interest (ROI) without normalization to the Montreal Neurological Institute (MNI) template, because it was impossible to normalize the brain contour owing to partial brain atrophy and ventriculomegaly.

RESULTS

1. Validation of motion synchronicity between the motors and AHRS sensors

Spatial and temporal synchronicity between both arms is essential to achieve the mirror effect in the mirror robot system. To validate the motion synchronicity, we compared the joint angles derived from the encoder of the motor in the hemiplegic arm and the AHRS sensor in the healthy arm in real-time. The error plots were depicted when performing the “dots tracing” task. As a result, the root mean square error (RMSE) between the motor and the AHRS sensor during elbow ROM was 0.07° and that during wrist ROM was 0.14°. This proved the existence of high synchronicity between the movements of both arms (Fig. 15). The average differential nonlinearity (DNL) of the elbow motor is 0.00018, and that of the wrist motor is 0.0238.

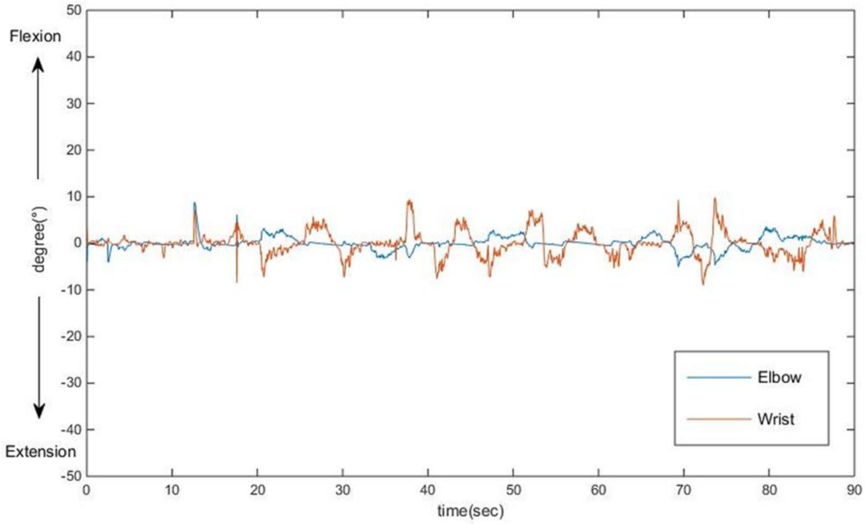


Figure 15. Error plots for motors and AHRS sensors at the elbow and wrist joints. The RMSE between the motor and AHRS sensor during elbow ROM was 0.07° and that during wrist ROM was 0.14°. The X-axis represents iterations per loop, and the Y-axis represents the error of degree for each joint.

2. A clinical study for healthy subjects

We conducted a clinical study on healthy subjects to confirm the safety and feasibility of the prototype. The instruction ("Do not move your hemiplegic arm on your own.") was given to the subjects for completely passive movement of the hemiplegic arm. We placed both forearms on the frames, and both hands on the handles. Then, we fixed the forearms with straps. Six healthy subjects conducted a 'pen marking task' (touching the two small boards alternately with a pen attached on the healthy hand as shown in Fig. 16) 10 times, which took on average 106 s per subject. No adverse events were observed, and robotic mirror therapy was proven to be feasible.

A 30-year-old healthy male conducted the fMRI. The blood-oxygen-level dependent (BOLD) signal was increased in the primary motor cortex during the active wrist ROM exercise. The p value was applied as < 0.01 and < 0.005 (Fig. 17).

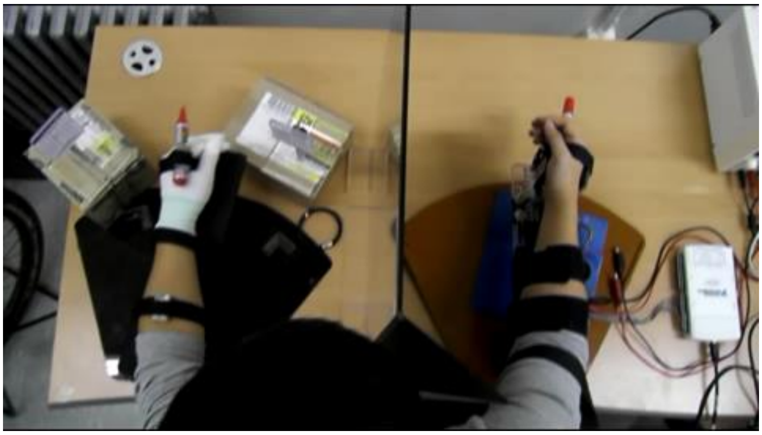


Figure 16. Pen marking task in six healthy subjects using a prototype of the mirror robot system. Conducting a pen marking task 10 times consecutively took, on average, 106 s per subject.

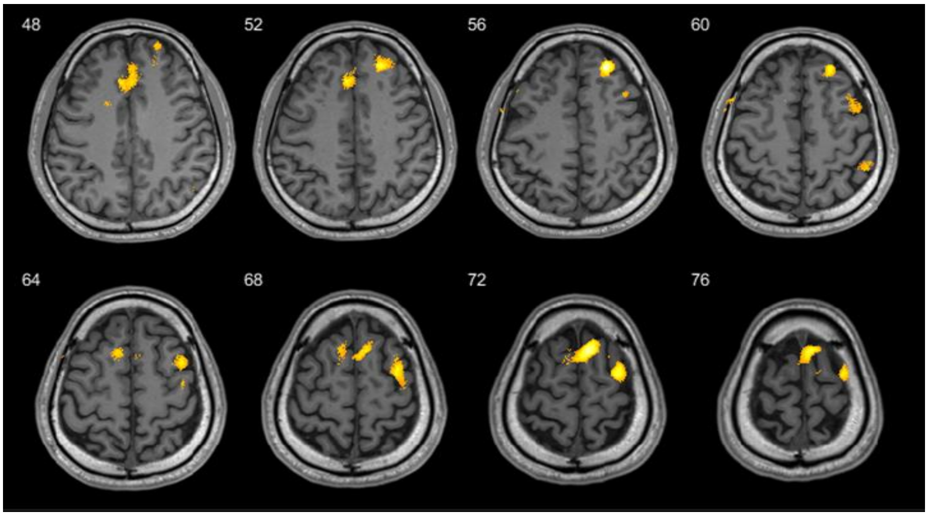


Figure 17. fMRI analysis in a healthy subject (30-year-old male). The BOLD signal was increased in the premotor cortex and prefrontal cortex during the active left wrist ROM exercise ($p < 0.01$).

3. Feedback from rehabilitation doctors

In addition, a clinical study with rehabilitation doctors was conducted. We requested expert opinions to determine appropriate tasks for effective robotic mirror occupational therapy. With feedback from six rehabilitation doctors, the degree of illusion elicited by the mirror robot was highest for “ball in holes” and “moving a cup” tasks (7.2 out of 10 on a numerical rating scale [NRS] for each), followed by “soccer game” (7.0/10) and “dots tracing” tasks (6.5/10). Regarding the synchronicity of movement between both arms during robotic mirror therapy, the “moving a cup” task had an NRS score of 7.0/10, followed by “soccer game” and “dots tracing” (6.8/10 each), and then “ball in holes” (6.2/10) (Fig. 3). Among these four tasks, rehabilitation doctors recommended “soccer game” as a useful task for ADL training in patients with stroke.

4. A case study for stroke patients

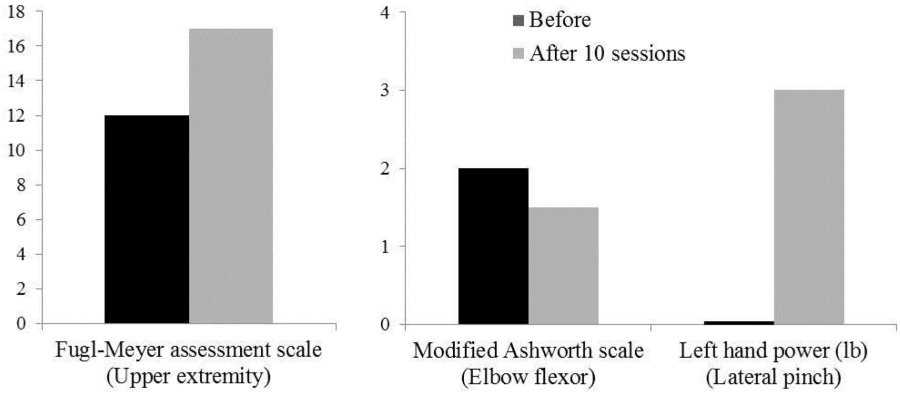
A. Case 1

A 60-year-old male stroke patient with a right basal ganglia hemorrhage and a left hemiplegia 19 months prior received robotic mirror therapy for two weeks. Robotic mirror therapy consisted of four tasks (“ball in holes”, “moving a cup”, “soccer game”, and “dots tracing”). After the patient accomplished the

10th visit, he conducted follow-up functional evaluations. The Fugl-Meyer assessment scale of the hemiplegic arm improved from 12 to 17 out of 66, and the modified Ashworth scale of elbow flexors (for spasticity) was reduced from grade 2 to 1+ (Table 1 and Fig. 18). Left lateral pinch power was increased from 0 to 3 lb. Other parameters revealed no difference before and after robotic mirror therapy.

Table 1. Functional evaluation of a 60-year-old male patient with chronic right basal ganglia hemorrhage (case 1).

	Before	After 10 sessions
Mini-mental state examination	29	-
Fugl-Meyer assessment scale (Hemiplegic upper extremity)	12	17
Shoulder/elbow	11	15
Wrist	0	1
Hand	1	1
Modified Ashworth scale		
Elbow flexor	2	1+
Wrist flexor	0	0
Modified Barthel index (Upper extremity)	25	25
Jebsen hand function test	Uncheckable	Uncheckable
Left hand power (lb)		
Grip	8	8
Lateral pinch	0	3
Palmar pinch	0	0
Hemispatial neglect test		
Line bisection test (left; middle; right)	6/6 each	6/6 each
Albert’s test (left; middle; right)	12/12 each	12/12 each
Motor evoked potential	No response	No response



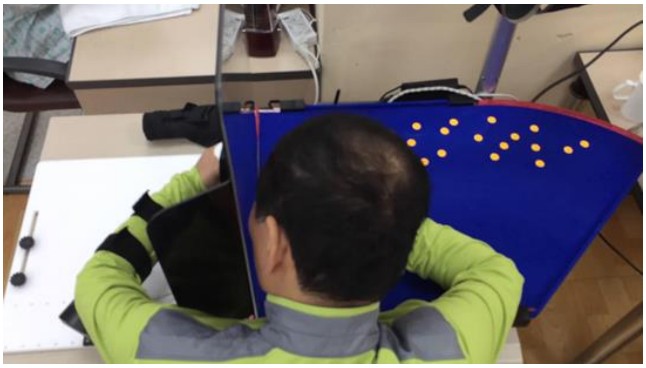


Figure 18. Functional evaluation of a 60-year-old male patient with chronic right basal ganglia hemorrhage (case 1). Main subsets of data that showed improvement after 10 sessions of robotic mirror therapy.

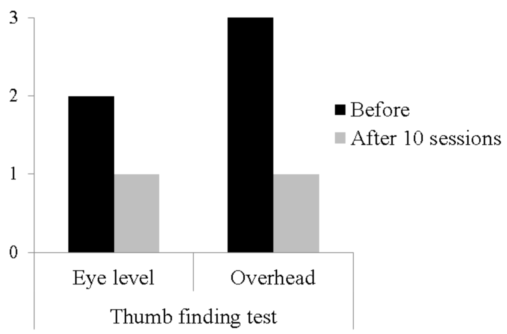
B. Case 2

A 56-year-old male stroke patient who had a right middle cerebral artery territory infarction and a left hemiplegia 11 months prior to his participation in this case study received robotic mirror therapy for two weeks. He had been receiving physical and occupational therapy in hospitals five days per week on an out-patient-basis. Robotic mirror therapy consisted of the four tasks that were mentioned above. At the follow-up functional evaluations after the 10th session, the TFT was considerably improved (Table 2 and Fig. 19). The TFT score at the eye level was improved from 2 to 1, and the TFT measured at the overhead level from 3 to 1. Albert's test score on the left side was improved from 6 to 11 out of 12 (Fig. 20). Other parameters revealed no difference before and after robotic mirror therapy. At the 2-month post-therapy follow-up, the TFT score was 1 at both the eye level and overhead level, and the Albert's test score on the left side was 11 out of 12.

In the fMRI study, there were no significant activation areas during the passive ROM task before the treatment sessions (Fig. 21A). However, after 10 sessions, the lower part of the superior parietal lobule (Brodmann area 7) and premotor cortex (PMC, Brodmann 6) were significantly co-activated during the passive ROM exercise. The percentage change in signal strength from the lower part of superior parietal lobule was 0.10 % before robotic mirror therapy and 0.38 % after 10 sessions of therapy. In the case of the active ROM task, the contralateral PMC and ipsilateral prefrontal cortex were mainly activated during the active ROM exercise in the post-treatment fMRI scan (Fig. 21C, 21D).

Table 2. Functional evaluation of a 56-year-old male patient with chronic right middle cerebral artery territory infarction (case 2).

	Before	After 10 sessions	At 2-month follow-up
Thumb finding test	Eye level: 2, Overhead: 3	Eye level: 1, Overhead: 1	Eye level: 1, Overhead: 1
Fugl-Meyer assessment scale (Hemiplegic upper extremity)	4	4	4
Shoulder/elbow	4	4	4
Wrist	0	0	0
Hand	0	0	0
Modified Ashworth scale			
Elbow flexor	1	1	1
Wrist flexor	1	1	1
Modified Barthel index (Upper extremity)	14	14	14
Jebsen hand function test	Uncheckable	Uncheckable	Uncheckable
Left hand power (lb)			
Grip	0	0	0
Lateral pinch	0	0	0
Palmar pinch	0	0	0
Hemispatial neglect test			
Line bisection test (left; middle; right)	5/6; 6/6; 6/6	4/6; 6/6; 6/6	4/6; 6/6; 6/6
Albert's test (left; middle; right)	6/12; 12/12; 12/12	11/12; 12/12; 12/12	11/12; 10/12; 12/12



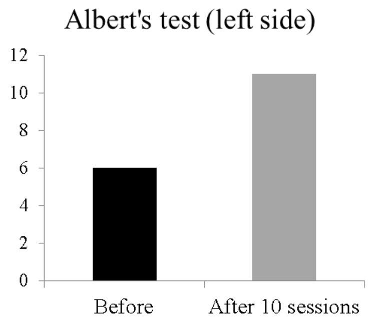
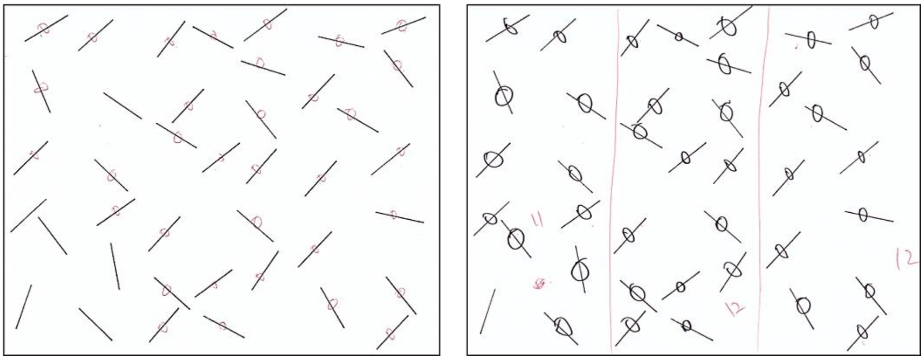


Figure 19. Functional evaluation of a 56-year-old male patient with chronic right middle cerebral artery territory infarction (case 2). Main subsets of data that improved after 10 sessions of robotic mirror therapy.

Figure 20. Albert's test of the case 2 patient. Albert's test before (A) and after 10 sessions (B) of robotic mirror therapy. The score in the left side was improved from 6 to 11 out of 12.

(A) (B)



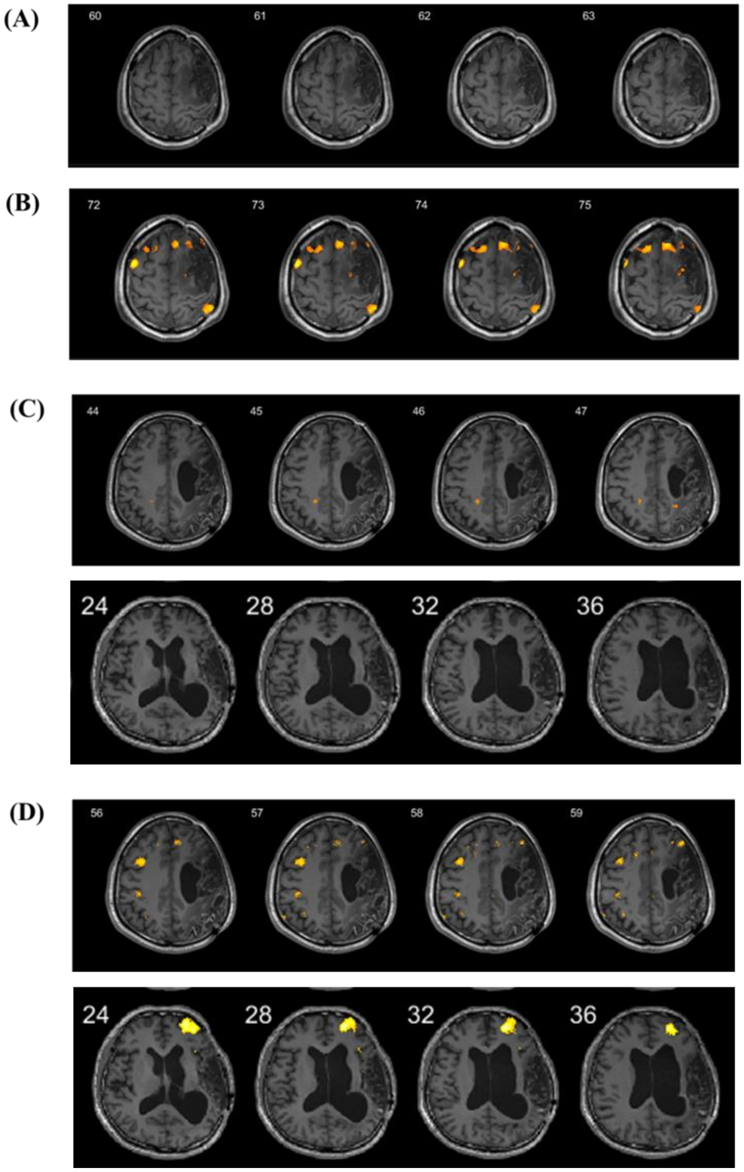


Figure 21. fMRI study in the case 2 patient. The BOLD signal was increased in the lower part of the right superior parietal lobule and left PMC during the passive left wrist ROM exercise before (A) and after 10 sessions of

robotic mirror therapy (B). The signal was increased mainly in the PMC and prefrontal cortex during the active ROM exercises before (C) and after 10 sessions of therapy (D) ($p < 0.01$ and < 0.005).

DISCUSSION

The primary purpose of this study was to develop a real-time mirror robot system for functional recovery of hemiplegic arms using an automatic control algorithm. The effect of robot-assisted therapy on long-term recovery of upper-limb impairment after stroke was proven beneficial in previous studies (19), and various kinds of arm robots have been introduced (20-27). However, previous studies of upper extremity robots that achieved bilateral arm movement applied mechanical connections without using a mirror, which is different from the concept of mirror therapy (19, 20).

To upgrade the conventional mirror therapy, we enabled the hemiplegic arm to move in real-time by applying AHRS sensors on the healthy arm and attaching motors to the hemiplegic elbow and wrist. Proprioceptive stimulus from the hemiplegic arm to the somatosensory cortex of brain can be enhanced through the mirror robot system. Therefore, our study is the first attempt that applied a real mirror with a robot system for facilitation of proprioception followed by motor recovery, which can be differentiated from others' work.

It is critical for the system to have minimum synchronization delay since the mirror effect will be maximized when the delay is minimized. To achieve this, we retrieved data from sensors with the minimum necessary byte count while reading them in parallel within a loop inside the software architecture. As a result, the synchronization delay between the healthy arm and the robot is only 0.04 – 0.40 sec. The RMSE between the motor and the AHRS sensor during wrist ROM is twice as much as that during elbow ROM, which could be because of possible accumulated error in an end-effector at the upper extremity.

The time from setup to operation of the mirror robot system takes only about 3-5 minutes. Therefore, this portable device can be easily installed and applied to stroke patients in an occupational therapy room, unlike the large-volume mirror image movement enabler (22).

In this case study, the chronic stroke patient (case 1) showed improvement in the Fugl-Meyer assessment scale and elbow flexor spasticity after two weeks of robotic mirror therapy. The minimal clinically important difference (MCID) of FMA-UE is known to be 4.25 to 7.25 in chronic stroke patients (28). Thus, the change of FMA-UE in the case 1 patient from 12 to 17 could be a clinically meaningful improvement. In addition, a decrease in elbow flexor spasticity might be partially due to the stretching effect of the mirror robot.

Importantly, the case 2 patient revealed improved proprioception (measured by the TFT) and hemispatial neglect after 10 sessions of robotic mirror therapy and 2-month post-therapy follow-up. Conventional mirror therapy is also known to be effective on hemispatial neglect (29-32). In the fMRI analysis after all the treatment sessions, the lower part of the superior parietal lobule and the PMC were co-activated during the passive ROM exercise. On the other hand, the PMC was mainly activated during active ROM exercise, which was probably due to the absence of somatosensory input. Because the patient could not move the hemiplegic wrist on his own due to severe weakness, the active ROM task was actually “motor imagery”. The previous studies showed that the PMC can be activated by motor imagery (33, 34). Because the patients conducted specific tasks with the robotic mirror system for two weeks, and fMRI tasks were simple ROM exercises, we assume that training effects on the study results could be excluded.

The lower part of the superior parietal lobule is known to receive inputs from the somatosensory cortex. Receipt of tactile and proprioceptive information from muscles and joints causes the superior parietal lobule to tap into its own memory stores (35). Meanwhile, the PMC receives a rich sensory input from the superior parietal lobule incorporating tactile and visuospatial signals. The PMC is usually active bilaterally, if at all (35).

There have been several studies on cerebral activation evoked by the mirror illusion (16, 17, 36-38). In healthy right-handed volunteers, there were increased BOLD responses in primary motor and somatosensory cortex (BA 2, 3b, and 3a), premotor and parietal areas, and V5 (36). The mirror illusion may be considered as not eliciting immediate changes in motor areas, whereas there is a direct effect on somatosensory areas, especially for left hand movements. In stroke patients, the fMRI results showed significant activation of the ipsilateral sensorimotor cortex, anterior prefrontal gyrus, and the occipital gyrus due to the mirror visual illusion of ankle movements (37). The ipsilateral prefrontal cortex was also activated during the active ROM task as part of post-treatment evaluation of our patient. In chronic stroke patients, who received mirror therapy for 8 weeks, there was an increase in the laterality index of ipsilesional BA 4 and BA 6 (38). This is slightly different from our study results.

The improvement of proprioception in our study may be related to the robotic mirror therapy setting. When the patient put on the exoskeleton, the forearm and hand were fixed with the strap throughout the treatment. Therefore, the tactile sensory input would have been nearly constant without significant variation. The most noticeable sensory change during the robotic mirror therapy was the movement of the elbow and wrist joints, which is a proprioceptive stimulation. The increased activity was dominant in the superior parietal lobule and not in the somatosensory cortex. The reason for this result may have been clearer if we had performed the somatosensory evoked potential examination. We need to further differentiate the contribution of robotic mirror therapy to sensorimotor processing from that of tactile stimulation or passive ROM exercise.

There are several limitations of this study. First, we could not include fine finger movements, such as grip or pinch, and 3-dimensional tasks of conventional mirror therapy. Second, we did not fix the elbow joint of the healthy arm to preserve physiologic movement as much as possible. However, restriction of the range of elbow motion would be helpful to enhance synchronicity with the opposite elbow, which is moved by the motor. Modifying the system by installing an additional structure that secures the healthy side elbow will improve the synchronicity and, therefore, will increase the effect of the therapy. Third, patients who had severe spasticity or stiffness could not be included because of insufficient motor power, even though the joint moved slowly. The system could be modified by replacing the motor with a motor with a higher torque output to overcome moderate stiffness. However, even with strong motor, treatment of patients with severe levels of spasticity or stiffness should be avoided to prevent tendon or bone injuries due to excessive force application to the joints. Fourth, we could not recruit a control group receiving conventional mirror therapy, which is needed to confirm the therapeutic effect of robotic mirror therapy.

The mirror effect may degrade proprioceptive information rather than integrate visual and proprioceptive information concerning hand position (39). The magnitude of this effect is linearly related to the size of the visual-proprioceptive conflict (39, 40). In this aspect, the robotic mirror therapy in our study can contribute to visual-proprioceptive integration. Therefore, it is expected to exert a synergistic effect in terms of proprioception compared to the simple passive ROM exercise without mirror therapy.

This mirror robot system can be easily developed and utilized effectively to advance occupational therapy. Future studies with a large sample size and longer follow-up period including functional brain MRI will be needed to confirm the effects on proprioception and functional recovery of hemiplegic arms in stroke patients.

CONCLUSIONS

This is the first report on robotic mirror therapy system using a real mirror that is differentiated from previous works on rehabilitation robots applying bilateral arm movement. We conducted a case study with chronic stroke patients, which revealed improvement in the Fugl-Meyer assessment scale and elbow flexor spasticity, proprioception, and hemispatial neglect after a two-week application of the mirror robot system. Visual-proprioceptive integration can be suggested as a therapeutic mechanism of robotic mirror therapy. This mirror robot system will pave the way for researchers in the field of neurorehabilitation to explore the effect of advanced occupational therapy to enhance proprioception in patients with brain lesions, such as stroke.

ACKNOWLEDGEMENTS

This work was supported by the Brain Fusion Program of Seoul National University (800-20120444). I would like to thank Hyung Seok Nam, Sukgyu Koh, Yoon Jae Kim, Wonshik Kim, Woo Hyung Lee, Sung Woo Park, Chiwon Lee, Jang Woo Park, Eun Sil Koh, Han Gil Seo, Byung-Mo Oh, and Sun Gun Chung for their contributions and assistance in this study.

REFERENCES

1. Hamzei F, et al. Functional plasticity induced by mirror training: the mirror as the element connecting both hands to one hemisphere. Neurorehabil Neural Repair. 2012;26:484-96.
2. Thieme H, Mehrholz J, Pohl M, Behrens J, Dohle C. Mirror therapy for improving motor function after stroke. Cochrane Database Syst Rev. 2012;3:CD008449.
3. Dohle C, et al. Mirror therapy promotes recovery from severe hemiparesis: a randomized controlled trial. Neurorehabil Neural Repair. 2009;23:209-17.
4. 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;97:575-81.
5. Hao Z, Wang D, Zeng Y, Liu M. Repetitive transcranial magnetic stimulation for improving function after stroke. Cochrane Database Syst Rev. 2013;5:CD008862.
6. De Santis D, et al. Robot-assisted training of the kinesthetic sense: enhancing proprioception after stroke. Front Hum Neurosci. 2015;8:1037.

7. Smorenburg AR, Ledebt A, Deconinck FJ., Savelsbergh GJ. Practicing a matching movement with a mirror in individuals with spastic hemiplegia. Res Dev Disabil. 2013;34:2507-13.
8. Semrau JA, Herter TM, Scott SH, Dukelow SP. Robotic identification of kinesthetic deficits after stroke. Stroke. 2013;44:3414-21.
9. Sanford J, Moreland J, Swanson LR, Stratford PW, Gowland C. Reliability of the Fugl-Meyer assessment for testing motor performance in patients following stroke. Phys Ther. 1993;73:447-54.
10. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther. 1987;67:206-7.
11. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel Index for stroke rehabilitation. J Clin Epidemiol. 1989;42:703-9.
12. Beom J, Jang HJ, Han TR, Oh BM, Paik NJ, Yang EJ, Lee SU. Fatty replacement of rotator cuff in brain-injured patients is associated with hemiplegic arm function, but not with tendon tear: A multicenter study. NeuroRehabilitation. 2015;37:213-9.
13. Hillier S, Immink M, Thewlis D. Assessing Proprioception: A Systematic Review of Possibilities. Neurorehabil Neural Repair. 2015;29:933-49.
14. Prescott RJ, Garraway WM, Akhtar AJ. Predicting functional outcome following acute stroke using a standard clinical examination. Stroke. 1982;13:641-7.

15. Brunner IC, Skouen JS, Ersland L, Grüner R. Plasticity and response to action observation: a longitudinal FMRI study of potential mirror neurons in patients with subacute stroke. Neurorehabil Neural Repair. 2014;28:874-84.
16. Wang J, Fritzsch C, Bernarding J, Krause T, Mauritz KH, Brunetti M, Dohle C. Cerebral activation evoked by the mirror illusion of the hand in stroke patients compared to normal subjects. NeuroRehabilitation. 2013;33:593-603.
17. Diers M, et al. Illusion-related brain activations: a new virtual reality mirror box system for use during functional magnetic resonance imaging. Brain Res. 2015;1594:173-82.
18. Promjunyakul NO, Schmit BD, Schindler-Ivens S. Changes in hemodynamic responses in chronic stroke survivors do not affect fMRI signal detection in a block experimental design. Magn Reson Imaging. 2013;31:1119-28.
19. Lo AC, et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. N Engl J Med. 2010;362:1772-83.
20. Ho NS, et al. An EMG-driven exoskeleton hand robotic training device on chronic stroke subjects: task training system for stroke rehabilitation. IEEE Int Conf Rehabil Robot. 2011;2011:5975340.
21. Hesse S, Schulte-Tigges, G., Konrad, M., Bardeleben, A., Werner, C. Robot-assisted arm trainer for the passive and active practice of bilateral

forearm and wrist movements in hemiparetic subjects. Arch Phys Med Rehabil. 2003;84:915-20.

22. Lum PS, et al. MIME robotic device for upper-limb neurorehabilitation in subacute stroke subjects: A follow-up study. J Rehabil Res Dev. 2006;43:631-42.

23. Yang CL, Lin KC, Chen HC, Wu CY, Chen CL. Pilot comparative study of unilateral and bilateral robot-assisted training on upper-extremity performance in patients with stroke. Am J Occup Ther. 2012;66:198-206.

24. Nef T, Mihelj M, Riener R. ARMin: a robot for patient-cooperative arm therapy. Med Biol Eng Comput. 2007;45:887-900.

25. Ozkul F, Barkana DE, Demirbas SB, Inal S. Evaluation of proprioceptive sense of the elbow joint with RehabRoby. IEEE Int Conf Rehabil Robot. 2011;2011:5975466.

26. Pehlivan AU, Celik O, O'Malley MK. Mechanical design of a distal arm exoskeleton for stroke and spinal cord injury rehabilitation. IEEE Int Conf Rehabil Robot. 2011;2011:5975428.

27. Zhang H, et al. Feasibility studies of robot-assisted stroke rehabilitation at clinic and home settings using RUPERT. IEEE Int Conf Rehabil Robot. 2011;2011:5975440.

28. Page SJ, Fulk GD, Boyne P. Clinically important differences for the upper-extremity Fugl-Meyer Scale in people with minimal to moderate impairment due to chronic stroke. Phys Ther. 2012;92:791-8.

29. Pandian JD, Arora R, Kaur P, Sharma D, Vishwambaran DK, Arima H. Mirror therapy in unilateral neglect after stroke (MUST trial): a randomized controlled trial. Neurology. 2014;83:1012-7.

30. Wang W, Zhang X, Ji X, Ye Q, Chen W, Ni J, Shen G, Zhang B, Yuan TF, Shan C. Mirror neuron therapy for hemispatial neglect patients. Sci Rep. 2015;5:8664.

31. 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;23:209-17.

32. 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. 2013;27:314-24.

33. Marins TF, Rodrigues EC, Engel A, Hoefle S, Basílio R, Lent R, Moll J, Tovar-Moll F. Enhancing Motor Network Activity Using Real-Time Functional MRI Neurofeedback of Left Premotor Cortex. Front Behav Neurosci. 2015;9:341.

34. Kraft E, Schaal MC, Lule D, König E, Scheidtmann K. The functional anatomy of motor imagery after sub-acute stroke. NeuroRehabilitation. 2015;36:329-37.

35. FitzGerald MJT, Gruener G, Mtui E. Clinical neuroanatomy and neuroscience. Fifth edition, pp.319, 324. Elsevier, 2007.

36. Fritzsch C, Wang J, Dos Santos LF, Mauritz KH, Brunetti M, Dohle C. Different effects of the mirror illusion on motor and somatosensory processing. Restor Neurol Neurosci. 2014;32:269-80.

37. Guo F, Xu Q, Abo Salem HM, Yao Y, Lou J, Huang X. The neuronal correlates of mirror therapy: A functional magnetic resonance imaging study on mirror-induced visual illusions of ankle movements. Brain Res. 2016;1639:186-93.

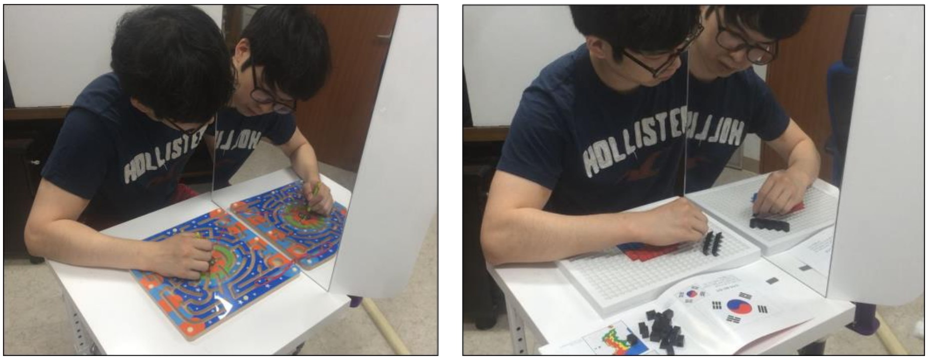
38. Bhasin A, Padma Srivastava MV, Kumaran SS, Bhatia R, Mohanty S. Neural interface of mirror therapy in chronic stroke patients: a functional magnetic resonance imaging study. Neurol India. 2012;60:570-6.

39. Holmes NP, Spence C. Visual bias of unseen hand position with a mirror: spatial and temporal factors. Exp Brain Res. 2005;166:489-97.

40. Moseley GL, Gallace A, Spence C. Is mirror therapy all it is cracked up to be? Current evidence and future directions. Pain. 2008;138:7-10.

SUPPLEMENTARY FIGURE AND TABLES

Supplementary figure 1. The tasks for conventional mirror therapy. The person in the figure is one of the researchers, Sukgyu Koh.



Supplementary table 1. Fugl-Meyer assessment scale.[9] Total motor score for the upper extremity is 66, and that for the lower extremity is 34.

UPPER EXTREMITY	
A. Shoulder/Elbow/Forearm	
I. Reflex activity	
Flexors —Biceps	☐
—Finger flexors	☐
Extensors—Triceps	☐
II. a. Flexor synergy	
Shoulder—Retraction	☐
—Elevation	☐
—Abduction	☐
—Outward rotation	☐
Elbow —Flexion	☐
Forearm —Supination	☐
b. Extensor synergy	
Shoulder—Adduction/inward rotation	☐
Elbow —Extension	☐
Forearm —Pronation	☐
III. Hand to lumbar spine	
Hand —Move to lumbar spine	☐
Shoulder —Flexion 0°–90°	☐
Elbow 90°—Pronation/supination	☐
IV. Shoulder —Abduction 0°–90°	☐
—Flexion 90°–180°	☐
Elbow 0° —Pronation/supination	☐
V. Normal reflex activity	☐
Total—Shoulder/Elbow/Forearm	☐
B. Wrist	
Elbow 90°—Wrist stability	☐
Elbow 90°—Wrist flexion/extension	☐
Elbow 0° —Wrist stability	☐
Elbow 0° —Wrist flexion/extension	☐
Circumduction	☐
Total—Wrist	☐
C. Hand	
Fingers mass flexion	☐
Fingers mass extension	☐
Grasp a	☐
Grasp b	☐
Grasp c	☐
Grasp d	☐
Grasp e	☐
Total—Hand	☐
D. Coordination/Speed	
Tremor	☐
Dysmetria	☐
Speed	☐
Total—Coordination/Speed	☐
Total Motor Score for the Upper Extremity	☐

LOWER EXTREMITY	
E. Hip/Knee/Ankle	
I. Reflex activity	
Flexors —Hamstrings	☐
—Achilles	☐
Extensors—Patellar	☐
II. a. Flexor synergy	
Hip —Flexion	☐
Knee—Flexion	☐
Ankle—Dorsiflexion	☐
b. Extensor synergy	
Hip —Extension	☐
—Adduction	☐
Knee—Extension	☐
Ankle—Plantar flexion	☐
III. Knee—Flexion	☐
Ankle—Dorsiflexion	☐
IV. Knee—Flexion	☐
Ankle—Dorsiflexion	☐
V. Normal reflex activity	
Flexors —Hamstrings	☐
—Achilles	☐
Extensors—Patellar	☐
Total—Hip/Knee/Ankle	☐
F. Coordination/Speed	
Tremor	☐
Dysmetria	☐
Speed	☐
Total—Coordination/Speed	☐
Total Motor Score for the Lower Extremity	☐

Supplementary table 2. Modified Ashworth scale[10]

Scoring	Description
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion (ROM) when the affected part(s) is moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

Supplementary table 3. Modified Barthel index[11,12]

Index item	Score				
Chair/Bed transfers	0	3	8	12	15
Ambulation	0	3	8	12	15
Ambulation/Wheelchair (if unable to walk)	0	1	3	4	5
Stair climbing	0	2	5	8	10
Toilet transfers	0	2	5	8	10
Bowel control	0	2	5	8	10
Bladder control	0	2	5	8	10
Bathing	0	1	3	4	5
Dressing	0	2	5	8	10
Personal hygiene (Grooming)	0	1	3	4	5
Feeding	0	2	5	8	10
Total score	100				

Supplementary table 4. Thumb finding test[13,14]

Scoring	Description
0	No difficulty: The patient is able to locate the affected thumb accurately.
1	Slight difficulty: The patient aims in the right general direction but missed the affected thumb by no more than 3 inches, and is able to locate it within 5 seconds.
2	Moderate difficulty: The patient finds the affected arm and then this leads him to the affected thumb.
3	Severe difficulty: The patient is unable to find his thumb and does not climb up the affected arm in order to locate it.

국문 초록

서론: 거울상 치료는 뇌졸중 환자의 편마비측 상지 기능 회복을 위해 임상 현장에서 효과적인 작업치료로 활용되어 왔다. 이것은 거울을 이용하여 건측 상지가 움직이는 동안 마치 환측 상지가 실시간으로 움직이는 것 같은 착각을 불러일으키는 것이다. 이 거울상 치료는 뇌의 감각운동피질을 활성화시켜 뇌가소성을 촉진시킬 수 있다. 하지만 기존의 거울상 치료는 실제로는 환측 상지가 움직이지 않는다는 중요한 제한점을 갖고 있다.

방법: 저자는 닫힌 피드백 기전을 활용하여 기존의 거울상 치료에 간단한 모듈을 추가한 실시간 2 축 거울상 로봇 치료 시스템을 개발하였으며, 이는 편측 상지가 실시간으로 움직이게 해 줄 수 있다. 이는 고유감각 촉진 및 그에 따른 운동기능 회복을 위해 실제 거울에 로봇을 결합한 최초의 시도이다. 저자는 3 개의 자세방위기준장치 센서, 팔꿈치 및 손목 관절에 2 개의 brushless 직류 모터 및 외골격 틀을 사용하였다.

결과: 환측 상지에 부착한 모터와 건측 상지에 부착한 센서 간 움직임의 동시성이 높은 것으로 검증되었다. 6 명의 정상인을

대상으로 수행한 적용 가능성 탐색 연구에서 거울상 로봇 치료는 안전하게 수행 가능하였다. 또한 저자는 재활의학과 의사들로부터 피드백을 받아 일상생활 동작수행 훈련에 유용한 작업 훈련 종류를 선택하였다. 2 주간 거울상 로봇 치료 시스템을 적용한 2 명의 만성 뇌졸중 환자들에서 각각 Fugl-Meyer 평가 척도 및 팔꿈치 굴곡근 경직, 고유감각 및 편측무시의 호전을 보였다. 고유감각의 호전은 뇌 기능적 MRI 에서 수동적 손목관절 운동시 상부 두정소엽의 하부 및 이로부터 신호를 전달받는 전운동피질 부위가 활성화된 점으로 설명된다.

결론: 거울상 로봇 치료는 뇌가소성 및 편마비측 상지 기능 회복에 중요한 감각피질에의 고유감각 경로를 촉진시킬 것으로 여겨진다. 본 연구의 거울상 로봇 치료 시스템은 간단히 개발할 수 있으며, 진보된 작업치료로 효과적으로 활용될 수 있을 것이다.

주요어: 거울상 치료, 고유감각, 재활로봇, 뇌졸중, 편마비, 센서

학 번: 2012-30553