Mirror feedback in virtual reality elicits ipsilesional motor cortex activation in chronic stroke patients

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Abstract—**We studied if mirror-visual feedback, presented in virtual reality (VR), could bolster the activity of the lesioned motor cortex in chronic stroke patients. 5 stroke subjects performed a simple finger movement using the non-paretic hand. During fMRI scanning, an MRI-compatible VR-motion capture interface was used to record their hand movement and actuate in real-time virtual hand models, which were presented in 1st person perspective as virtual feedback. Virtual hands' motion was manipulated by either actuating the hand model corresponding to the moving (unaffected) hand (veridical feedback) or the opposite (mirrored) virtual hand. Two additional types of feedback, in which the virtual hands were replaced with moving non-anthropomorphic shapes, served as control conditions. Subjects maintained consistent movement kinematics across conditions. In each of the 5 stroke subjects, mirrored feedback led to significant activation of the ipsilesional sensorimotor cortex, despite the affected hand remaining motionless during the task. An additional control experiment and conjunction analysis confirmed that the part of the motor cortex that was activated by mirrored feedback overlapped with the area of motor cortex involved in movement production of the affected hand. Our data suggest that mirrored visual feedback may be a feasible modality that can be used to recruit select brain regions in stroke patients as a means of facilitating neural reorganization and recovery.**

Keywords-component; Stoke; virtual reality; mirror feedback; fmri

I.   INTRODUCTION

In the next decade, more stroke survivors will live with major disability due to higher survival rate [1] and life expectancy. Large financial burdens related to stroke, with direct and indirect expenses in excess of $125 billion in FY 2005-06 [2], place unyielding demands on families and society. Though rehabilitation for stroke can have moderate benefits, current practice favors therapy of gait and proximal arm function over hand function [2] and therefore outcomes for the hand remain inferior to those of the arm and lower extremity [3, 4] [5-7]. Hand rehabilitation therefore remains a daunting challenge for patients and clinicians, particularly for individuals who are severely paretic and unable to perform therapeutic exercises.

Because corticospinal excitability is a strong predictor of recovery after stroke [8], it is urgent to develop interventions that can bolster activation in the motor cortex. Developing such treatments, which are grounded in neuroscientific principles, may advance the efficacy of therapeutic outcomes. Given empirical evidence for rich interconnections between visuomotor processing areas and interhemispheric motor centers, we hypothesized that mirrored visual feedback, paired with motor commands transferred interhemispherically, could facilitate activity in the lesioned motor system even in the absence of overt motor output.

In this study, we tested this prediction by using a virtual reality (VR) environment where motion of the ipsilesional (unaffected) hand is replicated in real time as movement feedback of a virtual hand corresponding to the contralesional (affected) hand. Such mirrored feedback has been suggested as a rehabilitation tool [9], especially for patients with severe hand paresis which prohibits individuals from actively participating in training. In those studies, subjects move both hands symmetrically, moving the affected arm to the extent possible, while watching the mirror reflection of their healthy hand in a sagittally oriented mirror. The reflection is overlapped with their affected hand, which remains hidden behind the mirror. Several small clinical studies have demonstrated promise of this approach for upper [10-12] and lower limb rehabilitation [13].

In the backdrop of this data, it becomes critical to understand the mechanisms by which mirrored feedback may operate, and perhaps mediate therapeutic effects. Functional MRI (fMRI) work in healthy subjects has revealed that mirrored feedback using a sagittally oriented mirror-box setup can be associated with increased activity in sensorimotor cortex (SMA, M1 and S1) ipsilateral to the moving hand. (However, Matthys et al., 2009 [14] found no activation in ipsilateral motor cortex.) Interestingly, individuals who have undergone amputation of the upper limb, but do not exhibit phantom limb pain, show similar effects while those who do experience phantom limb pain do not [15] suggesting that sensorimotor regions (which are thought to play a role in phantom sensations) may be mediating the mirror effects. Similarly, electrical [16] and neuromagnetic neuroimaging work in healthy subjects revealed increased lateralized readiness potentials and stimulus-induced 20-Hz suppression of the primary motor cortex contralateral to the inactive hand, both effects indicative of increased excitability of the motor cortex, during mirrored feedback. Direct facilitation of the healthy

corticospinal system has been demonstrated as increased motor evoked potentials (relative to baseline) in the motor cortex ipsilateral to the moving hand during mirrored feedback [17]. Interestingly, a recent fMRI study with stroke patients, who were provided mirror feedback with a mirror-box setup up while performing bimanual hand motion exhibited activation in precuneus and posterior cingulate cortex, but did no activation in sensorimotor areas of the lesioned hemisphere [18]. Thus, literature on whether the sensorimotor system is responsive to mirrored feedback in patient populations, particularly stroke, is scant, at best, and even in healthy individuals the data remain equivocal.

In our fMRI study, we overcame some of the limitations inherent in prior designs by using a virtual, rather than physical, mirror feedback. The advantages to using VR is that it allowed us to manipulate visual feedback in ways not possible in the natural world [19], thereby forcing subjects to focus exclusively on the mirrored feedback without the distraction of seeing the veridical hand moving. Second, we interlaced data collection gloves with the VR system and could thus record finger motion for offline analysis. This allowed us to exclude trials in which subjects did not conform to the task demands (i.e. due to inadvertent bilateral movements). Third, we used VR to provide a series of rigorous control visual feedback conditions to rule out confounds to activation that may be attributed motor output, visual field effects, or arbitrary visual motion effects. Fourth, because VR is rapidly infiltrating rehabilitation paradigms [20], our design allows us to draw direct predication on whether this would be a viable treatment possibility.

II. METHODS

A. Subjects

Five right-handed [21] subjects, with hemiparesis due to stroke (2 right-hemiplegics, 2F, mean age 56.6 ± 12 years, range: 37-73 years old) participated in the study after signing informed consents approved by the University of Medicine and Dentistry and the New Jersey Institute of Technology Institution Review Boards. All subjects were independent in basic activities of daily living; three of the subjects used a cane.

Table 1. Subjects clinical Information (Cerebral Vascular Accident (CVA), Chedokee-Master Arm score (CMA), Chedokee-Master Hand score (CMH))

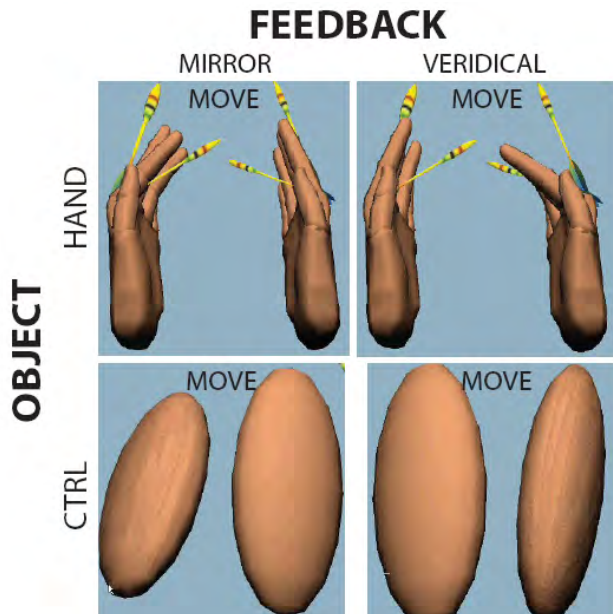| Pt	Age	Sex	Time Since CVA (Months)/ CVA side	CMA	CMH	Lesion Location
1	63	F	53/L	6	4	Left Occipital and Parietal Infarct, Small Bilateral Cerebellar Infarcts
2	55	M	41/L	5	4	Left thalamic nuclei
3	70	F	96/R	7	5	Right corona radiata infarct
4	58	M	132/R	5	4	Right MCA distribution infarct
5	37	M	92/R	5	4	Pons

Figure 1. The four VR visual feedback conditions

B. Setup and Proccedure

Subjects were positioned in the MRI scanner so that they could easily see a back-projected image on a semi-transparent screen through a rear-view mirror. Subjects wore a left and right MRI-compatible recording glove (Fifth Dimension Technologies, 5DT Data Glove 16 MRI). The gloves use fiber-optic sensors to measure metacarpophalangeal (MCP) and proximal interphalangeal finger joints to yield finger flexion and abduction angles. The gloves were interfaced with a virtual reality (VR) environment developed with Virtools software and a VRPack plugin that communicated with an open source Virtual Reality Peripheral Network. The VR environment showed left and right virtual hand models that were positioned in 1st person view, in semi-pronated positions (thumb toward the viewer), on the left and right side of the display (Fig. 1). The VR hands were actuated in real-time by data streamed from the 5DT gloves. Our previous experiments show that the 5DT gloves yield reliable measurements and can be effectively interfaced with VR in an fMRI environment [19]. The start of the VR simulation, data glove acquisition, and fMRI data acquisition were synchronized by a back-tick TTL trigger transmitted from the MRI scanner.

Subjects were trained to perform the task the day before scanning and were given a chance to practice just prior the start of the experiment. Their task was to perform whole hand finger movements with the paretic (Experiment 1) and non-paretic (Experiment 2) hand. Real-time left and right glove data was continuously streamed and used to animate the motion of the VR hand models in the following ways:

Experiment 1: Subjects performed the task only with the paretic hand, leaving the non-paretic hand at rest. The correspondence between data streamed from the gloves and the VR hands remained veridical, such that motion of the fingers on the left hand actuated the fingers of the left VR hand, and motion of the fingers on the right hand actuated the fingers on the right VR hand. This experiment was used to

understand if cortical regions in the lesioned hemisphere activated by mirrored feedback (see Experiment 2 below) overlapped with those regions associated with motion of the paretic hand.

Experiment 2: Subjects performed the task only with the non-paretic hand, leaving the paretic hand at rest. The correspondence between data streamed from the gloves and VR hands remained either veridical (as in Experiment 1) or was flipped (mirrored feedback) such that motion of the fingers on the left hand actuated the fingers of the right VR hand, and motion of the fingers on the right hand actuated the fingers on the left VR hand. This way, the VR hand moving either corresponded to the veridical moving hand, or in the case of mirrored-feedback, to the resting paretic side. A control feedback condition (CTRL) was also included to subtract out potential confounds of visual field position, gaze direction, and motion. For the control condition, the VR hands were replaced with a non-anthropomorphic object (ellipsoid) that was similar in size and color to the VR hands. The left or right control object rotated about an oblique axis (1 Hz) while the subjects moved their non-paretic hand, such that it either corresponded to the veridical or mirrored side (see Fig. 1).

The four visual feedback conditions (HAND [veridical, mirrored], CTRL [veridical, mirrored]) were presented in an event-related fashion and randomly interleaved with each other in each functional imaging run (8 trials per condition for four subjects and 10 trials per condition for one subject). Each subject performed four runs. Movement events (5 seconds duration) were separated by an inter-trial rest period that randomly varied between 3-7 seconds to jitter fMRI volume acquisition. Movement and rest events were cued by a word on the screen.

C. fMRI Acquisition and Analysis

fMRI data acquisition was performed using a 3-T Siemens Allegra head only scanner with a Siemens standard head coil. High resolution structural images (TR=2000 ms, TE= , voxel size 0.938x0.938x1, 176 slices, 1 mm slice thickness) and functional images (TR=2000 ms, TE=30 ms, FOV 100 mm, voxel size= 3x3x3 mm, number of slides 32, interslice time 62 ms, 175 number of volumes) were taken for each subject. All functional scans used a T2* weighted echo planar imaging sequence. fMRI data were preprocessed using SPM8. The first two dummy functional volumes were acquired to account for field inhomogeneities but not saved or included in data analysis. Each subject's functional volumes were realigned to the first volume and co-registered with the structural image. Slice timing correction was performed before all images were normalized to the SPM8 Montreal Neurological Institute template, and functional images were smoothed with an 8 mm Gaussian kernel. In the results section, all single-subject functional contrasts are overlaid onto the respective subject's high-resolution anatomical scan, which also shows their lesion.

A separate general linear model (GLM) was created for each subject and for each experiment. Run-to-run regressors were included in each GLM. Prior to creating the models, movement kinematics (see next section) were inspected to

make sure that subjects complied with the task. Individual trials in which subjects had inadvertent motion of the non-relevant hand were not modeled in the fMRI analysis (see Fig. 2).
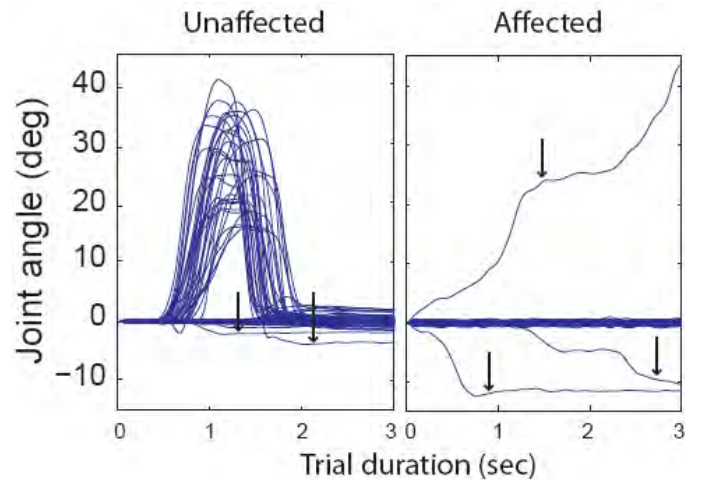

Figure 2. Example of a representative subject's (S2) index finger movement (metacarpophalangeal joint; 32 trials). The arrows mark trials in which the subject did not comply with the task, and thus were excluded from analysis.

fMRI Analysis of Experiment 1: To map regions in the lesioned hemisphere that were activated during motion of the paretic hand, we performed a movement > rest t-test contrast. Statistical significance was set to $p<0.01$ (FWE corrected) and a 10 voxel minimal extent.

fMRI Analysis of Experiment 2:

Single-subject analysis. To study subject-specific effects of mirrored visual feedback, we performed an F contrast with factors: OBJECT (HAND, CTRL) and FEEDBACK (veridical, mirrored). Specifically, we were interested in the following interaction: (HANDmirror – CTRLmirror) > (HANDveridical – CTRLveridical). Because subjects moved the non-paretic hand in each condition, all motor-related activation was subtracted out in this contrast. Also subtracted were effects of gaze, visual field, and arbitrary visual motion. The contrast was analyzed in an a-priori defined inclusive region of interest mask (WFUpickatlas SPM toolbox) that included bilateral frontal and parietal lobes, precuneus, and the superior temporal gyrus of the lesioned hemisphere.

Overlap between motor and feedback activations. To determine if mirror feedback-based effects recruited topographically similar regions in the sensorimotor cortex to those activated by movement of the paretic hand, we performed a conjunction analysis for each subject between the results of Experiment 1 and 2.

Group analysis. To determine if activation in sensorimotor areas was localized to a consistent topographic region, irrespective of hemisphere or lesion location, we flipped all of the left-lesioned subjects' raw functional images to the right, such that all subjects were "functionally lesioned" in the right hemisphere. The average image of the five subjects'

interaction contrast was then computed using Imcalc SPM8 toolbox.

D. Behavioral Measurements

Kinematic analysis was used to verify that movements of the non-paretic hand (the active hand involved in Experiment 2) were consistent across the different feedback conditions. For each trial, movement onset and offset was defined as the time at which the mean angular velocity of the four MCP joints exceeded and then fell below 5% of the peak mean angular velocity on the corresponding trial. Movement time was the interval between onset and offset. Movement onset and time were modeled in the GLM on a trial-by-trial basis to give a more temporally accurate convolution of the BOLD events with the hemodynamic response function. To verify that movements remained consistent, the peak angle attained (angular excursion) and movement time on each trial were submitted to a 1-way repeated measures analysis of variance (ANOVA) on the four feedback conditions. Statistical threshold was set at 0.05.

To verify that any mirror feedback-based effects in the fMRI data could not be accounted for by inadvertent motion of the paretic hand, we also performed the above analysis on the glove data acquired from the non-moving (paretic) hand. fMRI data corresponding to trials on which subjects moved their paretic hand were excluded from the GLM (see Fig. 2).

III. RESULTS

Experiment 1: FMRI: Regions activated during motion of the paretic hand: The contrast move>rest showed significant activation in a typical cortical network subserving visually guided hand movement. Significant activation was noted in the contralateral precentral and postcentral gyri, contralateral superior and inferior parietal lobules and ipsilateral insula, and to a lesser degree in ipsilateral sensorimotor areas.

Experiment 2: Behavior: Fig 2 shows a representative stroke subject's joint angle traces recorded from the paretic (static) and non-paretic (moving) hand during a functional run. Note that subjects generally maintained consistent movements with the non-paretic hand. However, occasionally, subjects either exhibited inadvertent motion of the paretic hand or missed required motions of the non-paretic hand. Such trials were excluded from behavioral and imaging analyses. A repeated measures ANOVA showed no effect of feedback condition (F=0.34, p=0.7969) for angular excursion and a marginal effect for movement duration (F=3.835, p=0.0418, with movement duration in the CTRL conditions (CTRLmirror and CTRLveridical) being slightly longer (by 103-114ms) than in the HAND conditions (see table 2).

Experiment 2: FMRI: Regions activated during mirror-based feedback: Fig. 3 shows regions with significant activation in the HANDmirr–CTRLmirr)>(HANDverid–CTRLverid) contrast. Significant activation was noted in the sensorimotor system of the ipsilesional hemisphere (ipsilateral to the moving hand). Topographic activation patterns across the five stroke subjects were remarkably similar, with clearly

Table 2. Statistics of Movement Angle Excursion (MAE) and Movement Duration (MD)

	Mirror		Veridical	
	HAND	**CTRL**	**HAND**	**CTRL**
MAE	0.92 (±0.53)	1.03 (±0.59)	0.91 (±0.49)	1.03 (±0.59)
MD	2.523 (±1.04)	2.81 (±1.25)	2.33 (±0.96)	2.86 (±1.26)
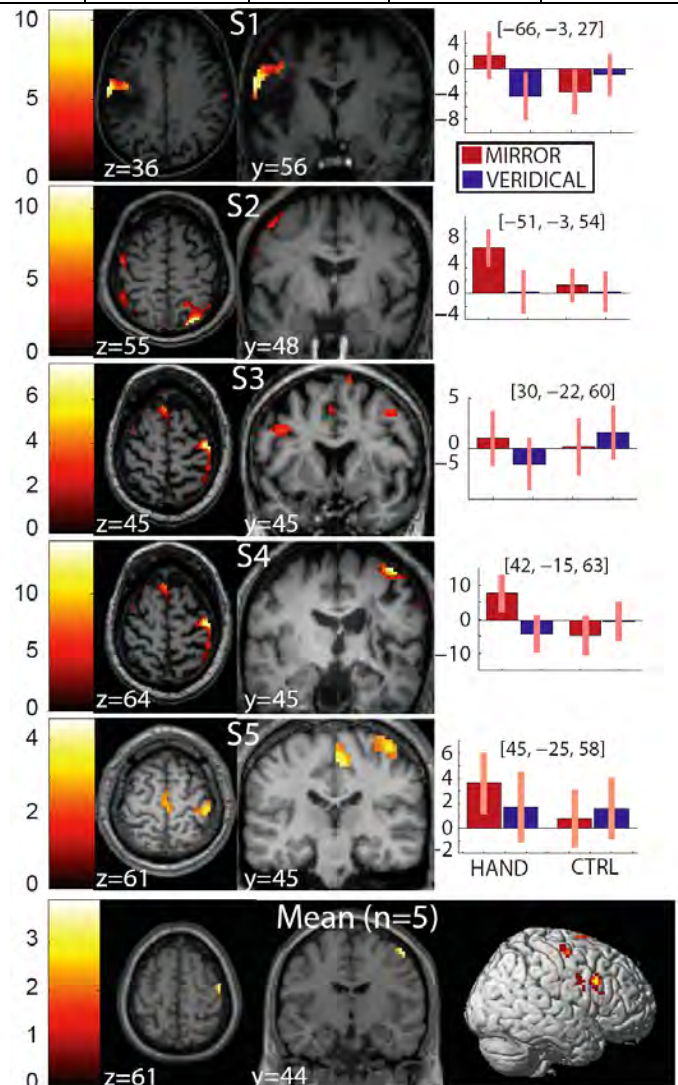
Figure 3. Bold activity for the contrast (HANDmirror-CTRLmirror)>(HANDveridical-CTRLveridical) of each individual subject (p<0.01). The results are overlaid on each subject's anatomical mprage scan. The bottom panel shows the average of these five subjects' activations after flipping the left hemisphere lesioned T-maps to the right hemisphere (p<0.01). The color bars on the left show t-values and the bar plots to the right show beta estimates in sensorimotor cortex clusters of each respective subject and for each condition.

activated clusters in the central sulcus as well as the precentral and postcentral gyri. In some cases, mirror visual feedback also led to recruitment of the superior and inferior parietal lobes (SPL, IPL), precuneus, supplementary motor area (SMA), and cingulate gyrus. Mean activation at the group

level was significant only in the ipsilesional primary and premotor cortex (see Fig. 3, Table 3).

Topographic overlap between motor- and feedback-based representations: We performed a conjunction analysis between Experiments 1 and 2 to test if motor regions activated by mirrored visual feedback overlap with motor centers engaged in producing movement of the paretic hand. An affirmative finding would suggest that mirrored feedback of the unaffected hand could be used to selectively activate relevant motor command centers giving rise to corticospinal projections to the paretic hand. Fig. 4 shows for each subject regions that were commonly activated in Experiment 1 (motion of the paretic hand) and Experiment 2 (mirrored feedback of the unaffected hand). In each of the five stroke subjects, a cluster in the lesioned motor cortex showed distinct topographic overlap across the two experiments.

IV. DISCUSSION

Our experimental design demonstrates that mirror visual feedback during unimanual motion of the unaffected hand can significantly activate the motor cortex of the lesioned hemisphere. Further, we show that this effect cannot be accounted for by arbitrary confounds related to visual motion, gaze effects, position of objects in a particular hemi-field, differences in movement kinematics, or especially to movement production (since activation attributed to these confounds was subtracted out). Finally, we show that regions showing mirror-based effects are topographically overlapping with those involved in producing movement of the paretic hand.

Our results are consistent with recent findings, that motor cortex can be modulated by action observation or perception, irrespective of overt movement [22, 23]. As mentioned in the introduction, other mirror visual feedback-based studies in healthy neural systems [16, 17, 24] have noted similar effects on motor cortex. Strangely, our data does not agree with the results of the only fMRI mirror feedback study conducted in stroke subjects [18] in which the authors did not note significant sensorimotor activation in response to mirror feedback. However, three critical differences between their design and ours may explain the discrepancy in the results. First, they used a mirror-box setup which did not prevent subjects from seeing both hands moving during the mirrored condition. Second, hand kinematics was not tracked in their study making it possible that trials with inadvertent motion (or lack of motion) washed the effects out. For these reasons, the absence of mirror-based effects in the sensorimotor cortex in the abovementioned study may be attributed to suboptimal (unfocused) presentation of mirror feedback.

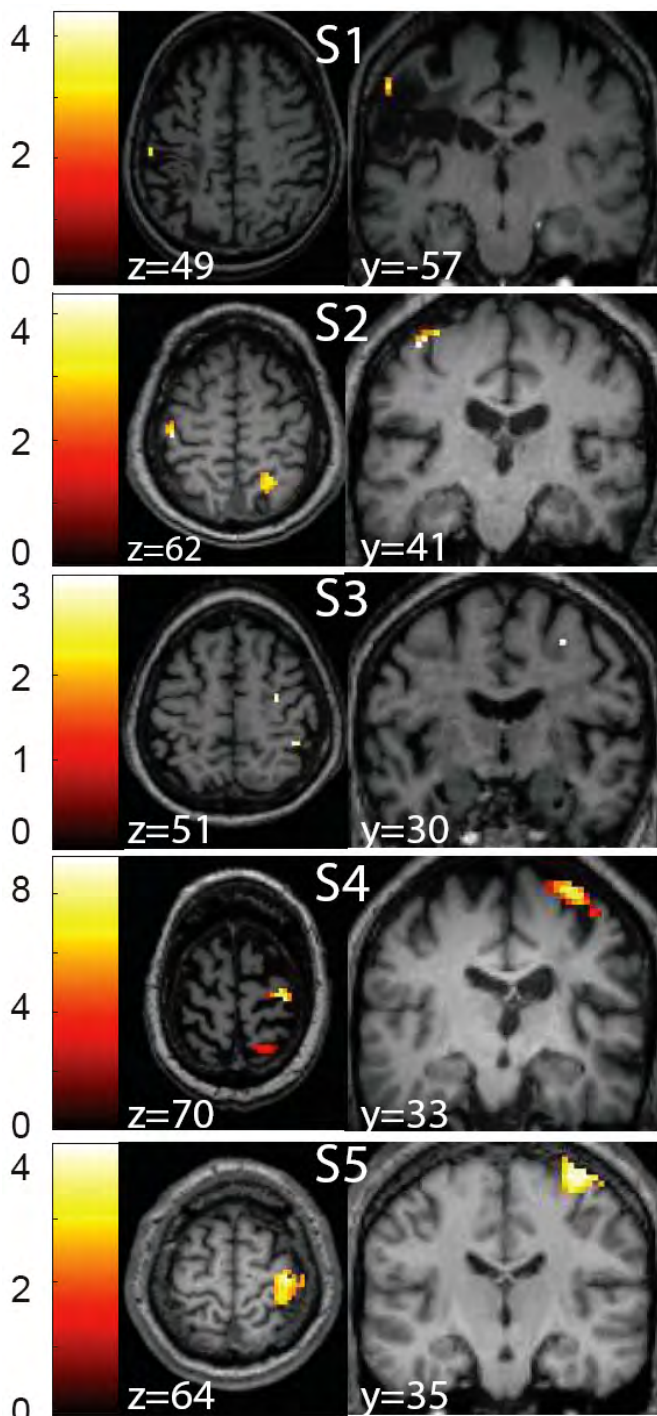
Figure 4. Conjunction analysis between contrasts of Experiment 1 and 2 on a subject-by-subject basis. Activated regions (p<0.01) show topographic overlap between mirror feedback-based activation and regions subserving control of the paretic hand.

Table 3. Ipsilesional hemisphere areas recruited in mirror hand visual feedback

equivk	T	F	x,y,z (mm)	Anatomical position
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(HANDmirror > HANDveridical)>(CTRLmirror>CTRLveridical) contrast
STATISTICS: p-values adjusted for search volume (p<0.01)

equivk	T	F	x,y,z (mm)	Anatomical position
Subject 1				
10	6.7973	0.55	-57 11 1	Inferior frontal opercularis
775	10.9552	0.73	-45 -31 67	precentral and postcentral gyrus, BA 2, 6, 9, 43
22	7.9145	2.18	-57 -46 49	inferior frontal lobule BA 40
36	5.8068	1.96	-21 -25 61	precentral gyrus
14	8.2823	1.12	-21 -43 76	Superior parietal lobule
18	8.3145	1.08	-18 -31 76	postcentral gyrus BA 1,2
Subject 2				
22	5.1139		-57 38 57	Inferior frontal gyrus BA 45,46
15	5.2758	1.51	-54 -19 13	Poscentral gyrus
9	3.4863	16.07	-63 -1 34	Precentral gyrus
23	7.9019	1.51	-12 -85 49	Superior parietal lobule BA 7
47	4.4677	1.79	-30 -49 49	Inferior/superior parietal lobule BA 7
30	3.2368	0.81	-48 -46 58	Inferior parietal lobule
72	6.2254	12.88	-39 -22 70	Precentral gyrus BA 4,6
Subject 3				
90	3.4283	0.46	51 11 -2	Inferior frontal and precentral gyrus
45	3.6024	3.13	45 -46 52	Inferior parietal lobule BA 40
14	3.2383	3.38	45 5 49	Precentral gyrus
130	4.368	1.99	3 14 49	L/R supplementary motor area, cingulated gyrus
18	3.996	2.85	30 -64 49	Superior parietal lobule, BA 7
22	3.6506	0.36	12 17 70	Supplementary motor area (SMA)
Subject 4				
459	11.262	2.39	60 14 31	Inferior/middle frontal gyrus, BA 6, 9, 45, 46, 47
14	3.5822	0.91	39 26 28	Inferior frontal triangularis
438	13.388	2.41	43 -13 64	Inferior parietal lobule and precentral gyrus, BA 6, 7, 40
260	14.423	0.88	12 -1 76	L/R SMA, cingulated gyrus, BA 8, 32
45	14.548	3.29	18 -58 73	Superior parietal lobule
Subject 5				
10	3.173	1.70	27 32 -17	Inferior frontal opercularis
210	4.4814	1.17	3 8 46	SMA BA 6, 24, 32
115	3.7553	1.35	45 -25 61	Precentral gyrus, BA 6
19	3.6966	2.24	9 -37 82	Postcentral gyrus
Average (n=5)				
30	3.53	NA	57 17 31	Inferior/middle frontal gyrus, BA 9
9	2.712	NA	66 2 28	Precentral gyrus, BA 6
13	3.88	NA	51 -10 58	Precentral gyrys, BA 6
9	3.41	NA	12 8 73	SMA

In conclusion this study demonstrates that VR may be an effective medium by which to provide mirror-based visual feedback to stroke patients with the aim of facilitating activity in topographically relevant sensorimotor areas of the lesioned hemisphere. Further study of the neural mechanisms underlying mirror-based feedback is critical to develop therapeutic interventions that boost activity in select brain networks and thereby enhance brain reorganization [8]. An interesting direction would be to explore the feasibility of combining this form of feedback with robot-assisted virtual reality training [19, 25-28] in maximizing recovery.

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