BRIEF REPORT

Cortical Reorganization and Associated Functional Motor Recovery After Virtual Reality in Patients With Chronic Stroke: An Experimenter-Blind Preliminary Study

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ABSTRACT. Jang SH, You SH, Hallett M, Cho YW, Park C-M, Cho S-H, Lee H-Y, Kim T-H. Cortical reorganization and associated functional motor recovery after virtual reality in patients with chronic stroke: an experimenter-blind preliminary study. Arch Phys Med Rehabil 2005;86:2218-23.

Objective: To investigate the effects of virtual reality (VR) on cortical reorganization and motor recovery.

Design: Nonparametric pre- and posttest design with experimenter blinded.

Setting: University medical center.

Participants: Five patients with hemiparesis (age, 59.8±3.4y) were recruited.

Intervention: Five patients received VR for 60 minutes a day, 5 times a week for 4 weeks. VR was designed to provide a virtual rehabilitation scene where the intensity of practice and sensory feedback could be systematically manipulated to provide the most appropriate, individualized motor retraining program.

Main Outcome Measures: Cortical activation and associated motor recovery were measured before and after VR using functional magnetic resonance imaging and standardized motor tests, respectively. Nonparametric tests were used at P less than .05.

Results: Prior to VR, the bilateral primary sensorimotor cortices (SM1s), contralesional premotor cortex, and contralesional or ipsilesional supplementary motor area were activated. After VR, the altered activations disappeared and predominantly the ipsilesional SM1 was activated ($P<.05$). Motor function was improved ($P<.05$).

Conclusions: This is a novel demonstration of VR-induced neuroplastic changes and associated motor recovery in chronic stroke.

Key Words: Computer-assisted instruction; Hemiplegia; Magnetic resonance imaging; Rehabilitation.

HEMIPARETIC STROKE IS A LEADING cause of disability in the affected limbs,[1] which may have a significant influence on disuse or learned nonuse of the affected limbs.[2] Consequently, this may result in suppression of the cortical representation of the affected limb (ie, hand) and further inhibit its spontaneous use.[3,4] Such cortical suppression has been shown to be evident in the cortical motor representation of the paretic hand that was decreased by one half of the size of the nonparetic hand after stroke.[3]

Several studies have attempted to investigate the efficacy of stroke rehabilitation approaches,[5-8] yet have yielded inconsistent results. Liepert et al[8] have reported enlarged cortical motor representation and associated hand motor recovery of selected stroke patients (highly motivated and relatively spared hand motor function) after intensive constraint-induced movement therapy (CIMT). However, major patient compliance, cost, and safety issues have been raised.[8,9] For example, a more recent CIMT case study noted that although highly motivated, the patient ". . . grew tired of wearing the mitt and had difficulty with full adherence at home . . . cheating with the uninvolved hand was a frequent temptation for the patient."[10(p851)] CIMT involves intensive intervention (6–8h daily for 6d/wk) and a home exercise program. Potential risk of serious falls may exist because the nonparetic hand is constrained, which may prohibit protective extension of the nonparetic arm if the patient falls.[7,9] Virtual reality (VR) studies have demonstrated that 45 to 60 minutes of VR intervention (3 times/wk) is effective in obtaining measurable motor recovery in stroke patients.[11,12] If this holds true, the cost of VR intervention would be considerably reduced. Because no constraint is involved in VR, patients can maintain their protective reaction if they lose their balance. Our VR is partially immersive and therefore does not present inherent lags and associated delayed latency, which could potentially produce symptoms similar to motion sickness reported in other full-immersion VR systems. VR studies have reported that patients consider VR intervention as interactive and enjoyable exercise games rather than therapy. Consequently, patients are likely to be more motivated by and compliant with the VR intervention than conventional therapy.[11] VR can provide both objective testing and motor retraining in simulated real-life environments, and that can be tailored based on an individual patient's baseline motor performance.[13] However, the neural control mechanisms supporting VR-induced motor recovery have never been investigated. We examined cortical reorganization and motor recovery, our basic hypothesis being that VR could produce practice-dependent enhancement of the

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Table 1: Clinical and Demographic History

Stroke Subject	Age/Sex	Handedness	Risk Factors	Site of Stroke (Topography)	Time From Stroke (mo)
Control group					
1	43/M	Right	Cig	Left corona radiata infarct	9.0
2	40/M	Right	Hchol, HTN	Right thalamic hemorrhage	12.0
3	63/F	Right	Hchol, NIDDM	Left corona radiata infarct	10.0
4	63/M	Right	HTN, Cig	Right corona radiata infarct	21.0
5	63/M	Right	HTN	Left thalamic hemorrhage	15.0
Mean	54.4				13.4
SE	5.3				2.2
VR group					
1	68/F	Right	Hchol, HTN	Left thalamic hemorrhage	24.0
2	55/M	Right	HTN, Cig	Right thalamic hemorrhage	21.0
3	50/M	Right	Afib	Right cortical infarct	9.0
4	66/F	Right	HTN, NIDDM	Left corona radiata infarct	7.0
5	60/F	Right	Hchol	Right corona radiata infarct	8.0
Mean	59.8				13.8
SE	3.4				3.6

Abbreviations: Afib, atrial fibrillation; cig, cigarette smoking; F, female; Hchol, hypercholesterolemia; HTN, hypertension; M, male; NIDDM, non-insulin-dependent diabetes mellitus; SE, standard error of measurement.

affected hand, which may help remediation of altered cortical reorganization by means of reversal or normalization of the aberrant organization.

METHODS

Participants

Ten patients with hemiparetic stroke (6 men, 4 women; mean age, 57.1±4.5y) were recruited. Inclusion criteria included: (1) more than 6 months elapsed from the onset of stroke, (2) ability to move the elbow against gravity, and (3) no prior stroke. Exclusion criteria included: (1) severe spasticity (Modified Ashworth Scale score >2) or tremor, and (2) severe visual and cognitive impairments. Informed consent was obtained from all subjects prior to the study. In an experimenter-blind randomized controlled trial, patients were randomized into either the control or intervention group. Intervention allocation was done by one of the experimenters who was unaware of the information obtained during the initial examination. The control group did not receive any intervention whereas the intervention group received VR training. Routine clinical examination was conducted to determine the presence of risk factors associated with stroke (table 1).

Procedure

Motor function. An experienced physical therapist performed the box and block test (BBT),[14] the Fugl-Meyer Assessment (FMA),[15] and the manual function test (MFT).[16] In addition, after completion of VR training, the therapist conducted the modified Motor Activity Log (MAL) interview[17] by asking each patient about amount of use (AOU) and quality of movement (QOM) of the affected upper extremity during ac-

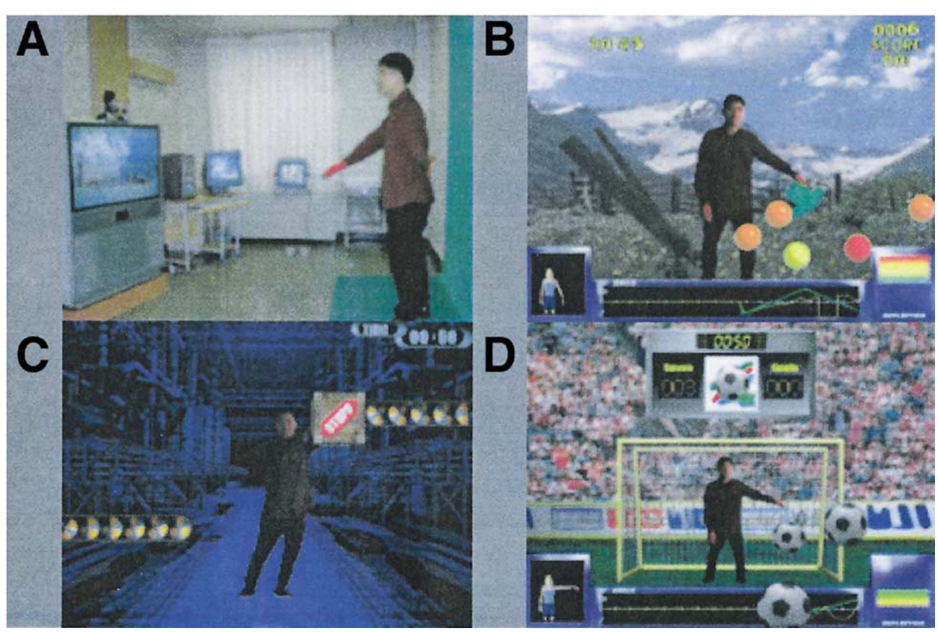

Fig 1. (A) VR exercise setup, (B) bird-ball exercise game, (C) conveyor exercise game, and (D) soccer exercise game. Reprinted with permission of Vivid Group Inc.[25]

tivities of daily living. Scores ranged from 0 (never used) to 5 (normal). The BBT was used to measure unilateral gross manual dexterity and hand manipulation skill. The test-retest reliability and validity were excellent (intraclass correlation coefficient [ICC] range, .90–.97; ICC=.91, respectively).[14] The upper-limb motor subset of the FMA was used to examine sensation, range of motion, reflexes, synergy, and fine and gross hand movements. Reliability and validity were good (ICC=.97; ICC range, .73–.85, respectively).[15] The MFT was used to measure gross and fine motor dexterity of the upper extremity. Reliability was excellent (ICC=.99).[16]

Functional magnetic resonance imaging. All patients were secured with a specially designed immobilizer and scanning was accomplished through use of a 1.5-T magnetic resonance imaging (MRI) scanner[a] with a standard head coil. This MRI system enabled whole-brain echo planar imaging (EPI). Imaging acquisition was performed using a gradient-echo EPI sequence based on the blood oxygenation level–dependent technique. The following data acquisition parameters were used: echo time, 60ms; repetition time, 3000ms; field of view, 210×210mm; matrix, 64×64; voxel dimensions, 4×4×4; and thickness, 5mm. Any signal intensity variation (>5%) during the control phase was removed due to possible confounding contributions from large brain vessels.[13,14] SPM-99 software[b] equipped with the Matlab program[c] was used to analyze raw image data. Significant voxels were obtained by applying a threshold of P less than .001.

For each patient, the bilaterally predefined regions of interest (ROIs), including the primary sensorimotor cortex (SM1), the premotor cortex (PMC), and the supplementary motor area (SMA), were used because most neuroplastic changes were observed to occur in these regions.[18,19] A normalized laterality index was then computed to compare any relative activity between the right and left hemispheres for each ROI.[18,19] The laterality index was defined as (C–I)/(C+I), where C and I indicate the total number of activated voxel counts in the region contralateral or ipsilateral to the forearm movement. Thus, the laterality index ranged from 1.0 (all contralateral activation) to –1.0 (all ipsilateral activation).[18,19]

VR Intervention

As depicted in figure 1A, the IREX virtual reality system[d] consisted of a television monitor, a video camera, cyber gloves, virtual objects and scenes, and a large screen.

The video camera captured the patient's whole body movement. These captured images were digitally converted and projected on an enlarged screen. The patient was able to view his/her own body movements in real time, which served to immerse them inside the virtual environment. Thus, the IREX was a more advantageous system associated with greater freedom of mobility than other existing VR systems that necessitate heavy and expensive devices, such as head-mounted displays, data gloves, and wires.[20,21]

Figures 1B through 1D show 3 interfaced virtual exercise protocols that were programmed in the IREX VR system. These VR protocols were designed to focus on the development of reaching, lifting, and grasping motor skills, with each game programmed to exercise 1 or multiple aspects of upper-extremity and trunk movement.[21] Further information about the IREX VR system and protocol can be found in the IREX manual.[21]

The task-oriented training paradigm with faded feedback was used to reinforce the patient to become an independent problem solver while decreasing negative dependence on the therapist's feedback. VR provides an augmented feedback about knowledge of results or knowledge of performance including error rate, speed, direction, joint position, and resistive force feedback. Because these motor tasks require complex intersegmental coordination and were initially difficult due to synergistic patterns, using the established IREX VR assessment and treatment protocol, VR-trained therapists determined the baseline performance, provided a customized treatment, and monitored the outcomes. Necessary adjustments in VR parameters such as speed, angle, and lifting force were made. For example, exercise progression was also obtained by increasing resistive force using hand and cuff weights. Initially, a simple-to-complex learning paradigm with a high frequency (>90%) of augmented knowledge of performance or knowledge of results feedback was given and gradually lessened as performance improved.[22] The exercise was performed 5 times for each game and was given for 60 minutes a day, 5 times a week for 4 weeks.

Statistics

Nonparametric tests were chosen due to the limited number of cases. The Mann-Whitney U test was used to compare age and stroke-onset duration between the groups. For the 2 groups, differences in the BBT, FMA, and MFT scores between the pretest and posttest were computed. The Mann-Whitney U test and the Wilcoxon 2-sample rank-sum test were used to com-

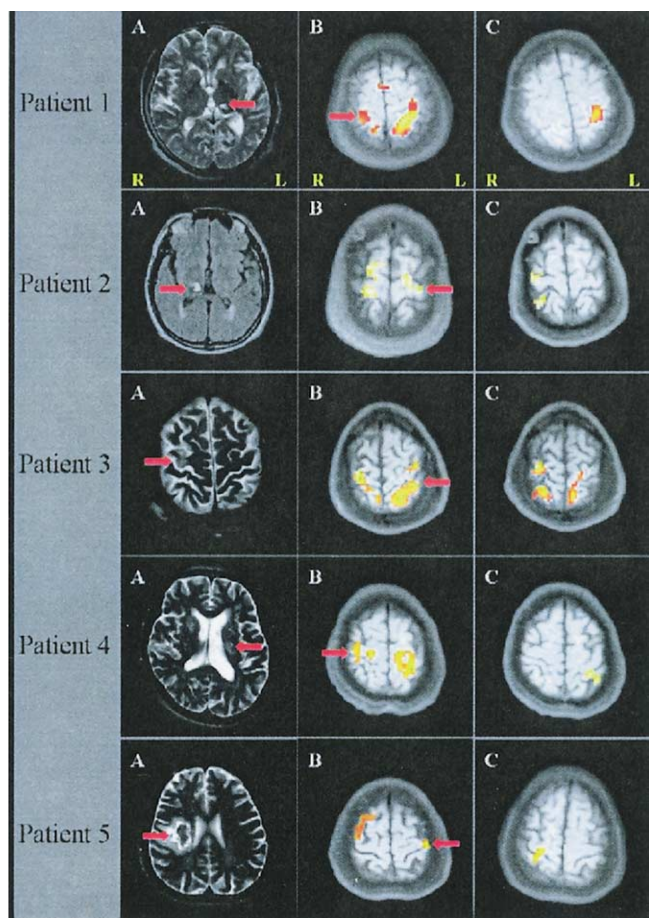

Fig 2. (A) T2-weighted diagnostic brain MR images. (B) Before VR, all patients showed bilateral activations at SM1s. (C) After VR, the aberrant bilateral or contralesional SM1 activity disappeared in patients 1, 2, 4, and 5 and decreased in patient 3 during the affected movement. The arrow indicates (A) lesion and (B) activation site. Abbreviations: L, left; R, right.

Table 2: Motor Function Test Scores

Subject	BBT VR Group	BBT Control Group	FMA VR Group	FMA Control Group	MFT VR Group	MFT Control Group
Pretest						
1	31.0	26.0	55.0	51.0	25.0	23.0
2	21.0	16.0	50.0	53.0	19.0	16.0
3	19.0	7.0	41.0	49.0	14.0	16.0
4	35.0	28.0	49.0	50.0	20.0	25.0
5	24.0	31.0	60.0	60.0	21.0	26.0
Mean	26.0	21.6	51.0	52.6	19.8	21.2
SE	3.0	4.4	3.2	2.0	1.8	2.2
Posttest						
1	38.0	23.0	62.0	53.0	28.0	23.0
2	24.0	19.0	59.0	56.0	20.0	17.0
3	22.0	8.0	49.0	50.0	17.0	17.0
4	39.0	20.0	55.0	56.0	24.0	23.0
5	27.0	30.0	65.0	60.0	23.0	26.0
Mean	30.0	20.0	58.0	55.0	22.4	21.2
SE	3.6	3.6	2.8	1.7	1.9	1.8
Z score*	2.3†		2.2†		2.3†	

*Mann-Whitney *U* test and Wilcoxon 2-sample rank sums test for 2 independent samples.
†$P<.05$ (2-tailed).

pare the differences in scores between the groups. The Wilcoxon signed-rank test for 2 related samples was used to evaluate differences in the laterality index scores. Significance level was set at .05.

RESULTS

Clinical and Demographic Data

Table 1 represents clinical and demographic information. The mean age of the control group did not differ significantly from that of the VR group (Wilcoxon test, $P>.05$). There were no significant differences in the prevalence of stroke risk factors and lesion sites (topography) between the control and VR groups (Fisher exact test, $P>.05$). T2-weighted diagnostic brain MRI results are shown in figure 2A. The Mann-Whitney *U* test revealed no significant differences in age and stroke-onset duration between the groups ($P>.05$), indicating that both groups had comparable clinical characteristics. All subjects were right handed (see table 1).

Motor Function

Table 2 shows the mean motor function tests scores for the pre- and posttest between the groups. Wilcoxon tests revealed that there was no significant difference between the groups for the BBT, FMA, and MFT scores at the pretest ($P>.05$), indicating that both groups had similar motor function to begin with. An independent Wilcoxon signed-rank test for the respective change of each mean BBT, FMA, and MFT score at the posttest revealed that there was a significant difference between the groups ($P<.05$), indicating that VR improved motor recovery. The control group did not show any significant change (see table 2). The mean AOU and QOM scores in the MAL increased from 0 to 1 (never used) to 3.6 (almost normal-use range, 2.9–4).

Cortical Reorganization

Table 3 compares the number of significantly ($P<.001$) activated voxels in SM1 between the pre-VR and post-VR conditions of the VR-trained group. The Wilcoxon signed-rank test showed that after the intervention all subjects significantly increased ipsilesional activation at the SM1 area during affected elbow movement ($P<.05$) (see table 3, fig 2C). However, the mean laterality index was not affected by the intervention during unaffected elbow movement ($P>.05$).

The laterality index ratio during affected movement increased from .08 to .90 ($P<.05$) while the ratio during unaffected movement remained unchanged (see table 3). Prior to VR, increased contralesional PMC, and contralesional or ipsilesional SMA and SM1 were bilaterally activated during affected movement. After VR, only ipsilesional SM1 was activated.

DISCUSSION

Our hypothesis was that cortical reorganization and motor recovery would improve after VR. As anticipated, cortical activation by the affected movements was reorganized from contralesional (before VR) to ipsilesional (after VR) activation in the laterality index. Our results were consistent with studies using transcranial magnetic stimulation and functional MRI that have demonstrated decreased ipsilateral

Table 3: Number of Significantly ($P<.001$) Activated Voxels in Primary Sensorimotor Cortex (SM1) of the VR-Trained Group

Subject	Affected Elbow MT Contra-SM1 Pre	Affected Contra-SM1 Post	Affected Ipsi-SM1 Pre	Affected Ipsi-SM1 Post	Affected LI Pre	Affected LI Post	Unaffected Elbow MT Contra-SM1 Pre	Unaffected Contra-SM1 Post	Unaffected Ipsi-SM1 Pre	Unaffected Ipsi-SM1 Post	Unaffected LI Pre	Unaffected LI Post
1	49.0	31.0	21.0	0.0	0.4	1.0	92.0	54.0	0.0	0.0	1.0	1.0
2	15.0	8.0	15.0	0.0	0.0	1.0	64.0	65.0	0.0	0.0	1.0	1.0
3	25.0	42.0	142.0	22.0	−0.7	0.3	91.0	73.0	0.0	0.0	1.0	1.0
4	163.0	112.0	103.0	0.0	0.2	1.0	42.0	29.0	0.0	0.0	1.0	1.0
5	21.0	15.0	8.0	0.0	0.5	1.0	11.0	20.0	0.0	0.0	1.0	1.0
Mean	54.6	41.6	57.8	4.4	0.1	0.9	60.0	48.2	0.0	0.0	1.0	1.0
SE	27.7	18.6	27.2	4.4	0.2	0.1	15.4	10.2	0.0	0.0	0.0	0.0
Z score†					−2.0*						0	

NOTE. SM1 activation of the nonparetic hand movement in the VR group was used as a comparison for motor activation of the paretic hand movement.[26]
Abbreviations: Contra-SM1, contralesional primary sensorimotor cortex; Ipsi-SM1, ipsilesional primary sensorimotor cortex; LI, laterality index; MT, movement; Pre, before virtual reality (VR); Post, after VR.
*$P<.05$ for 2-tailed.
†Wilcoxon signed-rank test.

cortical activation and increased contralateral activation as function of intensive practice of the affected limb.[8,18] In fact, the laterality index value of the subjects with stroke after the VR intervention was comparable to that of healthy elderly (.84).[18] Our finding demonstrates a shift in cortical organization of the affected limb from the ipsilateral hemisphere to the contralateral hemisphere after the VR intervention. It is plausible that VR may have motivated and promoted practice-dependent reorganization resulting from the increased AOU of the affected limb in relevant motor tasks. This may have led to an improvement of the cortical reorganization of the affected limb in the cerebral cortex.[8,18] Although the neural mechanisms associated with practice-dependent motor recovery are not clearly understood, it has been suggested that intensive use of the affected limb could generate effective synaptic potentiation, thereby increasing practice-induced neuroplasticity.[8]

Prior to VR training, among the principal ROIs activated, our analysis was focused on SM1 activation because of statistical significance and the consistent cortical activation pattern at the SM1 area in all subjects. There was increased contralesional PMC and contralesional or ipsilesional SMA activation and bilateral SM1 cortical activation during affected movement. After the intervention all subjects except patient 3 showed ipsilesional SM1 activation. During the unaffected movement, the majority of subjects showed relatively consistent ipsilesional SM1 activation before and after VR training. According to the laterality index analysis, before VR training, all subjects showed a laterality index score of close to zero, indicating bilateral cortical organization. After VR, they showed a laterality index score of close to 1, suggesting normalized ipsilesional cortical reorganization while inhibiting the aberrant contralesional cortical activation during affected elbow movement. These results are in agreement with previous neuroimaging studies,[18,23] which found increased ipsilesional SM1 activity in stroke patients who received rehabilitation. We also found that VR-induced neuroplasticity was closely related with hand motor recovery. According to the MAL interview, the functional hand motor gains from VR were transferred to real-world situations including spontaneous use of the affected hand for picking up a glass of water or buttoning a shirt. These activities were not possible prior to VR.

Presumably, a learning by imitation model has been suggested to induce an imitation-dependent organization around the motor cortex through "mirror" neural networks.[11,22] In an experimental study with a monkey, mirror neurons in the PMC were highly activated when the monkey observed a target movement and reproduced it.[22] It is believed that the mirror neuronal networks receive sensory feedback associated with joint kinematics or motor imagery of the observed motor behavior and then store the target motor memory in the PMC by a mechanism known as resonance (or mirror).[24] Similarly, it remains possible that the subjects who received sensory feedback during the VR training learned to internalize the motor representation of the target motor behavior using a notion of learning by imitation. This might have facilitated use-dependent cortical plasticity, which was primarily reorganized at the SM1 area. Consequently, this might result in the recovery of motor function and overcoming learned nonuse.

Further study may be necessary to determine if the VR-induced brain and motor recovery can be reproducible in a larger population of people with similar motor impairments, and to determine whether the VR technique is superior or more cost-effective than other stroke rehabilitations.

CONCLUSIONS

This novel study investigated VR-induced cortical reorganization and associated functional motor recovery in chronic stroke patients. We found that VR-induced cortical reorganization at the SM1 while inhibiting aberrant cortical activation, perhaps enhancing functional recovery in the affected limb. The clinical implication is that VR may be used as augmented chronic stroke rehabilitation.

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Suppliers

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