Virtual Reality–Induced Cortical Reorganization and Associated Locomotor Recovery in Chronic Stroke

An Experimenter-Blind Randomized Study

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Background and Purpose—Virtual reality (VR) is a new promising computer-assisted technology to promote motor recovery in stroke patients. VR-induced neuroplasticity supporting locomotor recovery is not known. We investigated the effects of VR intervention on cortical reorganization and associated locomotor recovery in stroke patients.

Methods—Ten chronic stroke patients were assigned randomly to either the control group or the VR group. VR was designed to provide interactive real-life practice environments in which practice parameters can be individualized to optimize motor relearning. Laterality index (LI) in the regions of interests (ROIs) and locomotor recovery were measured before and after VR using functional MRI (fMRI) and standardized locomotor tests, respectively. The *t* test and nonparametric test were performed to compare the mean differences at $P<0.05$.

Results—There was a significant difference in the interval change in the LI score for the primary sensorimotor cortex (SMC) between the groups ($P<0.05$), indicating that VR practice produced a greater increase in LI for the control group. However, the interval changes in the other ROIs were not significantly different ($P>0.05$). Motor function was significantly improved after VR ($P<0.05$).

Conclusions—Our novel findings suggest that VR could induce cortical reorganization from aberrant ipsilateral to contralateral SMC activation. This enhanced cortical reorganization might play an important role in recovery of locomotor function in patients with chronic stroke. This is the first fMRI study in the literature that provides evidence for neuroplasticity and associated locomotor recovery after VR. **(*Stroke*. 2005;36:1166-1171.)**

Key Words: gait ■ magnetic resonance imaging ■ rehabilitation

Stroke is a leading cause of chronic physical disability such as locomotion.[1] Underutilization of the affected limbs has been theorized to occur after neurological insult.[2] That is, a stroke patient's attempt to use the affected limb is often unsuccessful because of the sensorimotor impairments that are secondary to the underlying pathophysiology during the initial period of diaschisis.[2,3] The initial sensorimotor impairments may lead to long-term deconditioning of sensorimotor function in affected limbs because patients tend to compensate with the intact limbs rather than attempting to use the involved limbs.[2,3] Both no intervention and an intervention that emphasizes compensatory mechanisms contribute to underutilization of the impaired limb, resulting in suppression of the cortical representation of the affected limb and further inhibition of its use.[4]

To improve motor function, neurorehabilitations have been used, but the outcomes were variable and little is known about the neural mechanisms of locomotor recovery.[5,6] Only 2 studies represent the efforts to investigate the therapy-induced cortical reorganization and associated locomotor recovery.[7,8] However, its practicality and generalizability in the clinical setting warrant further studies because of labor-intensive cost-effectiveness and compliance issues.[6] Virtual reality (VR) is an interactive and enjoyable intervention that has recently shown to improve upper extremity motor function in adults with chronic hemiparesis with greater compliance.[9] VR has the capability to create a virtual rehabilitation scene in which the intensity of practice and sensory feedback can be systematically manipulated to provide the most appropriate, individualized real-life motor retraining.[9,10] However, the neural mechanisms supporting VR-induced locomotor recovery have never been investigated. The purpose of this study was to investigate cortical reorganization and locomotor recovery. Our premise was that VR might promote practice-dependent plasticity, thereby enhancing locomotor recovery.

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TABLE 1. Clinical and Demographic Characteristics

Subject	Age/Sex	Stroke Risk Factors	Site of Stroke (topography)	Time from Stroke to fMRI Date (mo)
VR Group				
1	55/M	Cig, HTN	Rt thalamic hemorrhage	25
2	54/M	HTN,Cig	Rt corona radiata hemorrhage	16
3	64/M	Cig, NIDDM, Hchol	Rt corona radiata infarct	13
4	45/F	HTN,NIDDM	Rt corona radiata hemorrhage	15
5	55/M	Hchol, Cig	Rt corona radiata infarct	22
Mean	54.60			18.20
Standard error of measurement	3.01			2.27
Control Group				
1	56/F	HTN, Hchol	Lt corona radiata infarct	12
2	55/M	Cig,HTN	Rt corona radiata hemorrhage	35
3	45/M	Hchol, Cig	Lt corona radiata infarct	13
4	66/F	HTN, NIDDM	Rt corona radiata infarct	22
5	51/M	Cig, HTN	Lt thalamic hemorrhage	15
Mean	54.60			19.40
Standard error of measurement	3.44			4.27

NIDDM indicates noninsulin-dependent diabetes mellitus; HTN, hypertension; Afib, atrial fibrillation; Hchol, hypercholesterolemia; cig, cigarette smoking.

Methods

Subjects

Ten stroke patients with hemiparetic stroke (6 men; mean age 57.1±9.8 years) were recruited. Inclusion criteria were: (1) $\geq$1 year after first stroke; (2) plateau in the maximum motor recovery after a conventional neurorehabilitation; and (3) the ability to extend $>60°$ at knee. Exclusion criteria were: (1) severe spasticity (modified Ashworth's scale >2) or tremor; and (2) severe visual and cognitive impairments. Informed consent was obtained from all subjects before the study, which was approved by a human subjects committee. Patients were assigned randomly to either the control group or the VR group. The control group did not receive any intervention, whereas the intervention group received the VR training. Routine clinical examinations determined the presence of stroke risk factors (Table 1).

Procedure

A procedural checklist and the standardized verbal instructions were used to ensure the uniformity of procedures during clinical and functional MRI (fMRI) testing. The investigators, unaware of the study, administered the assessment and intervention.

Motor Function

The locomotor function was determined by the standardized functional ambulation category (FAC) and modified motor assessment scale (MMAS; walking item only). The FAC is designed to examine the levels of required assistance during a 15-m walk without considering any assistive device used. There are 6 categories, ranging from 0 (nonambulatory) to 5 (normal).[11] The MMAS is a performance-based measure that was purported to assess motor function. Each item is scored on a scale from 0 (unable to stand or walk) to 6 (walk up and down 4 steps). The reliability and validity for the FAC and MMAS are well established.[11,12]

Functional MRI

Before neuroimaging, the patient's body parts, including head, pelvis, and hip, were secured with straps and trunk immobilizer specially designed to control successfully any undesirable translational movement during fMRI. All patients practiced the prepared motor task in supine position in the magnetic resonance (MR) scanner. The task involved a sequential knee flexion–extension with a predetermined angle of 60° at a metronome-controlled frequency of 0.5 Hz (cycle of 15 seconds of rest and 15 seconds of stimulus). A reference tape was placed on the scanner to indicate the corresponding angle position. Then the patient was instructed to touch the target line with the apex of the patella so as to control the amplitude of the movement. To control the consistency of rate, angle, and movement artifact, the 2 investigators carefully monitored the movement using a remote digital camera. If a mismatch between the target and actual performance or if any movement artifact was observed, the test was repeated.

Image signals were acquired using the echo planar imaging (EPI) sequence in accordance with the blood oxygenation level–dependent (BOLD) technique. A 1.5T MR scanner (Vision; Siemens) with a standard head coil was used. For the anatomic base images, 20 axial, 5-mm-thick, T_1-weighted, conventional spin echo images were obtained with a matrix size of 128×128 and a field of view (FOV) of 210 mm, parallel to the bicommissure line of the anterior commissure–posterior commissure. The EPI BOLD-dependent T2-weighted fMRI images in the transverse plane were acquired over the same 20 axial sections for each epoch, producing 1200 images for the entire cerebrum using the parameters: TE (echo time) 60 ms; TR (repetition time) 3000 ms; FOV 210×210 mm; matrix 64×64; voxel dimensions 4×4×4; and thickness 5 mm. A mask was applied to the imaging data such that any voxel variation in signal intensity $>5\%$ during the control period was discarded to remove large vessel contributions.[13,14] fMRI data were analyzed using SPM-99 software (Wellcome Department of Cognitive Neurology, London, UK) running under the MATLAB environment (Mathworks). Statistical parametric maps were obtained and voxels were considered significant at a threshold of $P<0.05$, corrected. The functional images were realigned and then smoothed by an 8-mm Gaussian filter before statistical analysis. Predetermined regions of interest (ROIs) were bilaterally drawn around the primary sensory cortex (S1), the primary motor cortex (M1), the primary sensorimotor cortex (SMC), the premotor cortex (PMC), and the supplementary motor area (SMA) because the areas have been reported to have neuroplastic recovery potentials.[14,15] S1 was defined as the postcentral gyrus and M1 the volume of cortex that included the posterior half of the precentral gyrus (including the anterior bank of the central sulcus). SMC was defined as the combination of S1 and M1, and PMC

A. Stepping up/down B. Sharkbait C. Snowboarding

Figure 1. VR exercise games. A, Stepping up/down; B, Sharkbait; C, Snowboarding. Reprinted with permission from IREX, JesterTek, Inc.

included the anterior half of the precentral gyrus as well as the anterior bank of the precentral sulcus. SMA was limited to the cortex on the medial wall of the hemisphere, extending from the top of the brain to the depth of the cingulate sulcus, including the dorsal bank of the cingulate sulcus. The posterior boundary was halfway between the extension of the central and precentral sulci onto the medial surface, and the anterior boundary was defined by the vertical line drawn from the anterior commissure.[16]

Because of a large within-subject variability in the BOLD signal, a normalized index, the laterality index (LI), was used to determine any shift in the symmetry of cortical activation between the 2 hemispheres for the ROIs as a function of intervention.[13,14] This index is expressed as $(C-I)/(C+I)$, where C is the active voxel count for the ROIs in the hemisphere contralateral to the leg performing the movement and I is the active voxel count for the corresponding region in the hemisphere ipsilateral to the performing leg. The possible range is from -1.0 (all activity in the ipsilateral hemisphere) to $+1.0$ (all activity in the contralateral hemisphere).[14,15]

Variations in movement parameters during imaging such as force[17] and frequency[18] may affect brain activation patterns. We attempted to control the basic parameters such as body position, rate, and amplitude of the movements from the preset to post-test to keep them as constant as possible. Furthermore, to ensure consistency of our fMRI measure, the test–retest reliability was established by determining the capability of our fMRI method to measure voxel counts activated in the contralateral hemisphere to the affected limb for the ROIs. Five age-matched patients with right hemiparesis participated in this reliability test. As per the fMRI protocol, a patient was positioned supine and instructed to perform the predetermined knee flexion–extension. Two investigators monitored any movement artifact using a remote digital camera. The reliability test was performed on 2 separate occasions, ≈30 days apart. All testing conditions, including the testers, procedures (ie, consistent instruction, calibration, knee position, rate, testing sequence, joint angular position), time of day and interval, and testing environment, were as consistent as possible. Individual LI data collected from the 2 points of time were then computed and used for analysis. Intraclass correlation coefficient ($ICC_{2,k}$) tests were calculated to determine the test–retest reliability. Correlations between the repeated measures were excellent, with $ICC_{2,k}$ ranging from 0.83 to 0.99 ($P<0.0001$).

VR Intervention

The IREX VR system requires a television monitor, a video camera, cyber gloves and virtual objects, scenes, and a large screen. The video camera was used to capture and track movement and immerse the patient inside VR scene. The system offers an alternative to the problems existing in other VR systems because the patients do not require head-mounted displays, data gloves, or other peripheral devices that connect to the computer. This enables them to move freely about in the real world while allowing manipulation of the virtual objects and navigation in the 3D virtual world.[10,19]

As illustrated in Figure 1, the Stepping up/down and the Sharkbait, Snowboard games were interfaced with virtual environments to facilitate range of motion, balance, mobility, stepping, and ambulation skills. The VR tasks were designed to focus on the development of the different skills as described previously, with each game programmed to exercise 1 or multiple aspects of trunk, pelvis, hip, knee, and ankle movement.[19] A detailed description of the VR intervention protocol is available in the Appendix (available online at http://www.strokeaha.org).

Augmented feedback about knowledge of results (KR), such as error rate and amount of lifting weights (resistive force), and knowledge of performance (KP), such as movement quality, was provided at the end of each game. Because these motor tasks require complex intersegmental coordination and were initially difficult for some patients because of synergistic patterns, we made a series of modifications in the VR parameter, including speed of a stimulus and resistive force based on their performance and progress.[10,19] As their ability to perform the exercise increased, we gradually challenged them by either increasing resistive force (ie, adding weights) or speed of the stimulus. Initially, a high frequency (>90%) of augmented KP or KR feedback was gradually lessened as performance improved.[10] Each game was played 5×, and depending on a game, within each game, there were 3 levels of 88 to 131 opportunities to perform the exercise. The intervention was given for 60 minutes per day, 5× per week for 4 weeks.

Statistics

$ICC_{2,k}$ test was used to determine the test–retest reliability of the fMRI measure. Mann–Whitney test was used to compare age and stroke onset duration between the groups. The Mann–Whitney-Wilcoxon (MWW) 2-sample rank sum test was used to compare the differences in FAC and MMAS and independent sample t test for LI scores for the predetermined ROIs at $P<0.05$.

Results

Motor Function

The locomotor function was determined by the standardized FAC and MMAS (Table 2). A separate MWW test revealed that there was significant difference in the interval changes in the FAC and MMAS scores between the groups ($P<0.05$), suggesting that the VR-trained group performed significantly better as a function of the intervention.

Cortical Reorganization

As shown in Figure 3, t test revealed that among the predefined ROIs, only LI in the primary SMC area was statistically significant ($t=-2.60$; $P<0.05$). This finding indicated that the LI in the VR group compared with the control group showed a significant increase as a function of the VR intervention (Figures 2 and 3). However, the interval cortical activation changes in the other ROIs were neither significantly different within the control group nor between the groups ($P>0.05$).

Discussion

The hypothesis of the study was that cortical reorganization and motor recovery would improve after VR. As anticipated, cortical activation by the affected movements was reorganized from ipsilateral (before VR) to contralateral (after VR) activation in LI. The LI value after VR was comparable to the

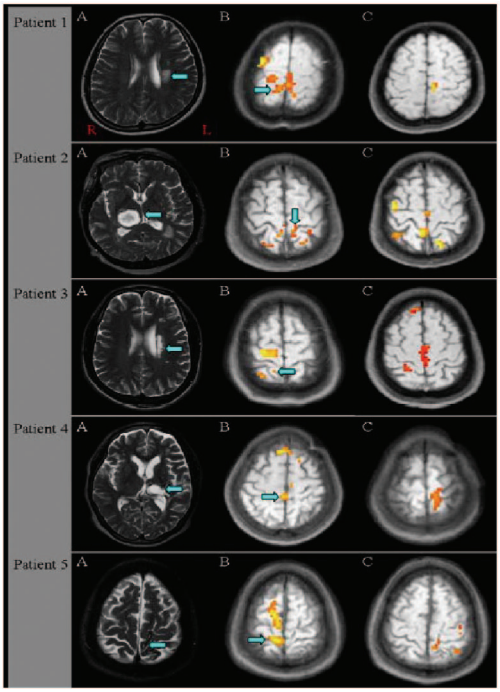

Figure 2. A, T2-weighted diagnostic brain MRI images. The arrow indicates the lesion site. B, Before VR, all patients showed the ipsilateral activations (arrow) at primary SMCs. C, After VR, the ispilateral SMC activity (arrow) disappeared (patient 1, 2, 4, and 5) or decreased (patient 3) during affected knee movement.

findings in normal subjects.[20] Our findings were consistent with the previous studies that showed a shift in the SMC activation from ipsilateral or bilateral to contralateral after intensive use of the paretic limb in adults.[4,7,8,14] This finding may support 2 possible neural mechanisms: (1) a migration from contralateral to ipsilateral (or bilateral) activation; or (2) reversion.[21] The former may involve cortical migration from the affected hemisphere to the intact hemisphere or neurons after diaschisis and during the course of natural recovery.[21] The latter may result from intensive use or practice-dependent neuroplasticity.[4,7,8,14] Although the neural mechanisms associated with practice-dependent motor recovery are not clearly understood, repetitive practice of the affected limb may generate effective synaptic potentiation, thereby increasing practice-induced neuroplasticity and associated motor improvement.[22] Certainly our neuroimaging findings suggest that VR could induce cortical reorganization of the neural locomotor pathways. This cortical reorganization was associated with notable gain in locomotor function. In fact, a majority of VR-trained subjects in the post-test questionnaire reported spontaneous uses and confidence of the affected limb during daily activities such as transferring in/out of the bathtub, putting on trousers, and stepping onto a step or curb. These functions were not possible before VR.

Among the other ROIs, the contralateral M1 and SMA activations may control the contralateral distal and the proximal musculature, respectively.[11] Interestingly, before VR, the bilateral M1s, ipsilateral SMC, and ipsilateral SMA were activated. Such a marked signal increase in the areas is never observed in normal brains, albeit a subtle signal increase may be noticed.[23] Thus, the present data combined with our previous finding[24] in adults with hemiparesis suggest that the ipsilateral corticospinal tract is responsible, in part, for the pathophysiology of such an aberrant cortical activation.

Before the VR intervention, the ipsilateral SMA, along with the bilateral M1 and SMC, was activated but was suppressed after VR. These activations are part of a distributed motor network, and the presence of this network has been suggested in adults with stroke during affected finger-

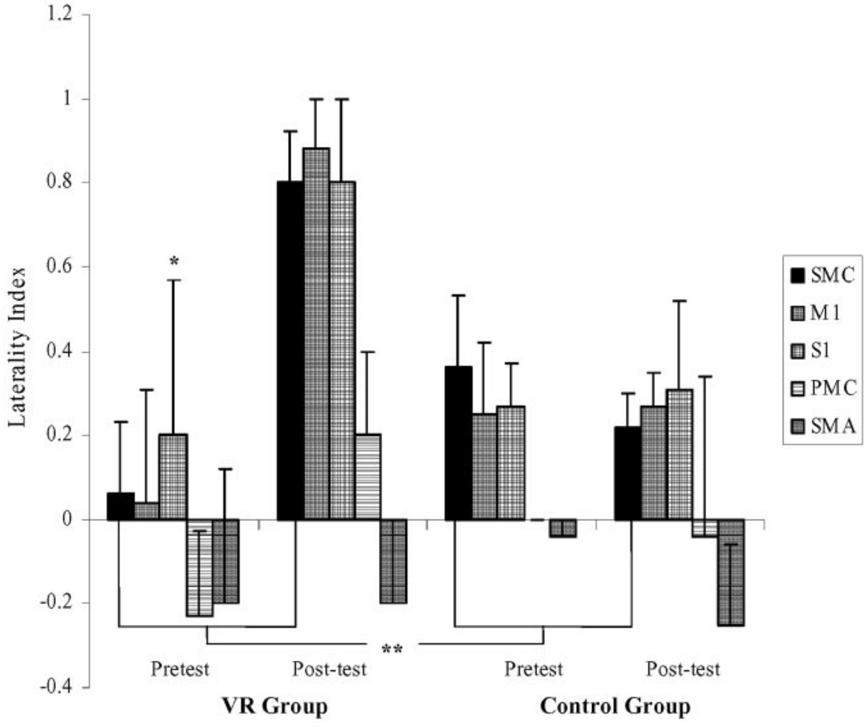

Figure 3. LI for each ROI during affected knee movement. *SEM; **independent sample *t* test revealed that the VR group compared with the control group showed significantly greater group mean LI difference (post-test–pretest) for SMC ($P<0.001$), suggesting that VR may be effective to induce measurable neuroplastic changes.

TABLE 2. Locomotor Function Test Scores

	FAC		MMAS	
VR Group	Pre-VR	Post-VR	Pre-VR	Post-VR
1	4	5	4	5
2	3	4	4	4
3	4	5	4	5
4	2	3	3	4
5	4	5	4	5
Mean	3.40	4.40	3.80	4.60
Standard error of measurement	0.04	0.04	0.20	0.24
Control Group	Pre-VR	Post-VR	Pre-VR	Post-VR
1	3	3	4	4
2	4	4	4	4
3	4	4	5	5
4	4	5	4	4
5	4	4	5	5
Mean	3.80	4.00	4.40	4.40
Standard error of measurement	0.20	0.32	0.24	0.24
Z-score	−2.45*		−2.45*	

*A separate MWW test revealed that there was significant difference in the interval changes (difference between post-test and pretest scores) in the FAC and MMAS scores between the groups (*P*<0.05), suggesting that VR produced significant improvement in gait.

tapping task.[25] Increased demand on the multiple areas in this network has been noticed with imposition of a complex motor task in normal subjects[26] as well as in the present study during a simple motor task in the adults with hemiparesis. In fact, a majority of subjects initially appeared to require much effort to use the paretic limb for a simple motor task, which was evident in their facial expression and increased association reaction during our clinical locomotor tests. As they advanced in their motor skills associated with locomotion, their mirror movement pattern gradually decreased or movement became less effortful. This finding lends considerable support to the notion that VR-induced motor recovery may be accompanied by normalization of the laterality and disappearance of the inappropriate involvement of the unaffected hemisphere motor network.

Despite our efforts to control the movement parameters during fMRI, a less-controlled aspect of the movement might have changed during the tests.[27] We conducted test–retest reliability to ensure consistency of our fMRI measure and found an excellent reproducibility of the fMRI measure. Therefore, it is unlikely that movement changes, if they occurred, would be able to account for all cortical activation observed in fMRI.

Conclusions

VR may have contributed to positive changes in neural organization and associated functional ambulation. Clinically, VR may be used as augmented chronic stroke rehabilitation. This study invites further investigations to explore the effectiveness of VR over other neurorehabilitations and whether VR-induced neuroplastic change is unique or comparable to those of other neurorehabilitations.

Appendix I

VR Intervention

Joint kinematics during each VR task was recorded by sophisticated camera technology that captures the patient's "mirror" image on a computer monitor. This allows the patient to see movement and interact with the objects in a virtual environment. Force exerted by the patient was manually estimated by determining the weights of hand/cuff weights or the conveyor box to provide feedback. The 3 virtual environments that were interfaced with the games include Stepping up/down, Sharkbait, and Snowboard. Specifically, Stepping up/down (Figure 1A) simulates functional stepping up and down the stairs. The exercise is designed for hip flexion and extension motions, weight shifting and bearing, and single limb stance balance, all of which are important neuromotor control elements in the swing phase of gait cycle. The patient was instructed to flex the hip to the target angle for a successful leg raise, which is visually guided by the virtual therapist (woman as appeared in Figure 1A) climbing 1 step. If the patient can flex the leg to >50% of the target angle but not all the way, the attempts increments but the successes does not. Lowering the hip to <25% of the target angle will reset and readjust the cycle and prepare for the next leg raise. Lateral or side-stepping activity can be incorporated in this VR environment. The output reports generated from this game included the number of matches versus misses of the target angle, as expressed in kinematic joint angle. Additional resistive force using weights or Theraband were added as the patient progressed to improve muscle strength and endurance.[18]

Sharkbait (Figure 1B) simulates deep sea diving with sharks, electric eels, and other sea creatures. The patient was instructed to capture as many stars as possible while avoiding sharks and eels. If the patient contacts a shark, he or she is virtually swallowed and spat out. If the patient contacts an electric eel, he or she is virtually shocked and is unable to move for a short time. This VR exercise involves weight shifting, stepping, protective strategy, and squatting. The patient can navigate sideways and vertically in this virtual underwater scene, and this mode requires actual stepping forward and backward or side to side. This exercise can be combined with reaching or other functional activities of daily living. The patient was instructed to face sideways for forward/backward stepping and forward (toward the camera) for lateral stepping. In addition, the stepping strategy can be practiced by manipulating the center of gravity outside the base of support with foam, rocker, and wobble board. A variation can be made to simulate a ski tuck position with instances of rising up (knee and hip extension) consistent with gaining air over a hill jump. The intersegmental control and strength of the knee and hip joint extension musculatures are important during stance phase of the gait cycle. The output reports generated from this game included the number of captures versus misses of the stars. The information was graphically presented to the patient as KR along with additional KP feedback at the end of each trial when appropriate. As with other VR exercises, the number of repetitions, direction, and speed of the stimulus (ie, stars) were customized on the basis of the patient's baseline performance.[18]

Snowboard (Figure 1C) simulates real snowboarding down a narrow slope. The patient was instructed to go over as many jumps as possible while avoiding all other obstacles. The patient can control motion by shifting weight to either side. When the game starts, the patient is asked to step sideways until he or she is centered over the snowboard to make navigation easier. The patient plays the game either facing the camera or sideways to the camera as if on a real snowboard. This mode requires actual stepping forward and backward or side-to-side weight shifting. In the forward/backward stepping task, the patient was asked to take a step with 1 leg to move right, then step backward to move left. In the lateral stepping task, the patient was asked to step laterally to the left to move left, and then step right to move right. Specific trunk (thoracolumbar) motions of flexion, extension, lateral bending, and rotation can be facilitated in this mode. The output reports generated from this game included the number of jumps versus misses.[18]

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Correction

In the June issue of *Stroke*, the article "Virtual Reality-Induced Cortical Reorganization and Associated Locomotor Recovery in Chronic Stroke: An Experimenter-Blind Randomized Study" by You et al[1] should have noted in the footnote that Sung H. You, Sung Ho Jang, and Yun-Hee Kim contributed equally to this work. The authors apologize for this error.

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[1] *[Correction for Vol 36, Number 6, June 2005. Pages 1166–1171.]*

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