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Mechanisms of Neural Reorganization in Chronic Stroke Subjects after Virtual Reality Training

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***Abstract*—This study investigates patterns of brain reorganization in chronic stroke subjects after two weeks of robot-assisted arm and hand training in virtual reality (VR). Four subjects were studied with event-related fMRI while doing simple paretic hand finger movements before (double baseline) and after training. Bilateral hand movements were recorded and used to provide real-time feedback to subjects during scanning to eliminate performance confounds on fMRI results. The kinematic parameters of each movement were also used in the general linear model with the BOLD signal to investigate training-induced changes in neuromotor coupling. Univariate analysis showed an increase in BOLD signal in the ipsilesional hemisphere in two subjects and a decrease in activity in the other two subjects. Seed voxel based functional connectivity analysis revealed an increase in connectivity between ipsilesional motor cortex and bilateral sensorimotor cortex during finger movements in all four subjects. Hemispheric laterality index values showed a tendency to decrease reflecting a reduction in the over-dominance of the contralesional hemisphere. The study is novel in terms of 1) tracking finger movement during a motor task in the scanner, 2) monitoring motor performance during the experiment and 3) giving online visual feedback of subjects' movement. This pilot study introduces a novel approach to study neural plasticity by combining measures of regional intensity, inter-regional interactions (using functional connectivity analysis and hemispheric laterality index), and modulation in the strength of neuromotor coupling.**

I. Introduction

STROKE is a leading cause of disability in the United States [1], with about 700,000 stroke cases occurring annually and a survival rate of about 54%. Though many therapeutic interventions for arm and hand rehabilitation exist, the neural mechanism of recovery remains poorly understood. However, given the possible relation between functional recovery and brain reorganization [2, 3], characterizing neural mechanisms of recovery is important for developing more effective, neuroscience-grounded, rehabilitation interventions. This study investigates neural reorganization of brain activity in four chronic stroke subjects after 2-weeks of intensive training of their affected upper extremity using New Jersey Institute of Technology robot-assisted virtual reality (NJIT-RAVR) adaptive training system, which was developed to re-train reaching, grasping, finger individuation, and coordination.

There are two main challenges in longitudinal fMRI designs. The first relates to the confound that altered motor performance has on interpreting changes in neural reorganization. The second relates to the effects that inadvertent movements (such as mirror movement) may have on interpreting changes in neural reorganization. To overcome these challenges, we provided subjects with online visual feedback of their finger movement through a virtual environment and analyzed their kinematics offline to identify and exclude from analysis those trials with inadvertent movements. While several studies have examined upper limb movements with online visual feedback in fMRI [4-6], none has analyzed finger movement in the scanner while providing online visual feedback using hand models in a virtual environment simulation.

Neural plasticity has been described as increases in BOLD signal in the ipsilesional sensorimotor cortex and higher excitability of the ipsilesional motor cortex, some other studies reported a decreases in sensorimotor activity [8]; this decrease can be interpreted as a possible increase in efficiency, especially if the sensorimotor cortex excitability was higher early in the recovery phase than the average activity in healthy controls [7] . Studies of the lateralization of brain activity has also demonstrated over-dominance of the contralesional hemisphere initially after stroke [3, 8], and that recovery associates with re-lateralization of motor cortical activity toward the ipsilesional hemisphere [8-14].

Based on this literature, we hypothesized that training in VR would be associated with (1) decrease in sensorimotor activity (increased efficiency), (2) increase in functional connectivity between the ipsilesional motor cortex and premotor-parietal regions within and between hemispheres, and (3) reduction in the over-dominance of the contralesional hemisphere.

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II. Methods

A. Subjects

Four right-handed[15] subjects, with hemiparesis due to stroke (2 right-hemiplegics, 2F, mean age 61.5 ± 7 years, range: 55-70 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.

TABLE I: SUBJECT INFORMATION

Age/ Gender	Time Since CVA	CVA side L/R	CMA	CMH	Ashworth scale	Infarct Location
63/ F	53	L	6	4	2	Left Occipital and Parietal infarct
70/F	96	R	7	5	1	Right corona radiata infarct
55/M	41	R	5	4	5	Left thalamic nuclei infarct
58/M	132	L	5	4	7	Right frontal temporal and parietal infarct

CVA (cerebrovascular accident); CMA/H (Chedoke-McMaster motor assessment arm/hand scale. L = left and R = right. F= female M = male. Ashworth scale is the summation of elbow, wrist and finger flexors scores.

B. Motor Training

Subjects trained using the NJIT- (RAVR) rehabilitation intervention 3 hrs/day for 8 days. Activities included reaching for and interacting with stationary and moving virtual targets and objects in 3D space (Fig. 1A-B). NJIT-RAVR intervention has been detailed in previous publications [16, 17].

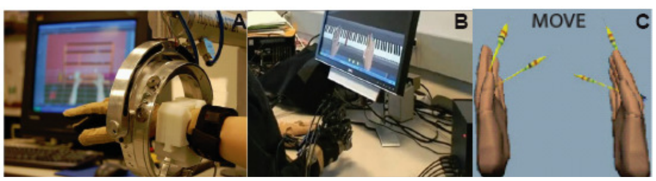

Fig. 1. A. B. Robotic arm, data glove and force-reflecting hand system used in the VR therapy. C. VR feedback during the fMRI movement task

C. Outcome Measures

Outcome measures were taken two weeks before the start of training (pretest 1), a day before start of training (pretest 2) and a day after the end of training (posttest).

Clinical: Jebsen Hand Function Test (JHFT) and Wolf Motor Function Test (WMFT).

Kinematic: Angular velocity, movement smoothness, finger individuation, and range of motion.

Neurophysiological: The functional task during fMRI was a simple whole-hand flexion movement of the paretic hand. The objective was to compare changes in brain activity between the posttest and pretests 1 and 2, under the same task performance constraints. Real-time visual feedback was provided by streaming data from an MRI-compatible data glove (5DT) to actuate VR hand models displayed on a screen. The first and second arrows (Fig. 1C.) assured that subjects kept a consistent start position and movement amplitude across trials. The angle of the second arrow was pseudo-randomly switched between 25 and 45 degrees (relative to the start position) to reduce the monotony of the task. Non-paretic hand data was also recorded to identify any trials with mirror movement. This VR-fMRI integration was described in a previous publication [18].

D. Behavioral Measures

Kinematics of the task in the scanner were analyzed to test for movement consistency across the three fMRI testing days. The peak movement angle (angular excursion) and movement time on each trial were submitted to a 1-way repeated measures analysis of variance (ANOVA) for the three days. Statistical threshold was set at 0.05. This analysis was not done for Subject 2 due to data corruption.

E. fMRI Data Acquisition

FMRI data was acquired in a 3-T Siemens Allegra head only scanner with a Siemens standard head coil. High resolution structural images (TR=2000 ms, TE= 4.38, 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, 156 volumes) were taken for each subject. All functional scans used a T2* weighted echo planar imaging sequence. FMRI data were preprocessed and analyzed using SPM5.

Each subject's functional volume was realigned to the first volume and co-registered with the structural image. All images were normalized to the SPM5 Montreal Neurological Institute template, and functional images were smoothed with an 8 mm Gaussian kernel.

F. fMRI Data Analysis

For each subject, a general linear model (GLM) was created using the canonical hemodynamic response function (hrf) [19]. Prior to creating the models, movement kinematics was 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 GLM. 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. To achieve a temporally accurate convolution of the BOLD events with the hemodynamic response function, movement onset and duration were modeled in the GLM on a trial-by-trial basis.

Movement>rest contrast were created between the posttest and the mean of the pretests 1 and 2 to identify regions with increased (posttest > pretest 1 & 2) and decreased (pretest 1 & 2 > posttest) activity

Functional Connectivity: Using the contrast move>rest we chose the most active cluster (8 voxels seed) in the ipsilesional motor cortex (precentral gyrus) as a region of interest (ROI). The time series of this cluster was extracted, normalized (zero-averaged) and used as a regressor into a second GLM for the same subject. Functional connectivity maps (temporal correlation between the seed voxel and the sensorimotor cortices) were compared between the three testing days.

TABLE II
WMFT AND JHFT CLINICAL SCORES IMPROVEMENT

Pt.	WMFT Pre	WMFT Post	JHFT Pre	JHFT Post	WMFT % change	JHFT % change
1	192.6	158.5	158.3	138.7	17.7	12.4
2	45.3	34.7	121.1	83.9	23.5	30.7
3	55.9	50.1	96.6	87.2	10.5	9.7
4	98.1	95.0	159.7	143.8	3.2	9.9

Parametric modulators: The mean angular velocity was modeled on a trial-by-trial basis as parametric estimator in the GLM. Contrasts between days were created comparing posttest to pretests 1 & 2. This measure represented changes in neuromotor coupling.

Laterality index: We used the LI toolbox [20] to calculate the number of significantly active voxels in each hemisphere and obtained a laterality index for each of the three testing days (pretest 1 & 2, and posttest) based on the equation $LI = \frac{(C-I)}{(C+I)}$ where C stands for the number of active voxels in the specific region contralateral to the moving paretic hand and I represents active voxels in the specific region ipsilateral to the moving paretic hand.

III. Results

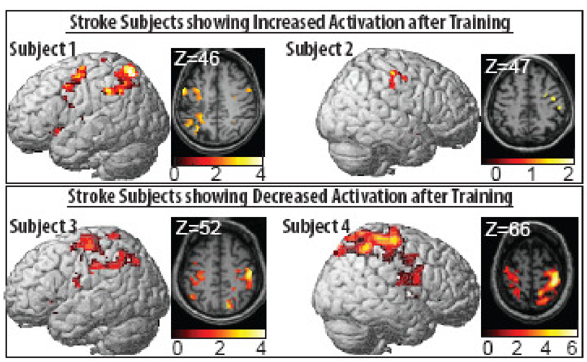

Fig. 3. Sensorimotor activation changes after training.

WMFT and JHFT scores show clinical improvements for the 4 subjects (Table II). Statistical comparisons of kinematics (movement duration, angular excursion, and angular velocity) revealed that for the most part, movements between testing days were relatively consistent, barring several exceptions. Movement duration was shorter during posttest in Subject 1 (F=62, p<0.001), Subject 3 (F=5.1, p=0.012), and Subject 4 (F=67, p<0.001). Angular excursion was significantly different between days for Subject 4 (F=77, p<0.0001). Angular velocity was different between days for Subject 1 (F=29.75, p<0.0001) and Subject 3 (F=13.27, p<0.0001,). The fMRI univariate data analysis showed increase in activation post- vs. pretest for Subjects 1 and 2, and a decrease in activation for Subjects 3 and 4 (Fig. 3). Functional connectivity between the ipsilesional motor cortex and bilateral sensorimotor areas during finger movement significantly increased in all four subjects (Fig. 4). Subjects 2 and 3, with subcortical lesions, show a smaller increase in bilateral connectivity of the bilateral

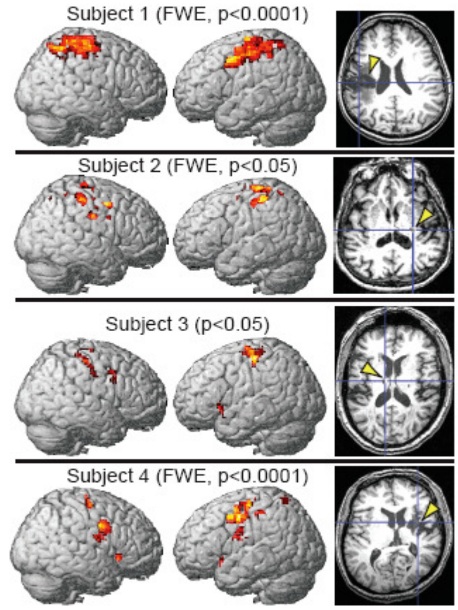

Fig. 4. Difference in functional connectivity maps after training (posttest) vs. before training (pretests 1 &2) for the four subjects.

sensorimotor cortex with the ipsilesional motor cortex relative to the other subjects. Further analysis showed that these 2 subjects have a more extensive bilateral neural network that was functionally connected with the ipsilesional motor cortex before training and this connectivity decreased after training. Analysis of the laterality index LI (Fig. 5) revealed that 3 of the 4 subjects

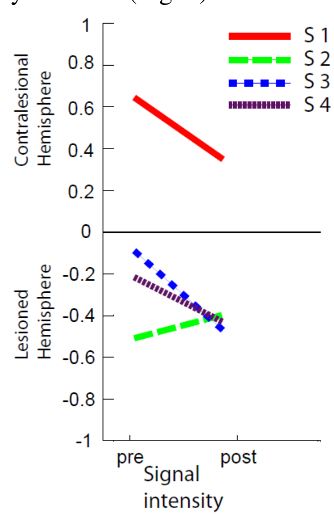

Fig. 5. Change in laterality index values after training. ‘Pre’ is the mean of pretest 1 and pretest 2, while ’post’ represents the posttest.

showed a shift toward greater involvement of the ipsilesional motor cortex. Subject 1's LI change indicates a reduction in the dominance of contralesional hemisphere after training, while subjects 3 and 4 show an increase in ipsilesional hemisphere activity. Subject 2 showed an opposite, though weaker, effect.

Analysis of neuromotor coupling revealed no significant change in correlation between BOLD and angular velocity for Subjects 1 and 2. Subjects 3 and 4 showed an increase in correlation between BOLD signal and angular velocity in (posttest vs. pretests 1 + 2) localized in the ipsilesional sensorimotor cortices (Fig. 6. left).

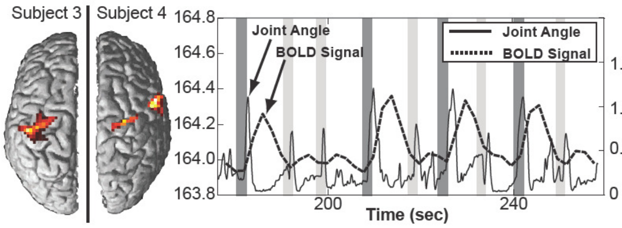

Fig. 6. Left. Difference in correlation between mean angular velocity and BOLD signal for the contrast posttest > pretests 1 & 2 for Subject 3 and 4. Right. Time traces of finger movement (solid) and the BOLD signal (dashed).

IV. Discussion

Our data demonstrate functional and clinical improvement in arm-hand function following 2 weeks of robot-assisted VR therapy. Neural reorganization was characterized as changes in recruitment of the ipsilesional sensorimotor cortex, increases in bilateral sensorimotor cortex connectivity with the ipsilesional motor cortex, and a general change in the interhemispheric balance. To summarize, the data suggests that comprehensive analyses need to be considered when studying brain reorganization.

Two of the subjects showed a decrease in the extent and intensity of the activity in the ipsilesional sensorimotor cortex. Moreover, they improved less in the WMFT and JHFT than the other 2 subjects (Table II). Finally, these 2 subjects showed change in the strength of correlation (neuromotor coupling) between bilateral motor cortex activity and subjects' mean angular velocity after training (Fig. 6). This suggests a possible relationship between the impairment level and the pattern of brain reorganization.

The differences in movement kinematics (i.e. performance) might have direct effects on the BOLD activity and this relationship should be considered when interpreting results from longitudinal intervention-based designs. Subjects 3 and 4 showed decreases in BOLD amplitude after training (Fig. 3.), which on the one hand may be explained as an increased efficiency of neural activity in these areas (per published literature), but may also be related to changes in movement kinematics. The increases in activity noted for Subjects 1 and 2 could be confounded by slight differences in motor performance which are noted by some of the kinematics variables. However, these same individuals did not show significant changes in neuromotor coupling, suggesting that the efficiency of processing in sensorimotor areas may not have changed after training for these individuals.

In summary, this study investigated mechanisms of neural plasticity after VR-based therapeutic intervention in stroke subjects. A critical component to this work was to integrate bilateral tracking of hand movement during fMRI acquisition and to model kinematics on a trial-by-trial basis in the GLM. This allowed us to regress out variance in activation that might be accounted (and confounded) by inadvertent motion (i.e., mirror movement) or inconsistent performance across fMRI sessions. In addition, this methodology allowed us to quantify neural plasticity at the level of regional changes in intensity of activation (Fig. 3.), inter-regional interaction changes (Fig. 4, 5), and changes in neuromotor coupling (Fig. 6).

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