Virtual reality-augmented rehabilitation for patients in sub-acute phase post stroke: a feasibility study

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ABSTRACT

Upper extremity (UE) rehabilitation is of utmost importance to the achievement of full inclusion and functional independence. Traditionally presented as well as technology-based therapeutic interventions have produced measurable changes in motor function and motor control but fall short of major reductions in disability. Animal models of stroke suggest that the first two weeks to one month post stroke may be a critical time period of increased brain plasticity. This study shows the feasibility of adding one hour of intensive robotic/virtual reality (VR) therapy to on-going rehabilitation in the acute phase of recovery post-stroke. All five of the subjects made substantial improvements in Upper Extremity Fugl-Meyer Assessment (UEFMA) scores (mean improvement = 6 points (SD=2)) as well as improvements in Wolf Motor Function Test (WMFT) time (average decrease = 41% (SD=35) after training with more consistent changes in the proximal arm portions of the WMFT and the UEFMA as well as in upper arm kinematics. Maps of cortical excitability indicate an increase in both the area of activation and the volume of activation of the first dorsal interosseous (FDI) muscle after a two-week training period.

1. INTRODUCTION

People post-stroke exhibit paresis of the upper and lower extremities. When a person with paresis uses their upper extremity (UE) for purposeful movement, the paretic movements differ from normal movements in that they are slower, less accurate, have delayed or reduced force, and are uncoordinated in terms of magnitude and timing of the movement (Sathian, et al, 2011). Upper extremity rehabilitation is of utmost importance to the achievement of full inclusion and functional independence. Plasticity-mediated therapies have evolved from the concepts of adaptive activity-based neuroplasticity, task- oriented motor training and the need for high doses of repetitive practice. One approach to plasticity-based therapy the combination of of virtual reality and rehabilitation robotics has offered new promise for enhanced outcomes for upper extremity rehabilitation. The literature shows a progression of articles, from feasibility studies, to small clinical trials and a recent Cochrane review suggesting the potential benefits of using virtual reality for rehabilitation. However, to date, the best efforts of groups studying technology-based therapeutic interventions have produced measurable changes in motor function and motor control, but fall short of major reductions in disability.

The prevalence of studies in people with chronic CVA stands in contrast to animal models of stroke that suggest that there may be a critical time period of increased brain plasticity (Biernaskie, Chernenko, and Corbett, 2004). During the first month post stroke the peri-infarct cortex regains responsiveness to cortical afferents with accompanying increased dendritic spine morphogenesis and axonal sprouting (Krakauer, Carmichael, Corbett, and Wittenberg, 2012). Rats trained with daily sessions of reaching showed significant gains in forearm reaching

ability when the training was started 5 or 14 days post infarct but not 30 days post infarct (Biernaskie et al, 2004). The important question these studies raise is whether early intensive training might be more effective.

To date only three studies have focused on task-based upper extremity interventions in persons in the acute period post-stroke. A study by da Silva Cameirão of persons less than thirty days after CVA, identified faster recovery of upper extremity motor function in patients performing virtually simulated rehabilitation activities (VSRA) for twenty minutes in addition to a standard inpatient rehab program (SIRP) when compared to controls who performed a dose matched increase in activity beyond their SIRP (da Silva Cameirão, Bermúdez i Badia, Duarte, and Verschure 2011). This finding is important because it establishes the feasibility of using VSRA in addition to an SIRP very early after a CVA.This study alsosuggests that VSRA might have an effect during the acute stages of stroke. The second study using a more traditionally presented intervention (CIMT) did not demonstrate additive benefits (Dromerick et al, 2009). A third study of subjects less than six months after a stroke by Levin demonstrated no difference in motor outcomes when comparing a group of subjects performing a nine session, VSRA program and a control group performing a dose-matched program of traditionally presented UE rehabilitation.

This study was designed to test the feasibility of training patients between one and eight weeks after a CVA using our intensive robotically facilitated, virtually simulated UE motor intervention (Adamovich et al, 2005; Fluet et al, 2012; Merians et al. 2011; Merians, Poizner, Boian, Burdea, and Adamovich, 2006). The intervention utilizes several innovative, technology based approaches such as simulated activities that adapt in difficulty based on patient performance, robotic antigravity support and trajectory shaping as needed and the virtual magnification of small active finger movements into meaningful virtual activities. We hypothesized that this intense, targeted intervention , would be tolerated well by persons in the first weeks following a stroke that were participating in inpatient or outpatient rehabilitation concurrently. In addition a battery of clinical, kinematic and neurophysiologic testing was performed to provide data to establish sample sizes for controlled studies of alternative treatments which will occur in the future

2. METHODS

2.1 Subjects

We performed feasibility testing with a single group of seven persons Subjects were recruited from a consecutive sample of patients from the in-patient department of a suburban hospital. After initial screening by the department's physician, a physical therapist screened subjects based on the following criteria: Inclusion: 1) within 2 months post stroke, 2) between the ages of 30 and 80, 3) partial active shoulder flexion, or abduction, elbow extension and wrist extension against gravity. 4) trace extension at the fingers (detected visually) that can be reproduced several times in a minute. Exclusion: 1) severe spasticity (Modified Ashworth 4), 2) cognitive deficits rendering them unable to follow three step commands or attend to task for at least ten minutes 3) hemi-spatial neglect rendering them unable to interact with an entire twenty four inch screen, 4) proprioceptive loss that rendered a potential subject unable to interact with a virtual environment without looking at their hand 5) unstable blood pressure and oxygen saturation responses to activity. A separate screening and consent process for the motor mapping evaluation using transcranial magnetic stimulation was conducted.

2.2 System

The NJIT RAVR System consists of an instrumented glove combined with the Haptic Master (Moog-NCS, The Netherlands), a 3 degrees of freedom, admittance controlled (force controlled) robot. Three more degrees of freedom (yaw, pitch and roll) are added to the arm by using a gimbal for pronation/supination (roll). A three-dimensional force sensor measures the external force exerted by the user on the robot. In addition, the velocity and position of the robot's endpoint are measured allowing the robotic arm to act as an interface between the participants and the virtual environments (described below), The Haptic Master allows one to program the robot to produce haptic effects, such as spring, damper and constant force and to create haptic objects like blocks, cylinders and spheres as well as walls, floors, ramps and complex surfaces. The users interface with the Haptic Master via a forearm trough that extends through the gimbal, allowing for partial support of the weight of the arm as needed, while maintaining the ability to produce and measure pronation and supination movement. The NJIT TrackGlove System consists of a CyberGlove™ (Immersion, USA), an instrumented glove for finger angle tracking, and a TrackStar™ three-dimensional magnetic tracking system (Ascension Technologies).

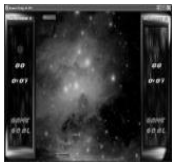
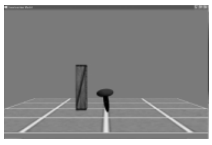
2.3 Simulations

We have developed a suite of simulations for training shoulder, elbow, wrist and finger movements using the Virtools software package (Dassault Systemes). See Table 1 for descriptions of simulations that were used and the movement constructs they target.

2.4 Training Protocol

To explore the feasibility of adding an hour of intense upper extremity activity to a standardized in-patient rehabilitation program, subjects received 60 minutes of training using the robot and the virtual reality gaming simulations in addition to their on-going in/out-patient physical, occupational and speech therapy for 5 days/week for two weeks.

Table 1. *Training Simulations.*

Simulation	**Training Goal**	**Game Play**	**Progression**	**Metric**
Monkey Business 	Improve pinch grip force modulation	Subject controls monkey with pinch grip. Height that monkey jumps is in proportion to force of pinch grip. Subject makes the monkey jump to branches of varying heights.	Height of jumps are increased and time between jumps decreases as time to successful completion of the task decreases	Time/Accuracy
Space Pong 	Finger Extension modulation	Subject plays a pong type game against the computer. Subject moves the paddle to the right by opening their fingers and to the left by closing them.	Decrease proportion of subject movement (finger extension) to paddle movement if accuracy does not improve with practice. Increase proportion when accuracy increases.	Accuracy
Space Ship 	Decreased arm elevation	Subject intercepts targets and avoids obstacles by piloting a spaceship with shoulder abduction and flexion movements	Increase target speed and obstacle density Increase workspace size as AROM increases.	Score increases with targets hit and obstacles avoided. Workspace size
Hammer 	Decreased Shoulder-Elbow Isolation	Subject hammers peg into the floor by pronating his forearm. Robot holds hammer stable over the target peg.	Decrease proportion of subject movement (pronation) to hammer movement as time to hammer pegs decreases	Peak pronation range of motion Time to hammer pegs
Piano 	Decreased Finger Individuation	Subject plays scales and simple songs. Each key is cued and the finger to press it designated.	Algorithm sets fractionation target based on performance. Utilize CyberGrasp™ to teach movement pattern if subject does not respond to algorithm.	Fractionation Time to press keys
Cups 	Decreased Shoulder-Trunk Isolation	Subject attaches virtual hand to virtual mugs and places them on virtual shelves in a 3-d workspace.	Increase volume of workspace as time to place cups on shelf decreases Recalibrate workspace weekly	Time to place nine cups on shelf Reaching trajectory length
Falling Objects 	Shoulder flexion towards midline	Subject moves a cursor to catch targets as they fall from the top of the screen. Targets drop centered on subject or in intact hemispace.	Recalibrate workspace weekly.	Time to catch 100 targets Height of targets caught

2.5 Outcome Measures

We examined the ability of our clinical, kinematic and neurophysiological measures to document changes in motor performance and neural control in persons having had their strokes less than thirty days prior to testing and training.

Clinical Assessment. Subjects were tested one day prior to training (pre-test) and one day after training (post-test). A physical therapist performed the Wolf Motor Assessment Function Test, (Wolf et al, 2001) and the upper extremity portion of the Fugl-Meyer Assessment (Fug l-Meyer 1979).

Kinematic Assessment. Pre/Post kinematic measures included changes in distal kinematics, proximal kinematics and force. All measures were collected with the patients seated with their trunks supported and their hands resting on a table. Performance for all tracing tasks was measured following a single familiarization trial which was not scored.

Finger angles were collected using a Cyberglove™ (Immersion, USA). **Finger range of motion** was measured as the difference between all of the joint angles with the fingers in a relaxed / flexed position and the joint angles of all of the fingers actively extending the fingers as much as possible. Larger differences indicated better active finger extension range of motion.

Finger Trace is the ability to modulate active finger extension and flexion between zero and eighty percent of max extension, measured by having the subject flex and extend their fingers to control a cursor tracking a sine function wave (period=.15 Hz, duration of 1 cycle≈ 6 seconds).Lower root mean square error values indicate better performance.

Shoulder and elbow coordination was measured by having the subject trace a figure of eight (diameter of each circle approximately 20cm, vertex at the midline of subject's body) on a low friction table top with their paretic hand. Lower root mean square error values indicate better performance. Hand path was measured with a TRACKSTAR™ three-dimensional magnetic tracker (Ascension, USA).

Pinch force was measured with an ATI Nano17™ force sensor (ATI Industrial Automation, USA). Pinch grip force is measured as the maximum voluntary force a subject can exert on a force sensor held between their paretic thumb and index finger, given two trials. Higher numbers indicate stronger pinch grip**.**

Pinch Trace is the ability to modulate pinch grip force between zero and eighty percent of max pinch force, measured by having the subject vary pinch grip force to control a cursor tracking a sine function wave (period=.15 Hz, duration of 1 cycle≈ 6 seconds). Lower root mean square error values indicate better performance.

TMS Mapping. Subjects were tested one day before the therapy onset and one day after the end of the therapy. Subjects were seated with their arm, hand, and fingers comfortably secured in a brace to limit motion. To assure spatial TMS precision, each subject's high-resolution anatomical MRI was used to render a 3D cortical surface that is co-registered with the subject's head for frameless neuronavigation (Advanced Neuro Technology). Transcranial Magnetic Stimulation (TMS) (Magstim Rapid2, 70mm double coil) was used to determine the hotspot for the contralateral first dorsal interosseus muscle (FDI). The TMS coil was held tangential to the scalp with the handle posterior 45° off the sagittal plane.Following determination of the FDI hotspot resting motor threshold (RMT) was calculated as the minimum intensity required to elicit MEPs >50μV in the FDI muscle on 50% of 6 consecutive trials (Butler, AJ et al. 2005). Surface electromyographic activity (EMG, Delsys Trigno, 2 kHz) was recorded from the FDI muscles of the limb contralateral to stimulation side.

Mapping was conducted on the lesioned hemisphere of both subjects. All mapping was performed with the subject at rest and stimulation intensity set to 110% of the determined RMT (Ngomoa, S et al. 2012) . A 10x10cm area surrounding the motor hotspot was marked using the neuronavigation software to provide consistent map boundaries. TMS pulses were delivered within the bounds with special attention paid to regions surrounding the hotspot territory. Real time visual feedback of the MEP time traces and neuronavigated coil position provided to the experimenter during testing maximized the map information obtained by allowing for increased density of points in excitable and border regions, with less attention given to far-away non-responsive areas (Niskanen, E et al. 2010). For each stimulation point we computed the following measures: (i) MEP as the peak-to-peak amplitude of the EMG signal 20-50ms after the TMS pulse, and (ii) background EMG, calculated as the EMG signal in the 50ms interval before the TMS pulse (2nd order Butterworth filter, 5-250 Hz band-pass, full-wave rectified, 20Hz low-pass envelope). A threshold of 50uV was used to identify MEPs from background EMG (Ngomoa, S et al. 2012). To allow comparisons across maps and sessions, MEP amplitudes and stimulation points were interpolated to a 10x10 cm mesh of 5 mm resolution centered on the M1 hotspot, using cubic surface interpolation (Borghetti, D et al. 2008, Weiss, C et al. 2012.) Outcome measures include map area and vlume, determined using double trapezoidal integration of the interpolated maps.

3. RESULTS

Table 2. *Initial Subject Characteristics.*

Subject	Age	Gender	Time Since CVA(Days)	Hemiplegic side	Lesion Location	Initial UEFMA total
1	67	M	47	R	MCA	43
2	62	F	39	R	Pons	25
3	57	M	6	R	Pons	30
4	57	M	5	L	Parietal	24
5	74	M	12	L	Cerebellum	55

We performed feasibility testing with a single group of seven persons. Training was initiated an average of 20 (SD=18) days post stroke. Average subject age was 63 (SD=6.3) years (See Table 2) Please note that subject numbers correspond to the same patients for Tables 2-5 and Figure 1. One subject discontinued the protocol after being screened but prior to testing due to a second stroke, a second discontinued training after one intervention session due to fatigue. The five remaining subjects completed 8 sessions of sixty to seventy five minutes of interaction with a set of 6 simulated rehabilitation tasks in addition to completing 100% of their scheduled SIRP treatment sessions (90 minutes of PT, 90 minutes of OT and 45-90 minutes of ST per day) during the study period suggesting feasibility of this protocol. No adverse events were noted during VR training. All five subjects were able to understand the simulations well enough to participate without extensive instruction in spite of a relatively simple screening process (one three step command). Two of the seven subjects could not participate in TMS testing due to a history of seizures and three more did not consent to participating in this aspect of the study.

All five subjects made substantial improvements in UEFMA scores (Mean improvement = 6 points (SD=2)) as well as improvements in WMFT time (average decrease = 41% (SD=35) (See Table 3). In addition, four of the 5 subjects completed at least one functional activity from the WMFT battery at posttest that they were unable to perform at pre-test. Four of the 5 subjects demonstrated improvements in clinical measures of proximal upper extremity function. In addition 3 of the 5 subjects demonstrated improvements in the kinematic measure of proximal UE coordination (Table 3). Distal UE function did not change as consistently. Only one of the five subjects demonstrated across the board improvements in all six measurements. Four of the five subjects demonstrated improvements in maximum pinch force. Four subjects demonstrated improvements in distal UEFMA. (Table 4). Fig. 1 shows the changes in the distribution of the pattern of activation for the first dorsal interosseous (FDI) muscle acquired pre and post training for two the two subjects from this sample that were appropriate for, and consented to TMS testing . The MEP maps indicate an increase in both the area of activation and the volume of activation after training.

Table 3. *Proximal UE Clinical and Kinematic Measurements.*

Subject	WFMT Proximal (sec)		UEFMA Proximal		Figure 8 RMSE	
	Pre	Post	Pre	Post	Pre	Post
1	11.5	13.46	35	40	3.66	2.67
2	135.7	15.7	28	33	17.39	1.49
3	128.03	30.51	19	23	1.15	1.39
4	376.14	251.43	10	17	11.36	13.72
5	12.67	11.51	23	24	1.35	0.55

4. DISCUSSION

This study demonstrated the feasibility of adding one hour of intensive robotic/VR therapy to on-going rehabilitation in the acute phase of recovery post-stroke. Five of the seven the subjects were able to participate in and tolerate the additional intensive activity with two of these five subjects beginning the robotic/VR therapy 5 days and 6 days post-stroke. Subjects vital sign responses to intense upper extremity activity remained stable throughout training. Subjects were supervised during 100% of the training sessions which is common for patients in the earliest phases of rehabilitation after a stroke.

Table 4. *Distal UE Clinical and Kinematic Measures.*

Subject	WMFT Distal (sec)		UEFMA Distal		Finger Range (deg)		Finger Trace RMSE		Pinch Force Max (N)		Pinch Trace RMSE	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	671.06	672.63	20	24	23.55	10.8	4.69	7.21	19.91	18.16	5.74	6.84
2	960.00	845.82	15	27	12.64	37.5	3.30	1.32	1.43	8.74	0.60	0.33
3	375.94	405.89	11	13	41.77	38.6	3.51	4.32	16.28	26.36	3.84	3.14
4	847.22	735.87	14	13	57.89	49.9	7.28	7.75	21.02	30.78	5.53	5.99
5	144.46	50.74	2	7	51.43	56.2	11.3	10.31	12.33	50.54	4.07	12.10

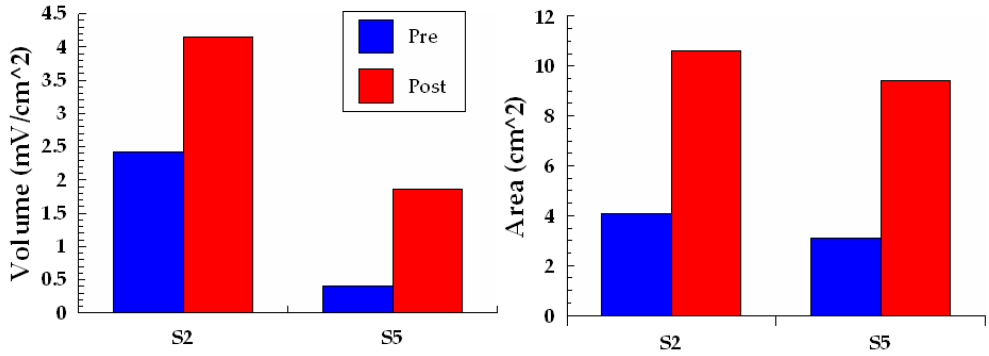


Figure 1: *Volume and Area of TMS maps of first dorsal interosseus muscle of paretic hand of two subjects (S2 and S5) measured before and after training.*

This study elucidated several important issues regarding determining the efficacy of such early intensive intervention. As a group the subjects showed a 41% change in the WMFT after the two-week training period. This change is double what we have found when training patients in the chronic phase (22%). It has been demonstrated that the effect sizes reported for several clinical measures (e.g the Frenchay, WMFT, TEMPA, ARAT, Jebsen) calculated at less than 3 months post-stroke were substantially larger than those calculated at three months or later post-stroke (Simpson and Eng, 2013). The authors speculated that the observed differences in effect sizes during this time period likely reflect the inherent neuroplasticity early after stroke. However, when subjects' outcomes were examined individually there was a noted variation in their response to treatment. Overall, there were more consistent changes in the proximal arm portions of the WMFT and the FM as well as in upper arm kinematics. Da Silva-Cameirão (2011) reported a similar response on the recovery of proximal movements in a pilot study using the Rehabilitation Gaming system in the acute phase post-stroke. This pattern of change was also noted in the kinematics of the movement. The changes in the distal clinical and kinematic measures were more varied with the exception of consistently robust changes in the maximum pinch force. The large changes in motor function, at least a portion of which will occur spontaneously, and the varied patterns of response in these subjects would suggest that large populations will be necessary to test hypotheses effectively in this population.

An important biomarker of functional recovery is the excitability of the corticospinal system (e.g., the integrity of the motor output) (Lazaridou et al, 2013; Qiu et al, 2011; Sampaio-Baptista et al, 2013). Transcranial magnetic stimulation (TMS) induced motor evoked potentials (MEP) are an established proxy of corticospinal excitability. The initial data in this feasibility study suggest that in the days following stroke, training and recovery may be associated with an expansion of the corticospinal network (area) and strengthening of corticospinal synaptic weights (volume). This said, testing corticospinal excitability using TMS in acutely ill patients can be challenging. Less than a third of our subjects (two of seven) were medically appropriate for TMS and consented to participate. Based on our participation rate, studies planning to use TMS measures to test hypotheses in subjects with acute CVA will need to recruit from large pools of potential subjects.

In this feasibility study we have shown that providing an intensive robotic/VR intervention in the early phases post-stroke and integrating it with on-going usual care rehabilitation is a definite possibility. There are multiple challenges to this type of intervention, the inherent heterogeneity of stroke, the variation in the time course of spontaneous recovery and the confounding effect of neural restitution and compensatory functional

movements. Improvements in motor performance are probably the result of several processes that occur in parallel to each other. We propose that our battery of clinical, kinematic and neurophysiological measures might be able to provide a window into the overlapping processes and help to sort out the confounding issues in the recovery of upper extremity function post-stroke.

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