Virtual reality-augmented rehabilitation in the acute phase post-stroke for individuals with flaccid upper extremities: A feasibility study

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***Abstract*— Rehabilitation of individuals with flaccid or severely affected upper extremities is challenging due to their limited motor ability and few options for therapeutic training. This initial study tested the feasibility of training individuals with severe hemiparesis using virtual reality (VR) based mirrored feedback and pinch force modulation tasks. The results demonstrated that the simulations were well tolerated early after stroke. Priming effects of the mirror tasks were suggested by increased maximal pinch force immediately after training. Furthermore, despite having no clinically observable movement distally, the subjects were able to consciously activate their muscles as shown by force traces and EMG recorded during the pinch trace task. Motor learning was also suggested by the decrease in Root Mean Square Error (RMSE) during this task. Lastly the benefits of using objective, technology based measurement tools was demonstrated by the ability of the force sensor to detect small changes in force production that could not be measured with a clinical scale of impairment.**

Keywords— Virtual reality-augmented rehabilitation, Acute phase, Stroke, Flaccid Upper Extremity

I. INTRODUCTION

Approximately 795,000 new or recurrent strokes (ischemic or hemorrhagic) occur each year in the United States [1] and stroke is the fourth leading cause of death with more than 130,000 deaths occurring yearly [2]. The incidence of mortality from stroke has been decreasing due to new technology, however this leaves a significant number of individuals with chronic disability. In fact, stroke is one of the leading causes of long-term disability in the United States [1]. Proportionally more stroke survivors are left with upper extremity impairment and disability than lower extremity. This may be due to greater emphasis placed on training ambulation for early mobilization, or due to more complex and multi-joint movements required by the upper extremity to interact with the environment [3]. In a population with mixed severity of stroke, 78% had not reached age matched upper extremity function at 3 months post stroke [4], and in severely affected individuals, only 11.6% had complete functional recovery at 6 months post-stroke [5]. Specifically with regards to hand function, grasp efficiency was found to be more impaired than proximal function at 1 year in individuals with mild to moderate stroke, with a possible explanation that alternate descending pathways such as the ipsilateral cortical and the reticulospinal tracts cannot compensate for distal fine motor control as well they can compensate for proximal motor control [6]. Recovery of the lateral corticospinal connections are needed for return of isolated distal hand function. After stroke there is an imbalance in inter-hemispheric inhibitory drive and excitability within M1 bilaterally with a resultant decrease in the affected M1 excitability. This has been associated with reduced functional recovery [7, 8]. Proof of principle studies in humans have shown that rebalancing of this excitability leads to better outcomes [8].

Unfortunately, despite research in humans and animals showing that most impairment based recovery after ischemic stroke occurs in the first 1-3 months due to spontaneous neuroplasticity that interacts with environmental factors and therapeutic training [9], the majority of studies using robotically facilitated VR are conducted in the chronic phase. Additionally, most of these studies enroll subjects with some active movement of the affected upper extremity.

To our knowledge, there have been only four groups that studied the use of upper extremity robotic training in the acute/sub-acute phase post-stroke. The results of these studies show that it is feasible to use robotic training in the acute/sub-acute phase of inpatient therapy without adverse effects. Furthermore, when robotic training was conducted in addition to regular therapy it led to

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improvements in function, impairment, and isolated active control of the upper extremity that was maintained in follow up ([10], [11], [12]). With regards to VR, three groups have studied this type of training in the acute/ sub-acute phase post stroke. Two of the three studies used dose matched controls and noted significant improvement favoring the treatment group in upper extremity function, speed, and impairment [13], [14] and [15]. All of the previous studies enrolled subjects with some active movement of the affected upper extremity.

The rehabilitation of individuals with flaccid or severely affected upper extremities is a greater challenge as these people are limited in the therapeutic tasks in which they can actively participate. As a result, they are taught compensatory techniques to accomplish necessary functional tasks. This can lead to "learned non-use" -a phenomenon in which the individual learns compensatory strategies early after stroke and thereby intentionally stops using the affected limb. Learned non-use can further hinder recovery of function in the impaired limb [16]. We hypothesize that tasks that engage the affected extremity to whatever capacity is possible may reduce the degree of learned non-use and potentially maximize the recovery process.

Priming the motor system using techniques such as somatosensory input, visual feedback, or movement-based strategies might promote plastic reorganization via intercortical rebalancing and increased ipsilesional M1 cortical excitability resulting in improved motor outcomes in individuals with severely affected upper extremities in the acute phase post-stroke [7]. One form of visual priming is VR based mirrored feedback. With this method, the subject watches a computer screen and moves their unaffected hand while a virtual hand representing their affected hand is actuated in real time by this movement. Our group has demonstrated in chronic stroke that virtual mirror training activates regions in the sensory-motor cortex similar to those activated by volitional movement of the affected hand, suggesting that this type of feedback may facilitate regions that are relevant for motor control in individuals with moderate hemiparesis post-stroke [17]. The idea of mirror training has been applied to the acute stroke population as well. In one instance, non-VR based mirror feedback training in individuals with severe upper extremity hemiparesis after acute stroke demonstrated greater distal motor recovery in the mirror therapy group as measured by the Upper Extremity Fugl-Meyer Assessment (UEFMA) [18, 19]. Another feasibility study using VR based mirror training in 6 acute stroke subjects with moderate to severe impairment found improved functional recovery of the affected arm after training. Furthermore this training was well tolerated and liked by the subjects [20]. Of interest, a study that compared VR based mirrored feedback to regular mirror therapy in a mixed population of mild to moderately impaired individuals with stroke found greater corticospinal excitability using the VR based method [21]. These data suggest that virtual mirror training may be beneficial in recruiting desired brain networks in individuals with chronic stroke, and in the case of both mirror-box and VR based training can be delivered successfully in those with acute stroke.

Priming can also be induced using movement-based strategies. One group developed a method called Active Passive Bilateral Therapy using a device that couples both hands such that active movement of the unaffected wrist produces mirror symmetric movements of the affected wrist. This training that was used in individuals with chronic stroke, starts with purely passive movement of the affected hand and progresses to active movement as able. The results showed improved and sustained upper extremity function of the affected hand, increased ipsilesional M1 excitability, increased transcallosal inhibition from the ipsilesional M1 to the intact M1 site and finally increased intracortical inhibition in the intact M1. These neurophysiological changes are associated with better motor outcomes [7].

The challenging task of rehabilitating individuals with paretic or severely affected distal upper extremities, in addition to the limited amount of prior research conducted in the acute phase using these types of techniques, led us to develop this study. Here we asked whether a combination of mirror visual and proprioceptive/movement-based priming in addition to training with a unique modulated pinch force task may be beneficial and effective for severely paretic individuals in the acute phase post-stroke. Specifically, in this early stage feasibility study, we tested the ability of training patients with severe hemiparesis (Stage 1 on Hand and Arm Impairment Inventory of the Chedoke-McMaster Stroke Assessment, [22]) using VR based mirrored feedback and pinch force modulation training. The mirrored feedback training involves two simulations: with and without the addition of an exoskeleton that passively moves the affected hand in synchrony with movement of the non-affected hand; thereby incorporating the benefits of movement-based priming to the mirrored feedback protocol. The pinch force task requires modulation of pinch force to track a sine wave. The instrumentation allows for force calibration such that small voluntary movements made by the individuals are represented as meaningful visual feedback [23]. This incorporates principles of motor learning to enhance its efficacy as a training tool. Additionally, this task is conducted with EMG recordings of hand and wrist muscles to determine any conscious activation despite the subjects' having no visible or palpable contractions distally.

We hypothesize that the combination of robotically facilitated VR-based mirror priming activities and the modulated pinch task will allow for meaningful active participation in distal motor training, despite severe paralysis that would render active participation with other training modalities impossible. We also hypothesize that this distally directed intervention will be feasible and well tolerated by these severely affected individuals in the first one to eight weeks post stroke.

II. Methods

A. Subjects

We performed feasibility testing with three subjects who were recruited from a consecutive sample of patients in an acute rehabilitation department of a suburban hospital. The three subjects were the first to meet the inclusion criteria and were selected without bias. After initial screening by the department's physician, a physical therapist screened subjects based on the following criteria: 1) within two months post stroke, and 2) between the ages of 30 and 80. Exclusion criteria included: 1) severe spasticity (Modified Ashworth of 3 or greater - [24]), 2) cognitive deficits rendering them unable to follow three step commands or attend to a task for at least ten minutes, 3) hemi-spatial neglect rendering them unable to interact with an entire twenty-four inch computer screen, 4) proprioceptive loss that renders potential subjects unable to interact with a virtual environment without looking at their hand, and 5) unstable blood pressure and oxygen saturation responses to activity. All subjects provided written consent prior to participating in this study.

Subject number 1 (S1) was a 75 year-old male six days post an ischemic stroke of the left basal ganglia and corona radiata. His UEFMA score was 2/66 [19] and his Chedoke-McMaster Stroke Impairment Inventory stage of the arm and hand were 1 at onset. Subject number 2 (S2) was a 57 year-old female ten days post-ischemic left pontine stroke. At onset, her UEFMA started at 2/66 and her Chedoke-McMaster Stroke Impairment Inventory stage of the arm and hand were also 1. Subject number 3 (S3) was a 55 year-old male nine days post ischemic stroke of the posterior limb of the left internal capsule. His UEFMA score was 2/66 and his Chedoke McMaster Stroke Impairment Inventory stage of the arm and hand were 1 at onset as well.

B. Training Protocol and Systems

All three subjects received interventional training consisting of two mirrored feedback tasks (flexion task without an exoskeleton and an extension task with an exoskeleton) and a pinch trace task. (see below for details) The training was daily Monday to Friday and lasted 45-60 minutes. In addition to this training subjects received their standardized in-patient rehabilitation program (including positioning, range of motion, supportive devices, and functional electrical stimulation to the affected upper extremity):

1- Pinch Trace Task:

Pinch force was measured with an ATI Nano17™ force sensor (ATI Industrial Automation, USA). The subjects pinched a force sensor placed between the index and thumb of the affected hand and modulated the force produced in accord with a sine wave seen on a computer screen in front of them. Subjects were observed carefully during this training and were cued as needed to only use their thumb and index finger.

Mirror Task:

2- Flexion Task Without Exoskeleton:

The subjects wore a CyberGlove™ (Immersion, USA) on the unaffected hand to track finger angles. They watched a computer screen that both shielded their hands and displayed the affected hand in neutral position in a first-person view. Subjects performed flexion/extension with their non-affected index finger. The goal of the movement was to flex their unaffected index finger to align the virtual finger to a visual line target. The virtual hand represented the affected finger in real time. Although the subjects only moved their non-affected hand, the visual feedback presented to them appeared as if they were moving their affected hand to the goal target. The number of repetitions were as tolerated with a minimum of sixty per session. This VR environment was developed with Virtools 4.0 software package (Dassault Systems) and a VRPack Plug-in that communicated with an open source Virtual Reality Peripheral Network VPRN interface [25] (see Figure 1).

Figure 1: View of the computer screen from the subject's perspective during the mirror flexion task.

3- Extension Task With Exoskeleton:
In addition to the above hardware, the subjects wore a CyberGrasp[TM] (Immersion, USA) on the affected hand that was actuated into extension by motion of the unaffected hand (e.g. the exoskeleton moved in synchrony with the unaffected hand while the subject hit a virtual ball with the this hand). This exoskeleton is lightweight, fits over the hand and assists hand extension via a system of cables affixed to the distal fingers. The amount of assistive force on the affected hand is proportional to the opening angle of the unaffected hand (see Figures 2 and 3).

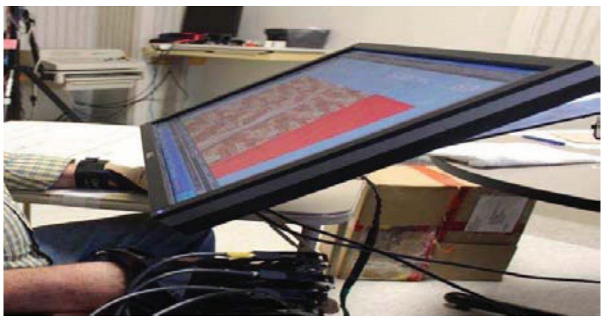

Figure 2: View of the Cybergrasp[TM] (Immersion, USA) on the affected hand.

Figure 3: View of the computer screen from the subject's perspective during the mirror extension task.

C. Outcome Measures

Clinical Assessment:

A physical therapist performed the UEFMA and Chedoke-McMaster Stroke Impairment Inventory of the Arm and Hand prior to each training session.

Pinch force and trace:

a) Pinch force measures the maximum voluntary force a subject can exert on a force sensor held between their paretic thumb and index finger, given two trials. Larger numbers indicate stronger pinch force**.**

b) Pinch trace measures the ability to control pinch force between 0% and 50% of maximum pinch force, measured by having the subject vary pinch grip force to control a cursor tracking a sine wave on a computer screen (duration of 1 cycle ≈ 6 seconds, period = 0.15 Hz). Root mean square error (RMSE) was calculated for the six-second interval and normalized by maximum force. RMSE is a measure of the difference between a sinusoid and the force values the subject actually generates. The formula is as follows:

$$RMSE = \sqrt{\frac{\sum_{t=1}^{n}(ActualForce(t) - ForceModel)^2}{n}}$$

Where Force Model is the sinusoid the subject was asked to trace, Actual Force is the force generated by the subject, and n is the number of samples collected over one trial. Smaller RMSE values indicate better performance.

Electromyographic (EMG) Assessment:

Surface EMG was recorded at 2 kHz (Delsys Trigno, Natick, MA, USA) from the First Dorsal Interosseous muscle, the Abductor Pollicis Brevis muscle, the Flexor Digitorum Superficialis muscle and the Extensor Digitorum Communis muscle of the affected upper extremity while the subjects performed the pinch force trace task. All data was imported into Matlab (The Mathworks, Inc., Natick, MA, USA) for custom processing and analysis. EMG data were filtered at 20 to 300 Hz, full wave rectified and a Root Mean Square average was applied with a 50 ms time window.

III. Results

We performed initial feasibility testing with three subjects. S1 received 7 sessions, S2 received 8 sessions and S3 received 9 sessions within a two-week period (45-60 minute sessions). Each subject trained on all three simulations during each session. All training was well tolerated without adverse side effects such as fatigue. Furthermore, the subjects were able to understand the simulations well despite having no prior instructions, and S1 showing signs of aphasia and S2 being a Spanish speaker.

Clinical Tests
S1 started with a score of 3/66 on the UEFMA at onset and this did not change over time. These scores represented reflex activity and active shoulder elevation. S1's Chedoke-McMaster arm and hand scores stayed the same throughout the training as well. S2 started with a score of 2/66 at onset and ended with a score of 11/66 on the UEFMA. These scores reflected primarily reflex activity at onset, in addition

to some proximal upper extremity active movement at discharge. S2's Chedoke-McMaster arm score improved slightly but the hand score stayed the same. S3 started with a score of 2/66 at onset and progressed to 29/66 on the UEFMA by the end of training. These scores represented reflex activity at the onset and mostly proximal movement with some partial grasp and hand opening at the end of training. S3's Chedoke-McMaster scores improved for both the arm and hand with more gains made proximally (see Table 1).

Subjects	Chedoke Arm		Chedoke Hand		UEFMA Proximal		UEFMA Distal	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
S1	1	1	1	1	3	3	0	0
S2	1	2	1	1	2	11	0	0
S3	1	5	1	3	2	21	0	8

Table 1. Clinical Measurements

Pinch Force/Trace and EMG Relationship

The maximum force the subjects could generate increased over time in days from 0.08 N on day 1 to 0.24 N on day 7 for S1, 0.10 N on day 1 to 0.34 N on day 8 for S2 and from 0.07 N on day 1 to 2.35 N on day 9 for S3 (see Figure 4).

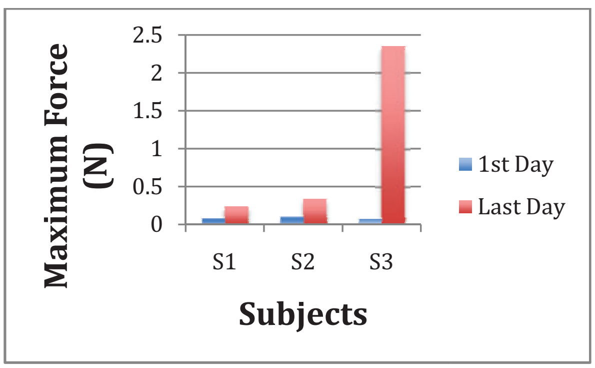

Figure 4. Maximum pinch force for the first and last day for all 3 subjects.

Additionally, all subjects demonstrated a decrease in RMSE over time. Subject 1 started at 0.49 on day 1 and ended at 0.20 on day 7. Subject 2 started at 0.29 on day 1 and ended at 0.16 on day 8. Subject 3 started at 0.21 on day 1 and ended at 0.03 on day 9 (see Figure 5).

Figure 5. Normalized RMSE over time in days for all 3 subjects.

Lastly visual inspection demonstrated that the subjects were able to modulate their active pinch force to track a sine wave displayed on a computer screen in front of them (see top of Figures 6 and 7). Despite showing no active movement in the hand, S2 showed discernable EMG activation of the APB muscle during the pinch trace task (see bottom of Figure 6). S3 demonstrated similar results (see bottom of Figure 7).

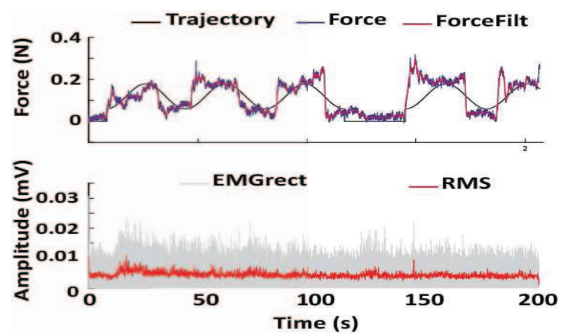

Figure 6. Top: Force Trace for S2. Bottom: EMG for the APB muscle in relation to force trace for S2.

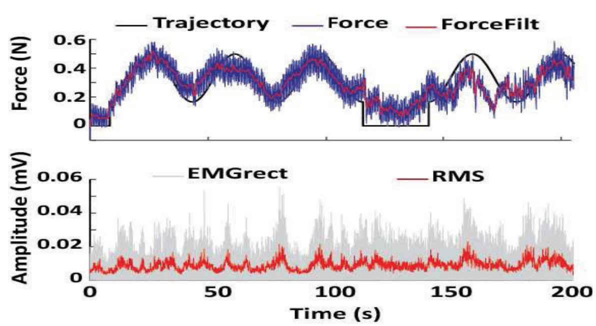

Figure 7. Top: Force Trace for S3. Bottom: EMG for the APB muscle in relation to force trace for S3.

Maximum pinch force of the affected hand was measured pre and post the mirror training task for several sessions with subject 3 and demonstrated increased force immediately after training as compared to pre training. For example maximum pinch force increased from 0.28 N pre to 0.33 N post on day 5.

IV. Discussion

This pilot feasibility study demonstrated the ability to use robotically facilitated VR based mirrored feedback and a pinch force trace task in the acute phase post stroke with three subjects who initially presented with flaccid upper extremities. All subjects tolerated the additional training well despite starting it within two weeks post-stroke when fatigue can be a factor limiting intense therapy.

In the past, VR based mirror simulations in chronic subjects have been shown to activate brain areas that partially overlap those that produce active movement of the hemiparetic arm [17]. Furthermore, a study conducted in the acute phase demonstrated that non-VR based mirror feedback therapy promotes greater recovery of the distal upper extremity at the impairment level as compared to a control group that consisted of similar training without a mirror [18]. Although there is no direct evidence, it is interesting to consider that the increase in maximal pinch force in the affected hand after the mirror training for subject 3 may have been due to an increase in ipsilesional cortical excitability induced by the mirror task. It has been shown that priming techniques may promote plastic reorganization in response to subsequent motor training and mirror therapies as well as the movement-based/proprioceptive task have been suggested as priming techniques [7, 26]. It is our hope that these interventions may lead to increased neural activity of the damaged cortex and promote more effective brain reorganization, which will perhaps facilitate optimal motor recovery.

The results from the pinch trace task suggest that even when the subjects' had no clinically measurable or observable active movement of the hand, they were able to modulate their pinch force in accord with a sine wave. This conscious activation was demonstrated by pinch force traces and EMG signals for subjects S2 and S3 (see Figures 6 and 7). This task can be modified such that minimal active movement is fed back visually as meaningful movement. A 2012 feasibility study using VR based gain scaling in the sub-acute phase post-stroke demonstrated that this method led to improved functional status in 6 subjects [27]. Furthermore it is known that increased salience of the training activity enhances neuroplasticity in both animals and humans [28]. A study in humans using TMS paired with median nerve stimulation showed that plasticity was blocked when the subjects' attention was taken away from the simulated extremity by a competing cognitive activity [29]. The visual feedback provided by the pinch trace task increases salience and motivation as the subject sees that they are actively controlling the cursor despite "not being able to move their fingers". This type of visual feedback can also affect motor learning and can be applied post-stroke [16]. Winstein [30] found that people post unilateral stroke were able to utilize augmented feedback to learn a discrete, coordinated motor task of the upper extremity.

The overall decrease in RMSE for force over the first few days with all subjects suggests that learning could in fact be occurring during our pinch force trace task (see Figure 5). However, we acknowledge that this could be due to becoming familiar with a new task rather than true motor learning. Finally, of further interest is the increase in maximum force noted over time for subjects S2 and S3 (see Figure 4) suggesting an improvement in motor output in the hand over time.

In this study, the pinch trace task was used both as a training method and an outcome tool. It demonstrated the benefits of objective, technologically based measurement tools. Clinically there was no visible or palpable movement seen in subject S2's distal hand however the force sensor was sensitive enough to measure minute maximal force generated by the subject and detect small changes over time. It has been noted previously that standard clinical measures used in clinical trials appear to have floor and ceiling effects and may not be sensitive to continuous change post stroke, whereas objective measures such as kinematics and kinetics continue to measure small changes in motor ability without these effects in either direction [31]. The superior ability to detect small changes was demonstrated by this objective measure, as the force trace was able to detect change in motor output to a greater extent than the UEFMA. The UEFMA score increased for S2 over time however this represented proximal movement; no active motor gains were seen at the hand. S3 made good gains in his UEFMA score however changes at the hand were only detectable with this clinical test once observable movement was present while the force sensor picked up change throughout.

In the future we plan to conduct a prospective, randomized controlled trial to determine whether this type of early intervention changes neural recovery differently as compared to usual acute rehabilitation. In monkeys it was shown that early, skilled training of the hand post infarct led to preservation of the intact hand in the surrounding tissue and “may direct the intact tissue to take over the damaged function” [32]. It is our hope that the skilled training of the affected hand provided by the pinch force task in conjunction with the motor priming from the mirror tasks, will also cause this type of reorganization in our subjects. The addition of TMS to our future study will be important to objectively determine any change in cortical excitability brought upon by our interventions.

V. Study Limitations

Specifically, as this is a pilot feasibility study, only three subjects were included and there were no control subjects. Our future study will be a randomized control trial that will address this limitation. Additionally, pinch force was used both as a training tool and evaluation tool hence decreasing generalizability. In the future we plan to assess other outcomes such as measuring EMG of the extensor group during maximal force production pre and post the mirror training to further determine any priming effects of this training method.

In general, there are drawbacks to conducting such a study in the acute care setting. One major drawback is the confounding factor of spontaneous recovery in the early phase post-stroke. Longitudinal studies have found that there is a non-linear, predictable functional recovery that occurs post-stroke that is independent of the dosage or type of therapeutic intervention provided. This recovery is based on processes such as “restitution of the non-infarcted penumbral areas, resolution of diaschisis, and brain plasticity based on anatomical and functional reorganization of the central nervous system” [33]. However, it has also been suggested that this phenomenon can be positively affected by the right type of training [9]. As stated previously it is our anticipation that the task specific training in conjunction with the mirrored feedback simulations, introduced during this unique time period, will enhance recovery at both the impairment and functional level, as well as positively affect neuroplasticity and motor learning.

A second challenge to the acute rehabilitation setting is the short length of stay that is seen with patients having persistent flaccidity of the affected extremities. Based on clinical experience it has been noted that due to their lack of ability to actively participate in therapeutic activities with the impaired side, these patients are often discharged to a less intense rehabilitation setting faster than someone with active motor control. For example, subject S1 was transferred to a sub-acute rehabilitation setting two weeks post admission due to limited functional improvement. As we recruit more subjects in the future, the shorter length of stay for these subjects may hinder our ability to provide sufficient amounts of training.

Finally, given the multifactorial approach with this combination training protocol, one limitation of a future RCT study is that it will be difficult to assess whether any anticipated enhanced recovery is due to the combination of interventions or a single intervention. If enhanced recovery is observed with the combination training protocol, then further studies could be designed to evaluate the clinical benefits of each training component separately.

VI. Conclusion

This initial part of the current feasibility study allowed us to demonstrate the ability to use a VR based mirror feedback simulation and a pinch trace task in the acute phase post-stroke in three people with flaccid upper extremities. These individuals are limited in the traditional therapy they can participate in and as a result are primarily taught compensatory techniques that may hinder their ability to improve at the impairment level. Furthermore lack of active finger extension early after stroke is associated with decreased prognosis to regain dexterity [34]. Our method allowed people without discernable motor ability distally to produce meaningful movement as reflected by EMG and a force modulation task. It is hypothesized that this combination training protocol based on principles of neuroplasticity and motor learning will affect neural recovery in a positive manner and help individuals with poorer prognosis. We will evaluate this with future research involving a larger scaled prospective randomized control trial.

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References

1] A. S. Go, D. Mozaffarian, V. L. Roger, E. J. Benjamin, J. D. Berry, M. J. Blaha*, et al.*, "Executive summary: heart disease and stroke statistics--2014 update: a report from the American Heart Association," *Circulation,* vol. 129, pp. 399-410, Jan 21 2014.

[2] K. D. Kochanek, J. Xu, S. L. Murphy, A. M. Minino, and H. C. Kung, "Deaths: final data for 2009," *Natl Vital Stat Rep,* vol. 60, pp. 1-116, Dec 29 2011.

[3] I. Aprile, M. Rabuffetti, L. Padua, E. Di Sipio, C. Simbolotti, and M. Ferrarin, "Kinematic analysis of the upper limb motor strategies in stroke patients as a tool towards advanced neurorehabilitation strategies: a preliminary study," *Biomed Res Int,* vol. 2014, p. 636123, 2014.
[4] N. E. Mayo, S. Wood-Dauphinee, S. Ahmed, C. Gordon, J. Higgins, S. McEwen*, et al.*, "Disablement following stroke," *Disability & Rehabilitation,* vol. 21, pp. 258-268, May-Jun 1999.
[5] G. Kwakkel, B. J. Kollen, J. van der Grond, and A. J. Prevo, "Probability of regaining dexterity in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke," *Stroke,* vol. 34, pp. 2181-6, Sep 2003.
[6] C. E. Lang, J. M. Wagner, D. F. Edwards, S. A. Sahrmann, and A. W. Dromerick, "Recovery of grasp versus reach in people with hemiparesis poststroke," *Neurorehabil Neural Repair,* vol. 20, pp. 444-54, Dec 2006.
[7] C. M. Stinear, P. A. Barber, J. P. Coxon, M. K. Fleming, and W. D. Byblow, "Priming the motor system enhances the effects of upper limb therapy in chronic stroke," *Brain,* vol. 131, pp. 1381-90, May 2008.
[8] F. C. Hummel and L. G. Cohen, "Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke?," *Lancet Neurol,* vol. 5, pp. 708-12, Aug 2006.
[9] S. R. Zeiler and J. W. Krakauer, "The interaction between training and plasticity in the poststroke brain," *Curr Opin Neurol,* vol. 26, pp. 609-16, Dec 2013.
[10] M. L. Aisen, H. I. Krebs, N. Hogan, F. McDowell, and B. T. Volpe, "The effect of robot-assisted therapy and rehabilitative training on motor recovery following stroke," *Arch Neurol,* vol. 54, pp. 443-6, Apr 1997.
[11] B. T. K. H. I. Volpe, Hogan N, Edelstein L, Diels C, Aisen M, "A Novel Approach to Stroke Rehabilitation: Robot Aided Sensorimotor Stimulation.," *Neurology,* vol. 54, pp. 1938-1944, 2000.
[12] S. Masiero, A. Celia, G. Rosati, and M. Armani, "Robotic-assisted rehabilitation of the upper limb after acute stroke," *Arch Phys Med Rehabil,* vol. 88, pp. 142-9, Feb 2007.
[13] C. W. Yin, N. Y. Sien, L. A. Ying, S. F.-C. M. Chung, and D. Tan May Leng, "Virtual reality for upper extremity rehabilitation in early stroke: a pilot randomized controlled trial," *Clinical Rehabilitation,* May 6 2014.
[14] G. Saposnik, R. Teasell, M. Mamdani, J. Hall, W. McIlroy, D. Cheung*, et al.*, "Effectiveness of virtual reality using Wii gaming technology in stroke rehabilitation: a pilot randomized clinical trial and proof of principle," *Stroke,* vol. 41, pp. 1477-84, Jul 2010.
[15] M. da Silva Cameirao, I. B. S. Bermudez, E. Duarte, and P. F. Verschure, "Virtual reality based rehabilitation speeds up functional recovery of the upper extremities after stroke: a randomized controlled pilot study in the acute phase of stroke using the rehabilitation gaming system," *Restor Neurol Neurosci,* vol. 29, pp. 287-98, Jan 1 2011.
[16] T. K. a. J. W. Krakauer, "Motor learning principles for neurorehabilitation," in *Handbook of Clinical Neurology, Neurological Rehabilitation*. vol. 110, E. B.V., Ed., ed: Elsevier B.V., 2013, pp. 93-104.
[17] S. Saleh, S. V. Adamovich, and E. Tunik, "Mirrored feedback in chronic stroke: recruitment and effective connectivity of ipsilesional sensorimotor networks," *Neurorehabil Neural Repair,* vol. 28, pp. 344-54, May 2014.
[18] C. Dohle, J. Pullen, A. Nakaten, J. Kust, C. Rietz, and H. Karbe, "Mirror therapy promotes recovery from severe hemiparesis: a randomized controlled trial," *Neurorehabil Neural Repair,* vol. 23, pp. 209-17, Mar-Apr 2009.
[19] A. R. Fugl-Meyer, L. Jaasko, I. Leyman, S. Olsson, and S. Steglind, "The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance," *Scand J Rehabil Med,* vol. 7, pp. 13-31, 1975.
[20] K. Eng, E. Siekierka, P. Pyk, E. Chevrier, Y. Hauser, M. Cameirao*, et al.*, "Interactive visuo-motor therapy system for stroke rehabilitation," *Med Biol Eng Comput,* vol. 45, pp. 901-7, Sep 2007.
[21] Y. J. Kang, H. K. Park, H. J. Kim, T. Lim, J. Ku, S. Cho*, et al.*, "Upper extremity rehabilitation of stroke: facilitation of corticospinal excitability using virtual mirror paradigm," *J Neuroeng Rehabil,* vol. 9, p. 71, 2012.
[22] C. Gowland, P. Stratford, M. Ward, J. Moreland, W. Torresin, S. Van Hullenaar*, et al.*, "Measuring physical impairment and disability with the Chedoke-McMaster Stroke Assessment," *Stroke,* vol. 24, pp. 58-63, Jan 1993.
[23] G. G. Fluet, A. S. Merians, Q. Qiu, I. Lafond, S. Saleh, V. Ruano*, et al.*, "Robots integrated with virtual reality simulations for customized motor training in a person with upper extremity hemiparesis: a case study," *J Neurol Phys Ther,* vol. 36, pp. 79-86, Jun 2012.
[24] R. W. Bohannon and M. B. Smith, "Interrater reliability of a modified Ashworth scale of muscle spasticity," *Phys Ther,* vol. 67, pp. 206-7, Feb 1987.
[25] S. V. Adamovich, G. G. Fluet, A. Mathai, Q. Qiu, J. Lewis, and A. S. Merians, "Design of a complex virtual reality simulation to train finger motion for

persons with hemiparesis: a proof of concept study," *J Neuroeng Rehabil,* vol. 6, p. 28, 2009.

[26] V. Pomeroy, S. M. Aglioti, V. W. Mark, D. McFarland, C. Stinear, S. L. Wolf*, et al.*, "Neurological principles and rehabilitation of action disorders: rehabilitation interventions," *Neurorehabil Neural Repair,* vol. 25, pp. 33S-43S, Jun 2011.

[27] S. Shiri, U. Feintuch, A. Lorber-Haddad, E. Moreh, D. Twito, M. Tuchner-Arieli*, et al.*, "Novel virtual reality system integrating online self-face viewing and mirror visual feedback for stroke rehabilitation: rationale and feasibility," *Top Stroke Rehabil,* vol. 19, pp. 277-86, Jul-Aug 2012.

[28] Kleim and Jones, "Principles of Experience-Dependent Neural Plasticity: Implications for Rehabilitation After Brain Damage," *Journal of Speech, Language & Hearing Research,* vol. 51, pp. S225-S239, February 2008.

[29] K. Stefan, M. Wycislo, and J. Classen, *Modulation of Associative Human Motor Cortical Plasticity by Attention* vol. 92, 2004.

[30] C. J. Winstein, A. S. Merians, and K. J. Sullivan, "Motor learning after unilateral brain damage," *Neuropsychologia,* vol. 37, pp. 975-987, July 1 1999.

[31] J. van Kordelaar, E. E. van Wegen, R. H. Nijland, J. H. de Groot, C. G. Meskers, J. Harlaar*, et al.*, "Assessing longitudinal change in coordination of the paretic upper limb using on-site 3-dimensional kinematic measurements," *Phys Ther,* vol. 92, pp. 142-51, Jan 2012.

[32] R. J. Nudo, B. M. Wise, F. SiFuentes, and G. W. Milliken, "Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct," *Science,* vol. 272, pp. 1791-4, Jun 21 1996.

[33] G. Kwakkel, B. Kollen, and E. Lindeman, "Understanding the pattern of functional recovery after stroke: Facts and theories," *Restorative Neurology & Neuroscience,* vol. 22, pp. 281-299, 2004.

[34] G. Kwakkel, C. G. Meskers, E. E. van Wegen, G. J. Lankhorst, A. C. Geurts, A. A. van Kuijk*, et al.*, "Impact of early applied upper limb stimulation: the EXPLICIT-stroke programme design," *BMC Neurol,* vol. 8, p. 49, 2008.