The Effects of Enhanced Self-Teleoperated Arm Therapy for Chronic Stroke Survivors

BY

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THESIS
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<td>AMFM</td>
<td>Arm Motor section of Fugl-Meyer test</td>
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<td>EA</td>
<td>Error Augmentation</td>
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<td>VRROOM</td>
<td>Virtual Reality Robotic and Optical Operations Machine</td>
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Summary

Stroke is a leading cause of disability in the United States with nearly 650,000 people each year experiencing upper extremity hemiparesis following a stroke. While several forms of rehabilitation exist in order to facilitate the motor recovery of post-stroke individuals, there is still significant room for improvement. An issue about current rehabilitation therapies, such as constraint-induced movement therapy and robotic-assisted movement therapy, is that they focus solely on the motor recovery of the more affected limb as opposed to the coordination of both limbs together. To solve this problem, bimanual movements are being integrated into current rehabilitation therapies. This recent integration of bimanual movements has shown to not only improve the functional coordination of both arms, but it can also lead to greater gains in the recovery of the hemiparetic limb. To further improve on current stroke rehabilitation, research on the neuroplasticity of motor control has been performed that suggests that the manipulation of error signals during repetitive reaching movements can also increase the coordination and motor recovery of both the hemiparetic limb as well as the less affected limb. While therapies involving bimanual reaching or error manipulation have been shown to be effective, very few studies have been performed on the efficacy of both treatments combined.

The purpose of this study is to determine the efficacy of self-teleoperated, robotic-assisted bimanual reaching therapy aimed at improving coordinated arm function. Specifically, I wanted to focus on the effects of error augmentation applied during bimanual reaching tasks. Twenty-six post-stroke individuals were asked to perform six, 45-minute bimanual reaching treatments while inside a Virtual Reality
Robotic and Optical Operations Machine (VRROOM). Participants were either assigned to an error augmentation treatment group or a standard treatment group. Those assigned to the error augmentation treatment would have their errors magnified both visually and haptically (through robotic forces) during the tasks, while those undergoing the standard treatment would perform the reaching tasks without any augmentations. Clinical scores as well as a quantitative assessment were recorded throughout the treatment period to determine motor recovery. While the results of the clinical measures were not able to determine a significant improvement between the error augmentation and standard treatments, the therapy, as a whole, indicated a clinically significant improvement in functional motor recovery. The quantitative assessment did, however, show that the error augmentation treatment was superior to the standard treatment in improving the bimanual coordination of post-stroke individuals. In determining the optimal method for post-stroke upper extremity rehabilitation, the findings of this study shed light on the future practicality of a self-rehabilitation technique.
1. INTRODUCTION

1.1 Motor Recovery After Stroke

A stroke, or cerebrovascular accident, is a leading cause of serious long-term disability in the United States with approximately 795,000 people suffering from one each year (Mukherjee and Patil 2011). Up to 85% of all stroke survivors also experience some form of hemiparesis, which results in the impairment of the upper extremities immediately following the incident (S. L. Wolf et al. 2006). Once medically stable, a post-stroke individual typically undergoes some form of rehabilitation to minimize impairments and promote the functional motor recovery required in many activities of daily living (Duncan et al. 2005). While existing therapies have been shown to be sufficient in recovering motor control, there is significant room for improvement. To facilitate upper extremity recovery in post-stroke individuals, many new therapeutic methods are emerging that allow for the “retraining” of the brain through a combination of bimanual reaching tasks, sensorimotor training, and self-rehabilitation.

1.2 Stroke Rehabilitation Techniques

There have been many studies conducted to determine the efficacy of traditional and modern therapeutic methods in regaining upper extremity function in stroke survivors. Traditional therapies, such as the Bobath concept, are the most well-known and widely used techniques for the rehabilitation of hemiparetic patients in the United States. Typically, this form of therapy involves a physical therapist that guides or facilitates the patient’s movements during different tasks (Ashburn 2000). Despite its widespread use, there is not a consistent methodology of the treatment across all
patients and there has been very little evidence that supports its clinical effectiveness as the optimal therapy for motor recovery (Paci 2003). Similar traditional approaches, such as those developed by Rood, Kabat, Brunnström and Perfetti, also lack sufficient evidence of their effectiveness as a viable therapy. With recent advances in the research of motor learning, many new techniques have emerged that could possibly redefine motor recovery therapies of post-stroke individuals.

Many recently developed therapeutic interventions have been clinically shown to substantially improve the motor control of post-stroke individuals with even long-term disabilities (S. L. Wolf et al. 2006). A common practice in many current therapies is the active practice of repetitive movements. This constant repetition of certain tasks, or “massed practice”, has been shown to greatly increase the motor recovery of chronic stroke survivors (Taub, Uswatte, and Pidikiti 1999). A relatively new technique utilized during repetitive reaching tasks is Constraint-induced movement therapy. This technique requires the stroke survivor to use their hemiparetic limb during repetitive reaching tasks (S. Wolf et al. 1989; Pierce et al. 2003) by physically constraining the movement of the stroke survivor’s less affected arm. This technique forces individuals to overcome a common issue in post-stroke individuals, called “learned nonuse”, wherein stroke survivors compensate for the lack of mobility in the hemiparetic arm by primarily using their less affected arm (Taub 1980; Taub et al. 1994). By refusing to use their hemiparetic arm during everyday tasks, the motor recovery of the more affected limb is greatly hindered, resulting in a distinct lack of function of the affected upper extremity. While constraint-induced movement therapy has been shown to produce clinically relevant improvements in upper arm motor function, it does have drawbacks. One major
drawback of this therapy is the lack of attention given to performing bimanual tasks and while the functional recovery of the more affected arm is important, there are many everyday tasks that require the coordination of both arms to complete. A modified form of constraint-induced movement that involves performing bimanual tasks has been shown to be effective in improving motor control, but this therapy only focused on sequential movements of both (Wu et al. 2007). While this is a step in the right direction towards implementing bimanual tasks in motor recovery, this excludes any tasks that require simultaneously coordinated movements of the arms.

Repetitive reaching tasks can also be accompanied by robotic interventions to aid in the movement of a participant’s arms. One of the main advantages to robotic-assisted rehabilitation is the ability to apply forces to a participant’s arm to further encourage motor recovery (J.L. Patton, Mussa-Ivaldi, and Rymer 2001; James L Patton and Mussa-Ivaldi 2004; Dancause, Ptito, and Levin 2002; Takahashi and Reinkensmeyer 2003). The application of these forces can then be used to either guide the participant’s arm toward the desired trajectory (Volpe et al. 1999; Peter S. Lum et al. 2002), provide resistance against the arm’s movement (Ouellette et al. 2004), or provide a force that amplifies a participant’s error. Regardless of the application of the robotic forces during the reaching tasks, studies have shown that robot-aided therapy of the upper limbs post-stroke are successful in improving short and long-term motor control (Prange et al. 2006). A difficulty with this type of treatment, however, is the implementation of both arms into the tasks to improve bimanual coordination. A preliminary study on the design of bimanual robotic therapy has showed the efficacy of
this type of treatment for improving performance of coordinated bimanual tasks (P.S. Lum, Reinkensmeyer, and Lehman 1993).

1.3 Bimanual Tasks

While most of the current stroke rehabilitation techniques typically increase the mobility and range of motion of the more affected arm, many do not focus on the coordination of both arms that are required in many activities of daily living such as buttoning a shirt or opening a jar. Many stroke survivors see this lack of attention to coordination as a flaw in current therapy techniques, and feel that the functional coordination of their arms is a more worthwhile form of recovery than being able to perform tasks perfectly with just one arm (Winstein et al. 2004). It has also been suggested that by employing the use of both arms during reaching tasks, the less affected arm has the ability to “retrain” the more affected arm in a way that increases coordination and functional recovery of the hemiparetic limb (Peter S. Lum et al. 2002; Hesse et al. 2003; MacClellan et al. 2005). This interaction has lead to the idea of bimanual tasks as a viable rehabilitation technique to further facilitate motor recovery in post-stroke individuals.

Plenty of research has been performed on the efficacy of bimanual training in the recovery of upper extremity motor control (Cobie Brinkman 1981; C Brinkman 1984; Sadato et al. 1997; Donchin et al. 1998; Nakanishi and Schaal 2004). This stems from the idea that bimanual movements require the activation of both cranial hemispheres (Kelso, Southard, and Goodman) and can produce an enhanced inter-hemispheric interaction (Peter S. Lum et al. 2002; Hesse et al. 2003). Bimanual movement control appears to involve a distributed network of cortical and subcortical areas as opposed to
being associated with just one neuroanatomical structure (Donchin et al. 1998; Kermadi, Y. Liu, E. M. Rouiller 2000; Swinnen 2002). Due to the interconnected nature of bimanual movements, it is suggested that most post-stroke individuals will experience some form of bimanual deficit, and should undergo at least some form of bimanual rehabilitation (Rose and Weinstein 2005).

An issue with bimanual training, however, lies in determining the most effective type of movement to encourage bimanual motion and facilitate coordinated motor learning. There are a wide variety of bimanual movements that can have any number of effects on bimanual coordination. Recent studies have shown that symmetrical movements, where bilateral homologous muscle groups are simultaneously activated, are easier to perform than asymmetrical movements (Heuer and Klein 2005; Diedrichsen et al. 2004). Symmetrical movements have also shown to activate neural networks in both hemispheres, which may allow the undamaged hemisphere to increase the activation of the more damaged hemisphere (Hallett 2001; Lacroix et al. 2004). These movements can then be further classified as parallel, such as reaching with both hands, or mirrored, such as pulling an object apart (Figure 1). A previous study on healthy individuals determined that the most intuitive mode of bimanual coordination is in-phase, parallel movements (Figure 1 right), such as pushing with both hands (Abdollahi, Kenyon, and Patton 2013b). These findings also coincide with the idea of “directional compatibility” wherein the coordination of limbs is seen more when performing parallel movements (Bogaerts and Swinnen 2001). While symmetrical and parallel movements were seen to increase the bimanual coordination of healthy
individuals, it is yet to be seen if these same results will translate to those that are post-stroke.

Figure 1- Symmetrical bimanual movements (Abdollahi, Kenyon, and Patton 2013a); hand movement (dashed arrow), cursor movement (solid arrow), targets (yellow spheres), left hand cursor (red square), right hand cursor (green square)

Another issue that can arise with bimanual training is the possibility that participants may be unable to divide their visual attention between both arms during
reaching tasks. When unilaterally reaching to targets, people typically look at the target location for course correction (Neggers and Bekkering 2000), but in the case of bimanual reaching to two targets, this is not possible. It has been suggested that by specifically orienting attention to one limb during reaching tasks, this limb will become “primed” and unfold more rapidly than the effector that has not been selectively given attention (Neely, Binsted, and Heath 2005). This can then lead to issues that would cause out of phase movements between the two upper extremities. A recent study in healthy subjects, however, found that focusing attention on one non-target location while reaching had a minimal effect on speed and efficiency compared to those who could freely focus their attention (Diedrichsen et al. 2004). These findings agree with the recent study performed by Abdollahi, Kenyon, and Patton that sought to determine the optimal way to perceive bimanual tasks in a virtual environment. They found that by translating the visual representation of a healthy participant’s arm across the midline in a virtual environment, such that they only needed to attend to one side of their view (Figure 2), decreased their ability to perform bimanual reaching tasks more so than those who did not experience the visual transformation (Abdollahi, Kenyon, and Patton 2013b). These findings suggest that the optimal reaching task and visual representation for bimanual coordination therapy in post-stroke individuals is a symmetrical, parallel reaching motion without a direct visual transformation across the midline.
1.4 **Error Augmentation in Motor Recovery**

Sensorimotor training, either through robotic assisted-movements or therapist-guided movements, has shown to be more effective in improving motor control than by
repetitive reaching movements alone (Feys et al. 1998; Jongbloed 1986; Volpe et al. 2000). While typically, this type of treatment involves the active guidance of the more affected arm toward a specific target by some force, recent research suggests that a resistive, namely error augmenting, force has shown to be the most effective (Stein et al. 2004). Error augmentation (EA) refers to the amplification of errors made during certain tasks. This error can be determined in many ways depending on the task required, and does not have a set definition. One example of determining error is seen in figure 3. In this figure, the optimal trajectory would be defined as a straight line path from the starting position to the end positions (dashed red line), and the error would be defined as the instantaneous perpendicular distance between the optimal trajectory and the actual trajectory (thin blue line). This error can then be magnified haptically, through robotic-assisted forces, or visually, in a virtual environment. In the case of visual error augmentation, the participant’s arms must first be hidden from sight, and then be represented visually in a virtual workspace. These representations can then be manipulated based on the participant’s error as they move through the workspace (Figure 3). While the mechanism behind the efficacy of amplifying a subject’s errors is not completely understood, it is believed that during error augmentation the natural adaptive behavior of the nervous system is engaged and stimulates motor learning (Lisberger 1988; Dancause, Ptito, and Levin 2002).

Research on the neuroplasticity of motor control suggests that the manipulation of error signals during repetitive reaching movements can further increase the coordination in bimanual tasks for stroke survivors (James L Patton and Mussa-Ivaldi 2004). The combination of these therapeutic techniques was shown to be effective in a
previous study where a therapist provided cues that the patient would reach toward. As the patient reached toward these cues, their error was magnified visually, through a virtual reality environment, and haptically, through resistive robotic forces. This study proved that intensive repetitive reaching combined with the augmentation of error signals was more advantageous than just the repetitive reaching alone (Abdollahi et al. 2014a). This coincides with previous research that determined that intensive repetitive movements combined with adaptive training are able to accelerate motor recovery in chronic stroke survivors (J. Patton et al. 2006; Dancause, Ptito, and Levin 2002). While the mechanism behind this adaptive training is not completely understood, it is thought to be dependent upon the internal forward model of learning, wherein the central nervous system makes use of sensory inflow (such as that of proprioception) and integrated motor outflow (such as the motor commands sent to the arm) combined with sensory correction to create an integrated process of motion (Wolpert, Ghahramani, and Jordan 1995). In these EA treatments, sensory correction is disturbed visually, haptically, or by a combination of both. This disturbance creates conflicting signals within the central nervous system, causing it to perceive mistakes more clearly and adapt to these errors accordingly (James L Patton, Kovic, and Mussa-Ivaldi 2006; Sharp, Huang, and Patton 2011).

Error augmentation typically occurs in one of two ways, an offset based approach, or a gain-based approach. In the case of an offset based error augmentation (Figure 3 left), a distinct error is added to a participant’s own movement errors such that the error perceived is less dependent on the actual error provided by the patient (Wei et al. 2005). In the case of a gain-based approach, the participant’s error is multiplied by a
set gain such that the error perceived is solely dependent on the error provided by the patient (Figure 3 right). Research has shown that while offsetting error results in a faster adaptation, error amplification provides a more complete adaptation (Huegel et al. 2009). A previous study has also speculated that a gain-based approach to error augmentation allows for participants to more clearly see mistakes and thus do not need to correct their movement as much as those who underwent an offsetting error treatment (Sharp, Huang, and Patton 2011). This research suggests that a gain-based visual and haptic error augmentation approach is the most viable for upper extremity rehabilitation in post-stroke individuals.

Figure 3- Error augmentation approaches (Wei et al. 2005); Offset-based (Left), Gain-based (right), Desired trajectory (dashed red line), Actual trajectory (thin blue line), Trajectory seen (thick blue line)
1.5 Objectives

While therapies involving bimanual reaching or error manipulation have been shown to be effective, very few studies have been performed on the efficacy of both treatments combined. The aim of this study is to determine if a self-rehabilitation therapy consisting of error augmentation is the optimal technique to use for motor recovery in post-stroke individuals. Specifically, I sought to discover if error augmentation applied during bimanual reaching tasks would result in greater motor recovery than by repetitive bimanual reaching tasks alone. The objectives of this study were to determine if error augmentation applied during bimanual reaching tasks is, first, able to increase the bimanual coordination of the upper extremities, second, result in an increased range of motion of the more affected arm, and third, increase the motor function of the hemiparetic arm.
2. MATERIALS AND METHODS

2.1 Participant Selection

Twenty-eight participants aged 18 or over that survived a single cortical stroke and were at least six-months post stroke agreed to participate in this study (detailed participant information in Table 1). Over the course of the treatment, two participants dropped out due to medical reasons and were excluded from the analysis (Figure 4). All participants were either recruited from a registry of post-stroke individuals or responded to postings around the Chicago area. The Institutional Review Boards of both Northwestern University and the University of Illinois at Chicago approved this study. All participants provided informed consent according to the Declaration of Helsinki prior to commencing the study. All participants were also required to have some proximal strength in the hemiparetic limb as confirmed by an upper extremity Fugl-Meyer score of 25-50. Exclusion criteria for this study included bilateral paresis, severe spasticity or contracture, multiple strokes, severe concurrent medical problems, severe sensory deficits, significant shoulder pain, cerebellar strokes resulting in severe ataxia, depth perception impairment (< 3/9 on Stereo Circle Test), visual field cut, cognitive impairment (Mini Mental State Examination < 23/30), severe aphasia, focal tone management with Botulinim Toxin (Botox®) injection to the hemiparetic upper extremity within the previous four months, and affective dysfunction or hemisensory neglect that would influence the ability to perform the experiment or provide informed consent. Participants were excluded if they received any other skilled upper extremity rehabilitation in a clinical setting.
Assessed for eligibility (n=62)

Excluded (n=34)
- Not meeting inclusion criteria (n=33)
- Declined to participate (n=1)
- Other reasons (n=0)

Randomized (n=28)

Allocated to Error Augmentation treatment (n=15)
- Received allocated intervention (n=15)
- Did not receive allocated intervention (n=0)

Allocated to Error Augmentation treatment (n=13)
- Received allocated intervention (n=13)
- Did not receive allocated intervention (n=0)

Lost to follow-up (n=0)
- One-week (n=0)

Discontinued intervention (n=2)
- Medical issues not related to treatment (n=2)

Lost to follow-up (n=0)
- One-week (n=0)

Discontinued intervention (n=0)
- Medical issues not related to treatment (n=0)

Analysis

Analyzed (n=13)
- Excluded from main-analysis (n=0)

Analyzed (n=13)
- Excluded from main-analysis (n=0)

Figure 4- Subject recruitment flow diagram
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F, female; M,male.
2.2 **Study Setting**

The study was performed using a three-dimensional haptic/graphic system called the Virtual Reality Robotic and Optical Operations Machine, or VRROOM (Figure 5). A cinema-quality digital projector (Christie Mirage 3000 DLP) combined with a semi-transparent mirror was used to obstruct the view of the participants’ arms. This also served to display stereo images in a five-foot-wide, 1280x1024 pixel display with a 110-degree wide viewing angle as a see-through augmented reality display. The display obstructed the view of the participant’s arms so that only cursors (representing hand locations) and targets were shown. The participants were also required to wear StereoGraphics liquid crystal shutter glasses to separate left and right eye images to give the perception that the workspace was three-dimensional. A SensAble Technologies Phantom Premium 3.0 robot was attached to the participant’s more affected wrist and was used to track the position of the arm as well as apply haptic feedback when necessary. An Ascension Flock of Birds sensor was used to track the participant’s head motion to display the appropriate perspective in the workspace. Another Flock of Birds sensor was used to track the position of the participant’s less affected arm. A Wilmington Robotic Exoskeleton was used to negate the effects of gravity on the participants more affected arm and thus reduce fatigue caused by any excessive motion.
2.3 Experimental Protocol

Each participant was randomly allocated to one of the two treatment groups such that the Fugl-Meyer scores from the initial screening were matched as closely as possible. The two treatments made use of robotic-assisted therapy wherein each participant would perform repetitive bimanual reaching movements with either no error augmentation added, named the “Standard Treatment Group”, or with the participant’s error visually and haptically magnified, named the “Error Augmentation (EA) Treatment”.

Figure 5- Experimental Setup of VRROOM
The entire study consisted of two weeks of six (three days per week) 45-minute treatment sessions followed by a one-week post-treatment follow-up evaluation (Figure 6).

Each of the treatment sessions began with five minutes of preparing the participant inside of the VRROOM. This set-up included comfortably sitting the participant inside the WREX and placing the patient’s more affected arm inside of an exotendon glove. The WREX and glove combination was used to reduce any muscle fatigue caused by the effects of gravity as well as aid the participant in keeping a neutral wrist alignment. By keeping a neutral wrist alignment during the procedure, the participant was able to create more functional hand and wrist movements. The
exotendon glove also served as an anchoring point for the robot to attach to the patient’s more affected arm, such that the patient would not be required to actively hold the handle. One Ascension Flock Of Birds sensor was placed on the participant’s less affected wrist in order to track its position in the workspace and another tracker was placed on the StereoGraphics shutter glasses to determine the participant’s head position and orientation. The robotic handle would then be attached to the WREX and exotendon glove with the center of the device located just above the radiocarpal joint. Forces for the error augmentation treatment group would then be applied through the robotic handle; the handle was attached to the participant’s more affected arm in both treatments in order to assist in the blinding of patients as well as to provide the instantaneous positions of the patient’s arm in the workspace.

Once the participant was set up inside the VRROOM, the treatment session would begin. The treatment would start with five minutes of a bimanual movement block, immediately followed by two minutes of rest. During these blocks, the patient’s arms were occluded by the visual display of the workspace such that only two red dots (representing the participant’s arm positions) and two yellow spheres (representing the targets) were visible (Figure 7). The bimanual movement block alternated between a bimanual reaching task and a free movement. The bimanual reaching task consisted of the patient coordinating their arms in order to reach to various targets in the workspace. During this block, the participant would alternate between reaching to a home position and then reaching outward to different targets. If the participants were able to successfully move within their targets at the same time and hold them inside the target for 0.02 seconds, a new set of targets would appear. A time limit of 10 seconds per
target was imposed in order to prevent sequential bimanual movements and promote simultaneous bimanual movements. This amount of time was insufficient to sequentially move both arms to their respective targets, so one coordinated movement of both arms was required to successfully pass the trial. If the participant was not able to pass the trial after the 10 seconds of reaching, the targets would disappear and a new set of targets would appear in the workspace.
To determine the optimal target distances for a challenging treatment, a test was put into place that would assess the range of motion for every patient separately. Prior to beginning the first treatment, each participant was asked to reach to four points at various distances within the workspace. If the participant was successful in reaching all of the points, the distance to the targets would increase and the participant would try again. Once the participant could no longer reach to all of the targets, this distance was used as an initial point to challenge the patients. No error augmentation was applied while determining the initial challenge point for the subject, regardless of treatment group. During each of the subsequent bimanual reaching blocks, if the participant was able to successfully reach to the four distinct targets, they would “level-up” and the distances for the next bimanual reaching block would increase.

During the free movement block, the participants were allowed to move freely around the workspace and were only instructed to move their arms together as much as possible. This gave the participants an opportunity to perform what they believed would be good therapy as well as work on any particular weaknesses they felt they had. During this block, the participants were once again only able to see their apparent arm positions and the two targets. This allowed the participants to reach to their targets for extra practice if they wanted to. If the participants were in the EA treatment group, they still received error augmentation during this block.

For the error augmentation treatment group, the position of the participant’s more affected arm was visually and haptically augmented. An error vector, e, was defined as the instantaneous difference between the patient’s wrist positions after accounting for the midline differences between the arms. This error vector was visually magnified by
1.5 to account for the visual error augmentation and was only applied to the participant’s hemiparetic arm. To haptically augment error, a force of 100 N/m (once again accounting for the midline differences) was applied in order to push the more affected arm away from the less affected arm. For safety purposes, this force was designed to saturate at 4 N/m.

2.4 **Error Metric Calculation**

Evaluations of bimanual coordination were performed three separate times during the study, prior to the treatment, 30 minutes after the last treatment, and one week following the final treatment. During these evaluations, every participant was asked to reach to targets at a set distance regardless of their challenge point. There was also no error augmentation added to these reaches, regardless of treatment group. To properly define how well both arms were coordinated during these reaching tasks, two metrics were used, the instantaneous error vector and the mean x-axis misalignment error angle. To calculate the mean x-axis misalignment error angle, the direction cosine between the error vector and the positive x-axis was found (eq. 1). The equation used was:

\[ a = \cos^{-1} \frac{v_x}{\sqrt{v_x^2 + v_y^2 + v_z^2}} \]  

(Equation 1)

where \(v_x, v_y, v_z\) refer to the x, y, and z components of the error vector between the instantaneous positions of the less affected arm to the more affected arm. An error angle of 0° is optimal and represents the exact coordination between the two arms.
2.5 **Clinical Evaluation**

Throughout the study, each participant’s bimanual coordination and function was also evaluated using various clinical measures. Prior to starting the treatment, a blinded evaluator administered clinical tests, such as the arm motor section of the Fugl-Meyer test, as well as the Wolf Motor Function Test. These evaluations were also performed 30 minutes after the final treatment as well as at the one-week follow up. The Fugl-Meyer assessment is useful in determining any changes in the range of motion of the more affected arm by rating the difficulty a patient may have moving their arm to various positions. The Wolf-Motor Function Test is useful in determining any changes in the functional use of the affected arm by rating the difficulty a patient may have performing specific tasks, such as folding towels or stacking checkers.

2.6 **Statistical Analysis**

To determine any treatment related changes in coordination or function, all outcomes were analyzed using a Mixed-Design ANOVA with factors of time (pre-treatment vs. post-treatment vs. follow-up) as the within-subjects variable, and the treatment type (Error Augmentation vs. Standard Treatment) as the between-subjects variable. Tukey’s honest significant difference post-hoc analysis was used when necessary to determine any detailed changes in the participant’s performance. All statistical tests were performed with an alpha of 0.05.
3. RESULTS

The first metric, mean instantaneous error, revealed a significant change in both treatment groups over the course of the three week study (F(2, 48)=20.98, p<0.01) with an average decrease in instantaneous error of 3 cm ± 3.37 cm (Figure 8). The post-hoc analysis did not reveal a significant difference between the error augmentation treatment and the standard treatment. The analysis did, however, reveal a significant decrease in error of 2.37 cm ± 1.95 cm over the course of the three-week study (t=-4.39, df=12, p<0.01). This group also showed a significant reduction in error of 2.82 cm ± 2.02 cm between the pre-treatment evaluation and the post-treatment evaluation (t=-5.05, df=12, p<0.01). Similarly, the standard treatment group showed a significant decrease in error of 3.62 cm ± 4.37 cm from pre-treatment to the one-week follow up (t=2.99, df=12, p<0.05). This group also showed a significant decrease in error of 2.43 cm ± 1.8 cm from the pre-treatment to the post-treatment (t=-4.88, df=12, p<0.01). These results also showed an uncharacteristically large amount of error reduction for three participants in the standard treatment group. A supplemental analysis that removed these participants revealed a much smaller decrease in error of 1.60 cm ± 1.82 cm between the pre-treatment and one-week follow-up evaluations (t=-2.7816, df=9, p<0.05). This change was also evident in the pre-treatment to post-treatment evaluation with a decrease in error of 1.82 cm ± 1.42 cm (t=-4.05, df=9, p<0.01). Despite the removal of these participants, there was still no significant difference between the two treatment groups. Separation of the participants based on their previously dominant hemisphere did not reveal a significant change in the results.
The other error metric, mean x-axis misalignment error angle, showed a significant difference between treatments ($F(1,24)=5.37, p<0.05$) with an average decrease in error angle of $3.26^\circ \pm 4.18^\circ$ for the error augmentation group (Figure 9). Further analysis found this change in error angle to be significantly different than the change in error angle for the standard treatment group ($t=2.07, df=24, p<0.05$). The post-hoc analysis also showed a significant decrease in error angle of $3.73^\circ \pm 5.23^\circ$ between pre-treatment and post-treatment for the error augmentation group ($t=2.57,$
df=12, p<0.05). Interestingly, there was no significant change between the one-week period of the post-treatment and follow up evaluation days. There was no significant change for the standard treatment group over the course of the three-week study.

Figure 9- Average Error Angle per Trial for Error Augmentation and Standard Treatment Groups; significant changes (solid lines), no significance (dashed lines); subject order within each group (color code); Average error per trial per subject (dots); 95% confidence intervals per subject (vertical lines); Phase averages (centers of diamonds); 95% confidence intervals per phase (top and bottom points of diamonds)
The main clinical outcome measure, Arm Motor Fugl-Meyer scores, showed a significant improvement for both treatments over the course of the three-week study (F(2, 48)=6.20, p<0.05) with an average gain of 2.92 ± 4.84 (Figure 10a). While post-hoc analysis could not reveal a significant change in scores between the error augmentation and standard treatment groups, the error augmentation group did significantly increase their scores over the three-week period with an average gain of 3.54 ± 3.73 (t=3.42, df=12, p<0.01). This group also showed an increase of Fugl-Meyer scores of 2.62 ± 3.43 over the one-week period without any treatment (t=2.75, df=12, p<0.05). The standard treatment group, on average, did not significantly increase their AMFM scores between the post-treatment evaluation and the one-week follow up evaluation.

The secondary clinical outcome measure, Wolf Motor Function scores, also showed a significant improvement over the three-week study period (F(2,48)=7.61, p<0.05) with an average gain of 0.23 ± 0.30 (Figure 10b). Similar to the Fugl-Meyer scores, further analysis failed to detect a significant difference between the two treatments. The error augmentation group, however, did show a significant average gain of 0.20 ± 0.14 points from the pre-treatment evaluation to the one-week follow-up (t=5.03, df=12, p<0.01). The standard treatment group also showed a significant average score gain of 0.16 ± 0.21 between the post-treatment evaluation and the one-week follow-up (t=2.78, df=12, p<0.05).
Figure 10- Clinical Score Change from the first visit, AMFM score (A), and WMFT score (B). Solid Lines (Blue- Standard Treatment; Red- Error Augmentation Treatment) show changes between treatments and dashed lines show changes between no treatment periods.
4. DISCUSSION

4.1 Viability as a Rehabilitation Methodology

This blinded, randomized study was successful in finding a benefit of self-teleoperated therapy in the upper extremity motor recovery of chronic stroke survivors. Over the course of the three-week treatment period, all outcome measures were shown to significantly improve, showing increases of bimanual coordination and function. The results of this study also show the potential benefit of combining self-rehabilitation therapy with visual and haptic error augmentation in accelerating motor recovery in chronic stroke individuals.

The results of the clinical measures, AMFM and WMFT scores, were able to show the efficacy of bimanual self-rehabilitation as a means of increasing bimanual function. Over the course of the three-week treatment period, both groups were able to improve their clinical motor function scores. While these effects could not be considered quite statistically significant, they might continue to improve with longer treatment periods. In the case of other robotic-assisted rehabilitation options, treatments that have shown to be clinically effective typically last for at least six weeks with various lengths of training per day (Fasoli et al. 2003). Because of the significant gains seen in just two weeks of self-teleoperated bimanual reaching, statistically significant gains may be observed during longer treatment periods.

Based on the results of the mean instantaneous error as well as the mean x-axis misalignment error angle, the error augmentation group average was able to significantly improve their bimanual coordination while performing reaching tasks. As evidenced by the mean x-axis misalignment error angle, this increase in bimanual
coordination for the error augmentation group was also significantly larger than that of
the standard treatment group, thus reinforcing the efficacy of error augmentation as a
viable therapeutic technique. The findings of this study suggest that the incorporation of
error augmentation into bimanual self-rehabilitation therapy may help facilitate motor
recovery more effectively than standard treatment alone. It is interesting to note,
however, that the significant reductions in error angle and instantaneous error did not
fully translate to significant gains in the clinical measures. One possible explanation for
this lack of consistency could be that the error metrics may be more powerful in defining
only minor changes in bimanual coordination, whereas clinical scores may require
larger gains to show improvement. While the results of the error metrics were able to
show a significant advantage to the error augmentation treatment, this study was not
able to show any significant improvements in the clinical measures between the two
treatment groups. Once again, longer periods of treatment may be necessary to detect
the larger functional improvements needed for clinical score measures.

While a clinically significant difference between the two treatments could not be
found, it is important to note that the point at which most of the changes in scores for
the error augmentation group occurred during the one-week follow-up evaluation. This
sudden jump in clinical scores for the EA treatment group may be attributed to a few
different factors. For one, it should be noted that the error augmentation treatment tends
to be more strenuous than the standard treatment, and thus can cause more fatigue
among the EA treatment group. While the participants were allowed to rest between the
final treatment and the post-treatment clinical score evaluation, there may have still
been some residual fatigue that could affect the participant’s ability to perform the given
tasks. Any difficulty seen when performing the clinical tests could result in a negative skewing of the clinical scores. This is further corroborated by the large gain of scores during the one-week follow-up evaluation. During the week without treatments, any possible muscle fatigue due to EA would go away and allow a more representative clinical score during the one-week follow-up.

4.2 Limitations

While performing this study, we noticed a few shortcomings that could potentially effect the participant’s improvement over the treatment period. One such shortcoming is the potential for a participant in the error augmentation group to pass a trial without successfully reaching to the given target. Due to the nature of error augmentation, a participant has the ability to shift the apparent position of the hemiparetic arm in the visual workspace. This shift can then be manipulated to successfully move the more affected limb’s cursor to the target without correctly moving the arm inside the target. While this was not seen during the course of this study, it is important to note the possibility of falsely passing certain reaching tasks.

While error augmentation is a well-studied technique of post-stroke rehabilitation, there is yet to be a consistent way to calculate error (Abdollahi et al. 2014b; Bajaj, Scheidt, and Patton 2005; Abdollahi, Kenyon, and Patton 2013b). With typical upper extremity error augmentation studies, the position of only one arm is taken into consideration when calculating error. This poses an issue in the scope of this study, due to the importance of coordinating both arms during the reaching movements. It is for this reason that we determined the distance in the instantaneous positions of both arms to
be the most effective way to calculate error. While this determination of error did seem to be effective, there is always the question as to whether a different calculation of error may be more effective.

Another possible concern discovered while performing this study is the effect that verbal encouragement and positive reinforcement may have on a participant’s ability to perform the reaching tasks. Throughout the duration of the study, subjects in both treatment groups would occasionally fail to move their arms simultaneously toward the targets. Due to the importance of bimanual coordination during each reaching movement, it was necessary to give verbal reminders to the participant in order to ensure they would move both arms accordingly. This type of encouragement can have unforeseen effects on the patient’s ability and motivation to perform the movements required and it has been found that verbal reinforcement during post-stroke rehabilitation may lead to larger gains in motor function compared to those that did not receive verbal encouragement (Dobkin et al. 2010). Due to the environment of the study, it is difficult to ensure that each participant received equal verbal reinforcement while performing the tasks. This potential issue could be resolved in further studies by employing an automated verbal or visual encouragement system in order to ensure that each participant receives the same level of encouragement. Automated encouragement also further presents the idea of this form of therapy as a viable self-rehabilitation, “patient solo” therapy.
5. CONCLUSION

This research indicates that a self-teleoperated therapy consisting of error augmentation applied to bimanual reaching tasks has been shown to be effective in increasing the bimanual coordination of post-stroke individuals. While these results fail to definitively prove that error augmentation on bimanual reaching tasks can produce larger changes in the clinical scores of motor recovery and function compared to a standard treatment, there is evidence that suggests error augmentation is at least somewhat successful in improving motor control. This study lays the framework for future studies on the efficacy of this treatment as a viable methodology to improve the bimanual coordination and function of the upper extremities of chronic stroke survivors.
References


Appendix

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Folk Street
Chicago, Illinois 60612-7227

Approval Notice
Initial Review – Expedited Review

October 10, 2014

Farnaz Abdollahi, MS
Bioengineering
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M/C 063
Chicago, IL 60612
Phone: (773) 524-7571

RE: Protocol # 2014-0707
“Error Enhanced Learning and Recovery in 2 and 3 Dimensions (re-submission of 2010-0209)”

Dear Dr. Abdollahi:

Your research protocol was reviewed and approved under expedited review procedures [45 CFR 46.110(b)(1)] on October 6, 2014. You may now begin your research.

The UIC Office for the Protection of Research subjects (UIC OPRS) recognizes Northwestern University as the IRB of Record for this research. This was determined based upon the IRB Authorization Agreement in place between the UIC IRB and Northwestern IRB which covers research conducted by Dr. James Patton.

Your research meets the requirement(s) for the following category - Expedited Review Approval Category 45 CFR 46.110(b)(1) and /or 21 CFR 56.110(b)(1):
(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving X-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

(7) Research on individual or group characteristics or behavior (including but not limited to research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Please note the following information about your approved research protocol:

Protocol Approval Period: October 6, 2014 - October 6, 2015
Phone: 312-996-1711 http://www.uic.edu/depts/ovcr/oprs/ FAX: 312-413-2929
Approved Subject Enrollment #: 10

Additional Determinations for Research Involving Minors: These determinations have not been made for this study since it has not been approved for enrollment of minors.

Performance Sites: UIC, Northwestern University

Sponsor: MARS3

PAF#: Not available

Grant/Contract No: ED-GRANTS-062012-003

Grant/Contract Title: Machines Assisting Recovery from Stroke and Spinal Cord Injury for Reintegration into Society

Research Protocol(s):

a) Error Enhanced Learning and Recovery in 2 and 3 Dimensions, 07/01/2014, Version #1 (footer notes: 10/01/2010, version 3)

Recruitment Material(s):

a) Research Studies, Are you a stroke survivor?, dated 04/13/2012

b) Recruitment Email (version 2.0), 05/31/2012

(Please note Northwestern University IRB has previously approved Recruitment Documents for use as part of this research)

Informed Consent(s):

a) STU00002311/Rev 14_STU00002311, version Date: 1/17/2014

(Please note Northwestern University IRB has previously approved Informed Consent Documents for use as part of this research)

Please note the Review History of this submission:

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<td>Initial Review</td>
<td>Expedited</td>
<td>10/06/2014</td>
<td>Approved</td>
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Please remember to:

→ Use only the IRB-approved and stamped consent document(s) enclosed with this letter when enrolling new subjects.

→ Use your research protocol number (2014-0707) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements on the enclosure, "UIC Investigator Responsibilities, Protection of Human Research Subjects" (http://tigger.uic.edu/depts/ovr/research/protocolreview/irb/policies/0924.pdf)

Please note that the UIC IRB has the right to ask further questions, seek additional information, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.
We wish you the best as you conduct your research. If you have any questions or need further help, please contact the OPRS office at (312) 996-1711 or me at (312) 355-4006. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Cynthia C. Tom-Klebb, M.A., C.I.P.
Associate Director
Office for the Protection of Research Subjects

Enclosure(s):

1. None. All documents previously approved by Northwestern University IRB

cc: James Patton, Bioengineering, M/C 063
    Thomas Royston, Bioengineering, M/C 063
    OVCR Administration, M/C 672
Vita

ERIK HAMMES

EDUCATION
University of Illinois at Chicago, Chicago, IL
M.A. Biomedical Engineering 2012- Expected 2014

Clemson University, Clemson, SC
B.S. Biomedical Engineering 2008-2012
Biomaterials Concentration

WORK EXPERIENCE
Clemson University, Clemson, SC
Supplemental Instruction Leader 2010-2011
Attended engineering course three times per week and provided tutoring for twenty students to aid in their success in the class

Supplemental Instruction Mentor 2012
Managed eighteen Supplemental Instruction Leaders to better present the material at their student review sessions

RESEARCH EXPERIENCE
Clemson University, Clemson, SC
Biofuel Production and Properties of Desert Bacterial Communities January 2010 – May 2012
Determined potential uses for bacterial waste during the production of biodiesel as well as assessing the extracellular polymeric substances of bacteria found in Navajo sandstone.

Improving Biotech Systems for Stem Cell Growth May 2011 – May 2012
Designed a multiple input PID control system to improve the efficacy of batch reactor throughput using online and offline measurements.

Modeling Fibroblast Migration During Wound Healing August 2011-May 2012
Used a system of physical barriers to determine fibroblast response to varying concentrations of growth factor.

Novel Designs for Ureteral Stents August 2011-May 2012
Designed ureteral stents of varying shape and composition to reduce the effect of in vivo encrustation.

PUBLICATIONS

MEMBERSHIPS
Biomedical Engineering Development Society