VIRTUAL REALITY AND ROBOTIC BASED TRAINING FOR THE UPPER LIMB IN THE ACUTE AND EARLY SUB-ACUTE PERIODS POST-STROKE.

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DEDICATION

Dedicated to my father - Dinesh Patel - 'the little ghost who has been watching over our family the past six years'.  I made it !!!
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ABSTRACT

Background

Stroke is a leading cause of long-term disability in adults. Functional use of the upper limb, specifically the hand, is essential for independent living. Despite important research efforts, many individuals do not regain long-term upper limb function after sustaining a stroke. Collectively, the work presented here addresses key issues in stroke rehabilitation for the upper limb - namely, evaluation of a novel training protocol for persons with severe impairment, determining the effects of a higher dose of upper limb training initiated in the acute and early sub-acute period post-stroke, and assessing the validity and effectiveness of two influential prediction models for stroke.

Methods

All studies were initiated within the first month post-stroke to take advantage of the unique neuroplasticity occurring at that time and were conducted on an inpatient rehabilitation unit. The first study was a longitudinal study which included five individuals with severe hand paresis post-stroke. This study evaluated the feasibility and outcomes of a priming method that utilized mirror visual feedback and contralateral passive range of motion combined with a force modulation task in persons with severe hand impairment. The outcomes included the Upper Extremity Fugl-Meyer Assessment (UEFMA), the Action Research Arm test (ARAT), maximum pinch force, and bilateral maps of cortical reorganization via Transcranial Magnetic Stimulation (TMS).
second study was a non-randomized, two armed intervention study that evaluated the benefits of eight additional hours of intensive upper limb training with individuals with moderate arm paresis. There were seven subjects in the Virtual Reality(VR)/robotic treatment group, and six in the control group. Outcomes included the Wolf Motor Function Test, the UEFMA, wrist AROM, and maximum pinch force, as well as bilateral maps of cortical organization using TMS. Lastly, the third study evaluated the validity and methodology of two influential prediction models for stroke – the Proportional Recovery Rule and the Predicted Recovery Potential (PREP2) algorithm.

Results

For the first study, results showed feasibility of performing this training so early after stroke, as well as clinically significant long-term gains on all clinical measures in this group. However, without a control group it was not possible to determine how much of these gains were from the additional training or from biological recovery combined with the usual care they were concurrently receiving. The second study showed the feasibility of performing intense hand focused upper limb training and multiple clinical and neurophysiologic tests within the first month post-stroke. Importantly, it also showed that an extra eight hours of intensive VR/robotic based upper limb training led to significantly greater gains in long-term impairment compared to usual care.

For the third study, trends showed that additional training initiated within one month post lesion may allow for greater than predicted proportional recovery
in persons with functional Corticospinal Tracts. The study results also showed that further evaluation of the method used to determine the presence of motor evoked potentials (an indicator of Corticospinal tract function) for the PREP2 algorithm is justified.

Conclusion
Although preliminary in nature, the results presented here may be useful for future development of effective upper limb training protocols for rehabilitation in the acute and early sub-acute periods for persons at all levels of impairment post-stroke.
CHAPTER 1

Introduction

1.1 Background

Approximately 795,000 new or recurrent strokes occur each year in the United States and the prevalence of chronic stroke is approximately 7 million (Benjamin et al., 2018). It is a leading cause of adult long-term disability in the United States with the financial burden of related care among the fastest-growing expenses for Medicare (Benjamin et al., 2018; Winstein, Stein, et al., 2016). Important advances in acute medical, surgical, and imaging interventions have made strides in prevention of deaths and reduction in disability post-stroke. Despite these advances and more than a decade of investigation of innovative upper limb motor therapies, long term upper limb deficits persist for a significant number of persons post-stroke. Proportionally, more stroke survivors are left with upper extremity impairment and disability than that of the lower extremity (Bruce H. Dobkin, 2005; Lee et al., 2015). At six months post-stroke, about 30-60% of affected individuals do not regain functional use and only 5-20% achieve full return of arm function (Morris, van Wijck, Joice, & Donaghy, 2013). Recovery of hand function is even more recalcitrant to recovery and at six months post-stroke ~65% of affected persons continue to have hand deficits that profoundly affect their ability to perform their usual activities and their independence (B. H. Dobkin, 2005; Lang, Wagner, Edwards, Sahrmann, & Dromerick, 2006; Morris et al., 2013).
Further, only 5% of those with initial severe hand paresis will have full recovery (Nakayama, Jorgensen, Raaschou, & Olsen, 1994). Importantly, impaired hand function is the most disabling deficit for many post lesion (Lum et al., 2009).

Recovery of the hand may be limited due to the greater complexity and heterogeneity of normal behavior compared to that of the lower extremity. Behavioral or ‘functional’ recovery after stroke occurs from both behavioral restitution/‘true recovery at the impairment level’ (a return to normal patterns of motor behavior and Electromyography (EMG) patterns) and via compensatory mechanisms (Bernhardt, Hayward, et al., 2017; N. Ward, 2011; Zeiler & Krakauer, 2013). This recovery can be defined as a change in neuromotor function over time (Bernhardt, Hayward, et al., 2017). ‘Most improvement at the impairment level occurs within the first 1-3 months post lesion from a combination of spontaneous recovery and from the heightened response of training from the unique plasticity occurring at that time’ (Zeiler & Krakauer, 2013). Despite this knowledge, traditional rehabilitation approaches in the current American healthcare system place greater emphasis on training ambulation for early mobilization and discharge, which can encourage adoption of compensatory strategies for the upper limb early post-stroke that may inhibit potential ‘true’ long-term recovery (Lum et al., 2009). Additionally, despite the need to develop effective interventions for greater distal recovery, most research studies focus on the proximal upper extremity - training ‘reach’
activities rather than hand movements. One reason being that it is difficult to initiate hand therapy in the acute phase post-stroke partly due to limited active movement and strength in the muscles of the arm and hand. A recent literature search looking for studies that evaluated interventions for severe paresis post-stroke yielded twenty-two intervention based studies of which only four focused on hand and wrist training. Further, when studies focus on the hand, many of these interventions do not show a consistent pattern of effectiveness (Langhorne, Coupar, & Pollock, 2009).

Beyond these issues, many studies of upper limb rehabilitation following stroke present a dichotomous pattern with one group of subjects achieving substantial recovery and a second group of non-responders that receive the same intervention achieving little to no recovery. It would be helpful to have valid prognostic indicators available early on in the clinical setting to appropriately determine if significant recovery is to be expected (Bernhardt, Borschmann, et al., 2017). Although instituted plans (rehabilitation interventions/goals, discharge planning) have important consequences, they are often made without objective guidelines. Not training the upper extremity to its full potential can lead to ‘learned non-use’ as well as ‘learned bad-use’ (Alaverdashvili, Foroud, Lim, & Whishaw, 2008) and trying to rehabilitate an arm that has no physiological potential is a poor use of resources and can lead to patient frustration (e.g. prognostic indicators can help determine the use of compensatory techniques versus normalizing motor function). Thus
valid prognostic factors are important for clinical treatment and goal planning, policy development, and for realistic assessment of intervention effects in research trials (e.g. can match the control and intervention groups based on recovery potential).

The vital need to develop effective hand-focused upper limb rehabilitation protocols that address some of the aforementioned issues has led to the formation of consensus documents from world leaders in stroke research. One such document outlines a “Roadmap for Research Priorities” that recommends that research trials evaluate the effect of dose response relationships in therapy (‘dosing’) and also investigate the benefits of early initiation of rehabilitation post-stroke (‘timing’) (Veerbeek et al., 2014). These are valid recommendations, as both dosing and timing of intervention have been suggested as two key ingredients required in an effective training program that drives beneficial neural plasticity and leads to greater recovery – a third crucial ingredient being ‘progressive skilled training’ (Bowden, Woodbury, & Duncan, 2013).

The three studies presented in this thesis address several key issues that have been deemed critically relevant to the development and evaluation of effective upper limb rehabilitation strategies post-stroke. First, the research follows consensus guidelines by investigating the effects of additional virtual reality (VR)/robotic based training introduced in the acute and early sub-acute period (Bernhardt, Hayward, et al., 2017) in both a group of individuals with
severe initial paresis and those with moderate initial paresis (addresses the question of the interaction of dosage and timing for persons at various levels of impairment - Aims 1 and 2). The research also evaluates the effects of ‘progressive skilled training’ and the issue of developing training protocols specialized for the hand by utilizing a VR/robotic system that provides skilled, intensive and progressive hand-focused training. Additionally, the research assesses the validity and methodology of two established and influential stroke recovery models (the Proportional Recovery Rule for stroke and the Predicted Recovery Potential algorithm 2 (PREP2)) in the acute and early sub-acute (< one month) phases post-stroke (Aim 3) (Prabhakaran et al., 2008; C. M. Stinear et al., 2017a). Lastly, the research follows recent recommendations from another consensus group regarding effective outcomes for stroke research - the Stroke Recovery and Rehabilitation Roundtable (SRRR). They recommend including the use of standardized outcome measures (including more objective ones such as kinematic and kinetic measures) tested for at least three months beyond onset of the lesion for all research studies assessing sensorimotor recovery post-stroke. This will advance understanding of recovery mechanisms, help with the development of more effective training methods, and help to consolidate knowledge using meta-analyses techniques (G. Kwakkel et al., 2017).

The following sections of this introduction provide a synopsis of the current literature addressing the previously identified key issues in stroke
rehabilitation: dosing, timing, type of intervention, predictive models post-stroke, and lastly the issue of using appropriate outcomes in research trials.

1.2 Review of the literature

1.2.1 Dosage

In animals, hundreds of task specific repetitions are performed to induce neuroplastic changes in both the ‘healthy’ and ‘stroke’ brain (Bell, Wolke, Ortez, Jones, & Kerr, 2015; Nudo, 2013). That repetition is necessary was demonstrated by an experiment with a skilled reaching task in rats. Increases in the number of synapses and motor cortex map size were not seen until after days 7 and 10 of training when sufficient repetition was introduced (Kleim et al., 2004). ‘The exact dose in animals is not known. However even if known, it could not be directly translated to humans due to differences in the motor system structures (i.e. role of the rubrospinal tract in animals versus humans) and the animal model of stroke is not exactly the same as human stroke’ (Lang, Lohse, & Birkenmeier, 2015). Determining optimal dosing in humans is challenging and one reason for this is that the definition of dose is not standard in therapy trials. Most clinical trials use total therapy time to represent the dose. However a more accurate definition of dose is the total amount of activity performed during a training regimen (including the duration of each session, the frequency of training sessions provided, and the intensity or amount of activity performed during each session (Page, Schmid, & Harris, 2012)). Thus, a more precise representation of dose would also include the
number of repetitions or amount of actual active therapy time during a session (Lang et al., 2015). Indeed, data is showing that the actual amount is the important factor and the duration or frequency are secondary factors (how the amount is spread over time) (Lang et al., 2015). Aside from these salient issues, it is important to note that all increases in therapy dose do not result in improved upper extremity recovery as time post-stroke may be a confounding factor.

1) *Late sub-acute to chronic phases post-stroke.* (late sub-acute = 3 – 6 months post, chronic = 6 months and beyond (Bernhardt, Hayward, et al., 2017))

Compiling a majority of studies conducted mostly in the late sub-acute to chronic phase (time post-stroke 3 months to 5.4 years), a 2015 meta-regression analysis comparing one dose of rehabilitation intervention to another (disregarding the specific intervention provided, addressing a variety of functional targets, and measuring outcomes with different assessments) found a modest benefit of more time scheduled in therapy (statistically significant Hedges effect size of 0.35). The higher dose groups received on average 57 hours of therapy and the lower groups 24 hours and every additional 10 hours of therapy increased the effect size by only a small amount (0.034) (Lang et al., 2015; Lohse, Lang, & Boyd, 2014). This alludes to the need for much higher amounts of therapy to affect change. This is corroborated by two recent research studies that incorporated between 90 -
300 hours of intense upper limb training (Daly et al., 2019; N. S. Ward, Brander, & Kelly, 2019). Both studies found clinically meaningful changes in impairment and behavior at follow up. Although showing compelling results, the dose in all these studies was measured by total therapy time and this may not be a precise enough measure of dose. Thus, Lang et al. conducted a randomized controlled trial (RCT) looking at functional outcomes using the Action Research Arm Test (ARAT (Yozbatiran, Donmez, Kayak, & Bozan, 2006)) between groups of subjects receiving different numbers of repetitions of task specific upper limb training - also in the chronic phase post-stroke. Importantly they found 'no evidence of a dose-response effect of task specific training on functional capacity in people with long-standing upper-limb paresis post-stroke'. The number of repetitions varied from 3200 – 9600 over an 8-week period (Lang et al., 2016). These findings are similar to two older reviews that mix acute and chronic studies and find no significant benefit of extra dosing on arm recovery (Cooke, Mares, Clark, Tallis, & Pomeroy, 2010; Galvin, Murphy, Cusack, & Stokes, 2008).

These results confound the dose question in the late sub-acute to chronic phases (3 months and beyond), add to the importance of using accurate measures of dose, and also add to the need for addressing this important question with further research.

2) Acute and early sub-acute phases post-stroke. (acute = 1 – 7 days post, early sub-acute = 7 days - 3 months post (Bernhardt, Hayward, et al., 2017))
In the acute and early sub-acute phases post-stroke, the results are also mixed. Four studies that specifically compared higher doses of upper limb therapy to lower doses and were initiated within the acute and early sub-acute phases found no statistically significant benefit of higher dosing on different outcomes measured at various time points post training (except for a trend favoring the higher dosed specialized training group in the Donaldson et al. (2009) study – importantly, their usual dosed group actually performed better than their higher dose group of regular therapy) (Donaldson et al., 2009; G. Kwakkel, Kollen, & Wagenaar, 2002; Lincoln, Parry, & Vass, 1999; Rodgers et al., 2003). Subanalysis from a 2004 review also found no additional benefits of augmented therapy time on the ARAT (G. Kwakkel et al., 2004). In contrast, a 2013 study by Han et al. that specifically compared one, two, and three hours a day of upper limb conventional therapy over a six week period did find significantly greater improvements on both the UEFMA and ARAT scores (Han, Wang, Meng, & Qi, 2013).

One influential study that is often cited against the use of larger dosing in the early period post-stroke is the VECTORS study, where a three hour dose of Constraint Induced Movement Therapy (CIMT) led to worse outcomes both immediately post intervention and 90 days post intervention on the total ARAT when compared to a two hour dose of CIMT or a two hour dose of conventional Occupational Therapy (Dromerick et al., 2009). In contrast, a similar sized study (Thrane, 2015) (NORCIMT – total N = 47) incorporating
the same dosage of 3 hours of CIMT and also conducted less than 30 days post-stroke found the CIMT group had significantly greater improvements on the log transformed Wolf Motor Function Test (WMFT (Wolf et al., 2001)) and the Nine Hole Peg Test (NHPT (Oxford Grice et al., 2003)) post treatment with no difference between the groups at the six months follow up (similar but not worse outcomes). This study did not dose match the control group and hence was similar to the comparison made by the VECTORS study with a 3-hour CIMT group and 2-hour control group (with a lower dosed control group). The NORCIMT study included participants with better NIH Stroke Scale (NIHSS) scores at onset as compared to the VECTORS study [1.7 (1.8) for the NORCIMT study treatment group - VECTORS, 5.3 (1.8)] and subjects initially had the ability to extend two fingers or their wrist – known positive prognostic factors for recovery. Additionally, a smaller (total N = 23), older study (Boake, 2007) also initiated within 30 days post-stroke, and comparing 3 hours of CIMT to a dose matched group receiving traditional therapy found significantly better outcomes post treatment on the Upper Extremity Fugl-Meyer Assessment (UEFMA (Fugl-Meyer, Jaasko, Leyman, Olsson, & Steglind, 1975) for the CIMT group but no between group differences at 3 months on all outcomes. Their subjects had active finger or wrist movement at onset and their NIHSS scores initially were: treatment group 4.9 (1.8) and control group 5.3 (3.4) (Boake et al., 2007). Lastly, another smaller (total N = 26) more recent study also conducted in the early phase post-stroke, utilizing
three hours of CIMT (10 days – similar to the VECTORS study) found a significantly greater improvement in the WMFT and Motor Activity Log (MAL) post treatment favoring the CIMT group and no difference between groups on the WMFT and the MAL at three months when compared to an equal dose of conventional Physical or Occupational Therapy (Yu et al., 2017). The participants had on average better NIHSS scores at onset (Yu et al., mCIMT 3.85 (1.63), VECTORS, 5.3 (1.8)), had active finger or wrist extension at onset (VECTORS study did not require active distal movement), and they only required restraint of the non-affected upper limb for 30% of waking hours (VECTORS required 90%). Importantly they did not compare treatment group outcomes to a lower dosed control so one cannot determine if a slightly lower control dose would have led to different outcomes. This is also true for the Boake (2007) study. All of these factors may have led to their ‘more favorable’ outcomes in the treatment group compared to the VECTORS study. Thus three studies with ‘similar’ dosing and intervention to the VECTORS study and initiated within 30 days post-stroke did not find detrimental effects compared to their control groups. However, importantly all three study participants had the ability to extend their distal upper limb and two of the three studies included participants with better NIHSS scores at onset (not Boake et al.) which may have resulted in the better outcomes compared to the VECTORS study.

A second large-scale study that is also often cited against the benefits of
additional dosing in the early phase post-stroke is the recent Interdisciplinary Comprehensive Arm Rehabilitation Evaluation (ICARE) study (Winstein, Wolf, et al., 2016). This study compared the Accelerated Skill Acquisition Program (ASAP) consisting of 30 1-hour treatment sessions (3 X/week over 10 weeks) of task oriented upper extremity training based on motor learning principles to dose equivalent usual and customary care (DEUCC) – 30 hours of outpatient Occupational Therapy, and to usual care (UC)- (whatever intervention/dose the subjects received without manipulation). The participants had moderate impairments initially (they had to have minimal active wrist and finger extension). The mean amount of hours received by the ASAP group over the 10 weeks was 28.3, the DEUCC group 26.6, and the UC 11.2. The study found no between group differences at 12 months on the log transformed WMFT (time score). The authors note that this apparent lack of benefit of a higher dose of therapy starting at a mean of 45.8 days post-stroke may be due to the effect of spontaneous recovery being greater than any treatment effect - as 16% to 42% of the observed improvements within 6 to 10- weeks post stroke are independently associated with time post stroke (Gert Kwakkel, Kollen, & Twisk, 2006). Hence perhaps they needed a much larger dose to overcome the spontaneous recovery – the ASAP program provided on average less than 30 hours of therapy over 10 weeks.

A third recently published randomized controlled trial initiated within 30 days post-stroke also did not find a benefit in long-term recovery from varied
amounts of upper limb therapy (C. M. Stinear et al., 2017b). The median amount of upper limb therapy provided in this study during their subjects inpatient rehabilitation stay was 0.7-2.7 hours. Again this may not have been of sufficient volume to induce change during this acute/early sub-acute period.

In summary, there is a unique period of plasticity post ischemic stroke when there is an opportunity to enhance impairment and behavioral recovery via the introduction of training that is based on sound principles of motor learning such as use of increased repetition, salience, and progressive skill oriented tasks. Unfortunately, there are mixed findings from a paucity of studies evaluating the benefits of using a higher dose of therapy whether introduced early or later. Looking at the early period post-stroke, the influential VECTORS trial found detrimental effects of increased dosing when introduced early, and several studies including a review, found that a higher dose of rehabilitation did not affect outcomes (Donaldson et al., 2009; G. Kwakkel et al., 2004; G. Kwakkel, Wagenaar, Twisk, Lankhorst, & Koetsier, 1999; Lincoln et al., 1999; Rodgers et al., 2003). However, it is important to note that other studies similar to VECTORS did find beneficial outcomes (Boake et al., 2007; Thrane, 2015; Yu et al., 2017). Additionally, the two large RCTs (C. M. Stinear et al., 2017b; Winstein, Wolf, et al., 2016) that found that the amount of dosing does not affect outcomes offered a substantially smaller dose of rehabilitation than studies that did find beneficial effects (Boake et al.,
To add to this literature and aide in answering the important question of the effect of higher dosing, it is vital to conduct research like that conducted here (second study - chapter 3) which is initiated within one month post-stroke and evaluates outcomes when a greater amount of training is provided (an additional eight hours of intensive (200 - 300 hand or arm repetitions per training session)) compared to previous non-conclusive studies.

1.2.2 Timing

There is a time limited, unique period of heightened plasticity post ischemic stroke that lasts about one to three months in humans. This plasticity mediates spontaneous biological recovery and produces an enhanced responsiveness to rehabilitative intervention introduced during that time. It is believed that during this time of unique plasticity, ‘true’ impairment based recovery is maximal and is mediated from both of these related processes – spontaneous recovery and enhanced responsiveness to training (Zeiler & Krakauer, 2013). Traditional rehabilitation approaches in the current American healthcare system tend to encourage mobilization and gait training for early discharge, which can lead to adoption of compensatory strategies at the upper limb in the early period post-stroke. This can potentially inhibit ‘true’ long-term recovery at the impairment level (Lum et al., 2009). Thus it is imperative to develop effective interventions that incorporate the right type of training, optimal amount of dosing, and are introduced during this early period.
(taking advantage of the unique plasticity, and enhanced responsiveness to intervention), to promote ‘true’ motor recovery.

There are important benefits of conducting research in the first month post-stroke: first, ‘one can assess the interaction between the unique, time limited plasticity (with its associated enhanced responsiveness to intervention) and the intervention provided’, second, ‘testing a novel intervention in the time and place of its intended use can help solve problems and reduce barriers to its eventual application in the clinic,’ – most rehabilitation is initiated within the first month after a stroke, and lastly, it will ‘provide evidence for the clinical guidelines that suggest that specific interventions be initiated early’ (C. Stinear, Ackerley, & Byblow, 2013). Despite these benefits only 6% of RCTs are conducted within the first 30 days post-stroke (Coleman et al., 2017; Fluet & Deutsch, 2013; Krakauer, Carmichael, Corbett, & Wittenberg, 2012; C. Stinear et al., 2013).

With regards to optimal timing, ‘concerns about initiating training too early after stroke arose from early animal research showing that forced use of the affected forelimb and forced disuse of the non-affected forelimb immediately after induced injury blocked potentially beneficial plasticity changes and/or exacerbated injury’ (Humm, Kozlowski, Bland, James, & Schallert, 1999; Kozlowski, James, & Schallert, 1996; Krakauer et al., 2012; Risedal, Zeng, & Johansson, 1999; Shen et al., 2016). However, in the animal model, it has now been agreed upon that starting five days after stroke
has no adverse effects (Krakauer et al., 2012). With humans, a consensus regarding the question of safe and effective timing has not been reached and can be addressed more closely by evaluating dose-matched interventions presented at various time points. Two studies have assessed the effect of time using dose matched upper extremity interventions presented early versus later – 1) Wolf et al. 2010 - EXCITE trial (Wolf et al., 2010), and 2) Stock et al. 2017 (Stock, Thrane, Anke, Gjone, & Askim, 2017)). The EXCITE trial compared CIMT 3-9 months post to 15-21 months post-stroke. Their participants had active movement at the wrist or fingers - an important positive predictor of recovery. Both the ‘early’ and ‘late’ groups improved significantly from pre to post and pre to 12 months post training, with significantly better gains for the early group (compared to late group) on the WMFT time, Motor Activity Log (MAL), and the hand domain of the Stroke Impact Scale (SIS (Duncan, Lai, Bode, Perera, & DeRosa, 2003)) from pre to 12 months post. Stock et al., (2017) compared CIMT early (< 28 days) to six months post-stroke in persons who also had active distal upper extremity movement. Again both groups made significant gains on all measures from pre to 12 months post. They also found significantly better scores for the early group compared to the late group on the log transformed WMFT, Modified Rankin Scale (MRS) and the Nine Hole Peg Test (NHPT) immediately post intervention but unlike the EXCITE trial, these differences were not maintained at 6 or 12 months follow up. These two studies show that dose
matched therapy presented earlier – in this case CIMT - effects a quicker recovery curve as the early groups show significantly better scores immediately post intervention for the Stock et al., (2017) study and at 12 months for the EXCITE trial, but that some of these change are not maintained at follow up (six and twelve months for the Stock et al., study and at the longer term follow up of 24 months in the EXCITE trial).

Due to the limited amount of research in this area – more research trials using matched dosing and asking the specific question of early versus late need to be conducted. As the severity of disability may affect tolerance to early therapy (seen with the VECTORS study), studies should be conducted that specifically look at which populations the early interventions are more effective for (not beneficial in more affected individuals?). Another important question is how much is too much? Is early still beneficial if doses are much higher than standard therapy? Lastly, it would be important to determine what training ‘ingredients’ provide retention of the higher gains made post intervention by the early groups.

The studies presented here are all initiated within one month post-stroke and will add to the literature regarding the feasibility, safety, and benefits of an additional 8-10 hours of therapy introduced early.

1.2.3 Type of training - including priming, Virtual Reality, and robotics

Specific interventions that are deemed effective to varying degrees post-stroke fall into three categories: 1) priming techniques that excite
sensorimotor areas prior to training (including mirror therapy, action observation, motor and visual imagery), 2) augmenting techniques that are applied during training to assist voluntary activation of weak muscles (including functional electrical stimulation, biofeedback, rTMS, robotic therapy), and 3) task-specific training (Pomeroy et al., 2011). The training techniques that are investigated in this proposal utilize a combination of these three types of interventions.

1) Priming techniques

Providing effective rehabilitation techniques acutely for persons with severe initial impairment is a challenge as they are limited in the therapeutic tasks in which they can actively participate. One technique that may be beneficial in this group is priming. Priming the motor system using techniques such as somatosensory input, visual feedback, repetitive TMS, or movement-based strategies might stimulate plastic reorganization (e.g. rebalancing intercortical asymmetries in activation and activating appropriate circuitries) and thereby promote improved motor outcomes (Pomeroy et al., 2011; C. M. Stinear, Barber, Coxon, Fleming, & Byblow, 2008). One form of priming is mirror therapy. A thorough literature review found four studies that evaluated the use of mirror therapy as a treatment intervention for those with severe paresis of the hand and/or arm post-stroke (Colomer, E, & Llorens, 2016; Dohle et al., 2009; Radajewska et al., 2013; Thieme, Mehrholz, Pohl, Behrens, & Dohle, 2013). Dohle et al. (2009), Radajeska et al. (2013), and
Thieme et al. (2013) were conducted in the early sub-acute phase and Colomer et al. (2016) in the chronic phase. Radajewska et al. (2013) and Dohle et al. (2009) focused on the distal upper extremity. Dohle et al. (2009), Thieme et al. (2013), and Colomer et al. (2016) used dosed matched controls thereby strengthening their findings. All four studies did not find any additional benefit of adding mirror therapy for persons with initial severe paresis for most of their main outcomes - exception being, a greater number of distally plegic subjects made functional gains on the ARAT in the mirror group in the Dohle et al. (2009) study, and light touch improved significantly more in the mirror group in the Colomer et al. (2016) study. Based on these specific studies, the use of mirror therapy does not appear to add any extra benefit in this group of sub-acute and chronic subjects. However, this is based on only four studies of ‘smaller’ size. To definitively answer this question, more research needs to be conducted especially - in the acute time post lesion, and perhaps the type of mirror intervention needs to be different. It is known that mirror visual feedback stimulates activity within primary and higher order visual areas ipsilateral to the moving arm (Deconinck et al., 2015). All four of these studies did not use visually directed training movements (movements with visual goals) and adding visual targets to the task may tap into visual systems to a greater extent hence adding to the effect of the mirror therapy. Hence, the mirror therapy used in the first study presented in this thesis utilizes a visual target. This study is also initiated in the acute and early sub-acute periods to
add to the limited literature in this time period.

Priming can also be induced using contralaterally controlled passive movement. Byblow and colleagues (Byblow et al., 2012) used a method they call Active Passive Bilateral Therapy using a device that couples both hands such that active movement of one wrist produces mirror symmetric movements of the opposite wrist in a group of healthy subjects. A similar method was also used previously by Boos et al. (Boos, Qiu, Fluet, & Adamovich, 2011). In the Byblow et al. (2012) study, movement priming was found to facilitate corticomotor excitability as measured by increased TMS induced MEP amplitudes in the ipsilesional hemisphere for ≥ 30 minutes in the passive hemisphere. When used with individuals post-stroke, this is hypothesized to create a period of time where plastic reorganization may be facilitated within the affected motor cortex (Byblow et al., 2012).

In another study, active passive bilateral therapy was used in individuals with chronic stroke, starting with purely passive movement of the affected hand and progressing to active movement as able. The results showed improved and sustained upper extremity function of the affected hand, increased ipsilesional M1 excitability (S-R slope), increased transcallosal inhibition from the ipsi- to the contralesional M1, and increased intracortical inhibition within contralesional M1 (C. M. Stinear et al., 2008). More recently, the same group used this method in the sub-acute phase and noted similar neurophysiological changes along with accelerated time to
functional recovery (C. M. Stinear, Petoe, Anwar, Barber, & Byblow, 2014). This is the second form of priming utilized in the first study presented in this thesis.

2) Progressive skilled training

Data suggest that skilled, challenging, and progressive training involving many repetitions leads to neural changes that are linked to motor learning and recovery of impairment and behavior in human adults after stroke (French et al., 2016; Lohse et al., 2014). On a neurophysiologic level, repeated practice of a skilled and challenging movement ‘potentiates the pathways used to produce that movement. Prolonged potentiation via long-term practice facilitates motor system connectivity via mechanisms of synaptogenesis, axonogenesis, and angiogenesis, leading to enhanced motor representations at the cortical level’ (Lang et al., 2015; Nudo, 2013). This was shown elegantly in both primate and rat models where novel and progressively more difficult reaching tasks led to reorganization of the motor cortex representation compared to performing only known and stable tasks (J. A. Kleim, Barbay, & Nudo, 1998; Plautz, Milliken, & Nudo, 2000). In humans this was demonstrated by Perez et al. (2004). They measured performance, intra-cortical excitability, and motor evoked potentials (MEPs) of the Tibialis Anterior (TA) muscle pre and post skilled and unskilled training of the ankle joint in humans. They found that only skilled training (active movement of the ankle joint by following a series of patterns on a computer screen) led to
increased Transcranial Magnetic Stimulation (TMS) induced MEPs at the TA muscle, improved performance on the motor task, and decreased intracortical inhibition (Perez, Lungholt, Nyborg, & Nielsen, 2004).

It is especially difficult to initiate hand therapy immediately after a stroke due to limited active movement and strength in the muscles of the hand. Haptic robots integrated with complex gaming and virtual reality (VR) simulations are ideally suited to overcome these obstacles and may be a solution for delivery of early hand training programs that incorporate progressive skilled training (Fluet et al., 2017). These systems offer several advantages in the ability to deliver goal oriented activities, including the ability to provide highly repetitive practice with systematic increases in task difficulty, fine-tuned assistance when needed, and the ability to turn small active movements into goal directed activities (Duret, Grosmaire, & Krebs, 2019; G. Kwakkel, Kollen, & Krebs, 2008; Mehrholz, Platz, Kugler, & Pohl, 2008).

a) Virtual reality

To our knowledge, there are only eight published research articles using VR that are initiated within the acute and early sub-acute phases (Aminov, Rogers, Middleton, Caeyenberghs, & Wilson, 2018; Brunner et al., 2017; da Silva Cameirao, Bermudez, Duarte, & Verschure, 2011; Kong et al., 2016; Kwon, Park, Yoon, & Park, 2012; Saposnik et al., 2010; Vanbellingen, Filius, Nyffeler, & van Wegen, 2017; Yin, Sien, Ying, Chung, & Tan May Leng, 2014; Yong Joo et al., 2010). The early publication by Kong et al., (2010) was a
feasibility study for the Kong et al., 2016 study so there are only seven actual studies - six of which are RCTs in design (except Vanbellingen et al., 2017). Four of the six (except Kong et al., 2016 and Brunner et al., 2017) have small sample sizes, ranging from 8-13 subjects per group which can underpower study results. They are all dose-matched except for the Kwon et al., 2012 study, and the actual amount of VR therapy varies. Of the five dose matched studies, Saposnik et al. (2010) and Da Silva et al. (2011) did find significant improvement favoring the treatment group in the WMFT, arm movement speed, UEFMA, and the arm portions and the Chedoke-McMaster Stroke Impairment Inventory Stage of the arm and hand. However this was not maintained at 12 weeks in the second Spanish study presented (Da Silva 2011). The other three studies find within group improvements but no between group differences. This finding is similar to the Kwon et al. 2012 study that is not dose matched. Thus, only two of the six RCT studies providing varied amounts of dosing, and initiated early post-stroke found between group differences favoring VR. Vanbellingen et al. (2017) published a longitudinal study that found additional VR training resulted in a significant increase in hand dexterity measured by the Nine Hole Peg Test.

These mixed results from a small number of studies emphasize the importance of conducting similar research using VR in the future to find more definitive answers. The studies presented in this thesis utilize a VR based system in the acute and early sub-acute periods post-stroke to provide mirror
visual feedback (first study - chapter 2) and intensive upper limb training (second and third studies - chapters 3 and 4).

b) Robotic systems

With regards to the use of robotics in the acute and early sub-acute period post-stroke, twelve studies were found using six different robot systems: the MIT-MANUS (Aisen, Krebs, Hogan, McDowell, & Volpe, 1997; Rabadi et al., 2008; Sale, Franceschini, et al., 2014; Sale, Mazzoleni, et al., 2014; B. T. K. H. I. Volpe, Hogan N, Edelstein L, Diels C, Aisen M, 2000; B. T. Volpe et al., 1999), the Bi-Manu-Track (Hesse et al., 2005), the MIME (Mirror Image Movement Enabler) (Burgar et al., 2011), the ReoGo (Takahashi et al., 2016), the NeReBot (S. Masiero, Celia, Rosati, & Armani, 2007; Stefano Masiero, Armani, Ferlini, Rosati, & Rossi, 2014), and the end-effector REA plan robot (Dehem et al., 2019). As a group, these studies show that it is feasible to use robotic training in the acute/early sub-acute phases of therapy without adverse effects. When the robotic training was in addition to regular therapy, without dose matching, most studies showed greater improvements in function, impairment, and isolated active control of the upper extremity that was maintained in follow up favoring the robotic group ((Aisen et al., 1997), (B. T. K. H. I. Volpe, Hogan N, Edelstein L, Diels C, Aisen M, 2000), (Hesse et al., 2005; S. Masiero et al., 2007)). This was proposed to be from the increased repetitions performed by the trained arm with the robot. However, when the robotic therapy was dose matched, several of the studies found that
it did not produce any benefit over traditional therapy (Stefano Masiero et al., 2014), (Rabadi et al., 2008) and (Burgar et al., 2011). The only exception is the Dehem et al. (2019) study that did find significantly greater outcomes on the Box and Blocks and UEFMA test at six months in their VR group (Dehem et al., 2019). Thus intensity may be the main component necessary to interact with the spontaneous reorganization occurring in this sensitive period post lesion. Importantly, only one of the twelve studies used a hand specific robot for training. Study number two (chapter 3) compares intensive VR/robotic based upper limb training to usual care in the acute and early sub-acute periods post-stroke. This study adds to the controversial literature regarding the benefits of additional training early on. As it is not a dose matched study, it does not add to the literature regarding the specific benefits of robotics.

1.2.4 Predictive models post-stroke

Valid prognostic factors for post-stroke recovery are important to help institute appropriate rehabilitation interventions, allocate limited resources, provide realistic goals for patients and their families, and stratify subjects in clinical trials. Prognostic factors or biomarkers for prediction post-stroke can include the outcomes from neurological scales, amount of initial motor recovery (e.g. ability to grasp, extend fingers, abduct the shoulder), cognitive status, medical comorbidities (e.g. diabetes), physical activity, presence of inattention or neglect, and neurophysiological and neuroimaging measures such as TMS and MRI to determine corticospinal integrity and amount of corticospinal tract
damage respectively. Functional MRI can also utilize the amount of motor cortex excitability, as well as functional connectivity measures to predict outcomes (Cramer et al., 2007). Well established theories describing recovery from stroke propose a time limited and unique period of heightened plasticity post ischemic lesions lasting about one to three months in humans when ‘true’ impairment based recovery is optimal (Zeiler & Krakauer, 2013). An important model of recovery, the Proportional Recovery Rule for stroke states that the early spontaneous biological recovery described above, follows a proportional pattern based on initial impairment (measured using the Upper Extremity Fugl-Meyer – UEFMA (Fugl-Meyer et al., 1975)). This rule predicts that people will experience a recovery of approximately 70% of the maximal recovery possible based on the initial impairment that they demonstrate during the first week following a stroke (Prabhakaran et al., 2008). This rule was corroborated to varying degrees by five other studies – Byblow et al., (2015), Buch et al., (2016), Feng et al., (2015), Winters et al., (2015), and Stinear et al., (2017) (Buch et al., 2016; Byblow, Stinear, Barber, Petoe, & Ackerley, 2015; Feng et al., 2015; C. M. Stinear et al., 2017b; Winters, van Wegen, Daffertshofer, & Kwakkel, 2015). This proportional recovery rule was extended by Stinear et al. (2017) who state that the neurological process for this impairment based recovery involves the integrity of the corticospinal tract (CST) and that proportional recovery will occur regardless of severe initial impairment or the volume of rehabilitation provided if the CST is functional.
(indicated by the presence of TMS induced motor evoked potentials (MEPs)) (C. M. Stinear et al., 2017b). This group has developed their own widely accepted impairment and TMS based algorithm – the Predicted Recovery Potential algorithm 2 (PREP2) (C. M. e. a. Stinear, 2016). Although widely accepted, there are important issues with both these models. First, the statistical/mathematical premises of the proportional recovery rule have been challenged recently by three groups (Hawe, Scott, & Dukelow, 2018; Hope et al., 2019; Senesh & Reinkensmeyer, 2019). Hawe et al. and Hope et al., show that mathematical coupling and the ceiling effect of the UEFMA are largely responsible for the 0.70 variance explained in the linear regression, and using published scores, they show that actual recovery is much more variable than the rule predicts and Hope et al., also note that the model can be overly optimistic. Senesh et al., propose that the slope is actually the average probability of scoring across the remaining items at follow up. Besides these fundamental issues, both models emphasize biological recovery that occurs spontaneously, without systematically examining the impact of interventions utilized to modify or augment this spontaneous recovery. In the third study presented here (chapter 4), the validity of these two widely used predictive models was evaluated by comparing outcomes from these two models when a greater amount of training than that used to develop these models was used. This third study also evaluated how initial MEP status affected recovery compared to predicted outcomes from the
Proportional Recovery Rule. Additionally, the methodology used to develop the PREP2 algorithm was re-examined. The PREP2 algorithm uses MEPs obtained while the hand is at rest to assess CST integrity (resting method). Active methods (assessing MEP presence while the affected hand is contracting), utilized in several studies to increase the sensitivity of TMS tests for CST evaluation may have detected minimal residual CST function resulting in more accurate predictions (Cruz Martinez, Tejada, & Diez Tejedor, 1999; Heald, Bates, Cartlidge, French, & Miller, 1993). It was hypothesized that measuring initial MEPs with active methods will lead to more accurate long-term predictions using the PREP2 algorithm than using resting methods.

1.2.5 Outcome measures
Recent recommendations from the Stroke Recovery and Rehabilitation Roundtable (SRRR) include the use of standardized outcome measures – tested at least three months post - for all research studies assessing sensorimotor recovery post-stroke. This will advance understanding of recovery mechanisms, help with the development of more effective training methods, and help to consolidate knowledge using meta-analyses techniques (G. Kwakkel et al., 2017). These outcomes are based on the International Classification of Function and Disability definitions. The UEFMA is recommended to assess status at the body structure and function level. The ARAT is recommended to assess status at the activity limitation level. Both of
these measures were utilized at the recommended measurement times in the studies presented here. It has been noted previously that standard clinical measures used in research 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 can measure small changes in motor impairment without these effects in either direction (van Kordelaar et al., 2012). Thus, the SRRR recommends that ‘all future stroke trial should include kinematic and kinetic measures as they are the best way to distinguish between behavioral restitution and compensation’ (including the ability to determine patterns of learned bad-use (Alaverdashvili et al., 2008))(G. Kwakkel et al., 2017). In both study 1 (chapter 2) and 2 (chapter 3), recovery was evaluated using a combination of clinical, and kinematic/kinetic measures to incorporate these recommendations.

Additionally, TMS measures of cortical excitability were obtained in all three studies. Specifically for studies 1 and 2, TMS mapping allowed the assessment of neurophysiological changes occurring bilaterally both during the trial and up until the six-month follow up. Associations between ipsilesional TMS map changes with clinical and kinematic/kinetic outcomes were also evaluated in study 2. This helped determine the role of reorganization of cortical motor output in recovery post-stroke in this group of subjects (Chieffo et al., 2013). Four studies have used TMS based mapping in chronic stroke patients to quantify the recovery of the corticospinal system (Bastings,
Greenberg, & Good, 2002; Butler & Wolf, 2007; Liepert, Graef, Uhde, Leidner, & Weiller, 2000; Thickbroom, Byrnes, Archer, & Mastaglia, 2004); all noting an increase in the peak MEP amplitude and area of MEPs representing the hand in the ipsilesional sensorimotor cortex. Additionally, TMS based maps acquired early and 1-month after stroke showed that recovery of the impaired upper limb was associated with increased area in the ipsilesional hemisphere (Chieffo et al., 2013; Yarossi et al., 2019). To date, we know of only two studies that have sought to quantify the neuroplastic changes (via TMS mapping) evoked by an intervention in this same early stage following stroke (Boake et al., 2007; Platz et al., 2005). Results from Boake et al. (2007) indicated that an increased number of MEP-active sites in the ipsilesional hemisphere was associated with increased functional improvement in individuals receiving CIMT compared to controls receiving usual care. In contrast, Platz et al. (2005) did not find any change in the number of active sites in their two treatment groups (Bobath or Impairment Oriented Arm Training). In addition to TMS mapping, in the third study of this thesis, both active and resting TMS induced MEP status was used as an indicator of initial CST integrity. As noted previously, active methods may lead to more precise predictions on the PREP2 algorithm.

1.3 Aims/Rationale/Hypotheses

Literature review suggests important concepts related to effective upper limb rehabilitation post stroke. These include the interaction between dosage and
time, type of intervention used, biomarkers for prediction of stroke recovery, and appropriate outcome measures for stroke research. The studies presented in this thesis address and in some cases incorporate these issues.

The following section presents the three study aims with rationales and hypotheses. This is followed by the thesis body which is organized into three chapters - each a research study corresponding to the specific aims described below.

Aim 1: To investigate the feasibility, outcomes, and cortical motor changes of using virtual mirror feedback and passive movement priming prior to a hand training task that is initiated within one month post-stroke in persons with initial severe hand paresis.

Rationale

More individuals are left with greater upper limb deficits than lower limb deficits post-stroke. This is especially true for those with severe impairment initially. In a population with mixed severity of stroke, 78% had not reached age matched upper extremity function at 3 months post-stroke (Mayo et al., 1999), and in severely affected individuals, only 11.6% had complete functional recovery at 6 months post-stroke (G. Kwakkel, Kollen, van der Grond, & Prevo, 2003). One reason for this may be that persons with severe paresis post-stroke are limited in their ability to rehabilitate their upper extremity as they cannot participate in interventions that have been determined to be effective, for example task oriented practice or CIMT
(Pomeroy et al., 2011). Due to the unique, enhanced, and time limited neuroplasticity occurring initially post-stroke, the acute period is the optimal time for restorative methods of training (Zeiler & Krakauer, 2013). However, often these individuals are taught compensatory techniques using adaptive devices or the non-impaired arm (Krakauer et al., 2012). This can lead to the development of ‘learned non-use’ and further hinder recovery (Kitago et al., 2013; Lum et al., 2009). Indeed, focused use of the unimpaired arm immediately post lesion was shown to affect recovery of the impaired arm in a 2005 rat study (Allred, Maldonado, Hsu, Je, & Jones, 2005). Priming techniques may be beneficial in this group. One such technique is mirror therapy which can increase stroke affected sensorimotor cortical excitability without movement and thus assist in preserving neural circuits/promote plasticity in response to subsequent training thereby enhancing motor learning (Pomeroy et al., 2011; Saleh, Adamovich, & Tunik, 2014). Another priming technique that may be beneficial in this group is contralaterally controlled passive movement. The pilot investigation conducted to answer Aim 1 was initiated within the first one month post-stroke to tap into the enhanced plasticity and utilized our unique VR system that allowed hand training even for those with minimal movement. Specifically, the study evaluated the feasibility and clinical and kinetic outcomes induced by a novel combination of VR based mirror visual feedback with a visual cue and contralaterally controlled passive movement priming prior to a scaled pinch
training task. Cortical motor maps using TMS were obtained to assess changes in bilateral cortical representation associated with this novel intervention (Patel et al., 2017).

Hypotheses

Hypothesis 1a: The hand-focused virtual mirror feedback and passive movement priming coupled with a force modulation pinch task will be feasible and well tolerated by individuals with severe paresis when initiated within the first month post-stroke.

Hypothesis 1b: The hand-focused virtual mirror feedback and passive movement priming coupled with a force modulation pinch task will lead to clinically meaningful changes on measures of impairment and function in a group of individuals with severe paresis post-stroke.

Aim 2: To investigate whether an intensive hand focused upper limb virtual reality/robotic training program initiated within one month post-stroke leads to greater improvement on impairment and activity/functional outcomes compared to usual care in a group of persons with moderate initial impairments. Additionally, to investigate whether these changes in outcomes are associated with changes in cortical maps (an assay of cortical excitability/plasticity).

Rationale

There is controversy regarding the benefits of higher dosed interventions introduced in the early period post-stroke. Literature review of studies
addressing the benefits of additional dosing in the acute and sub-acute phases post-stroke finds mixed results. Two recent randomized controlled trials performed in the acute/early sub-acute period after stroke found that the dose of rehabilitation did not affect outcomes (C. M. Stinear et al., 2017b; Winstein, Wolf, et al., 2016). However, these studies offered a substantially smaller dose of rehabilitation than early studies that did find beneficial effects (Stock et al., 2017; Yu et al., 2017). A feasibility study initiated within one month post-stroke was conducted to address Aim 2. Specifically, an additional eight hours of hand focused upper limb VR/robotic training was compared to usual care in a group of individuals with moderate impairments. Associated, bilateral cortical map changes were evaluated using TMS mapping.

Hypotheses

*Hypothesis 2a:* The VR/robotic training group will demonstrate greater improvement on impairment and functional outcomes when compared to the usual care group.

*Hypothesis 2b:* The VR/robotic training group will demonstrate greater changes in ipsilesional cortical somatotopy when compared to the usual care group and this change in cortical somatotopy will be associated with affected upper extremity impairment and functional recovery.

Aim 3: To investigate whether an intensive hand focused upper limb VR/robotic training program initiated within one month post-stroke leads to
greater recovery than predicted from the Proportional Recovery Rule and the PREP2 algorithm compared to usual care in a group of persons with moderate impairment. In addition to evaluate how initial MEP status affects recovery compared to predicted outcomes from the Proportional Recovery Rule. Lastly, to investigate whether MEPs measured during attempted muscle contraction (active method) will be a better predictor of recovery than MEPs obtained while the hand is at rest (resting method).

Rationale
Valid prognostic factors for post-stroke recovery are important to help institute appropriate rehabilitation interventions, allocate limited resources, provide realistic goals for patients and their families, and stratify subjects in clinical trials. This research study further evaluated two algorithms, the Proportional Recovery Rule and the PREP2 algorithm in a new cohort of subjects. Both models emphasize biological recovery that occurs spontaneously, without systematically examining the impact of interventions utilized to modify or augment this spontaneous recovery. The study performed to address Aim 3 examined the impact of specific interventions and dosing on both models’ predictions by comparing the achieved motor recovery outcomes between high dose training and usual care groups - with a hypothesis that individuals in the higher dose VR/robotic group will achieve greater recovery then that predicted from both models’ predictions and that this recovery will also be greater than the control group.
Additionally, this study re-examined the methodology used to develop the PREP2 algorithm. The PREP2 algorithm measures CST functionality using the presence or absence of TMS evoked MEPs while the subjects are at rest. It is possible that testing MEPs actively during affected hand contraction may lead to fewer false negatives (subject ‘falsely’ categorized as MEP negative initially and hence with a worse predicted prognosis) and allow for more precise long-term predictions.

Hypotheses

Hypothesis 3a: Individuals in the higher dose VR/robotic group will show greater recovery than predicted from both the PREP2 and the Proportional Recovery Rule, and this will also be greater than a control group receiving usual care.

Hypothesis 3b: Measuring initial MEPs with active methods will lead to more accurate long-term predictions using the PREP2 algorithm than using resting methods.
CHAPTER 2

EXPLORING THE IMPACT OF VISUAL AND MOVEMENT BASED PRIMING ON A MOTOR INTERVENTION IN THE ACUTE PHASE POST-STROKE IN PERSONS WITH SEVERE HEMIPARESIS OF THE UPPER EXTREMITY.

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2.1 Abstract

Purpose: Explore the potential benefits of using priming methods prior to an active hand task in the acute phase post-stroke in persons with severe upper extremity hemiparesis.

Methods: Five individuals were trained using priming techniques including virtual reality (VR) based visual mirror feedback and contralaterally controlled passive movement strategies prior to training with an active pinch force modulation task. Clinical, kinetic, and neurophysiological measurements were taken pre and post the training period. Clinical measures were taken at 6 months post training.

Results: The two priming simulations and active training were well tolerated early after stroke. Priming effects were suggested by increased maximal pinch force immediately after visual and movement based priming. Despite having no clinically observable movement distally, the subjects were able to volitionally coordinate isometric force and muscle activity (EMG) in a pinch tracing task. The Root Mean Square Error (RMSE) of force during the pinch trace task gradually decreased over the training period suggesting learning may have occurred. Changes in motor cortical neurophysiology were seen in the unaffected hemisphere using Transcranial Magnetic Stimulation (TMS) mapping. Significant improvements in motor recovery as measured by the Action Research Arm Test (ARAT) and the Upper Extremity Fugl Meyer Assessment (UEFMA) were demonstrated at six months post training by
three of the five subjects.

Conclusion: This study suggests that an early hand-based intervention using visual and movement based priming activities and a scaled motor task allows participation by persons without the motor control required for traditionally presented rehabilitation and testing.

Key words: Acute phase, cortical priming, virtual reality-augmented, cerebral vascular accident, flaccid upper extremity

2.2 Introduction

Approximately 795,000 new or recurrent strokes occur each year in the United States (Go et al., 2014). Furthermore, stroke is one of the leading causes of long-term disability in the United States (Go et al., 2014). Proportionally more stroke survivors are left with upper extremity impairment and disability than lower extremity (Dobkin, 2005). 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 (Aprile et al., 2014; Duncan et al., 1994). In a population with mixed severity of stroke, 78% had not reached age matched upper extremity function at 3 months post-stroke (Mayo et al., 1999), and in severely affected individuals, only 11.6% had complete functional recovery at 6 months post-stroke (G. Kwakkel, Kollen, van der Grond, & Prevo, 2003). 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 as they can compensate for proximal motor control (Lang, Wagner, Edwards, Sahrmann, & Dromerick, 2006). Recovery of lateral corticospinal connections is needed for return of isolated distal hand function (J.W. Krakauer, 2005).

Unfortunately, despite research in humans and animals showing that most impairment based recovery after ischemic stroke occurs in the first 1-3 months (Zeiller & Krakauer, 2013) the majority of neuro-rehabilitation studies are conducted in the chronic phase (J.W. Krakauer, Carmichael, Corbett, & Wittenberg, 2012; C. Stinear, Ackerly, & Byblow, 2013). Additionally, most of these studies enroll subjects with some active movement of the affected upper extremity.

To our knowledge, there have been only three groups that have studied virtual reality (VR) 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 (da Silva Cameirao, Burmudez, Duarte, & Verschure, 2011; Saposnik et al., 2010; Yin, Sien, Ying, Ching, & Tan May Leng, 2014).

Importantly, none of these studies investigated the rehabilitation of individuals with flaccid or severely paretic upper extremities. This population is challenging because they are limited in the therapeutic tasks in which they
can actively participate. Consequently, emphasis is placed on teaching compensatory movements to accomplish necessary functional tasks (J. W. Krakauer, Carmicheal, Corbett, & Wittenberg, 2012) that can lead to “learned non-use” - a phenomenon in which the individual tapers use of the affected limb. Learned non-use has been shown to hinder the ultimate recovery of function in the impaired limb (Kitago & Krakauer, 2013). We surmise that tasks that engage the affected extremity early after stroke, however small that engagement is, may reduce the degree of learned non-use and potentially maximize the recovery process.

After stroke, it is hypothesized that there is an imbalance in inter-hemispheric inhibitory drive and motor cortex (M1) excitability, most notably reflecting a decrease in the excitability of ipsilesional M1. These changes have been associated with reduced functional recovery (Hummel & Cohen, 2006; Stinear, Barber, Coxon, Fleming, & Byblow, 2008). Proof of principle studies in humans have shown that restoring this balance is associated with better outcomes (Hummell & Cohen 2006).

In individuals with severe paralysis in the acute phase, priming the motor system using techniques such as somatosensory input, visual feedback, repetitive TMS, or movement-based strategies might stimulate plastic reorganization (e.g. rebalancing inter-cortical asymmetries in activation and activating appropriate circuitries) and thereby promote improved motor outcomes (Pomeroy et al., 2011; Stinear, Barber, Coxon, Fleming, & Byblow,
2008). One form of visual priming is VR based mirror feedback. For this, 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. Beneficial effects of visual priming have been found in both healthy and stroke affected individuals. In a healthy population, ipsilateral M1 corticospinal excitability (as measured by TMS) was facilitated when unilateral hand movement was fed back visually via a regular mirror box setup (Garry, Loftus, & Summers, 2005). Parallel results were found when visual mirror feedback was paired with repetitive motor training in a healthy group, and this facilitation was associated with improved motor performance of the untrained hand (Lappchen et al., 2012; Nojima et al., 2012). Similar effects have been demonstrated in persons with stroke. A study that compared VR based mirror feedback to regular mirror therapy in a sample of subjects with mild to moderate upper extremity hemiparesis found increased corticospinal excitability of the ipsilesional M1 in both treatment groups; with the VR based method showing the larger change in MEP amplitude and latency (Kang et al., 2012). However, it is important to note that this single study does not provide definitive support that VR based visual priming is superior to traditionally presented visual priming. With regards to neural correlates, 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 (Saleh, Adamovich, & Tunik, 2014). Taken together, these data suggest that VR based visual mirror feedback may be a useful priming tool to increase the excitability of and sensitivity to rehabilitation activities in desired brain networks in individuals post-stroke, and perhaps aid in functional recovery of the affected arm.

Priming can also be induced using contralaterally controlled passive movement. As an example, Byblow and colleagues (Byblow et al., 2012) used a method they called Active Passive Bilateral Therapy using a device that couples both hands such that active movement of one wrist produces mirror symmetric movements of the opposite wrist. A similar method was used previously by Boos et al. (Boos, Qiu, Fluet, & Adamovich, 2011). Movement priming was found to facilitate corticomotor excitability for ≥ 30 minutes in the passive hemisphere in healthy subjects. When used with individuals post-stroke, this is hypothesized to create a period of time where plastic reorganization may be facilitated within the affected motor cortex (Byblow et al., 2012).

In another study, active passive bilateral therapy was used in individuals with chronic stroke, starting with purely passive movement of the affected hand and progressing 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 ipsi- to the contralesional M1, and increased intracortical inhibition within contralesional M1 (Stinear, Barber, Coxon, Fleming, & Byblow, 2008). More recently, the same group used this method in the sub-acute phase and noted similar neurophysiological changes along with accelerated time to functional recovery (Stinear, Petoe, Anwar, Barber, & Byblow, 2014).

The challenging task of rehabilitating individuals with severely affected distal upper extremities, in addition to the limited amount of prior research conducted in the acute phase using these types of techniques, makes this a ripe time to ask whether a combination of VR based visual mirror and proprioceptive/movement-based priming prior to a scaled active training task may be feasible and beneficial for those in the acute phase post-stroke and with severe paresis (Stage 1 on Hand and Arm Impairment Inventory of the Chedoke-McMaster Stroke Assessment (Gowland et al., 1993)).

Specifically, this study aims to uncover the strengths and weaknesses of using visual and movement based priming techniques prior to a force modulation task in addition to usual care in persons with flaccid hemiplegia in the acute phase post-stroke. Additionally, clinical measures at 6 months will allow us to evaluate recovery patterns over time. This study will also elucidate the requirements for a future randomized controlled trial. We hypothesize that this unique combination of priming and training will allow for meaningful active participation in distal motor training despite severe paralysis that would render active participation with other training modalities impossible. Furthermore, we
hypothesize that the hand-focused intervention will be feasible and well tolerated by individuals with severe paresis in the first month post stroke. Finally, we propose that any changes in motor recovery will be associated with changes in cortical neurophysiology as assayed via TMS mapping.

2.3 Methods

A. Participants and Protocol

1) Participants

Five subjects were recruited from an acute rehabilitation department of a suburban hospital. After initial screening by the department’s physician, a physical therapist screened subjects based on the following criteria: 1) within one month post-stroke, 2) between the ages of 30 and 80, and 3) with severe upper extremity paresis (Stage 1 on Hand and Arm Impairment Inventory of the Chedoke-McMaster Stroke Assessment, (Gowland et al., 1993)). Exclusion criteria included: 1) severe spasticity (Modified Ashworth score of 3 or greater – (Bohannon & Smith, 1987)), 2) cognitive deficits rendering them unable to follow three step commands or attend to a task for at least ten minutes (based on review of the Speech Therapist’s evaluation using the Montreal Cognitive Assessment), 3) hemi-spatial neglect rendering them unable to interact with an entire twenty-four inch computer screen (based on review of the physiatrist’s admission evaluation), 4) proprioceptive loss that renders potential subjects unable to interact with a virtual environment without looking at their hands (tested clinically by the physical therapist), and 5)
unstable blood pressure and oxygen saturation responses to activity. Between January 2015 and October 2015, 80 subjects were screened by a physical therapist and 5 met the above criteria. Subjects ranged in age from 51 to 66 years (58.2 SD 6.91). Four of five subjects had subcortical lesions. Their initial Upper Extremity Fugl-Meyer Assessment (UEFMA) (Fugl-Meyer, Jaasko, Leyman, Olsson, & Steglind, 1975) scores ranged from 2 to 6 and represented reflexive and active scapular movement only (Table 1). All subjects provided written consent prior to participating in this study.

Table 1. Demographic and baseline data

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age</th>
<th>Days Post Stroke</th>
<th>Lesion Site</th>
<th>UEFMA Pre</th>
<th>Chedoke Pre</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prox</td>
<td>Distal</td>
</tr>
<tr>
<td>S1</td>
<td>Male</td>
<td>55</td>
<td>9</td>
<td>L Internal Capsule</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>S2</td>
<td>Male</td>
<td>51</td>
<td>27</td>
<td>L Basal Ganglia</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>S3</td>
<td>Male</td>
<td>53</td>
<td>7</td>
<td>R Frontal and Parietal</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>S4</td>
<td>Female</td>
<td>65</td>
<td>5</td>
<td>L Pons</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>S5</td>
<td>Male</td>
<td>66</td>
<td>16</td>
<td>R Pons</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

2) Protocol

All subjects were projected to receive 8 1-hour training sessions over a two-week period. All received 8 sessions except S5 (received 7 sessions) due to early discharge. All subjects received 15 minutes of each of the two priming methods (60 to 120 repetitions per priming protocol depending on their speed
of movement) followed by 15 minutes of training using the force modulation pinch trace task. In addition, subjects received their standard in-patient rehabilitation program (which included positioning, range of motion, supportive devices, and functional electrical stimulation to the affected upper extremity).

B. Training Systems and Simulations

1) System

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 (Adamovich et al., 2009).

2) Priming Tasks

The priming involves two simulations. The first is a visual priming task consisting of a flexion task of the unaffected index finger without coupled passive movement of the affected hand. The second is a movement based priming task consisting of an extension task of the unaffected hand coupled to movement of the affected hand via an exoskeleton. The flexion task was chosen because our group has demonstrated in chronic stroke that this type of virtual mirror training activates regions in the sensory-motor cortex similar to those activated by volitional movement of the affected hand (Saleh, Adamovich and Tunik., 2014). This is followed by the extension task that incorporates contralaterally controlled passive movement as a priming
technique (Boos, Qiu, Fluet, & Adamovich, 2011; Byblow et al., 2012). These two tasks were chosen to increase cortical excitability of the hand area of M1 immediately prior to the scaled active pinch force modulation task. This sequence was followed for all subjects.

- Flexion Task Without Exoskeleton (visual based priming; Saleh, Adamovich, & Tunik, 2014):

The subjects wore a CyberGlove™ (Immersion, USA) on the unaffected hand to track finger angles. They watched a computer screen that shielded their hands from view and displayed virtual feedback of 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. Although the subjects only moved their non-affected index finger, the visual feedback presented to them in real time appeared as if they were moving their affected finger to the goal target. The subjects spent 15 minutes on this priming method (60 to 120 repetitions depending on their speed of movement) (Figure 1).
- Extension Task With Exoskeleton (movement based priming) (Boos, Qiu, Fluet, & Adamovich, 2011):

In addition to the above hardware, the subjects wore a CyberGrasp™ (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 this hand). The 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 (Figures 2 and 3). This simulation was performed after the flexion task and all subjects spent 15 minutes on this task (60 to 120 repetitions depending on their speed of movement).
Figure 2: View of the CyberGrasp™ (Immersion, USA) on the affected hand.

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

3) Training Intervention

Pinch Trace Task:

For the training task we have chosen an isometric pinch force task to control the vertical motion of a cursor in order to trace a sinusoidal wave on a
computer screen. The advantage of this task is that the instrumentation allows for calibrating the force demands to accommodate minimal voluntary movements available to the subjects while still preserving meaningful visual feedback (Fluet et al., 2012). This incorporates principles of motor learning such as enhancing salience and thus motivation to increase its efficacy as a training tool. This task was used as both a training task and an outcome measure (see below). Pinch force was measured with an ATI Nano17™ force sensor (ATI Industrial Automation, USA). Subjects pinched the sensor placed between the index and thumb of the affected hand in order to control the vertical displacement of a cursor along a sinusoid that was moving along the horizontal dimension of a computer screen. Subjects’ finger position on the force sensor was inspected throughout the session to ensure that they pinched with the thumb and index finger, and did not compensate by using alternate strategies. Subjects spent 15 minutes on this training task.

C. Outcome Measures

1) Clinical Assessments

A physical therapist performed the UEFMA, the Chedoke-McMaster Stroke Impairment Inventory Stage of the arm and hand, and the Action Research Arm Test (ARAT) at baseline, prior to each training session, immediately post intervention, and again 6 months after the intervention. The UEFMA and the Chedoke-McMaster Inventory measures were chosen as both can be used with people who have severe paresis and are recommended for use in the
acute and sub-acute phase post stroke (APTA - StrokEdge - neuropt.org).

2) Kinetic- Pinch force and trace

Pinch force was used as an outcome measure because the sensitivity of the load sensor used is such that it can detect minute levels of force and therefore it is sensitive to small changes in motor function which could not be detected using clinical measures.

a) Pinch force measures the maximum voluntary force a subject can exert on a force sensor held between their paretic thumb and index finger. Larger numbers indicate stronger pinch force. Subjects were given two attempts and the largest number was used.

b) Pinch trace measures the ability to control pinch force between 0% and 50% of maximum pinch force in order to control the vertical motion of a cursor tracking a horizontal sine wave (duration of 1 cycle ≈ 6 seconds, period = 0.15 Hz) on a computer screen. Force data was collected at 100 Hz over the 4-minute trace. RMSE is a measure of the difference between a sinusoid and the force values the subject actually generates. It is normalized by maximum force because the amplitude of the sinewave is determined by the maximum force generated during calibration prior to each training session. These values are very different between subjects and within each subject per training day and therefore are normalized by this maximum force calibration value in order to allow comparison between subjects and across days.

The formula is as follows:
\[
RMSE = \sqrt{\frac{\sum_{t=1}^{n} (\text{ActualForce}(t) - \text{ForceModel})^2}{\text{MaxForce}}}
\]

where Force Model is the sinusoid that the subject was required 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.

3) Electromyographic (EMG) Assessment

Surface EMG was recorded at 2 kHz (Delsys Trigno, Natick, MA, USA) from the First Dorsal Interosseous (FDI) muscle, the Abductor Pollicis Brevis (APB) muscle, the Flexor Digitorum Superficialis (FDS) muscle and the Extensor Digitorum Communis (EDC) muscle of the affected upper extremity while the subjects performed the pinch force and 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, (as well, 60Hz noise was notch filtered out) full wave rectified and a Root Mean Square average was applied with a 50 ms time window.

4) Transcranial Magnetic Stimulation (TMS) Mapping

To assay the neurophysiological underpinnings of performance and recovery, we measured the EMG activity of hand muscles during the pinch trace task, and mapped the motor evoked potentials (MEPs) bilaterally (using Transcranial Magnetic Stimulation – TMS) pre/post the training period.

In subjects one to four, topographic representations of finger-hand
muscles were mapped bilaterally pre and post training. Motor evoked potentials (MEPs) were recorded from surface electrodes (Delsys Trigno, 2 kHz sampling) placed on the first dorsal interosseous [FDI], extensor indicis longus [EI], abductor pollis brevis [APB], abductor digiti minimi [ADM], flexor digitorum superficialis [FDS], and extensor digitorum communis [EDC] muscles of the limb contralateral to the stimulated hemisphere. Subjects were seated with their arms comfortably positioned in front of them and EMG was monitored to ensure that the upper extremity was at rest. Frameless neuronavigation (Advanced Neuro Technology) was used to monitor and record TMS coil (Magstim Rapid2, 70 mm AFC coil) position during and across sessions. All stimulation was conducted with the TMS coil held tangential to the scalp with the posterior handle 45° off the sagittal plane (Littmann, McHenry, & Shields, 2013). Mapping began by identifying the site at which the minimal stimulator output produced the strongest consistent MEPs in the contralateral FDI muscle (motor “hotspot”). Following determination of the FDI hotspot, resting motor threshold (RMT) was calculated as the minimum stimulus intensity required to elicit motor evoked potentials (MEPs) > 50 µV in the FDI muscle for 50 % of 6 consecutive trials (Butler, Khan, Wolf, & Weiss, 2005). A 10 x 10 cm area surrounding the motor hotspot was marked using the neuronavigation software to provide consistent map boundaries across sessions. If a reliable hotspot for the lesioned hemisphere could not be determined due to the absence of MEPs,
the hotspot and map boundaries from the contralesional hemisphere were mirrored to the lesioned side and mapped at 100% of stimulator output. All mapping was performed with the subject at rest and stimulation intensity set to 110% of the determined RMT (Ngomo, Leonard, Moffett, & Mercier, 2012). TMS pulses were delivered within the bounds with special attention paid to regions surrounding the hotspot territory (Niskanen et al., 2010). For each stimulation point MEPs were calculated as the peak-to-peak amplitude of the filtered (2nd order Butterworth filter, 5-250 Hz band-pass) EMG signal 20-50ms after the TMS pulse. MEP amplitudes were interpolated to a 10 x 10 cm mesh of 5 mm resolution centered on the M1 hotspot, using cubic surface interpolation (Borgehetti et al., 2008; Weiss et al., 2013). Map area, the extent of the representation producing corticospinal output, was calculated as the product of the number of interpolated scalp sites eliciting MEPs > 50uV and the map resolution (0.25 cm²) (Bastings, Greenberg, & Good, 2002; Borgehetti et al., 2008; Flament, Goldsmith, Buckley, & Lemon, 1993; Sparing, Buelte, Meister, Paus, & Fink, 2008; Wassermann, McShane, Hallett, & Cohen, 1992; Weiss et al., 2013).

2.4 Results

Five subjects were recruited for this study. They received 7 or 8 sessions (45 minute sessions) of training. Each subject participated in the 2 priming tasks (visual and movement based) and 1 training task (pinch force modulation) at each session. All training was well tolerated without adverse side effects such
as fatigue. Furthermore, the subjects were able to understand the simulations despite having no prior instructions.

1) Maximum Pinch Force Pre and Post Priming

Maximum pinch force of the affected hand was measured pre and immediately post priming during each training session. This was used as a proxy measure of excitability changes induced from the priming. Table 2 shows the mean change (with SEM) per person. Four of the 5 subjects demonstrated a mean increase in change in pinch force following priming. This may reflect the hypothesized increase in excitability caused by the two priming tasks. These changes are small and would not be considered clinically significant but they may represent small positive changes in motor function elicited by a 30 minute priming intervention.

Table 2. Mean of the change in maximum force pre to post priming per subject.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Mean of change in maximum force</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>0.042 N</td>
<td>0.007 N</td>
</tr>
<tr>
<td>S2</td>
<td>-0.016 N</td>
<td>0.17 N</td>
</tr>
<tr>
<td>S3</td>
<td>0.006 N</td>
<td>0.032 N</td>
</tr>
<tr>
<td>S4</td>
<td>0.34 N</td>
<td>0.235 N</td>
</tr>
<tr>
<td>S5</td>
<td>2.9 N</td>
<td>1.878 N</td>
</tr>
</tbody>
</table>

2) Pinch Trace Task Performance and EMG Relationship

The pinch trace training task allowed active participation by these individuals despite having no observable voluntary movement of the affected hand. Figure 4 is a representative example of one subject's change in force and control over the training period while continuing to have a clinically flaccid hand. For example, initially on day 1 of training, S1 had no active hand
movement and was unable to actively modulate pinch force to track a sine wave. Despite this, EMG demonstrated some minimal muscle activation of the APB muscle (Figure 4, left panel). On day 3, the same subject continued with a “flaccid” hand, however showed improved tracking ability with corresponding improvement in APB muscle EMG amplitude and pattern (Figure 4, middle panel). With continued training, this improvement increased to the last day with both APB and FDI muscles showing corresponding EMG activation (Figure 4, right panel). Subjects S2, S4, and S5 also demonstrated improved performance on this force modulation task with corresponding improvements in FDI and APB activation as measured by EMG.

Figure 4. Force and EMG relationship for S1.

Four of the five subjects demonstrated a decrease in RMSE during the pinch trace task over time. Subject 1 started at 0.206 on day 1 and ended at 0.047 on day 8. Subject 2 started at 0.259 on day 1 and ended at 0.16 on day 8. Subject 4 started at 0.41 on day 1 and ended at 0.16 on day 8. Subject 5
started at 0.209 on day 1 and ended at 0.031 on day 7. Subject 3 could not perform the task adequately at any time point (Figure 5). The gradual decrease in RMSE over the course of the intervention demonstrated by these four subjects may reflect task learning despite their poor levels of overall motor performance.

![Normalized RMSE over time in days for 4 subjects. Subject 3 was unable to perform the task adequately therefore RMSE could not be calculated.](image)

3) Maximum Pinch Force Measured Pre and Post Training

Maximum pinch force was also measured at testing sessions pre and post training. Figure 6 indicates that four of the five subjects generated an increased pinch force after the training. The maximum pinch force the first 2 subjects could generate increased over time from 0.07 N to 2.34 N for S1 and 0.13 N to 2.41 N for S2. S3 did not make any gains (0.10 N to 0.11 N) The last two subjects also made gains, 0.12 N to 0.30 N for S4, and 0.32 N to 17.86 N for S5 (Figure 6).
4) Clinical Tests Measured Pre/Immediately Post Training and 6 months Post Training

Pre and post training:

S1 started with a score of 2/66 at onset on the UEFMA and progressed to 29/66 by the end of training. These scores represented reflex activity initially and mostly proximal movement with some partial grasp and hand opening at the end of training. S1’s Chedoke-McMaster scores improved for both the arm and hand with more gains made proximally. Their ARAT score was a 0 at onset and improved to a 6/57 reflecting proximal movement. S2 had an initial score of 6/66 on the UEFMA reflecting reflex and proximal scapular movement. After training this improved to 13/66 and again the majority of gains were made proximally. S2’s Chedoke-McMaster scores improved minimally for both the arm and hand scores. Their ARAT score only improved to 3/57 after training and again this represented minimal active proximal
movement. S3 scored 4/66 on the UEFMA initially (reflex and scapular movement) and made only proximal gains by the end of training. Similar gains were seen on the Chedoke-McMaster assessment. As well, their ARAT score improved minimally to a 3/57 post training. S4’s initial UEFMA score was 3/66 and improved to 9/66. This subject’s Chedoke-McMaster score changed from 1 on both the hand and arm sections initially to a 2 on the arm section post. Their ARAT score improved minimally to a 3/57 after intervention. This subject had only reflex and scapular movement at onset and made only proximal gains. Finally, S5 started with a 4/66 on the UEFMA (reflexive and scapular movement) and progressed to a 9/66. Their Chedoke-McMaster scores changed from 1 to 2 on both the arm and hand sections and their ARAT improved minimally to 3/57 (Table 3).

Six months after training:

All participants made gains clinically at 6 months after training with subjects 1, 3, and 4 showing the greatest functional and impairment based recovery (Table 3).

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Chedoke Arm</th>
<th>Chedoke Hand</th>
<th>UEFMA Proximal</th>
<th>UEFMA Distal</th>
<th>ARAT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>6 mths</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>S1</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>S2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>S3</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>S4</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>S5</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
4) TMS Maps

TMS motor maps of the non-lesioned side for subjects 1-4 showed an increase in area for the FDS and EDC muscles from pre to post training (Figure 7). No MEPs were demonstrated at the lesioned hemisphere for any muscles tested at both time frames (pre and post training) in all 4 subjects. This increase in motor map representations in the contralesional M1 may reflect early cortical reorganization required to support the impaired hand’s function as this has been shown to correlate with improving upper extremity function in this early time post-stroke (Rehme, Fink, von Cramon, & Grefkes, 2011).

![Figure 7. TMS motor maps pre and post training for FDS and EDC muscles for subjects 1-4 (the group average area is shown with standard error of the mean).](image)

2.5 Discussion

There are several relevant findings from this group of subjects that provide evidence for further study. First, it may be possible to develop an intervention specifically targeted to the hand of persons with a clinically flaccid
arm. Second, although this study is conducted in the very early phase post-stroke, the subjects were able to tolerate an additional 45 minutes of hand therapy. Third, despite having an initially flaccid upper extremity at onset, several subjects demonstrated important clinical gains at 6 months after training. Lastly, results from the pinch trace task demonstrated that even when subjects had no clinically measurable or observable active movement of the hand, there was some initial minimal muscle activation that could be detected by an instrumented force sensor and EMG. Notably, the force and EMG modulation improved over time (Figure 4). It may be the case that visual feedback provided by the pinch trace task increased the salience and motivation as subjects could unequivocally see that they were able to actively control the cursor despite “not being able to move their fingers”. 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 (Shiri et al., 2012). Furthermore it is known that increased salience of the training activity enhances neuroplasticity in both animals and humans (Kleim & Jones, 2008).

In the past, VR based visual mirror simulations in chronic stroke subjects have shown to activate brain areas that partially overlap those that produce active movement of the affected arm (Saleh, Adamovich, & Tunik, 2014). Furthermore, a study by Kang et al. (2012) demonstrated greater cortical excitability of the affected hemisphere using VR based visual mirror
feedback as compared to a mirror box or control. Although there is no direct
evidence, it is interesting to consider that the increase in maximal pinch force
in the affected hand after the priming tasks for four of the five subjects may
have been related to an increase in ipsilesional cortical excitability induced by
these tasks. 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 (Pomeroy, et al., 2011; Stinear, Barber, Coxon, Fleming,
& Byblow, 2008). We hope that our priming interventions will lead to
increased neural activity of the damaged cortex and promote more effective
brain reorganization, which will perhaps facilitate optimal motor recovery.

Although small, the increase in maximum force noted for four of the
subjects suggested an improvement in motor output in the hand over time
(Figure 6). Additionally, the overall decrease in RMSE seen for the pinch
trace task over the first few days with four of the subjects suggests that
learning might be occurring (Figure 5). However, we acknowledge that this
could be due to becoming familiar with a new task rather than true motor
learning.

In this study, the pinch trace task was used both as a training method
and an outcome measure. It demonstrated the benefits of objective,
technologically based measurement tools. 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 can measure small changes in motor ability without these effects in either direction (van kordelaar et al., 2012). 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. For example, S1 made distal 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 detected change starting on day 1.

TMS maps were obtained for four of the subjects and demonstrated an increase in map area for the FDS and EDC muscles in the unaffected hemisphere from pre to post testing. Using fMRI, Rehme et al. (Rehme, Fink, von Cramon, & Grefkes, 2011) found additional recruitment of the unaffected M1 and premotor areas over the first two weeks post acute stroke in their severely impaired subgroup that was correlated with functional recovery of the affected arm (measured with the ARAT and maximum grip force). They suggested that this reflected stroke induced early reorganization that might represent an enhanced effort by severely impaired individuals to move their affected side, and support arm function during this acute time. A similar reorganization in the unaffected hemisphere may be occurring in the subjects in this current study and merits further investigation.

Finally, establishing rehabilitation prognoses for persons with upper
extremity hemiplegia has been a topic of discussion for many years. It has
been suggested that persons with minimal active movement of the arm and
hand be taught compensation techniques emphasizing the use of the
unimpaired upper extremity. More recently, Stinear et al. (2012), suggested
that people post stroke without active shoulder abduction or finger extension
(tested at 72 hours post event) and without motor evoked potentials at 2
weeks post-stroke have “limited or no predicted potential for upper extremity
recovery” at 12 weeks after stroke. None of the 5 the subjects in this study
demonstrated active shoulder abduction or finger extension at pretest (tested
at a mean of 11.6, range 5 to 27 days after CVA). In addition, none
demonstrated lesioned hemisphere motor evoked potentials at the extensor
carpi radialis muscle during pre or post training evaluations. Contrary to their
findings, 3 of our 5 subjects showed good gains in all clinical measures made
at 6 months after training (Chedoke Inventory arm and hand progressed to 4-
5, the UEFMA improved to a range of 44-48/66, and their ARAT scores
increased to 26-35/57). These findings suggest that there could be potential
for recovery and functional use of the upper extremity in those with severe
impairment at onset that persists beyond two weeks post-stroke, and that
continued attempts to develop evaluation and rehabilitation techniques to
identify and maximize this potential are indicated.

In the future we plan to conduct a larger scale randomized controlled
trial to determine whether this type of early intervention changes motor and
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” (Nudo, Wise, SiFuentes, & Milliken, 1996). 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 elicit this type of reorganization in our subjects. The addition of TMS mapping and excitability measures for all subjects in our future work will be important to objectively characterize any changes in cortical neurophysiology that is associated with improvement in motor outcome brought upon by our interventions.

2.6 Study Limitations

We were primarily interested in testing our ability to provide a scaled hand intervention in this early period post-stroke and determining if priming had any measurable effect on motor function and therefore we did not have a usual care or non-priming control. Our future study will be a randomized control trial that will address some of these limitations.

There are natural challenges to conducting such a study in the acute care setting. A major one 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” (Kwakkel, Kollen, & Lindeman, 2004). However, it has also been suggested that recovery can be positively affected by the right type of training (Zeiler & Krakauer, 2013). As stated previously, it is our anticipation that the task-specific training immediately after the priming techniques, 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, patients with persistent severe hemiparesis are often discharged to a less intense rehabilitation setting faster than someone with active motor control. 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 priming method separately in order to tease apart which method is more beneficial.

2.7 Conclusion
This initial study allowed us to demonstrate the ability to use VR based visual mirror feedback and movement based priming techniques in conjunction with a pinch trace force modulation task in the acute phase post-stroke in five people with flaccid upper extremities. Traditional rehabilitation options are limited for those with severe paresis, and may encourage compensatory movements that can potentially lead to learned non-use. Our method allowed people without discernable motor ability distally to produce meaningful movement that could be quantified with objective measures and instrumented technology. Furthermore, 3 of the 5 subjects demonstrated important clinical gains at 6 months after training suggesting that developing effective rehabilitation strategies for this group is warranted. We suggest 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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Declaration of Interest Statement

There are no declarations of interest.

References


CHAPTER 3

INTENSIVE VIRTUAL REALITY AND ROBOTIC BASED UPPER LIMB TRAINING COMPARED TO USUAL CARE, AND ASSOCIATED CORTICAL REORGANIZATION, IN THE ACUTE AND EARLY SUB-ACUTE PERIODS POST-STROKE: A FEASIBILITY STUDY.

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3.1 Abstract

Background

There is conflict regarding the benefits of greater amounts of intensive upper limb rehabilitation in the early period post-stroke. This study was conducted to test the feasibility of providing intensive therapy during the early period post-stroke and to develop a randomized control trial that is currently in process. Specifically, the study investigated whether an additional eight hours of specialized, intensive (200 – 300 separate hand or arm movements per hour) virtual reality (VR)/robotic based upper limb training introduced within 1-month post-stroke resulted in greater improvement in impairment and behavior, and distinct changes in cortical reorganization measured via Transcranial Magnetic Stimulation (TMS), compared to that of a control group.

Methods

Seven subjects received 8–1hr sessions of upper limb VR/robotic training in addition to their inpatient therapy (PT, OT, ST). Six subjects only received their inpatient therapy. All were tested on measures of impairment [Upper Extremity Fugl-Meyer Assessment (UEFMA), Wrist AROM, Maximum Pinch Force], behavior [Wolf Motor Function Test (WMFT)], and also received TMS mapping until six months post training. ANOVAs were conducted to measure differences between groups across time for all outcome measures. Associations between changes in ipsilesional cortical maps during the early
period of enhanced neuroplasticity and long-term changes in upper limb impairment and behavior measures were evaluated.

Results
The VR/robotic group made significantly greater improvements on UEFMA and Wrist AROM scores compared to the usual care group. There was also less variability in the association between changes in the First Dorsal Interosseus (FDI) muscle map area and WMFT and Maximum Force change scores for the VR/robotic group.

Conclusions
An additional eight hours of intensive VR/robotic based upper limb training initiated within the first month post-stroke may promote greater gains in impairment compared to usual care alone. Importantly, the data presented demonstrated the feasibility of conducting this intervention and multiple outcome measures (impairment, behavioral, neurophysiological) in the early period post-stroke.

Keywords Stroke, Upper Limb, Acute, Early Sub-acute, Virtual Reality, Robotic Therapy, Transcranial Magnetic Stimulation

3.2 Background
Approximately 795,000 new or recurrent strokes occur each year in the United States and the prevalence of chronic stroke is approximately seven million (Mozzaffarian et al., 2016). It is a leading cause of adult long-term disability in the United States with the financial burden of related care among
the fastest-growing expenses for Medicare (Mozzaffarian et al., 2016). Proportionally more stroke survivors are left with upper extremity impairment and disability than that of the lower extremity (Dobkin, 2005). At six months post-stroke only 5-20% achieve full return of arm function (Colomer, E, & Llorens, 2016; Heller et al., 1987). It is thus imperative to develop and test innovative upper extremity training protocols that are based on sound principles of motor learning (as skilled, challenging, and progressive training involving many repetitions leads to neural changes that are linked to motor learning and recovery of impairment and behavior in human adults after stroke (French et al., 2016; Lohse et al., 2014)), and also to compare changes in impairments, behavior, and brain organization to help identify the neural substrates of recovery.

There is a time-limited period of unique neuroplasticity post ischemic stroke that lasts about one to three months in humans. This plasticity mediates spontaneous biological recovery and produces enhanced responsiveness to rehabilitative intervention introduced during that time (Zeiler & Krakauer, 2013). It is believed that during this time of unique plasticity, impairment based recovery is maximal and is mediated from both of these related processes - spontaneous recovery and enhanced responsiveness to training (Zeiler & Krakauer, 2013). Consequently, it would be logical to assume that additional hours of intensive training initiated within the acute and early sub-acute period post-stroke (acute: 1 – 7 days post,
early sub-acute: second week - 3 months post (Bernhardt et al., 2017) would interact with this distinct type of plasticity and result in better outcomes compared to conventional rehabilitative care. Careful review of the literature suggests that the relationship may not be so straightforward. For example, a 2014 meta-analysis found a positive relationship between increased therapy time and clinical measures of function and impairment overall (Lohse, Lang, & Boyd, 2014). However, other individual studies (including a large randomized controlled trial (RCT)), and a sub-analysis from a 2004 review, that have focused on therapy within this early phase, and specifically compared higher amounts of upper limb therapy to lower amounts, found no statistically significant benefit of higher amounts of intervention on different outcomes measured at varied time points post training (Kwakkel, Kollen, & Wagenaar, 2002; Kwakkel et al., 2004; Lincoln, Parry, & Vass, 1999; Rodgers et al., 2003; Weinstein, 2015). Additionally, an influential study by Dromerick et al. found that three hours of Constraint Induced Movement Therapy (CIMT) led to worse outcomes on the Action Research Arm Test (ARAT) – (Yozbatiran, Der-Yeghiaian, & Cramer, 2008) when compared to two hours of CIMT or two hours of conventional occupational therapy (Dromerick et al., 2009).

Mechanisms of neuroplasticity such as the formation of new synaptic connections with concomitant modification in the cortical excitability and somatotopic remapping can be positively influenced by training methods that are developed from established principles of motor learning (Kleim & Jones,
The study presented here was performed to determine feasibility, and to help develop a large scale randomized controlled trial (RCT) that we are currently conducting at a nationally recognized rehabilitation center [(https://ClinicalTrials.gov (NCT03569059)]. Specifically, the research was formulated to help fill a gap in the literature by testing whether gains in upper limb impairment and behavior are greater if an additional eight hours of intensive, motor learning based VR/robotic training (VR group) is provided during the first month post-stroke compared to usual care alone (UC group). The VR/robotic system enables 200-300 activity based hand and arm movements per hour of training. This volume is necessary to elicit neuroplastic changes (Nudo, 2013), and is much greater than the average of 40.64 (32.14) repetitions per session provided by conventional rehabilitation in similar settings (Kimberley, Samargia, Moore, Shakya, & Lang, 2010). Bilateral cortical reorganization was evaluated via changes in Transcranial Magnetic Stimulation (TMS) induced maps. In contrast to trends in the literature, we hypothesized that participants in the VR/robotic training group would demonstrate greater gains on both impairment (assessed with the Upper Extremity Fugl-Meyer Assessment - UEFMA (Fugl-Meyer, Jaasko, Leyman, Olsson, & Steglin, 1975), wrist active range of motion – Wrist AROM, and Maximum Pinch Force) and behavioral measures (assessed with the Wolf Motor Function Test - WMFT (Wolf et al., 2001)) compared to the UC group due to preferential
effects of the VR/robotic training on the unique plasticity occurring during the first month post-stroke.

Topographic patterns of reorganization of the corticospinal system can be quantified using TMS induced motor evoked potentials (MEPs) to assay the integrity of the sensorimotor cortex representation of arm and hand muscles. Although some studies using TMS mapping to track ipsilesional motor reorganization over the first months to one year following stroke have indicated that increased excitable areas in the ipsilesional hemisphere are associated with recovery of the upper limb (Chieffo et al., 2013; Freundlìb et al., 2015; Traversa, Cìcinelli, Bassì, Rossìni, & Bernardì, 1997; Yarossi et al., 2019), other studies have found no change in ipsilesional excitable area over the same period (Cìcinelli, Traversa, & Rossìni, 1997; Delvaux et al., 2003). This contradiction of findings is part of a larger current controversy over the interpretation of M1 reorganization as it relates to recovery. Further research is necessary to better understand the complex relationship between effector specific M1 reorganization, amenability of the effector to training, and behavioral and impairment based gains. To date, we know of only two studies that have sought to quantify the neuroplastic changes (via TMS mapping) evoked by an intervention in this same early stage following stroke (Boake et al., 2007; Platz et al., 2005). Results from Boake et al. (2007) indicated that an increased number of MEP-active sites in the ipsilesional hemisphere was associated with increased functional improvement in individuals receiving
CIMT compared to controls receiving usual care. In contrast, Platz et al. (2005) did not find any change in the number of active sites in their two treatment groups (Bobath or Impairment Oriented Arm Training). We surmised that if greater impairment and behavioral-based gains in the VR group is attributed to bolstering neuroplastic changes that normally occur during this time period, the VR/robotic training would be associated with a greater expansion in ipsilesional M1 hand muscle representations (measured via TMS) compared to the hand muscle territory measured in the UC group (which would be reflective of neuroplastic changes attributed to spontaneous mechanisms and usual care).

3.3 Methods

Subjects and protocol

Thirteen subjects were recruited from a small (20 bed) inpatient rehabilitation unit of a suburban hospital and participated in this feasibility study following institutionally approved informed consent. After initial screening by the department’s physician, a physical therapist screened subjects based on the following criteria: Inclusion: 1) within 1 month after first time unilateral ischemic or hemorrhagic stroke, 2) between the ages of 30 and 80, 3) participants were able to actively: perform mass finger flexion and extension a minimum of 5 degrees, 5 times in 1 minute with their arm at the side of their body and their elbow flexed; perform elbow extension a minimum of 5 degrees, 5 times in 1 minute (returning to original position after each
movement); lift the affected hand up off of their lap and place it onto a table located in front of them (table height a few inches taller than lap), and 4) participants were able to tolerate passive ROM of the shoulder to 90 degrees in flexion and abduction without neck, shoulder or hand pain. Exclusion: 1) severe spasticity (Modified Ashworth score of 3 or greater (Bohannon & Smith, 1987)), 2) cognitive deficits rendering them unable to follow three step commands or attend to a task for at least ten minutes (based on review of the Speech Therapist’s evaluation using the Montreal Cognitive Assessment (Nasreddine et al., 2005)), 3) hemispatial neglect rendering them unable to interact with an entire twenty-four inch computer screen (based on review of the physiatrist’s admission evaluation), 4) proprioceptive loss that rendered them unable to interact with a virtual environment without looking at their hands (tested clinically by the physical therapist), and 5) unstable blood pressure and oxygen saturation responses to activity. Exclusion criteria for TMS included: 1) diagnosis of epilepsy, 2) implanted metal in the head or neck, 3) the subject was pregnant, and 4) implanted electronic devices. After screening and consent, participants were alternately assigned to the treatment (VR) group or usual care (UC) group.

Virtual reality protocol (VR group): This group began training as inpatients within the first month post-stroke. This was initiated as soon as possible after PRE testing was completed. The VR group received eight 1-hour sessions (one hour of training provided 200-300 separate hand or arm movements) of
hand-focused upper extremity VR/robotic training in addition to their usual three hours of rehabilitation (Physical, Occupational, and Speech Therapy - on consecutive days Monday-Friday).

Usual care protocol (UC group): This group of participants were also inpatients within the first month post-stroke and received a combination of physical, occupational, and speech therapy for 3 hours a day. This therapy consisted of adaptive and progressive task and impairment based therapy including strengthening, ROM, mobility, activities of daily living, and transfer training. Subjects with finger and wrist weakness typically also received electrical stimulation of the finger and wrist extensor muscles. Electrical stimulation was not provided to the VR group.

VR/robotic system

For the intensive VR/robotic training, we used the NJIT-RAVR system. This system provides an adaptive and progressive motor learning environment through sensory and perceptual modifications such as force modulation, activity and workplace scaling, gain manipulation and error augmentation (A.S. Merians, & Fluet, G.G., 2014). Notably, the NJIT-RAVR system was shown to be effective at reducing impairments in a chronic stroke population (Adamovich, Fluet, Merians, Mathai, & Qiu, 2009; Fluet, Merians, Qiu, Davidow, & Adamovich, 2014; Merians et al., 2011).

Hardware
The NJIT-RAVR system comprises both an arm training robot (Haptic Master [Moog NCS, The Netherlands]) and an integrated system for the hand consisting of an instrumented measurement glove (CyberGlove [Immersion, USA]), a cable actuated hand exoskeleton that facilitates finger extension for those persons with more severe impairment (CyberGrasp [Immersion, USA], and a 3-dimensional magnetic tracking system that tracks hand and arm position (TrackSTARTM [(Ascension Technology, USA)] – the NJIT Track–Glove System. The Haptic MASTER is an admittance-controlled robot with six degrees of freedom. A three-dimensional force sensor measures the external force exerted by the user on the robot. In addition, it provides tracking of multiplanar movements in a 3D workspace and enables programmable haptic effects, such as variable anti-gravity support, springs and dampers, and haptic objects, such as walls, floors, tables and other complex-shaped objects (Adamovich, Fluet, Merians, Mathai, & Qiu, 2009; Fluet, Merians, Qiu, Davidow, & Adamovich, 2014). 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 pronation and supination movements. It was individually programmed to provide assistance to lower functioning subjects with progressive adaptations that lessened the help provided as subjects improved over time. Adaptations were made manually by the controlling engineer based on therapist feedback and success scores obtained from the simulations.
Training simulations and interventions

The VR environment was developed with the Virtools 4.0 software package (Dassault Systemes, Velizy-Villacoublay, France) and a VRPack Plug-in that communicates with an open source Virtual Reality Peripheral Network (VRPN) interface. The NJIT-RAVR robotic system that interfaces with our suite of impairment and activity based VR simulations was used to train the hand and arm separately. This training system can be readily adapted in terms of speed, accuracy, amount of assistance provided by the robots, and the ratio of patient movement amplitude to avatar movement amplitude. The treatment group performed three simulations for the hand, and three for the arm - training approximately ten minutes on each of the six simulations during each session (the number of repetitions per game varied however on average, each participant performed between 200 -300 repetitions of hand or arm movements in a one hour session). Each training simulation was designed to use an activity to address an impairment commonly experienced by persons with stroke. The hand simulations consisted of the games: Monkey Business, Space Pong, and Piano Trainer. Their forearm was supported on a table during these hand activities. The arm simulations consisted of the games: Space Ship, Hammer Trainer, and Placing Cups (please refer to Fluet et al. 2017 for details (Fluet et al., 2017)). The CyberGrasp was used initially with persons with severe hand impairment who
could not extend their fingers without assistance (Adamovich et al., 2009; Patel et al., 2017).

Outcome measures

All outcomes were measured at baseline (PRE), immediately post intervention (POST), and again one (1M) and six months (6M) after the intervention.

Impairment (body structure/function) measures

1) The Upper Extremity Fugl-Meyer Assessment (UEFMA): is an index of global UE motor recovery at an impairment level. The arm subsection was used with a total score of 66. This test measures single and multi-joint movement in and out of synergy, digit individuation, speed, dysmetria, ataxia, and reflexes. This is a widely used tool that is both reliable and valid in acute stroke populations (Deakin, Hill, Pomeroy, 2003; Duncan, Propst, & Nelson, 1983; Fugl-Meyer, Jaasko, Leyman, Olsson, & Steglind, 1975; Malouin, Pichard, Bonheau, Durand, & Corriveau, 1994).

2) Wrist active range of motion (Wrist AROM): measures the average difference between maximum active wrist flexion and extension. This was measured using an industry standard, precise 3-dimensional magnetic tracking system that tracks hand and arm position (TrackSTARTM [(Ascension Technology, USA] – precision: 1.4mm RMS, 0.5 degrees RMS).

To increase reliability of the measure, the same person followed the same,
set protocol at each test session (Fluet et al., 2017; Patel et al., 2017; Qiu et al., 2009).

3) Maximum pinch force: measures the maximum voluntary force that a subject can exert on an industry standard, precise force sensor [ATI Nano17™ force sensor (ATI Industrial Automation, USA) – precision: 0.318 grams-force] held between their paretic thumb and index finger. Larger numbers indicate stronger pinch force. Subjects were given two attempts and the largest pinch force value was used. To increase reliability of the measure, the same person followed the same, set protocol at each test session (Fluet et al., 2017; Patel et al., 2017; Qiu et al., 2009).

Behavioral measure

The Wolf Motor Function Test (WMFT): measures participants’ capacity to use their recovering motor abilities to perform goal-oriented tasks. It is a quantitative measure of upper limb motor ability assessed via timed functional tasks. It is reliable and valid for use in the stroke population (Wolf et al., 2001). The log of the mean timed scores for 15 items was used in this study (weight to box and grip strength were not measured).

TMS mapping procedure (previously described in (Yarossi, Adamovich, & Tunik, 2014)).

Surface electromyographic activity (EMG, Delsys Trigno, at 2 kHz) was recorded to measure the MEPs elicited by TMS. EMG was recorded from 5 hand muscles contralateral to the stimulation side: first dorsal interosseus
[FDI], abductor pollis brevis [APB], abductor digiti minimi [ADM], flexor digitorum superficialis [FDS], and the extensor digitorum communis [EDC]. Consistent placement of electrodes was achieved by palpation of maximal muscle contraction. Motion of the contralateral arm was limited during TMS mapping by securing the arm and hand in a splint and via verbal cueing. To ensure spatial TMS precision for the repeated assessments, each subject's head was coregistered to a canonical high-resolution anatomical MRI for frameless neuronavigation (Advanced Neuro Technology). All TMS measures were taken at rest and background EMG was monitored to ensure that muscles remained relaxed. The TMS coil (Magstim, 70 mm double coil) was held tangential to the scalp, with the handle held posteriorly and at 45° off the sagittal plane (Littman, McHenry, & Shields, 2013). MEPs were sampled until the location with the largest MEP was determined (Koski, Mernar, & Dobkin, 2004; Sollman et al., 2013). This method affords high intra- and inter-experimenter reliability (Sollman et al., 2013), has been cross-validated with fMRI, and is robust in identifying the location of greatest activation for a given muscle (Sparing, Buelte, Meister, Paus, Fink, 2008). Resting motor threshold (RMT) was determined at this location as the minimum intensity required to elicit MEPs >50 uV in the FDI muscle on 50% of 6 sequential trials (Butler, Kahn, Wolf, & Weiss, 2005). The hotspot and RMT were determined at each mapping session. All mapping was performed with the stimulation intensity set to 110% of the determined RMT (Ngomo, Leonard, Moffet, & Mercietr,
A 7x7cm area surrounding the motor hotspot was marked using the neuronavigation software to provide consistent map boundaries. One hundred and fifty TMS pulses were delivered at a 4 second interstimulus interval within the grid boundaries with special attention paid to regions surrounding the hotspot territory. Real time feedback of multi-muscle MEPs and neuronavigated coil position was used to maximize the map information obtained by increasing the density of points in excitable and the ‘hotspot’ region while giving less attention in far-away non-responsive areas (Niskanen et al., 2010). Mapping procedures were conducted for both the ipsilesional and contralesional hemispheres. The MEP for each stimulation point was calculated as the peak-to-peak amplitude of the EMG signal 20-50ms after the TMS pulse.

TMS mapping analysis

Map area has been used extensively to describe sensorimotor cortex reorganization after stroke (Cortes, Black-Schaffer, & Edwards, 2012). A threshold of 50uV was used to identify MEPs from background EMG (Ngomo, Leonard, Moffet, & Mercier, 2012). MEP amplitudes and stimulation points were interpolated to a 7x7 cm mesh of 0.375 mm resolution (centered on the M1 hotspot) using cubic surface interpolation (Borghetti et al., 2008; Weiss et al., 2012) allowing comparisons across maps and sessions. Extent of the representation producing corticospinal output (MEPs) for individual muscles,
or map area, was calculated using double trapezoidal integration of the interpolated map (Yarossi, Adamovich, & Tunik, 2014).

Statistical analysis
Baseline status between groups was compared using Mann-Whitney U tests. A 2-way mixed ANOVA was conducted with a between factor of treatment Group (VR and UC) and a within factor of Time (PRE, POST, 1M, 6M) to evaluate the difference over time on impairment and behavioral measures. Effect size using Partial Eta Squared ($\eta^2$) is provided for all findings to show the amount of variance in the outcome variables explained by group membership. This was used in part to determine the sample sizes required for the RCT. Log WMFT and Wrist AROM data were normalized prior to performing the ANOVAs due to issues with normality in these data sets. The other two outcomes had no such issues (UEFMA PRE and Wrist AROM PRE: $SW(13) = 0.944, p = 0.513$ and $SW(11)) = 0.923, p = 0.36$ respectively). PRE to 6M changes in ability to perform items on the WMFT were evaluated using a Mann-Whitney U test. Alpha was set at 0.05 for all comparisons. The association between changes in ipsilesional FDI muscle area representations during the early, critical period of enhanced neuroplasticity and long-term Maximum Pinch Force and WMFT change scores was evaluated via scatterplots.

3.4 Results
Thirteen individuals with first time stroke occurring less than one month prior to enrollment participated in the study. There were no statistically significant differences in age, days post-stroke, or in UEFMA scores between groups at baseline – PRE (Mann-Whitney U test – age: $U = 18$, $p = 0.67$, days post-stroke: $U = 19.5$, $p = 0.825$, UEFMA: $U = 19.5$, $p = 0.83$). Participant characteristics are listed in Table 1. All training was well tolerated without adverse incidents such as fatigue, medical complications, or interference with regularly scheduled therapies.

### Table 1 Participant characteristics.

<table>
<thead>
<tr>
<th>Group/Subject</th>
<th>Age</th>
<th>Sex</th>
<th>Days post-stroke</th>
<th>Lesion location</th>
<th>UEFMA at PRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>VR1</td>
<td>45</td>
<td>M</td>
<td>12</td>
<td>Corona radiata and putamen</td>
<td>32</td>
</tr>
<tr>
<td>VR2</td>
<td>62</td>
<td>F</td>
<td>8</td>
<td>R middle cerebral artery</td>
<td>47</td>
</tr>
<tr>
<td>VR3</td>
<td>76</td>
<td>M</td>
<td>7</td>
<td>L frontal, parietal and occipital cortex</td>
<td></td>
</tr>
<tr>
<td>VR4</td>
<td>43</td>
<td>F</td>
<td>7</td>
<td>R middle and anterior cerebral arteries</td>
<td></td>
</tr>
<tr>
<td>VR5</td>
<td>60</td>
<td>M</td>
<td>7</td>
<td>L periventricular white matter</td>
<td>11</td>
</tr>
<tr>
<td>VR6</td>
<td>53</td>
<td>M</td>
<td>13</td>
<td>R temporal and parietal cortex</td>
<td>21</td>
</tr>
<tr>
<td>VR7</td>
<td>60</td>
<td>M</td>
<td>30</td>
<td>R posterior limb of the internal capsule and putamen</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>57.14(11.3) years</td>
<td>12(8.3) days</td>
<td></td>
<td>28.43(11.3)</td>
<td></td>
</tr>
<tr>
<td>UC1</td>
<td>59</td>
<td>F</td>
<td>6</td>
<td>L internal capsule</td>
<td>49</td>
</tr>
<tr>
<td>UC2</td>
<td>80</td>
<td>F</td>
<td>11</td>
<td>R frontal and insular cortex</td>
<td>19</td>
</tr>
<tr>
<td>UC3</td>
<td>52</td>
<td>M</td>
<td>7</td>
<td>L pons</td>
<td>30</td>
</tr>
<tr>
<td>UC4</td>
<td>70</td>
<td>M</td>
<td>7</td>
<td>L basal ganglia</td>
<td>21</td>
</tr>
<tr>
<td>UC5</td>
<td>56</td>
<td>M</td>
<td>17</td>
<td>L thalamus</td>
<td>49</td>
</tr>
<tr>
<td>UC6</td>
<td>55</td>
<td>M</td>
<td>30</td>
<td>R deep matter under the frontal lobe and R basal ganglia and thalamus</td>
<td>4</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>62(10.8) years</td>
<td>13(9.3) days</td>
<td></td>
<td>28.67(17.8)</td>
<td></td>
</tr>
</tbody>
</table>
Impairment and behavioral outcomes

Mann-Whitney U tests revealed no significant differences between groups at PRE for all four measures, indicating baseline function was similar between the two groups. Table 2a shows the results of these tests at PRE, as well as the means (standard deviations) for all outcome measures, for both groups at each time level (non-normalized values). A 2-way mixed ANOVA with a within factor of Time and a between factor of Group was used to test for main effects and interactions for the four impairment and behavioral outcomes (Table 2b). Log WMFT and Wrist AROM data were normalized prior to performing the ANOVAs due to issues with normality in these two data sets. Effect size using Partial Eta Squared ($\eta^2$) is provided for all findings. A Time X Group interaction was significant for the UEFMA [$F(3,33) = 3.59, p = 0.024, \eta^2 = 0.246$] and Wrist AROM [$F(3,27) = 3.93, p = 0.019, \eta^2 = 0.304$].

Preplanned contrasts (Tukey’s Least Significant Difference) between the two groups to test for differences in the amount of change from PRE to 6M are provided for the significant interactions. For the UEFMA, between group differences in PRE to 6M change scores were significant and greater for the VR group [$F(1,11) = 5.83, p = 0.034, \eta^2 = 0.346$]. For Wrist AROM, between group differences in PRE to 6M change scores were significant and also greater for the VR group [$F(1,9) = 5.342, p = 0.046, \eta^2 = 0.372$]. Importantly, 6/7 VR subjects versus only 2/6 UC subjects surpassed the minimal clinically important difference (MCID – value of 9 or 10) for the UEFMA from PRE to
POST (during the training period) (Arya, Verma, & Garg, 2011). A Time X Group interaction was not significant for Log WMFT \([F(3,33) = 1.18, p = 0.332, \eta^2 = 0.097]\) and Maximum Pinch Force \([F(1.81,19.96) = 1.02, p = 0.372, \eta^2 = 0.085]\) scores. As well, the main effects of Group and Time were not significant for the WMFT and Maximum Pinch Force. PRE to 6M changes scores for the number of WMFT items performed were not significantly greater in the VR group [5.57(3.4)] than in the UC group [3.12(3.1)]; Mann-Whitney U test: \(U = 12.5, p = 0.22\). Figure 1 shows the individual data over time for all four measures.
Table 2a Independent t-test results at PRE and means (SDs) for all measures over time.

<table>
<thead>
<tr>
<th>Outcome/Group</th>
<th>PRE/between group</th>
<th>POST</th>
<th>1M</th>
<th>6M</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mann-Whitney U tests</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UEFMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VR</td>
<td>28.43 (11.3)</td>
<td>45.96</td>
<td>54.29 (7.1)</td>
<td>58.43 (7.2)</td>
</tr>
<tr>
<td>UC</td>
<td>28.67 (17.8)</td>
<td>37.83 (16.4)</td>
<td>44.67 (16.2)</td>
<td>46.67 (17.8)</td>
</tr>
<tr>
<td>U = 19.5, p = 0.83</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wrist AROM (deg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VR</td>
<td>34.75 (10.6)</td>
<td>74.27 (17)</td>
<td>95.11 (13)</td>
<td>108.51 (16.2)</td>
</tr>
<tr>
<td>UC</td>
<td>51.62 (11.1)</td>
<td>58.72 (18.3)</td>
<td>64.71 (13.7)</td>
<td>72.36 (17.7)</td>
</tr>
<tr>
<td>U = 9, p = 0.27</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max Pinch Force (N)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VR</td>
<td>12.89 (20.4)</td>
<td>16.49 (17.2)</td>
<td>21.47 (21.2)</td>
<td>30.65 (23.4)</td>
</tr>
<tr>
<td>UC</td>
<td>14.01 (15.3)</td>
<td>21.91 (21)</td>
<td>18.05 (19.7)</td>
<td>22.09 (25)</td>
</tr>
<tr>
<td>U = 20, p = 0.89</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log WMFT (sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VR</td>
<td>3.75 (0.3)</td>
<td>2.45 (0.4)</td>
<td>1.79 (0.5)</td>
<td>1.44 (0.5)</td>
</tr>
<tr>
<td>UC</td>
<td>3.99 (0.3)</td>
<td>3.04 (0.5)</td>
<td>2.49 (0.5)</td>
<td>2.57 (0.5)</td>
</tr>
<tr>
<td>U = 20.5, p = 0.94</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2b Two-Way Mixed ANOVA results for all measures.

<table>
<thead>
<tr>
<th>Test</th>
<th>Time</th>
<th>Group</th>
<th>TIME X Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>UEFMA</td>
<td>F(3,33) = 60.44</td>
<td>F(1,11) = 1.02</td>
<td>F(3,33) = 3.59</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.001</td>
<td>p = 0.333</td>
<td>p = 0.024</td>
</tr>
<tr>
<td>Wrist AROM (deg)</td>
<td>F(3,27) = 11.58</td>
<td>F(1,9) = 0.80</td>
<td>F(3,27) = 3.93</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.001</td>
<td>p = 0.394</td>
<td>p = 0.019</td>
</tr>
<tr>
<td>Maximum Pinch Force (N)</td>
<td>F(1.81,19.96) = 0.006</td>
<td>F(1,11) = 0.005</td>
<td>F(1.81,19.96) = 1.02</td>
</tr>
<tr>
<td></td>
<td>p = 0.99</td>
<td>p = 0.944</td>
<td>p = 0.372</td>
</tr>
<tr>
<td>Log WMFT (sec)</td>
<td>F(3,33) = 0.094</td>
<td>F(1,11) = 0.731</td>
<td>F(3,33) = 1.18</td>
</tr>
<tr>
<td></td>
<td>p = 0.963</td>
<td>p = 0.411</td>
<td>p = 0.332</td>
</tr>
</tbody>
</table>

Greenhouse-Geisser corrected
Six individuals in the VR and 5 in the UC group met the inclusion criteria for TMS mapping. TMS maps of the cortical representation of five hand muscles (FDI, APB, ADM, FDS, EDC) were obtained bilaterally in these individuals.
The maps representing the FDI muscle are presented here (Figure 2). The ipsilesional cortical area representing the FDI muscle in both treatment groups was reduced compared to the contralesional side at PRE. The ipsilesional TMS map area for the FDI muscle increased from PRE to POST and POST to 1M (significant for both study groups, at p < 0.05 for PRE to 1M) with a non-significant reduction in size from 1M to 6M for both groups. There was no difference between groups over time ipsilesionally. Contralesional area for the FDI muscle monotonically increased from PRE to 6M in the UC group. Conversely, in the VR group, contralesional area decreased from PRE to 1M and then increased from 1M to 6M.

Figure 2. Comparison of ipsilesional and contralesional TMS maps for the FDI muscle.

The association between PRE to 1M changes in ipsilesional FDI area and PRE to 6M changes in Maximum Pinch Force and WMFT scores for both treatment groups was evaluated via scatter plots (Figure 3). Of the four outcome measures, these two were chosen as the FDI muscle is required to
pinch the index and thumb together (as measured by the Maximum Pinch Force test), and five of the fifteen WMFT items require FDI muscle usage. Statistical correlation analysis was not conducted due to the small sample sizes. PRE to 1M TMS induced map changes were chosen as we wanted to capture expansion during the enhanced period of neuroplasticity. PRE to 6M changes in outcomes were chosen as we wanted to evaluate the association between cortical reorganization during the critical, early period and long-term changes in impairment and behavior.

Figure 3 Association between change in 1M-PRE FDI area and change in 6M-PRE Pinch force and WMFT scores.

3.5 Discussion
This feasibility study, initiated within one month post-stroke, was performed to aid in the development of a large scale RCT that we are currently conducting.
Specifically, we compared an additional eight hours of intensive VR/robotic based upper limb training to conventional therapy. There is enhanced neuroplasticity during this early time post-stroke which is proposed to interact with training and thus lead to enhanced recovery (Zeiler & Krakauer, 2013). However, there have been contradictory results from studies evaluating additional therapy provided during this time. Our approach is distinguished from previous approaches in that it provides a unique combination of focused, high intensity, and progressive training that facilitates a repeatable trajectory. Specifically, this system provides 200-300 upper extremity movements per hour of training which is had been proposed to enhance neuroplasticity (Nudo, 2013). Based on this, we hypothesized that gains in upper limb impairment and behavior in our VR group would be greater than our UC group. We feel that the differences between the two groups in PRE to 6M changes scores suggest that the hypothesis may be correct and warrant larger scale examination. Specifically, PRE to 6M change scores were significantly greater for the VR group for UEFMA scores [F(1,11) = 5.83, p = 0.034, η2 = 0.346], and Wrist AROM scores [F(1,9) = 5.342, p = 0.046, η2 = 0.372]. Notably, 6/7 of the VR subjects surpassed the MCID for the UEFMA during the training period compared to only 2/6 of the UC group. In this pilot set, improvements in PRE to 6M change scores were not significantly different between groups for the WMFT, WMFT items performed, and Maximum Pinch Force. However, we were encouraged that the VR group
could perform an average of 2 items more on the WMFT compared to the UC group from PRE to 6M. The ability to perform an item within 120 seconds at a post-test that a participant was previously unable to perform at baseline has been cited as a clinically meaningful change in persons with stroke (Wolf et al., 2006).

Current evidence indicates that ipsilesional M1 excitation may be important for functional improvement of the upper limb post-stroke (Dodd, Nair, & Prabhakaran, 2017). We thus hypothesized that enhanced long-term gains in impairment and behavior in the VR group would be associated with greater expansion in TMS based ipsilesional cortical hand representations. For the map representations, our results showed that at PRE, the cortical representation area for the FDI muscle in both groups was reduced on the ipsilesional side compared to the contralesional side. This decreased area representing the more affected hand before therapy reflects a reduced excitability of the motor cortex in the ipsilesional hemisphere that may be the result of the infarct itself (Liepert et al., 2000). Subsequently, in both groups, there was an increase in ipsilesional map size from PRE to POST, and again from POST to 1M, with a decrease thereafter. Boake et al. (2007) found a similar finding at PRE, as well as the pattern of enlargement in the ipsilesional hemisphere from PRE to POST. The reduction in area size from 1M to 6M may represent central focalization as movement stabilizes and recovery starts to plateau (Liepert et al., 2000). In contrast to our hypothesis, there were no
differences between the two groups in the pattern of change for the FDI muscle representation. Statistical correlations between ipsilesional map changes and long-term changes in outcomes were not possible at this time due to small sample sizes, however associations were less variable for both the WMFT and Maximum Pinch Force scores for the VR group compared to the UC group. Larger sample sizes from the RCT will allow for a more objective evaluation of these associations.

3.6 Study limitations

We recognize that a limitation in presenting any feasibility work is a small sample size. This precluded our ability to perform statistical correlations between TMS map changes and clinical measures. Nonetheless, this data was invaluable to develop our current RCT. As an example, for the behavioral outcome WMFT, a power analysis using these results (with an alpha of 0.05 and an estimated power of 0.8) determined that a sample size of 25 subjects would be needed in each group to show a significant difference between groups in PRE to 6M change scores. Similar analyses, as well as the effect sizes from this data, were used to determine the sample sizes for the different study arms of the current RCT, and to justify an increase in the amount of additional hours of training provided from eight to ten. Another limitation of the study was that this was a non-randomized design. However, all baseline demographic and outcome measures were statistically similar between the two groups thus eliminating potential selection bias. Additionally, although
highly precise equipment was used to measure Maximum Pinch Force and Wrist AROM, a formal assessment of the reliability of our measurement technique was not conducted. Thus our method for obtaining these values could potentially have some measurement error. That being said, the same person obtained these measures throughout and followed the same set protocol at each test session to improve measurement consistency. We also plan to formally evaluate these measurement techniques during the RCT. Lastly, TMS maps for more proximal arm muscles (wrist and elbow) were not obtained with the first few subjects. This limited our ability to adequately evaluate associations between UEFMA and Wrist AROM scores and proximal TMS based muscle representations. These limitations were also addressed during the development of the RCT. Barring these limitations, the data we present here nevertheless demonstrates feasibility of conducting this intervention and multiple outcome measures (impairment, behavioral, neurophysiological) in this relatively fragile patient population, and helps guide our predictions about future results.

3.7 Conclusions
This feasibility study initiated in the acute and early sub-acute period post-stroke compared an additional eight hours of specialized and intensive VR/robotic training to conventional rehabilitation. Long-term gains in impairment reflected by UEFMA and Wrist AROM PRE to 6M change scores was enhanced in the VR group. These greater changes in the VR group were
not paralleled with augmented changes in ipsilesional FDI muscle cortical organization that were unique to this group, as similar patterns of change were demonstrated in the UC group as well. Associations between PRE to 1M change scores in ipsilesional FDI area representation and PRE to 6M change scores for the WMFT and Maximum Pinch Force measures were less variable in the VR group.

Abbreviations

Transcranial Magnetic Stimulation TMS
Upper Extremity Fugl-Meyer Assessment UEFMA
Wolf Motor Function Test WMFT

Declarations

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The authors thank Dr. Supriya Massood DO, and the clerical, nursing, and rehabilitation staff of the Acute Rehabilitation Department at St. Joseph’s Hospital, Wayne, NJ for their assistance with medical advisement, subject recruitment, and scheduling. We also thank Amanda Cronce, BA for her technical support, and James Scott Parrott, PhD for his invaluable statistical assistance.

Funding

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Independent Living and Rehabilitation Research grant [RERC 90RE5021 (SA)].

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors’ contributions
Data was collected by JP, MY, QQ, and GF. QQ performed the design and implementation of the virtual reality video games used in the interventions. AM, ET, GF, and SA were involved in designing the training protocol. Data analysis was performed by JP. Manuscript writing was performed by JP, and revised by MY, SA, ET, QQ, AM, and GF.

Ethics approval and consent to participate
All subjects provided written and verbal informed consents approved by Institutional Review Boards of the New Jersey Institute of Technology (HHS FWA 00003246, IRB Protocol Number: F 165-13), Rutgers University (Pro0120090144 Visual Augmentation Through Virtual Reality to Rehabilitate the Hand After Stroke), and St. Joseph’s Hospital-Wayne prior to participating.

Competing interests
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Consent for publication

Not applicable

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reorganization in subacute and chronic stroke: A neuronavigated TMS


CHAPTER 4

EVALUATING PREDICTION MODELS IN THE ACUTE AND EARLY SUB-ACUTE PERIODS POST-STROKE.

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4.1 Abstract

It is important to be able to predict the potential for recovery after a stroke as accurate prognoses allow for development of appropriate rehabilitation goals, realistic expectations, and efficient use of limited resources. Two models that have been developed to predict the course of stroke recovery are the Proportional Recovery Rule and the Patient Recovery Potential (PREP2) algorithm. Both models are based on biological recovery that occurs spontaneously and neither question how this recovery can be modulated by the type and amount of training provided. The main goal of this exploratory study was to evaluate whether additional Virtual Reality (VR)/robotic based upper limb training initiated within the first month post-stroke leads to greater than predicted recovery and/or outcomes when compared to usual care (UC). Recovery and outcomes of both groups were compared against the two models’ predictions as well as between the two groups. A secondary aim was to evaluate the methodology used in the PREP2 algorithm, specifically whether testing Corticospinal Tract (CST) integrity while the affected hand is contracting (active method) leads to fewer false negatives and hence a more accurate model compared to testing CST function with the hand at rest (resting method). A total of 27 (14 in the VR, 13 in the UC) individuals participated in the main study question, five of whom participated in the secondary question as well. Primary analyses show trends indicating that there may be greater than predicted proportional recovery when additional
VR/robotic training is initiated early after stroke, especially for those individuals who have residual CST function. Secondary analyses also support the need to further evaluate the methodology of the PREP2 algorithm.

Key words Stroke, CVA, upper limb, virtual reality, robotics, Proportional Recovery Rule, Patient Recovery Potential (PREP2)

4.2 Introduction

Stroke is a leading cause of long-term disability in adults with the financial burden of related care among the fastest-growing expenses for Medicare (Benjamin et al., 2018). Proportionally more stroke survivors are left with upper extremity impairment and disability than that of the lower extremity (Dobkin, 2005). Maximal upper extremity function is critically important to restore full independence and reduce the need for costly supportive care. Although innovative upper limb motor therapies, (French et al., 2016; Duret, Grosmaire, & Krebs, 2019; Aminov, Rogers, Middleton, Caeyenberghs, & Wilson, 2018) have attempted to reduce upper extremity impairment and functional loss after stroke, substantial improvement has not been made as over 80% of people post-stroke continue to have sensorimotor deficits that affect their self-care and ability to participate in daily activities (Morris, van Wijck, Joice, & Donaghy, 2013). Further recovery of function is variable and the potential for independence is unpredictable.

Disease specific models designed to predict recovery (change in neuromotor function over time) (Prabhkaran et al., 2008) and/or outcomes
(ultimate motor ability at a set point in time) (Stinear et al., 2017a) from motor impairment and functional loss are important because accurate prognoses allow clinicians to develop optimal rehabilitation programs with appropriate goals, allow patients and families to have realistic expectations, and allow for effective allocation of time and resources. Additionally, prediction models enable valid assessment of intervention effects in research because they allow comparison of outcomes between individuals with similar recovery potential (C. M. Stinear, 2017).

There are two established and influential stroke prediction models for the acute and early sub-acute periods (< 1 month) post-stroke - the Proportional Recovery Rule (Prabhakaran et al., 2008) and the Predicted Recovery Potential algorithm 2 (PREP2) (Stinear et al., 2017a). The Proportional Recovery Rule predicts that people will experience a recovery of approximately 70% of the maximal recovery possible based on their initial impairment during the first few days following a stroke as measured by the Upper Extremity Fugl-Meyer Assessment (UEFMA - Fugl-Meyer, Jaasko, Leyman, Olsson, & Steglin, 1975). This rule was corroborated to varying degrees by five other studies (Buch et al., 2016; Byblow, Stinear, Barber, Petoe, & Ackerley, 2015; Feng et al., 2015; C.M. Stinear et al., 2017b; Winters, van Wegen, Daffersthofer, & Kwakkel, 2015). It was extended by Stinear et al. (2017b) who propose that the neurological process for this impairment based recovery involves the integrity of the Corticospinal tract
(CST) and that proportional recovery will occur regardless of severe initial impairment or the volume of rehabilitation if the CST is functional (indicated by the presence of Transcranial Magnetic Stimulation (TMS) induced motor evoked potentials (MEPs)) (C.M. Stinear et al., 2017b). This group developed their own widely accepted algorithm – the PREP2 (C.M. Stinear et al., 2017a; C.M. Stinear et al., 2016) which combines clinical and neurophysiological biomarkers of Corticospinal integrity obtained within days of stroke to predict upper limb motor outcomes three months after stroke (with predictions stable at 2 years post (Smith et al., 2019). However, there are two problematic issues with these models.

First, both models emphasize biological recovery that occurs spontaneously without systematically accounting for the impact of interventions utilized to modify or augment this spontaneous recovery. The PREP2 was developed using subjects from previous studies who on average received less than 15 hours of upper extremity training throughout their rehabilitation (Byblow, Stinear, Barber, Petoe, & Ackerley, 2105; Stinear, Barber, Petoe, Anwar, & Byblow, 2012). In this study we evaluated the validity of these two widely used predictive models by using higher amounts of training than that used to develop these models to determine whether higher amounts leads to greater recovery/outcomes than predicted by these models. Specifically, this study, initiated within one month post-stroke, compared recovery between two groups – a higher dosed intervention group that
received 8-10 hours of Virtual Reality (VR)/robotic based upper limb training (VR group) in addition to their prescribed therapy and a control group that received usual care only (UC group). Our primary hypothesis was that individuals in the higher dose VR/robotic group would achieve greater recovery than that predicted from both models compared to a control UC group.

The second issue is that the predictive quality and validity of a model can be significantly affected by its methodology. The PREP2 algorithm has traditionally utilized resting methods to determine MEP status (Stinear, Barber, Petoe, Anwar, & Byblow, 2012; Stinear et al., 2017a). Currently, Stinear and group have added active methods to their algorithm but there is no indication that a comparison of prediction accuracy is being made between the two methods (personal communication with Cathy Stinear). It is feasible that testing MEPs actively during affected hand contraction may lead to fewer false negatives (subject ‘falsely’ categorized as MEP negative initially and hence with a worse predicted prognosis) and allow for more precise long-term predictions. Active methods, utilized in several studies to increase the sensitivity of TMS tests for CST evaluation may have detected minimal residual CST function resulting in more accurate predictions (Cruz Martinez, Tejada, & Diez Tejedor, 1999; Heald, Bates, Cartlidge, French, & Miller, 1993). Thus, our second aim was to re-examine the methodology used to evaluate MEP status in the PREP2 algorithm. Specifically, a secondary
analysis was performed to determine whether evaluating CST function using active methods of TMS induced MEP determination (affected hand is contracting during the assessment) provides more accurate predictions using the PREP2 algorithm compared to resting methods (affected hand is at rest). We hypothesized that active methods will indeed lead to more accurate predictions compared to resting methods.

4.3 Methods

4.3.1 Subjects and protocol

Participants were recruited from two acute inpatient rehabilitation centers between July 2013 and May 2019. The first 21 individuals were recruited from St. Joseph’s Hospital, Wayne, New Jersey as part of a pilot study that was conducted prior to a large scale randomized controlled trial (RCT) currently occurring at the Kessler Institute for Rehabilitation, Saddlebrook, New Jersey [(https://ClinicalTrials.gov (NCT03569059)]. The last six were recruited for this RCT. The RCT will continue to address the research questions at hand in a larger cohort. All participants provided institutionally approved informed consent (Rutgers University, St. Joseph’s Hospital, Wayne, and The Kessler Institute of Rehabilitation, Saddlebrook). After initial screening by a physician at St. Joseph’s Hospital or a study coordinator at the Kessler Institute, a Physical or Occupational Therapist further screened subjects based on the following criteria: Inclusion: 1) within 1 month after first time unilateral ischemic or hemorrhagic stroke, 2) between the ages of 30 and 80, and 3)
participants were able to actively - 3a: perform mass finger flexion and extension a minimum of 5 degrees, 5 times in 1 minute with their arm at the side of their body and their elbow flexed, 3b: perform elbow extension a minimum of 5 degrees, 5 times in 1 minute (returning to original position after each movement), 3c: lift the affected hand up off of their lap and place it onto a table located in front or next to them (table height a few inches taller than lap), and 3d: participants were able to tolerate passive ROM of the shoulder to 90 degrees in flexion and abduction without neck, shoulder or hand pain.

Exclusion: 1) severe spasticity (Modified Ashworth score of 3 or greater (Bohannon & Smith, 1987)), 2) cognitive deficits rendering them unable to follow three step commands or attend to a task for at least ten minutes, 3) hemispatial neglect rendering them unable to interact with an entire twenty-four inch computer screen, 4) proprioceptive loss that rendered them unable to interact with a virtual environment without looking at their hands, and 5) unstable blood pressure and oxygen saturation responses to activity.

Exclusion criteria for TMS included: 1) diagnosis of epilepsy, 2) implanted metal in the head or neck, 3) the subject was pregnant, and 4) implanted electronic devices. After screening and consent, the first 21 participants were alternately assigned to the treatment (VR) group or usual care (UC) group (pilot study at St. Joseph’s Hospital), and the last six subjects were randomly assigned to either group (RCT at the Kessler Institute).

VR/robotic system
For the intensive VR/robotic training, we used the NJIT-RAVR system. This system provides an adaptive and progressive motor learning environment through sensory and perceptual modifications such as force modulation, activity and workplace scaling, gain manipulation and error augmentation (Merians & Fluet, 2014). Notably, the NJIT-RAVR system was shown to be effective at reducing impairments in a chronic stroke population (Adamovich, Fluet, Merians, Mathai, & Qiu, 2009; Fluet, Merians, Qiu, Davidow, & Adamovich 2014; Meraians et al., 2011).

**Hardware**

The NJIT-RAVR system comprises both an arm training robot (Haptic Master [Moog NCS, The Netherlands]) and an integrated system for the hand consisting of an instrumented measurement glove (CyberGlove [Immersion, USA]), a cable actuated hand exoskeleton that facilitates finger extension for those persons with more severe impairment (CyberGrasp [Immersion, USA], and a 3-dimensional magnetic tracking system that tracks hand and arm position (TrackSTAR™ [(Ascension Technology, USA)] – the NJIT Track–Glove System. The Haptic MASTER is an admittance-controlled robot with six degrees of freedom. A three-dimensional force sensor measures the external force exerted by the user on the robot. In addition, it provides tracking of multiplanar movements in a 3D workspace and enables programmable haptic effects, such as variable anti-gravity support, springs and dampers, and haptic objects, such as walls, floors, tables and other complex-shaped objects.
(Adamovich, Fluet, Merians, Mathia, & Qiu, 2009; Fluet, Merians, Qiu, Davidow, & Adamovich, 2014). 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 pronation and supination movements. It was individually programmed to provide assistance to lower functioning subjects with progressive adaptations that lessened the help provided as subjects improved over time.

*Training simulations and interventions*

The VR environment was developed with the Virtools 4.0 software package (Dassault Systemes, Velizy-Villacoublay, France) and a VRPack Plug-in that communicates with an open source Virtual Reality Peripheral Network (VRPN) interface. The NJIT-RAVR robotic system that interfaces with our suite of impairment and activity based VR simulations was used to train the hand and arm separately. This training system can be readily adapted in terms of speed, accuracy, amount of assistance provided by the robots, and the ratio of patient movement amplitude to avatar movement amplitude. The treatment group performed three simulations for the hand, and three for the arm - training approximately ten minutes on each of the six simulations during each session. Each training simulation was designed to use an activity to address an impairment commonly experienced by persons with stroke. The hand simulations consisted of the games: Monkey Business, Space Pong, and Piano Trainer. Their forearm was supported on a table during these hand
activities. The arm simulations consisted of the games: Space Ship, Hammer Trainer, and Placing Cups (please refer to Fluet et al. 2017 for details (Fluet et al., 2017)). The CyberGrasp was used initially with persons with severe hand impairment who could not extend their fingers without assistance (Adamovich et al., 2009; Patel et al., 2017).

**Virtual reality/robotic group (VR):** This group began training as inpatients within the first month post-stroke. This was initiated as soon as possible after baseline testing (PRE) was completed. The VR group received 8-10 1-hour sessions (one hour of training provided 200-300 separate hand or arm movements) of hand-focused upper extremity VR/robotic training in addition to their usual three hours of rehabilitation (Physical, Occupational, and Speech Therapy - on consecutive days Monday-Friday).

**Usual care group (UC):** This group of participants were also inpatients within the first month post-stroke and received a combination of Physical, Occupational, and Speech therapy for three hours a day. This therapy consisted of adaptive and progressive task and impairment based training including strengthening, ROM, mobility, activities of daily living, and transfer training. Individuals with finger and wrist weakness typically also received electrical stimulation of the finger and wrist extensor muscles.

4.3.2 Proportional Recovery and PREP2 classifications and methods

1) Proportional Recovery Rule:
Maximal predicted recovery for all participants was calculated using the following equation: (Krakauer & Marshall, 2015; Prabhakaran et al., 2008)

\[
\Delta \text{UEFMA} = (0.70) \cdot (66 - \text{acute UEFMA}) + 0.4
\]

(UEFMA = Upper Extremity Fugl Meyer score)

This rule was developed with baseline measures taken within three days post-stroke and recovery measures taken between 3-6 months post-stroke.

2) PREP2 algorithm: predicted outcomes for all subjects with TMS and ARAT data were calculated using the PREP2 algorithm (Stinear et al., 2017a).

SAFE Scores: An identical approach to Stinear et al. (2017) was utilized (Stinear et al., 2017a). Shoulder abduction and finger extension (SAFE) strength was scored from zero to five using the standard approach described by the Medical Research Council (MRC). A total score was used to assess the initial level of motor impairment. Patients with a SAFE score above 5 in the first week post-stroke have a good to excellent prognosis for recovery (> 34 on the ARAT) (Stinear et al., 2017a).

PREP2

The PREP2 algorithm was developed with baseline measures taken within
three days post-stroke and outcomes measured at ~ three months post-stroke.

4.3.3 Transcranial magnetic stimulation (TMS) evaluation of Corticospinal Tract function (CST)

TMS was performed using a Magstim 70 mm double coil. This technique was used to assay CST function (via presence or absence of motor evoked potentials – MEPs) for all subjects that met the inclusion criteria for TMS. The TMS coil was placed at 45 degrees to the sagittal plane and consistency of position was assured using a neuronavigation system. For the primary hypothesis, participants’ MEP status at rest was used in the PREP2 algorithm classification. The presence of MEPs was measured using surface EMG collected at the first dorsal interosseous (FDI) muscle. Initially, subjects were seated with the upper extremity comfortably at rest. They were categorized as MEP positive at rest if MEPs of any amplitude were observed at a consistent latency (20 – 50 msec) in the FDI muscle while the muscle remained at rest (C.M. Stinear et al., 2017a). If this criterion was not met with stimuli delivered at maximal stimulator output then the participant was categorized as MEP negative at rest. A participant was categorized as ‘positive’ (P) if resting MEPS were present at baseline, as a ‘convert’ (N/C) if they were MEP negative at baseline and then converted to MEP positive (at rest) at any of the subsequent testing sessions, and as MEP negative (N) if they never had MEPs (at rest) at any testing session (Delvaux et al., 2003; Hendricks,
Zwarts, Plat, & van Limbeek, 2002; Pennisi et al., 1999, Cicinelli, Traversa, & Rossini, 1997; Traversa, Cicinelli, Bassi, Rossini, & Bernardi, 1997; Yarossi et al., 2019). For the secondary analysis, five participants, also had their MEP status determined while their affected hand was contracting (active method). For active methods, participants were asked to pinch their affected index and thumb at 20% of maximal FDI EMG signal to trigger the TMS pulse (Rossini et al., 2015)). They were categorized as MEP positive actively if distinct MEPs were seen with consistent waveforms and at a consistent latency (20 – 50 msec) in the FDI muscle during the active contractions on 10/20 stimulations (personal communication with Cathy Stinear, PhD).

4.3.4 Outcome measures

The Upper Extremity Fugl-Meyer Assessment (UEFMA) and the Action Research Arm Test (ARAT) are the two outcome measures utilized by the Proportional Recovery Rule and the PREP2 algorithm prediction models respectively. Model based predictions were calculated immediately post the baseline (PRE) measures. UEFMA and ARAT scores were measured at baseline (PRE), immediately post training (POST), one month post training (1M), and six months post training (6M) for the main hypothesis.

1) The Upper Extremity Fugl-Meyer Assessment (UEFMA): is an index of global UE motor recovery at an impairment level. The arm subsection was used with a total score of 66. This test measures single and multi-joint movement in and out of synergy, digit individuation, speed, dysmetria, ataxia,
and reflexes. This is a widely used tool that is both reliable and valid in acute stroke populations (Deakin, Hill, & Pomeroy, 2003; Duncan, Propst, & Nelson, 1983; Fugl-Meyer, Jaasko, Leyman, Olsson, & Steglind, 1975; Malouin, Pichard, Bonneau, Durand, & Corriveau, 1994).

2) The Action Research Arm Test (ARAT) consists of a battery of 19 activities that assess a person’s ability to handle and manipulate objects differing in size, weight and shape and therefore can be considered to be an arm-specific measure of behavioral ability. It is a reliable and valid test for use in stroke populations (Croarkin, Danoff, & Barnes, 2004; Platz et al., 2005; Yozbatiran, Der-Yeghiaian, & Cramer, 2008). The ARAT is responsive to change in the early period after stroke (Beebe & lang, 2009).

4.3.5 Statistical Analysis

Non-parametric statistical tests were used throughout due to the small group sizes which can affect normality of data. Baseline status of age, days post-stroke, UEFMA and SAFE scores between groups was evaluated using Mann-Whitney U tests.

1) Proportional Recovery Rule

The Proportional Recovery Rule was developed without differentiating individuals' recovery based on the integrity of the CST. Hence, a statistical analysis was performed comparing the two groups as a whole to determine whether the VR group had greater than predicted outcomes compared to the UC group. Specifically, Mann-Whitney U tests were performed to determine
the statistical difference between the two groups on the difference between their observed and predicted UEFMA outcome scores at 1M and 6M (significance set at $\alpha < 0.05$).

Recent investigations have found that the prediction success of the Proportional Recovery Rule is dependent on integrity of the CST (Byblow, Stinear, Petoe, & Ackerley, 2015; Stinear et al., 2017b). Based on this, a descriptive visual analysis was performed to determine whether individuals in the VR group recovered more compared to those in the UC group based on the integrity of each person’s CST function. This was also performed both at 1M and 6M. Lastly, linear regression modeling was conducted to parallel the process performed to develop the Proportional Recovery Rule and to also determine how this data would be represented by regression models using an independent variable of maximal possible recovery ($66 – \text{PRE UEFMA score}$) and a dependent variable of UEFMA score at 1M (significance set at $\alpha < 0.05$)).

2) PREP2 Algorithm

For the primary hypothesis (higher amounts of training would lead to greater than predicted outcomes compared to usual care), a Fisher’s Exact test comparing the proportion of subjects in each group that achieved $>$ than their predicted outcome on the PREP2 at 1M was performed (significance set at $\alpha < 0.05$). For the secondary hypothesis (the PREP2 algorithm would be more accurate if active TMS methods were used to assess CST function), a
retrospective descriptive analysis was performed (see *TMS Evaluation of Corticospinal Tract Function (CST)*).

4.4 Results

Fourteen individuals were recruited in the VR group and thirteen in the UC group - all returned for 1M testing. Of these individuals, nine in the VR group and seven in the UC group returned for 6M testing. Mann Whitney U tests found no difference between groups on baseline scores (table 1).

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>VR group (mean(SD))</td>
</tr>
<tr>
<td>VR group (n = 14)</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Days post-stroke</td>
</tr>
<tr>
<td>UEFMA PRE</td>
</tr>
<tr>
<td>SAFE PRE</td>
</tr>
</tbody>
</table>

Additionally, there was no statistical difference in UEFMA scores between 1M (VR n = 9, UC n = 7, 67.96(13.6) days) and 6M (235.75(73.6) days) for both groups (Wilcoxon Signed Rank test - VR: Z = -1.83, p = 0.067; UC: Z = -1.44, p = 0.15). This is in line with popular theory in stroke recovery namely that the majority of recovery at the impairment level occurs within the first three months post-stroke (Zeiler & Krakauer, 2013; Smith et al., 2019). This was the same for ARAT scores (Wilcoxon Signed Rank test - VR: Z = -2.2, p =
Thus 1M scores were used for the primary prediction model comparisons. However, 6M data is also shown for completeness.

4.4.1 Proportional Recovery

1M data:

Data from all 27 participants was available for this analysis at 1M (mean days VR group: 71(14.6), UC group: 64.2(11.4), Mann Whitney U = 211, p = 0.23).

Group analysis (without accounting for individuals’ CST function): The individual difference between the observed and predicted UEFMA scores for both groups at both 1M and 6M is shown in table 2. The mean difference at 1M between the observed and predicted UEFMA scores for the VR group was -1.3(7) and the mean difference for the UC group was -10.37(9.5). A Mann-Whitney U test of differences between observed and predicted values between the VR and UC groups was significant favoring the VR group (U = 38, p = 0.01).
Table 2. Individual difference between the observed and predicted UEFMA scores for both groups at both 1M and 6M.

<table>
<thead>
<tr>
<th>VR group/ MEP status</th>
<th>Observed - Predicted UEFMA score</th>
<th>UC group/ MEP status</th>
<th>Observed - Predicted UEFMA score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1M</td>
<td>6M</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>-16.6</td>
<td>-</td>
<td>NA</td>
</tr>
<tr>
<td>NA</td>
<td>5.2</td>
<td>-</td>
<td>N</td>
</tr>
<tr>
<td>N</td>
<td>-2.8</td>
<td>-</td>
<td>N</td>
</tr>
<tr>
<td>P</td>
<td>4.3</td>
<td>-</td>
<td>NA</td>
</tr>
<tr>
<td>P</td>
<td>3.6</td>
<td>-</td>
<td>N/C</td>
</tr>
<tr>
<td>N</td>
<td>-5.8</td>
<td>-3.8</td>
<td>NA</td>
</tr>
<tr>
<td>N/C</td>
<td>2.5</td>
<td>9.5</td>
<td>N/C</td>
</tr>
<tr>
<td>N</td>
<td>-0.9</td>
<td>3.1</td>
<td>N/C</td>
</tr>
<tr>
<td>P</td>
<td>-6.9</td>
<td>-1.9</td>
<td>N/C</td>
</tr>
<tr>
<td>N/C</td>
<td>-0.9</td>
<td>5.1</td>
<td>N</td>
</tr>
<tr>
<td>P</td>
<td>5.3</td>
<td>5.3</td>
<td>N/C</td>
</tr>
<tr>
<td>NA</td>
<td>0.9</td>
<td>5.9</td>
<td>P</td>
</tr>
<tr>
<td>N/C</td>
<td>-12.7</td>
<td>-16.7</td>
<td>NA</td>
</tr>
<tr>
<td>N/C</td>
<td>6.8</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mean (SD): -1.3(7)</td>
<td>mean (SD): 1.4(7.9)</td>
<td>mean (SD): -10.37(9.5)</td>
</tr>
</tbody>
</table>

Individual analysis based on CST function: In the VR group, three of the five individuals with positive MEPs (P) at PRE recovered more than predicted compared to none in the UC group. Two of the four converts in the VR group recovered more than predicted compared to one of the five in the UC group. Lastly, no individuals with negative MEPs recovered more than predicted in either group (figure 1).
Figure 1. Observed versus predicted UEFMA outcomes at 1M.

Blue circles = individual scores predicted from the Proportional Recovery Rule, blue line = regression
Red circles = individual observed UEFMA scores at 1M
P = person with positive MEPs at PRE, N/C = person with positive MEPs at any test time after PRE, N = person never had MEPs

Linear regression modeling:

VR group:
\[ \Delta \text{UEFMA} = 0.38(66 - \text{PRE UEFMA}) + 10.07 \]
\[ R^2 = 0.28, F(1,13) = 4.58, p = 0.054 \]

The model is not significant for the VR group, however a trend is seen as \( p = 0.054 \).

UC group:
\[ \Delta \text{UEFMA} = 0.77(66 - \text{PRE UEFMA}) + 25.73 \]
\[ R^2 = 0.31, F(1,12) = 5.02, p = 0.047 \]

The model is significant for the UC group - maximal possible outcome explains about 31% of the variance in the UEFMA score at 1M.
6M data:

Group analysis (without accounting for individuals' CST function): At 6M, (mean days VR group: 229.2(45.7), UC group: 244(103.1), Mann Whitney U = 83, p = 0.57) with nine participants in the VR group, and seven in the UC group, the mean difference between observed and predicted scores for the VR group was 1.4(7.9), and the mean difference for the UC group was -8.4(12.6) (table 2). A Mann-Whitney U test of differences between observed and predicted scores between the VR and UC groups was not significant (U = 94, p = 0.07).

Individual analysis based on CST function: In the VR group, two of the five positive MEP individuals returned for 6M testing and one of the two surpassed their predicted outcome at 6M. All four individuals who converted in MEP status returned at 6M (N/C) and three of them surpassed their predicted outcomes. Two individuals with negative MEPs returned at 6M and only one of the two surpassed their predicted outcome. In the UC group, the one positive individual completed their 6M testing and did not surpass their predicted outcome at this time. Four of the five converts returned at 6M and only one of them surpassed their predicted outcome. One of the three individuals with negative MEP status returned for 6M testing and did not surpass their predicted outcomes (figure 2).
Figure 2. Observed versus predicted UEFMA outcomes at 6M.

Blue circles = individual scores predicted from the Proportional Recovery Rule, blue line = regression
Red circles = individual observed UEFMA scores at 1M
P = person with positive MEPs at PRE, N/C = person with positive MEPs at any test time after PRE, N = person never had MEPs

4.4.2 PREP2 Algorithm

Ten participants in the VR group, and seven in the UC group had the required TMS and ARAT data for this analysis at 1M (mean days VR group: 69.9(14.6), UC group: 64.4(12.2), Mann Whitney U test = 98.5, p = 0.43). Five out of ten participants in the VR group surpassed their predicted outcomes at 1M compared to three of the seven UC participants. A Fisher’s Exact test did not find a significant difference between the two groups in the number of people who surpassed the predicted outcomes from the PREP2 algorithm at 1M (p = 0.99). When comparing 6M to 1M data, only one person from the total of twelve with 6M data did not surpass their predicted outcome at 1M but did so at 6M (table 2).
The PREP2 algorithm only requires evaluation of MEP status initially, hence anyone who becomes MEP positive at a subsequent test time is still only described as MEP negative. It is of interest to evaluate whether our convert group (N/C) had better outcomes than our negative group. However, the number of individuals in each group thus far was too small to make any objective assessments at this time.

### Table 3. PREP2 outcomes for VR and UC groups at 1M and 6M.

<table>
<thead>
<tr>
<th>VR group</th>
<th>Mep status</th>
<th>SAFE score pre</th>
<th>predicted ARAT</th>
<th>ARAT 1M</th>
<th>ARAT 6M</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>4</td>
<td>34-48</td>
<td>57***</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>4</td>
<td>34-48</td>
<td>43**</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>2</td>
<td>34-48</td>
<td>27*</td>
<td>32*</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>6</td>
<td>50-57</td>
<td>57**</td>
<td>57**</td>
<td></td>
</tr>
<tr>
<td>N/C</td>
<td>2</td>
<td>0-31</td>
<td>34***</td>
<td>48***</td>
<td></td>
</tr>
<tr>
<td>N/C</td>
<td>2</td>
<td>0-31</td>
<td>52***</td>
<td>54***</td>
<td></td>
</tr>
<tr>
<td>N/C</td>
<td>4</td>
<td>13-31</td>
<td>21**</td>
<td>24**</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>4</td>
<td>0-31</td>
<td>42***</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>3</td>
<td>0-31</td>
<td>29**</td>
<td>38***</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>4</td>
<td>0-31</td>
<td>36***</td>
<td>41***</td>
<td></td>
</tr>
<tr>
<td>UC group</td>
<td>N/C</td>
<td>3</td>
<td>0-9</td>
<td>54***</td>
<td>NA</td>
</tr>
<tr>
<td>N/C</td>
<td>2</td>
<td>0-31</td>
<td>47***</td>
<td>57***</td>
<td></td>
</tr>
<tr>
<td>N/C</td>
<td>4</td>
<td>0-31</td>
<td>26**</td>
<td>16**</td>
<td></td>
</tr>
<tr>
<td>N/C</td>
<td>4</td>
<td>0-9</td>
<td>15***</td>
<td>35***</td>
<td></td>
</tr>
<tr>
<td>N/C</td>
<td>5</td>
<td>50-57</td>
<td>38*</td>
<td>48*</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>2</td>
<td>0-31</td>
<td>17**</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>0</td>
<td>0-31</td>
<td>4**</td>
<td>8**</td>
<td></td>
</tr>
</tbody>
</table>

* actual score less than predicted score, **actual score within predicted range, *** actual score exceeded predicted score

4.4.3 Outcomes comparing resting and active methods of evaluating CST function

A secondary hypothesis predicted that measuring initial MEPs with active methods (assessing MEP presence while the affected hand is contracting) would lead to more accurate long-term predictions using the PREP2 algorithm.
than using resting methods (assessing MEP presence while the affected hand is resting). Five participants were included in this analysis from both the VR and UC groups. Only one person had no MEPs at rest but did so actively. Using resting methods, this individual was predicted to be at Poor level of outcome at three months post-stroke (0-9 on the ARAT), and predicted to have a Good outcome (34-48 on the ARAT) if MEP positive. This participant attained a score of 54 on the ARAT at 71 days post-stroke (Excellent on the ARAT: 50-57), thus surpassing even the prediction based on a positive MEP status. Of the four individuals without active MEPs, two exceeded their predictions at 1M - one of whom was a convert. Of the two that only met their predicted outcomes, one was also a convert.

4.5 Discussion
The primary aim of this exploratory study was to evaluate whether additional therapy, when compared to a usual care control group, led to greater than predicted recovery/outcomes in both the Proportional Recovery Rule and the PREP2 algorithm. The results support this type of inquiry as we do show trends representing a difference in proportional recovery with additional therapy, thus challenging the assumption that these algorithms are solely dependent on spontaneous biological plasticity. At 1M, when comparing the group scores as a whole, the VR group showed significantly greater recovery compared to the UC group than is predicted by the Proportional Recovery Rule (VR group mean: -1.3 (7), UC group: -10.37(9.5)). This recovery
however did not surpass the predicted amounts for either group (both mean values are negative). The 1M data in this study was collected ~ two months post-stroke. The average time post-stroke for the cohort used to develop the Proportional Recovery rule was ~ 4 months. This two-month difference may have caused the overall observed recovery to be less than the predicted for both groups. At 6M post-training (~ 7.5 months post-stroke), the VR group on average recovered more than predicted, and more than the UC group - but these findings were not significant. This cohort was much smaller, therefore statistically underpowered. For the PREP2 algorithm, we show no significant differences between groups on the number of participants who surpassed their predicted outcomes at 1M. Again, this is a smaller cohort and the results may be statistically underpowered. At 6M, only one person from the whole group surpassed outcomes at this time that did not at 1M.

Recent investigations have found that the prediction success of the Proportional Recovery Rule is dependent on integrity of the CST (Byblow, Stinear, Barber, Petoe, & Ackerley, 2105; Stinear et al., 2017b). Thus we also compared recovery between groups based on the MEP status of each individual, as this may be a more valid comparison. In general, individuals with positive MEPS typically show a greater recovery or outcome post-stroke (Stinear et al., 2017). In this study, we identify individuals who were MEP negative at PRE but then converted to positive at any of the subsequent testing sessions as ‘converts’. Understanding the recovery patterns of these
individuals is a poignant topic and a key aim of our current RCT. Several studies (Chieffo et al., 2013; Freundlib et al., 2015; Veldema, Bosl, & Nowak, 2017) have included these individuals but did not report specific analyses or descriptions of converters. Instead, these individuals were grouped as MEP- for their analyses. In those studies that provide at least some description of this group, conversion to MEP+ at a later time point has not always been found to indicate more favorable clinical improvement (Delvaux et al., 2003; Hendricks, Zwarts, Plat, & van Limbeek, 2002; Pennisi et al., 1999). However, contradictory reports exist and in four studies, individuals who gained MEP+ status at a later time point showed consistent clinical improvement’ (Cicinelli, Traversa, & Rossini, 1997; Traversa, Cicinelli, Bassi, Rossini, & Bernardi, 1997; Yarossi et al., 2019; Birchenall et al., 2019). In our study, in the VR group, more individuals with either positive MEPS or ‘converters’ recovered more than predicted compared to the UC group at both 1M and 6M.

Lastly, persons without MEPs generally recover less (Stinear et al., 2017). In this study, no individuals without MEPs recovered more than predicted at 1M, and only one person in the VR group did so at 6M. Overall, these are important findings as they may indicate that training amount may affect recovery in persons with intact CSTs.

With regard to our secondary analysis, the one participant that did have MEPs when measured actively but not passively, showed much greater recovery than predicted using resting methods. Hence this individual's
recovery followed that of someone with a functional CST (positive MEP status). Further research with more subjects is needed to clarify whether CST function should be determined actively to increase the validity/accuracy of the PREP2 algorithm.

4.6 Study Limitations

This was an exploratory study including mostly participants from a pilot study conducted at a small, 20 bed inpatient rehabilitation center. Thus the sample sizes were small overall, but especially for the PREP2 analyses, 6M analyses for both models, and the active/resting comparison. Additionally, in the pilot study, we did not use the ARAT as an outcome measure initially and this further reduced the sample size in the PREP2 analyses. The small sample sizes may have underpowered the results overall.

The majority of participants were not randomly allocated to their group assignment thus introducing the potential for selection bias. This said, the two groups were equal at baseline on measures of impairment and initial MEP status was relatively equivalent. Another important limitation is that our PRE, 1M, and 6M collection time points are different than that used to develop both prediction models. The differences in measurement times leads to difficulties in comparing our results with the models’ as there is important biological recovery occurring within the first three months post-stroke. However, we would argue that the timing of the baseline measurement in this study, which occurred at an average of ~12 days after stroke (without the two 30 day
outliers) is closer to the timeframe for inpatient rehabilitation stays (admission to inpatient units occur at a median of ~ 4-7 days post-stroke and the average stay is two weeks (Winston et al., 2016; http://strokeconnection.strokeassociation.org)), and hence is a more ecologically valid timeframe to include in a prediction model than between 24 - 72 hours after stroke which is the baseline score collection time for both the Proportional Recovery Rule and the PREP2 algorithm.

Despite these overall limitations, importantly, we do show feasibility of conducting a study that is initiated within one month post-stroke, involves intense training, and requires neurophysiologic measures acutely, with multiple clinical measures over an extended time period. We also show trends supporting both our hypotheses that warrant further exploration.

4.7 Conclusion
Primary results show trends indicating that there may be greater than predicted proportional recovery when additional VR/robotic training is initiated early after stroke, especially for those individuals who have residual CST function. These findings warrant further research with a larger cohort to better answer the questions proposed here. Secondary results also support the need to further evaluate the methodology of the PREP2 algorithm.

References


5.1 Conclusion

Stroke is a leading cause of long-term disability in adults (Benjamin et al., 2018). Despite more than a decade investigating innovative training protocols, many individuals are left with upper limb deficits that hinder their ability to function independently (Kwakkel et al., 2013).

World leaders in stroke care and research have developed consensus papers that outline key issues/recommendations in stroke rehabilitation research (Veerbeek et al., 2014; Bernhardt, Borschmann et al., 2017; Kwakkel et al., 2017). These include determining the most effective type and amount of training, as well as the time to initiate this training for optimal recovery/outcomes. They also suggest using kinematic and kinetic measures to provide more objective evaluations without floor and ceiling effects. Importantly, these measures can determine whether behavioral changes are from return of previous patterns of muscle and joint use or from the development of compensatory movement patterns. A key recommendation is to use neurophysiologic measures such as Transcranial Magnetic Stimulation (TMS), Functional Near-Infrared Spectroscopy (FNIRS), Electroencephalogram (EEG), and Functional MRI to permit a more indepth understanding of the neural mechanisms of recovery. Additionally, the consensus papers recommend developing valid models that allow long-term prediction of recovery/outcomes for persons with stroke. Finally, they
advocate the establishment and use of common language and definitions for stroke research. The three studies presented in this thesis address or incorporate several of these key issues/recommendations.

Importantly, all three studies were initiated within the first month post-stroke to take advantage of the unique neuroplasticity occurring within the first one to three months in humans. This distinct neuroplasticity is thought to induce spontaneous biological recovery and enhanced responsiveness to training (Zeiler & Krakauer, 2013). It is thus vital to conduct research in the first month post-stroke so that interaction between this unique plasticity and the intervention being evaluated can be tested. Also the greatest intensity of rehabilitation is usually provided within the first month post-stroke, so testing an intervention in the time and place it will be used can provide insight into potential barriers. Despite this, the majority of studies on therapeutic interventions have focused on individuals in the chronic phase after stroke with limited work looking at interventions during the acute and early sub-acute phases (Coleman et al., 2017; Krakauer et al., 2012; Fluet & Deutsch, 2013; Kwakkel, Kollen, & Krebs, 2008). Indeed, a 2013 review found that only 6% of all stroke motor rehabilitation trials have enrolled all patients within the first 30 days post-stroke (C.M. Stinear, Ackerley, & Byblow, 2013). The three studies presented in this thesis will add to this limited body of work.

The first study addressed the need to expand the therapy available to those with severe loss of impairment and function initially after stroke. These
individuals are limited in their ability to rehabilitate their upper extremity as they cannot participate in interventions that have been determined to be effective, for example task oriented practice or Constraint Induced Movement Therapy (CIMT) (Pomeroy et al., 2011). Due to the aforementioned neuroplasticity occurring initially post-stroke, the acute and early sub-acute periods are considered the optimal time for restorative methods of training (Zeiler & Krakauer, 2013). This study evaluated the feasibility and clinical and kinetic outcomes induced by a novel combination of priming prior to a scaled pinch training task. Cortical motor maps using Transcranial Magnetic Stimulation (TMS) were also obtained to assess changes in bilateral cortical representation associated with this novel intervention (Patel et al., 2017). Five individuals with severe hand paresis post-stroke were included. The intervention utilized multiple priming techniques (mirror visual feedback and contralaterally controlled passive movement) in conjunction with a pinch trace force modulation task with people who had very minimal use of their affected hand. This method allowed people without discernable motor ability distally to produce meaningful movement that could be quantified with objective measures and instrumented technology. Subjects demonstrated clinical gains at six months after training suggesting that developing effective rehabilitation strategies for this group is warranted. One important limitation of this study was the lack of a control group. Thus it was not possible to discern what proportion of the gains seen in this cohort were due to the additional training
compared to spontaneous biological processes. However, this pilot study allowed us to demonstrate the feasibility of providing hand focused rehabilitation to persons with severe strokes, in the earliest stages of recovery.

The second study addressed the interaction between focused, intense rehabilitation interventions and heightened levels of neuroplasticity seen immediately after stroke. This was a feasibility study that compared an additional eight hours of specialized and intensive hand focused upper limb VR/robotic training to conventional rehabilitation (UC group) in a cohort with moderate impairment post-stroke. Currently there are contradictory results from a small number of studies and reviews at all the different time points post-stroke. The primary hypothesis of the study was that participants in the VR/robotic training group would demonstrate greater gains on both impairment and behavioral measures compared to the UC group due to preferential effects of the VR/robotic training on the unique plasticity occurring during the first month post-stroke. A secondary hypothesis was that the VR/robotic training would be associated with a greater expansion in ipsilesional M1 hand muscle representations (measured via TMS) compared to the hand muscle territory measured in the UC group.

Results showed significantly greater long-term gains in impairment reflected by UEFMA and Wrist AROM PRE to 6M change scores in the VR group. However these enhanced changes were not associated with greater
changes in cortical reorganization as ipsilesional FDI map changes were similar for both groups. One important study limitation was the small sample sizes. This may have underpowered results precluding significant differences in gains on Maximum Pinch Force and the WMFT (although importantly, non-significant trends favoring the VR group were seen for both measures). Additionally the small sizes prevented statistical correlations between outcomes and TMS map changes. Lastly, the small groups may have resulted in the lack of difference seen in ipsilesional cortical reorganization between the two groups. Although, it may be that this lack of difference is a basic physiological mechanism for plasticity post-stroke and the amount of additional intervention provided was not sufficient enough to alter this mechanism. This said, there was a larger translation of neurologic adaptations into function in the VR group as opposed to the UC group. Based on these disparate findings, impairment and behavioral based recovery following stroke might involve a more complicated set of adaptations involving multiple areas of the brain. We only mapped M1, but recovery may have occurred from changes in bilateral ‘premotor’ areas (Premotor and Supplementary Motor area via cortico-cortical influence or through Reticulospinal connections) (Ward, 2011). Despite limitations, this study showed the feasibility and safety of performing high intensity, hand focused upper limb training, as well as numerous clinical, and neurophysiologic tests with this fragile population within one month after stroke, and extending many
months post. Importantly, the results did not find any detrimental outcomes from providing such intense training so early on. Our results are in contrast to the highly cited VECTORS study that showed that three hours of CIMT led to worse outcomes compared to two hours of either CIMT or dose matched usual care. Their high intensity group had to wear a constraint mitt on the unimpaired side for 90% of waking hours thus forcing use of the impaired side throughout the day. This may have been too high of an intensity so early after stroke (Dromerick et al., 2009). Our results also differ from the ICARE study - another influential study conducted early after stroke - that found no differences in outcome despite varied treatment amounts. Their high intensity program provided on average less than 30 hours of upper limb therapy over 10 weeks which was only a few hours more on average than their dose matched control group, and about 17 hours more than their usual care group. This may not have been enough to overcome the effects of spontaneous biological recovery happening during the intervention period (Winstein et al., 2016).

A fourth topic important for stroke rehabilitation is prediction models. Two established models are the Proportional Recovery Rule (Prabhakaran et al., 2008) and the Predicted Recovery Potential (PREP2) algorithm (C.M. Stinear et al., 2017a)(Smith, Ackerley, Barber, Byblow, & Stinear, 2019). They have far reaching influence not only at the individual level of care, but also at policy levels (i.e. reimbursement schedules). Both models emphasize biological
recovery that occurs spontaneously, without systematically examining the impact of interventions utilized to modify or augment this spontaneous recovery. However, the PREP2 was developed using subjects from previous studies who on average received less than 15 hours of upper extremity training throughout their rehabilitation (Byblow, Stinear, Barber, Petoe, & Ackerley, 2015; Stinear, Barber, Petoe, Anwar, & Byblow, 2012). Thus is critically important that the validity of both models is evaluated against different types and amounts of training. Additionally, their methodology needs to be scrutinized carefully for optimal prediction accuracy. The third study which included 27 participants with moderate impairment, addressed both of these issues. Primarily, the study evaluated whether an additional 8-10 hours of VR/robotic based upper limb training initiated within the first month post-stroke led to greater than predicted recovery and/or outcomes compared to that of a usual care group (UC). Recovery and outcomes of both groups were compared against the Proportional Recovery Rule and PREP2 algorithm predictions respectively, as well as between the two groups. Limitations in this third study were a lack of randomization between groups and the use of different time points for baseline and recovery/outcome measures for this study compared to the two models. Despite these limitations, primary study results support the importance of conducting such research as trends indicated that there may be greater than predicted proportional recovery when additional VR/robotic training is initiated early after stroke, especially for those
individuals who have residual CST function. Krakauer and Marshall (2015) state that proportional recovery depends primarily on spontaneous biological recovery and is not affected by type nor amount of training. Our results may be different because we provided high amounts of intense upper limb training to our intervention group. The developers of the rule utilized data from participants already enrolled in a prospective study and hence no treatment protocols were manipulated (one can assume that these individuals only received usual care). The rule was further investigated by Stinear et al., (2017b) whose study cohort only received a median of 0.7 - 2.7 hours of upper limb training during their three month trial. Again, this is far less than what our high intensity group received. The developers of the rule also did not evaluate recovery based on CST function and we find a difference between groups more so in individuals who have functional CSTs.

A secondary aim of this third study was to evaluate the methodology used in the PREP2 algorithm, specifically whether testing CST integrity while the affected hand is contracting (active method) leads to fewer false negatives and hence a more accurate model compared to testing CST function with the hand at rest (resting method). Secondary results also support the need to further evaluate the methodology used for MEP assessment for the PREP2 algorithm.

5.2 Closing remarks and future direction

All participants in the three studies presented in this thesis, except for the last
six, were recruited as part of a pilot study conducted from July 2013 until May 2018 at St. Joseph’s Hospital, Wayne. Data and insight from this pilot study were used to develop a large scale randomized controlled trial (RCT) occurring presently at the Kessler Institute for Rehabilitation, Saddlebrook. Importantly, all three studies show the feasibility of providing additional training and performing multiple tests in the acute and early sub-acute periods post-stroke. The first study also showed that persons with initially severe hand impairment could train effectively with our novel intervention, and that this training led to clinically important long-term gains in this group. The second study revealed that additional VR/robotic training led to significantly greater gains in long term upper limb impairment compared to usual care. Lastly, the third study demonstrated that additional VR/robotic training may give rise to greater than predicted proportional recovery compared to usual care in individuals with function CSTs. These results warrant additional evaluation with larger groups and proper study methods that rectify the limitations present in these three thesis studies. Currently, the research questions put forth in Aims 2 and 3 are being further evaluated within the RCT at Kessler using larger groups, appropriate methods of randomization, and additional clinical, kinematic (Reach to Grasp), and neurophysiologic outcome measures (EEG). The additional kinematic data will help us to evaluate more clearly whether behavioral gains are made from compensatory mechanisms or from return of premorbid patterns of movement and muscle recruitment.
The EEG data will add to our prediction questions. The RCT also uses four months as the primary outcome measurement time to parallel the time frames used by the prediction models. Additionally, the RCT includes a dose matched control group that receives equivalent amounts of additional usual care. This will allow us to determine whether gains are solely from additional amounts of training or from the unique aspects of VR/robotic training. Lastly, we are quantifying the amount of training received by each group at Kessler as the number of arm and hand repetitions performed. This will allow for a more direct and objective comparison of dosing between groups. Discussions have been initiated to add the research questions addressed in Aim 1 to the RCT as well. If and when initiated, larger groups, and a dose matched control group would be used for this Aim as well.

Maximal return of arm function is critical for return to independent living. With the current rehabilitation approaches, only 5-20% achieve full return of arm function at six months post-stroke (Colomer & Llorens, 2016). It is thus imperative to continue to develop and test innovative upper extremity training protocols that are based on sound principles of motor learning, and also to compare changes in impairments, behavior, and brain organization to help identify the neural substrates of recovery. The research conducted in the RCT will provide more definitive answers to the preliminary results presented here. It will also add to the sparse and at times contradictory body of research in this early time frame post-stroke.
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