

Medical University of South Carolina Protocol
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Study Title: Patient-Targeted Upper Extremity Rehabilitation After Stroke

Version 4.0

Date: 08/01/2016

TABLE OF CONTENTS

Specific Aims	p.1
Background and Significance	p.2
Preliminary Studies	p.7
Research Design and Methods	p.12
Protection of Human Subjects	p.20
References/Literature Citations	p.25
Consultants	p.28
Facilities Available	p.29
Investigator Brochure	p.30
Appendix	p.30

A. SPECIFIC AIMS

Exciting advances in rehabilitation research have increased knowledge about the potential for upper extremity (UE) motor recovery after stroke. Experimental models provide strong evidence that intensive task practice which is made progressively more and more challenging drives cortical reorganization. We restructured the Fugl-Meyer UE Assessment (FMA-UE) to reflect a progression of UE motor recovery typically seen in individuals with stroke. This novel restructuring (1) allows the identification of unique categories of UE motor impairment that can be the target for specific treatment, and (2) maps increasingly more difficult movement tasks for task-practice sessions. The restructured FMA-UE is the first comprehensive framework with which to link measurement of patient-specific UE motor ability to personalized treatment.

The Specific Aims of this VA funded (VA Merit Award, #1I01RX000799, Woodbury PI) project are to:

Aim #1: Compare the effects of targeted rehabilitation to non-targeted rehabilitation on UE motor function.

Hypothesis: Targeted intervention will result in a greater pre- to post-intervention reduction of UE motor impairment when compared to non-targeted intervention. **Approach:** This is a prospective double-blind RCT with parallel arm design. 130 individuals with mild, moderate, and severe post-stroke UE hemiparesis will be enrolled. Subjects within each impairment level will be randomly assigned to either a targeted or non-targeted treatment group for 2 hr rehabilitation sessions 3x/week for 4 weeks (a total of 12 sessions). Targeted practice is defined as a treatment targeted at specific UE motor deficits characterizing each UE impairment level enabled by our original measurement method. Non-targeted practice is a standard of care treatment that consists of task practice with no guidance from measurement to choose appropriate tasks or address specific underlying deficits.

Aim # 2: Determine critical neuromechanical factors influencing response to targeted or non-targeted therapy

Hypothesis: Response to targeted therapy will be associated with recovery of more normal UE movement and muscle activity patterns. **Approach:** Our measurement framework successfully allows us to target therapy. However detailed neuromechanical analysis is critical for documenting the baseline status of motor control process in order to quantify treatment-related changes in these processes. Multiple regression models will be used to determine the influence of pre- to post-intervention changes in neuromechanical factors and UE motor impairment as measured by the Rasch FMA-UE change score. This knowledge will enable further refinements of existing treatments and facilitate development of new treatments to target underlying factors.

Aim #3: Determine critical predictors of the time-course of response to rehabilitation.

Hypothesis: People with stroke have different patterns of recovery; key neuromechanical variables predict these patterns. Approach: Growth mixture modeling (GMM) will be applied to longitudinal Rasch FMA-UE measures. GMM separates a sample into subgroups of people showing similar recovery patterns, and specifies neuromechanical factors predicting these patterns. Using GMM within our measurement framework is a highly innovative method to identify distinct groups with similar recovery trajectories and describe each group's behavior in terms of FMA-UE items that can/cannot be performed over the time course of treatment.

B. BACKGROUND AND SIGNIFICANCE

Each year over 795,000 individuals in the USA have a stroke.¹ Stroke causes brain cell damage or cell death which then leads to altered patterns of connectivity in cortical and sub-cortical neural networks supporting movement.² Over 75% of stroke survivors experience some degree of upper extremity (UE) paralysis.³ Unfortunately, UE motor function rarely recovers completely; 85% of those who survive stroke report residual arm/hand motor impairment severe enough to interfere with performance of daily tasks at 4 years post-stroke.⁴

Recent progress in neuro- and rehabilitation science has advanced the understanding of the potential for neuronal recovery after stroke-related brain damage.⁵ These advances stem from investigations of the brain's natural "plasticity" or propensity to organize/reorganize.^{6,7} Neural plasticity is the mechanism by which the brain encodes experience and learns new behaviors, and is also the mechanism by which the damaged brain relearns lost behavior in response to rehabilitation.⁸ A growing body of experimental evidence in animal models of stroke and translational studies in humans have shown that the amount of practice and skill training are fundamental aspects of rehabilitation that drive recovery.⁹

2a. Amount of practice is a critical component of effective UE rehabilitation

In the healthy nervous system, repetitive use of a limb induces plasticity of neuronal structures and networks within regions supporting motor control.⁹⁻¹¹ Animal models show altered motor representations, dendritic branching, increased synapse growth and more efficient synaptic responses throughout motor cortical areas corresponding to repetitively practiced movements, suggesting possible mechanisms of use-dependent neural reorganization.^{7,12,13} In healthy humans, extensive practice of specific UE movements alters cortical motor representations, such that the territory representing the practiced movement expands, while territories representing non-practiced movements do not expand or shrink.^{14,15}

Similarly, repetitive use of a limb after a brain lesion promotes neural reorganization of damaged networks. In rat and primate models of cortical stroke, UE limb motor representation loss was prevented and cortical reorganization was promoted with extended task-practice.^{16,17} In humans with stroke, imaging studies show that task-practice rehabilitation programs increase the excitability of the damaged hemisphere, alter motor cortex topology, and contribute to the restoration of balanced inter-hemispheric facilitation and/or inhibition.¹⁸ Repetitive use of the more affected UE may "force" activation of neural circuitry that the patient is not using, or only minimally using, thereby inducing reorganization or strengthening neural adaptations that in turn enhance the use of that circuitry and the behavior(s) dependent upon it.

2b. Skill training is a critical component of effective UE rehabilitation

The greatest neuroplastic changes in cortical areas supporting UE motor control are associated with the repetition of new skills rather than repetition of existing skills.¹⁶ In a classic series of studies Plautz and Nudo showed that training a primate to retrieve a food pellet using a novel pattern of forelimb and digit coordination increased the size of cortical representational areas for the trained limb.^{11,19} In contrast, repeating an already-known limb coordination pattern to retrieve the pellet did not alter the movement representational area. Other studies have shown that skill training results in reorganization of movement representations within the motor cortex,²⁰ endurance training induces angiogenesis but does not alter movement representations,²¹ and strength training alters spinal motor neuron excitability but does not alter motor map organization.²² These findings imply that the type of tasks practiced impart structural and functional adaptive reorganization across the motor system which are dependent on the content of the practice sessions.

Accumulated evidence linking skill-training to neural plasticity has led to modern “task-oriented training” rehabilitation approaches.²³ In a task-oriented approach, a patient is challenged to accomplish a specific goal (e.g., pick up and drink from a soda can) thereby engaging the patient’s visual, perceptual, cognitive and motor systems as he/she problem-solves how to achieve the goal.²⁴ Each practice trial provides information to the patient (feedback) which forms the basis for strategizing the next attempt.²⁵ Applied to stroke rehabilitation, the approach assumes learning-dependent functional recovery which is measured in terms of the patient’s ability to perform a specific task. For example, several large randomized controlled clinical trials have shown that high-dose repetitive task-oriented practice improves a patient’s perceived ability to use his/her affected UE for daily tasks.²⁶⁻²⁸

2c. The specific treatment effects of repetitive task-practice UE rehabilitation are not clear

Although task-oriented approaches are efficacious, the specific effects of the treatment on motor control processes supporting task performance are not clear. For example, a large clinical trial of constraint induced movement therapy, a type of task-oriented training, enabled participants to perform tasks faster.²⁸ Yet the outcome measures used in the trial do not provide data on how participants accomplished the tasks.

There are very few studies investigating the effects of task-oriented treatments on specific motor behaviors and/or underlying mechanisms. Those studies that have been conducted provide conflicting results. On the one hand, studies have shown the therapy improves underlying motor control strategies thereby enabling more efficient motor planning.^{29,30} On the other hand, studies have shown the therapy exaggerates compensatory movement patterns thereby reducing movement efficiency^{31,32} and possibly interfering with longer-term recovery.^{33,34} Knowledge of how motor behaviors and/or neuromechanical factors are affected by treatment is key for establishing clear guidelines about the treatment, i.e., for which patients it is optimal, and for which patients it is not optimal.

Current neurorehabilitation practice guidelines direct therapists to implement task-oriented training but the lack of knowledge regarding treatment effects may limit this implementation.^{35,36} In order to determine the most appropriate treatment strategy for a given patient a therapist must 1) clearly define specific UE movements that patient can/cannot perform, 2) determine the impact of underlying factors on his/her performance, and 3) plan an expected time-course of treatment. To do this, a therapist must have an assessment of UE motor function that reflects contemporary theoretical expectations of deficit and recovery by clearly identifying where the patient is in the UE recovery process and specifying the expected next steps in recovery.³⁷ Without this information, a therapist is unable to tailor a repetitive task-oriented training approach to the needs of his/her patient. Unfortunately many assessments widely used in stroke rehabilitation are not useful for this purpose because their score is not meaningful.

For example, the Fugl-Meyer Upper Extremity Assessment (FMA-UE) is the most commonly used tool used to measure post-stroke UE motor impairment in rehabilitation research studies.^{38,39} The FMA-UE is scored by assigning each item an ordinal rating (0=unable to perform, 1=partial performance, 2=near normal performance), then summing item ratings for an aggregate score. However the sum score does not reveal how an individual performs on specific items. What does it mean for a patient to receive a 30 on the FMA-UE? Is the client able to extend his/her elbow? Is s/he able to keep the elbow in full extension while elevating the shoulder to 180 degrees? These are important questions because judgments regarding impairment severity, interpretations of treatment effects or response to therapy and, most importantly, decisions about treatment rely in a clear understanding of what a FMA-UE score means.⁴⁰

2d. Rasch measurement theory improves the meaning of the FMA-UE score

A person’s rating on an assessment item is an interaction of the person, given his/her skill level, and an item which has a level of difficulty.⁴¹ Item Response Theory statistical methods such as the Rasch measurement model connects person-ability to item-difficulty thereby linking a score to a description of item performance.⁴² We applied the Rasch model⁴³ to FMA-UE data obtained from 512 persons with stroke.⁴⁴ The analysis calibrated measures of item-difficulty and person-ability to the same metric and arranged items according to difficulty (less to more difficult) and persons according to ability (less to more ability). Through Rasch measurement, FMA-UE items represent difficulty makings along the continuum of the instrument’s construct (UE motor ability). The placement of person-ability on this measurement continuum enables a person’s location along the measurement metric, i.e., a person-ability measure, to reflect the “amount” of the construct, UE motor ability that he/she exhibits.

This Rasch analysis was the basis for developing a classification system which formed groups of patients having similar amounts of UE motor ability. In ongoing work funded by Dr. Woodbury's CDA-2 (see **Table 1**, and **Preliminary Studies**) item response theory staging methods⁴⁵ were applied to the Rasch FMA-UE item difficulty hierarchy to establish 3 stages of UE motor impairment; mild, moderate, and severe. Stages can be understood as several hierarchic levels along the continuum of a construct. To avoid confusion with the classic "Brunnstrom Stages"⁴⁶ we will refer to *ability levels* or *categories* instead of *stages*. Cut score values were determined from FMA-UE items corresponding to evidence-based milestones marking a progression of post-stroke UE recovery; concurrent shoulder flexion/elbow extension,⁴⁷ and wrist flexion/extension while keeping the proximal joints still.⁴⁸

The idea of partitioning post-stroke UE recovery into stages is not new. In 1951 Twitchell described a predictable, stepwise course of post-stroke UE recovery.⁴⁹ Brunnstrom, furthering Twitchell's work, mapped a sequential 6-stage recovery process beginning with flaccidity (stage 1), advancing to proximal gross whole arm synergistic

Table 1: The Rasch FMA-UE UE Impairment Categories

Impairment Level	Description of movements below ability level (easy), matched to ability level (matching), and above ability level (difficult).	Key UE motor behavior marking transition to the next impairment level.
Mild	<p>Easy: Single joint movements into the body and movements requiring simultaneous control of two joints</p> <p>Matching Ability: Hook grasp, Wrist circumduction</p> <p>Difficult: No FMA-UE items represent this level of difficulty</p>	n/a
Moderate	<p>Easy: Single joint movements into the body (e.g., elbow flexion), mass finger flexion and cylindrical grasp</p> <p>Matching Ability: Fluctuating between partial ability and near normal ability to perform movements requiring simultaneous control of two joints (e.g., pronate/supinate forearm with elbow extended) and perform distal movements requiring precise muscle coordination (e.g., lateral prehension)</p> <p>Difficult: Hook grasp, wrist circumduction</p>	Reacquisition of near normal ability to flex and extend the wrist while keeping the elbow straight and the shoulder flexed to 30 degrees
Severe	<p>Easy: Single joint movements into the body (e.g., elbow flexion), mass finger flexion and cylindrical grasp</p> <p>Matching Ability: Fluctuating between unable and partial ability to perform movements requiring movement of arm away from body (e.g., extend elbow, abduct shoulder, flex shoulder to 90 degrees). Partial ability to externally rotate shoulder, utilize palmar pinch.</p> <p>Difficult: Unable to perform movements requiring simultaneous control of two joints (e.g., pronate/supinate forearm with elbow extended), or perform distal movements requiring precise muscle coordination.</p>	Reacquisition of partial ability to simultaneously flex the shoulder while extending the elbow

movements (stage 3) and onto recovery of distal isolated fine motor coordination (stage 6).⁴⁶ Fugl-Meyer applied a numeric rating scale to Brunnstrom's taxonomy thereby echoing her stages in the FMA-UE item order.³⁹

The progression of FMA-UE items reflected in the progression of UE impairment levels differ from the classic Brunnstrom stages in content and meaning. Rasch analysis of the FMA-UE challenged the assessment's construct validity and item-difficulty order (see **Preliminary Studies**).⁴⁴ The Rasch FMA-UE item-difficulty order provided a framework to interpret contemporary data providing evidence that arm movements are easier or more challenging based on the inherent task-specific computational demands of a movement task.⁵⁰

We argue that this Rasch FMA-UE measurement framework is a valuable foundation for designing treatment. We hypothesize that for each level of UE motor impairment, the Rasch FMA-UE classification system defines task-practice conditions that are the just-right balance between person-ability and task-difficulty and therefore provides a platform for designing patient-targeted therapy, investigating the specific effects of treatment and identifying responders/non-responders.

2e. The Rasch FMA-UE measurement framework as the basis for designing patient-targeted UE rehabilitation

According to the Challenge Point Framework,²⁴ optimal practice sessions occur when a learner is challenged by the tasks being practiced because they are well matched to his/her ability level, i.e., neither too easy nor too difficult. Appropriately scaling task-difficulty to match patient-ability motivates repeated attempts and optimizes sensorimotor feedback.^{24,51} In contrast, repetition of "easy" tasks (difficulty below patient-ability) may not promote cortical reorganization because tasks are already known.²² Repeated attempts to perform very difficult tasks (well-

above patient-ability) may elicit altered, compensatory movement configurations which may interfere with long term recovery.^{33,34}

A Rasch FMA-UE person-measure (in contrast to a sum-score) defines individuals' response to specific FMA-UE items, thus a classification system based on the person-measure specifies how ability-level members respond to FMA-UE items. The Rasch FMA-UE metric indicates what items (UE movements) were easy enough for patients with poor UE motor ability and what items were challenging enough for patients with good UE motor ability. It therefore forms the basis for designing optimal task-oriented practice sessions.

For example, when a person's ability measure matches an item's difficulty measure then it is expected that s/he would have a 50% probability of being able to perform this item successfully because it represents the "just right challenge" for the individual. Items at this level reflect movements that the patient is expected to recover in the short-term, i.e., as the expected-next-steps in the post-stroke UE motor recovery process. Therefore these items (movements) provide optimal challenge and should be targeted in task-practice sessions. A person has a greater than 50% probability of accomplishing items with difficulties below the person measure ("easy" items). Items at this level reflect movements that have already recovered and therefore do not need to be practiced in task-practice sessions. A person has a less than 50% probability of accomplishing items with difficulties above the person measure ("hard" items). Items at this level reflect movements that are too difficult for the patient at his/her current level of ability. As the patient recovers, these items may indicate appropriate goals for future task-practice sessions.

2f. Determining neuromechanical influences on UE recovery

One purpose of the present proposal is to explore the neuromechanical mechanisms contributing to post-stroke UE recovery. There is evidence supporting the hypothesis that several neuromechanical (i.e., kinematic and electromyographic (EMG)) factors are key to recovery. Individuals with stroke demonstrate reduced voluntary elbow extension range of motion⁵² which may be at least partially explained by abnormal elbow muscle co-activity between biceps and triceps.⁵³ Together, these impairments contribute to reduced ability make smooth reaching movements throughout the workspace.⁵⁴ Given this limitation, people with stroke recruit the trunk as an extra degree of freedom.⁵⁴ Anterior trunk flexion is used in place of elbow extension for reaching movements. UE motor recovery is characterized by improved elbow extension,⁵⁵ reduced anterior trunk motion,⁵⁶ and reduced muscle co-activity.⁵⁷

Here we aim to investigate the influence of neuromechanical mechanisms contributing to the treatment related changes in participants' Rasch FMA-UE person ability measure. By investigating the relationship of neuromechanical factors to a person's FMA-UE measure, we will learn more about what neuromechanical factors or mechanisms underlie a person's location within this classification system. As noted in the brief literature review above, several studies relate neuromechanical factors to UE recovery. But in these studies, UE recovery is defined in terms of performance of a single task (e.g., reach-to-point) or in terms of a patient's aggregate score on an assessment. Here, our measurement framework enables us to investigate how neuromechanical factors influence re-acquisition of the underlying construct "UE motor ability" which is defined in terms of specific FMA-UE items that a patient could/could not perform prior to rehabilitation but gained the ability to perform after rehabilitation.

2g. The time-course of UE recovery

Identifying and describing those that respond and do not respond to rehabilitation treatment is a growing area of interest in rehabilitation science. Here we aim to differentiate patterns of recovery in our sample by integrating Growth Mixture Modeling (GMM) into our Rasch FMA-UE measurement framework. This is a highly novel method for defining responders and non-responders. Although well established in educational and psychological literature, GMM is a new to rehabilitation science and has been used in only a few stroke rehabilitation studies to date.^{55,58,59}

GMM offers a robust method of identifying subgroups of people with stroke who follow distinct trajectories of UE recovery. In contrast to analyses that focus on mean-level change in a sample, GMM elucidates how different people recover in different ways. GMM separates repeated measurements of a sample into groups of individuals showing similar patterns of change over time. In addition, the analysis specifies factors predicting these distinct patterns. When placed into the Rasch FMA-UE measurement framework, the results of the GMM analysis will

enable a clear description of each subgroup because the subgroup's pattern of UE recovery will be directly connected to a description of the specific FMA-UE items that can/cannot be performed.

2h. Pilot study: targeted-rehabilitation versus non-targeted rehabilitation

Our recent pilot work³² provides evidence that a targeted rehabilitation intervention maximizes UE motor function when compared to non-targeted intervention. We conducted a pilot study (n=12, with 6 subjects per intervention group) which investigated the effects of an intervention targeted at participants with moderate post-stroke UE motor impairment, specifically those individuals who displayed reduced shoulder-elbow interjoint coordination and

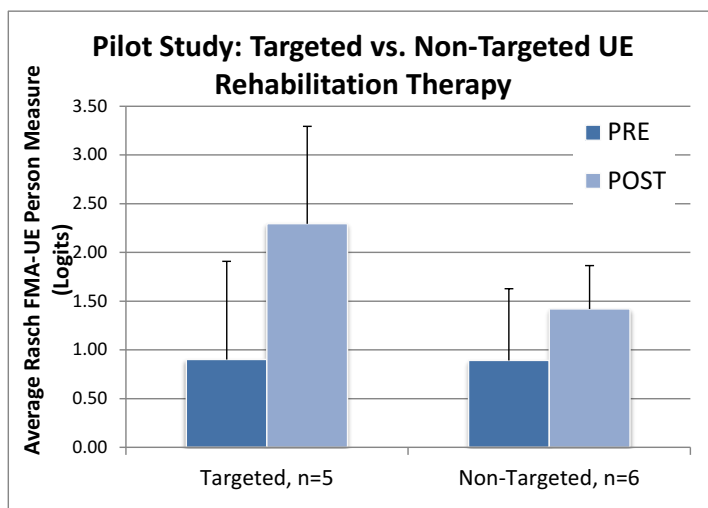


Figure 1: Rasch FMA-UE measure pre- and post-treatment

excessive anterior trunk flexion. The intervention was “targeted” meaning that it afforded opportunity for participants to practice a more normal reaching pattern characterized by concurrent shoulder flexion-elbow extension while cueing participants to avoid using excessive anterior trunk flexion. The trunk cue was provided with a trunk restraint that was loosely fit across the subject's chest. Participants were randomly assigned to a high-intensity task practice group with trunk restraint (targeted) or a high intensity task practice group without trunk restraint (non-targeted). Both groups were matched on amount of time spent in therapy (4 hrs/day, over 10 days). The FMA-UE was administered 1 week prior to be start of therapy, and then administered again within one week after the conclusion of therapy. Each subject's FMA-UE was converted to a person-ability measure with Rasch analysis. The average Rasch FMA-UE measure for each group is shown in **Figure 1**. Pre-intervention, the targeted

group scored an average of 0.90 (± 1.01) logits and the non-targeted group scored a similar 0.89 (± 0.74) logits. After the intervention subjects in the targeted group scored 2.30 (± 1.0) logits while the non-targeted subjects scored 1.42 (± 0.45) logits. These data demonstrate the feasibility of targeting an intervention at a specific UE motor impairment and suggest that targeted therapy holds potential for reducing UE motor impairment (as measured by the FMA-UE) to a greater degree than a non-targeted intervention. See **Preliminary Studies** for more information on this pilot study.

Significance and Innovation: A modern measurement method, such as the Rasch model, presents an innovative way to think about measurement and treatment. We built an original post-stroke UE measurement framework with Rasch analysis. For the first time a methodology is available to researchers and therapists offering an evidence-based method to directly connect a patient's UE motor-ability measure to a description of movements that can/cannot be accomplished. This connection, not only allows us to re-evaluate traditional expectations of post-stroke UE recovery, but also maps recovery as a progression of item difficulties. The progression of item difficulties provides a basis for interpreting and/or elucidating emerging data about post-stroke UE impairment and recovery. Moreover, the framework provides an innovative platform to determine the influence of neuromechanical factors on recovery of specific motor behaviors and determine how these specific motor behaviors evolve over time. No similar measurement framework exists. Indeed, standardized assessments have offered the practicing clinician little benefit for making day-to-day clinical practice decisions. By restructuring the FMA-UE with Rasch analysis, we anticipate that the framework will provide a tool for therapists to make theoretically-grounded clinical decisions, set patient-tailored goals, plan optimal treatment, and clearly monitor patient progress. We anticipate that the aims of the present study, if successfully achieved, will lead to refinements of existing interventions in order to more accurately target critical underlying impairments and patterns of recovery. In addition, the investigation will be a tool for future investigations of therapy targets and novel interventions as of yet unconsidered. Efforts such as these may show promise for closing the gap between research and practice in rehabilitation.

C. PRELIMINARY STUDIES

3a. Development of the Rasch FMA-UE measurement framework

In published research⁴⁴ we restructured the FMA-UE to reflect a progression of UE motor recovery typically seen in individuals with stroke thereby challenging the traditional reflex-hierarchical theoretical construct of post-stroke UE recovery underlying the assessment.³⁹ We applied the Rasch polytomous measurement model⁴³ to FMA-UE data obtained from 512 individuals, ages 69.8 ± 11.1 years, 0–145 days post-stroke. Factor loadings and item infit statistics suggested that the three reflex items were empirically disconnected from other assessment items. The reflex items were removed.

The analysis simultaneously calibrated measures of item-difficulty and person-ability to the same metric and arranged items according to difficulty (less to more difficult) and persons according to ability (less to more ability). The analysis illustrated what movements were able to be performed by individuals with less motor ability (i.e., greater impairment) and what movements were able to be performed by individuals with more motor ability (i.e., less motor impairment).

The Rasch-derived FMA-UE item difficulty hierarchy is presented in **Table 2**. Items are ordered in decreasing order of difficulty so that the most challenging items are at the top of the table and least difficult items are at the bottom of the table. Item difficulty calibrations are given in the middle column (measure) along with the standard error of the measure in the right column. This item order was consistent in 98% of the 512 person sample in this study. In a subsequent study we showed that it was invariant in 377 people tested across two time periods.⁶⁰

The FMA-UE item difficulty order is not entirely consistent with the traditional recovery model because items do not progress in a strict synergistic-to-isolated, proximal-to-distal order. For example, Table 1 shows that some

Table 2: The Rasch FMA-UE Item Difficulty

FMA-UE item	Measure	Error
Wrist circumduction	1.67	0.10
Hook grasp	1.33	0.10
Shoulder flexion to 180°, elbow extended	1.26	0.10
Spherical grasp	1.20	0.10
Lateral prehension	1.08	0.10
Wrist flexion-extension, elbow extended	1.06	0.10
Pronation-supination, elbow extended	1.00	0.10
Wrist stable, elbow extended	0.95	0.10
Movement with normal speed	0.89	0.10
Forearm supination	0.65	0.10
Shoulder abduction to 90°, elbow extended	0.28	0.10
Movement without dysmetria	0.27	0.10
Shoulder external rotation	0.24	0.10
Wrist stable, elbow at 90°	0.18	0.10
Wrist flexion-extension, elbow at 90°	0.12	0.10
Palmar prehension	0.06	0.10
Scapular retraction	0.03	0.10
Pronation-supination, elbow at 90°	-0.17	0.11
Shoulder flexion to 90°, elbow extended	-0.21	0.11
Hand to lumbar spine	-0.40	0.11
Shoulder abduction	-0.56	0.11
Elbow extension	-0.64	0.11
Forearm pronation	-0.87	0.11
Movement without tremor	-0.91	0.11
Cylindrical grasp	-1.10	0.12
Finger mass extension (relax flexion)	-1.25	0.12
Scapular elevation	-1.40	0.12
Finger mass flexion	-1.44	0.12
Shoulder adduction with internal rotation	-1.56	0.12
Elbow flexion	-1.76	0.13

proximal arm motions are located near the bottom of the table. These “easy” items are expected to be among the first motions to recover after stroke (e.g., elbow flexion, shoulder adduction with internal rotation). But unexpectedly, some distal arm motions are also located near the bottom of the table. They are also “easy” items and also are expected to recover early after stroke (e.g., finger mass flexion, cylindrical grasp).

The FMA-UE item difficulty hierarchy provides a framework to elucidate and interpret contemporary research. Our results suggest that the FMA-UE items are arranged according to the difficulty of motion. That is, arm movements are “easier” or “more challenging” based on the inherent task-specific demands of the movement. Elbow flexion may be “easier” than wrist circumduction because the movement is inherently less complex, i.e., requires less agonist-antagonist coordination. Shoulder flexion to 180 degrees with the elbow extended may be “difficult” because of the influence of gravity on a long lever arm.

3b. Use of the framework to match person-ability to item-difficulty

In a separate study we aimed to illustrate the connection between a Rasch FMA-UE person-ability measure and FMA-UE item-difficulties. The data shown here were generated from Dr. Woodbury's funded VA RR&D CDA-2 project. For this project, 55 participants (52 completed testing), ages 45–88 years who were an average of 7 years post first time ischemic stroke were enrolled into a prospective cross-sectional study of UE reaching ability.

Figure 2, a Rasch FMA-UE person-item map, presents the sample ability (n=52) measured on the same metric as item difficulty in order to illustrate the link between person-ability and item-difficulty. The column of numbers to the left is the measurement metric (logits). The center line represents the FMA-UE's latent trait, UE motor ability. The "x" symbols to the left of the center line represent each participant's person ability measure. Items are displayed to the right of this line. The map is arranged so that the most able people and the most difficult items are at the top and the least able people and least difficult items are at the bottom. A curve representing the distribution of the sample's UE motor ability has been overlaid onto the figure to illustrate the relationship of the sample's ability to assessment's item-difficulties. The location of each item on the metric corresponds to its average difficulty across all categories, that is, the item difficulty measure in Table 2. However, item difficulties actually range over the metric because each item has a rating scale. The dotted rectangular box surrounding items illustrates this range.

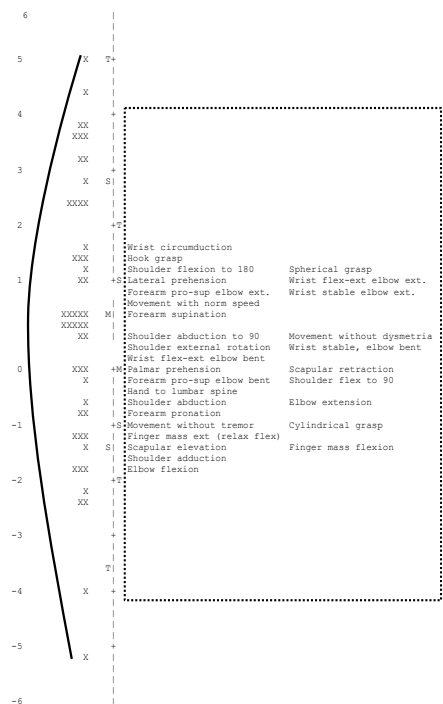


Figure 2: Rasch FMA-UE person-

exhibit control of 1 joint (e.g., items at the bottom of the figure such as elbow flexion or shoulder adduction); persons with higher scores were likely to exhibit control of multiple joints (e.g., items at the top of the figure such as shoulder flexion to 180 degrees, wrist circumduction). The map suggests that UE motor recovery corresponds with an increased probability of performing tasks requiring synchronous control of agonist-antagonists to overcome gravity, rotate joints or achieve dexterous prehension patterns.

3c. Use of the framework to link measurement to rehabilitation treatment design

In a recent publication⁶¹ we demonstrated a method to link a Rasch FMA-UE person-ability measure to a patient-specific rehabilitation treatment plan. The data shown here were generated from Dr. Woodbury's funded VA RR&D CDA-2 project.

Figure 3 presents a Rasch FMA-UE Keyform Recovery Map. A keyform looks similar to a survey questionnaire with the items of the survey on one side of the form and numbers corresponding to the rating scale of each item, placed on the other side of the form. While the keyform is similar to a survey questionnaire, it has two additional features. First, the items of the assessment are ordered on the basis of Rasch item-difficulty calibrations. The items progress from the easiest item on the bottom of the form to the hardest items on the top of the form. Second, the ratings for the items are not lined-up in straight vertical columns as on a typical survey. Instead each rating for each item is associated with a difficulty calibration. Item ratings stair-step from left to right to correspond with increasing amounts of person-ability required to perform more difficult items. The form enables one to view the specific items that a client can or cannot perform. This information can assist a therapist to tailor treatments to a client's individual ability-level.

To illustrate the use of a keyform, one individual with moderate UE motor impairment (defined by the Rasch FMA-UE impairment categories) enrolled in Dr. Woodbury's CDA2 was randomly selected. This person's performance on each FMA-UE item is displayed on the keyform. Item ratings show a pattern of what the client can do, can partially do, and cannot do. This individual shows near normal performance (rating of "2") on five of the six easiest items and partial performance (rating of "1") on four of the nine of the most difficult items. The area boxed by the dashed-line in the figure (i.e., items from movement without tremor to forearm supination) illustrates the "transition zone" where the client's performance fluctuates between partial performance (rating of "1") and near normal performance (rating of "2"). This transition zone can be the basis for goal setting and treatment planning.

Because items in the transition zone are at the “just right challenge” for the individual, the position of items in relationship to this zone reflect the client’s expected next steps in the post-stroke UE motor recovery process. Motor behaviors (items) within the lower parts of the transition zone may suggest appropriate shorter term functional goals, while motor behaviors (items) within the upper parts or well above the transition zone may form

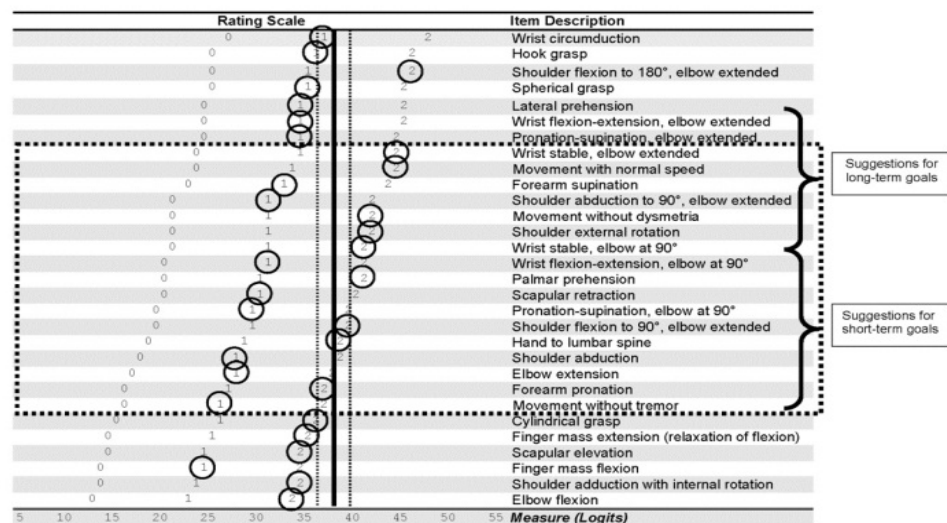


Figure 3: Rasch FMA-UE Keyform Recovery Map

methods^{45,62,63} were used to differentiate 3 levels of UE motor impairment; severe, moderate and mild. **Table 3** presents the Rasch FMA-UE Keyform Staging Chart. Rows of FMA-UE items are listed in order of decreasing difficulty level. The 3-point rating scale for each item is presented to the left of each item label. The blue shaded

Table 3: Rasch FMA-UE Keyform Staging Chart

Table 3. Rasch FMA-UE Keyhole Staging Chart									
Severe			Moderate		Mild				
-6	-4	-2	0	2	4	6			
		0	1	1	2		Wrist circumduction		
		0		1	2		Hook grasp		
		0		1	2		Shoulder flexion to 180°, elbow extended		
		0		1	2		Spherical grasp		
		0		1	2		Lateral prehension		
		0		1	2		Wrist flexion/extension, elbow extended		
		0		1	2		Pronation-supination, elbow extended		
		0		1	2		Wrist stable, elbow extended		
		0		1	2		Movement with normal speed		
		0		1	2		Forearm supination		
		0		1	2		Shoulder abduction to 90°, elbow extended		
		0		1	2		Movement without dysmetria		
		0		1	2		Shoulder external rotation		
		0		1	2		Wrist stable, elbow at 90°		
		0		1	2		Wrist flexion/extension, elbow at 90°		
		0		1	2		Palmar prehension		
		0		1	2		Scapular retraction		
		0		1	2		Pronation-supination, elbow at 90°		
		0		1	2		Shoulder flexion to 90°, elbow extended		
		0		1	2		Hand to lumbar spine		
		0		1	2		Shoulder abduction		
		0		1	2		Elbow extension		
		0		1	2		Forearm pronation		
		0		1	2		Movement without tremor		
		0		1	2		Cylindrical grasp		
		0		1	2		Finger mass extension (relaxation of flexion)		
		0		1	2		Scapular elevation		
		0		1	2		Finger mass flexion		
		0		1	2		Shoulder adduction with internal rotation		
		0		1	2		Elbow flexion		
-6	-4	-2	0	2	4	6			
Severe			Moderate		Mild				

sequence of critical milestones marking post-stroke UE recovery; the ability to (1) simultaneously flex the shoulder and extend the elbow,⁴⁷ and (2) rotate the distal forearm while keeping the proximal joints still.⁴⁸ We identified FMA-UE items corresponding to the critical milestones then calculated Rasch-Andrich step thresholds⁴³ to mark boundaries between categories. Threshold values correspond to the vertical lines in the figure; the threshold marking the transition from severe to moderate = -0.12 logits, and from moderate to mild = 2.44 logits.

This classification system defines UE motor behaviors characterizing each impairment level. Characteristic behaviors are illustrated by the expected FMA-UE item ratings for each stage’s column in the figure. For example, people classified in the FMA-UE “severe” category are partially able to accomplish (grey shaded bars) elbow flexion, scapular elevation, shoulder adduction, mass finger flexion and more difficult movements such as

the foundation for appropriate longer term functional goals.

3d. The Rasch-derived FMA-UE impairment categories

The purpose of this ongoing work is to build a classification system depicting how people with various levels of UE motor impairment (severe, moderate, mild) interact with FMA-UE items. The data shown here were generated from Dr. Woodbury’s funded VA RR&D CDA-2 project.

Item response theory staging

bars designate each item’s “0” rating, grey shaded bars designate the “1” rating, and green shaded bars designate the “2” rating. The numbered scale at the top and bottom of the chart represents the “amount” of the underlying construct, UE motor ability, progressing from less ability (left) to more ability (right) and measured in log-equivalent units (logits). As item difficulty increases, the rating scale stair-steps to the right to illustrate the concept that more UE motor ability is required to accomplish more difficult items. Three cut scores (vertical lines) divide the FMA-UE scale into 3 impairment levels.

Cut-scores marking boundaries between UE impairment levels were based on an extensive literature review to identify a

shoulder abduction, elbow extension, shoulder flexion, forearm pronation/supination. They will be unable to perform (blue shaded bars) all other items. Initial reacquisition of the ability to simultaneously flex the shoulder while extending the elbow (transition from scoring 0 to scoring 1 on the corresponding FMA-UE item) marks entry to the next category. People in the “*moderate*” category have near normal ability (expected score =2, green shaded bars) on items addressing elbow flexion, scapular elevation, finger flexion, relaxation of a tight fist. They should have partial ability (grey shaded bars) items addressing shoulder flexion to 90 degrees while keeping the elbow straight, external rotation, individual finger movements and some prehension skills. People in the “*mild*” category will exhibit “2” on the majority of items (green shaded bars) but may have partial ability (grey shaded bars) to perform the most difficult items such as wrist circumduction and hook grasp. The results of this analysis are also summarized in **Table 1**.

3e. Kinematic and EMG findings to validate the Rasch-derived FMA-UE impairment categories

The purpose of this ongoing work is to validate the Rasch FMA-UE impairment categories with neuromechanical analyses. The 55 person sample enrolled in Dr. Woodbury’s CDA2 study was divided into subgroups according to the FMA-UE impairment category definitions described above. Extensive kinematic, EMG analyses were conducted while subjects performed 5 repetitions of an unrestrained reach-to-grasp task at a fast pace.

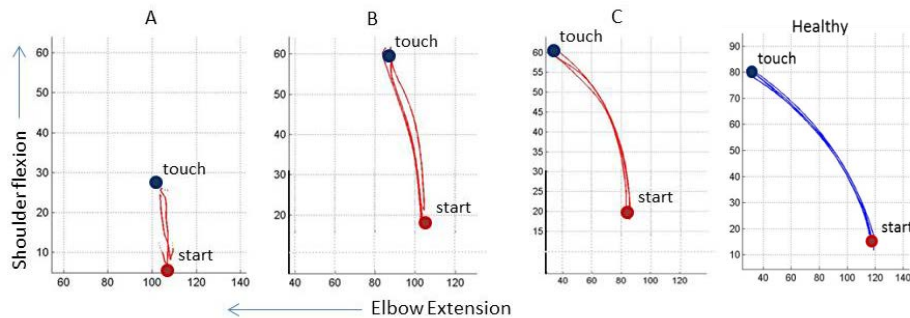


Figure 4: Angle-angle plots (red= stroke, blue = healthy)

Figure 4 presents angle-angle plots. Panels A-C in red present kinematic data from 3 representative individuals with stroke. The rightmost panel in blue presents kinematic data from a neurologically healthy individual. Elbow extension (x-axis) is plotted with shoulder flexion (y-axis) for the 4 individuals. Person A (left panel) has severe UE motor impairment as evidenced by

utilizing approximately 20 degrees of shoulder flexion and virtually no elbow extension during the task. Person B (middle panel) with moderate impairment utilized approximately 40 degrees of shoulder flexion, and 20 degrees of elbow extension. Person C (right panel) with mild impairment utilized approximately 40 degrees of shoulder flexion and 45 degrees of elbow extension during the task. The performance of Person C, the mildly impaired individual is similar to the healthy individual whose data is presented in the rightmost panel. The healthy individual utilized approximately 70 degrees of shoulder flexion and 80 degrees of elbow extension to accomplish the task.

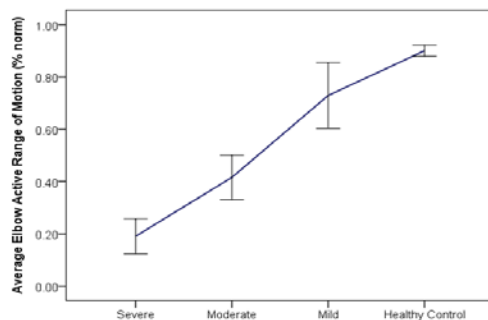


Figure 5: Elbow active range of motion

We tested the hypothesis that the groups formed by the Rasch FMA-UE impairment categories differed according to (1) elbow active range of motion (AROM), (2) hand path curvature (HPC), and (3) muscle onset. These neuromechanical variables were chosen because they measure critical aspects of motor control. Elbow active range of motion measures the ability to execute a goal directed movement, HPC is a surrogate measure of shoulder-elbow interjoint coordination, and muscle onset indicates the activation of key agonistic and synergistic muscles, thus indicates the integrity of descending motor tracts and motor neurons. Neuromechanical variables were averaged for the 5 trials, and compared with ANOVA and Tukey’s HSD post-hoc comparisons with significance defined as $p < 0.05$.

Figure 5 presents elbow AROM (y-axis) averaged for each FMA-UE impairment category (x-axis). Elbow AROM is shown as a percentage of normal range of motion. As expected, and consistent with Figure 4 above, those with severe UE impairment exhibited the lowest elbow AROM and those with mild impairment exhibited more normal elbow AROM. Post-hoc pairwise comparisons were all statistically significantly different (all comparisons $p < 0.05$).

Figure 6 illustrates HPC (y-axis) averaged for each FMA-UE impairment category (x-axis). HPC was calculated

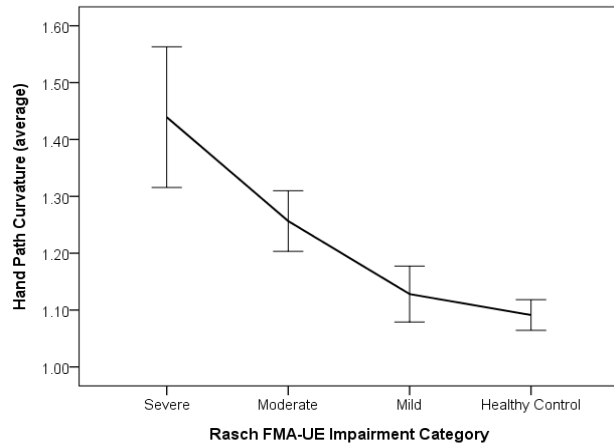


Figure 6: Hand Path Curvature

as a ratio of the distance that the lateral wrist marker actually traveled to the target divided by the most direct distance between the hand and target at the beginning of movement. More direct, efficient paths have values close to 1. Higher values indicate more curved hand path trajectories. The variable is a surrogate measure of shoulder-elbow interjoint coordination such that healthy individuals who exhibit normal shoulder-elbow coordination demonstrate HPC values near 1. As expected, and consistent with Figure 4 above, those with severe UE impairment exhibited the highest HPC values which indicated impaired shoulder-elbow coordination. Those with mild impairment exhibited more normal HPC values. Post-hoc pairwise comparisons were all statistically significantly different ($p < 0.05$) except for the comparison between the moderate and mild categories ($p = 0.07$).

Figure 7 illustrates muscle onset (y-axis) averaged for each FMA-UE impairment category (x-axis). Muscle onset

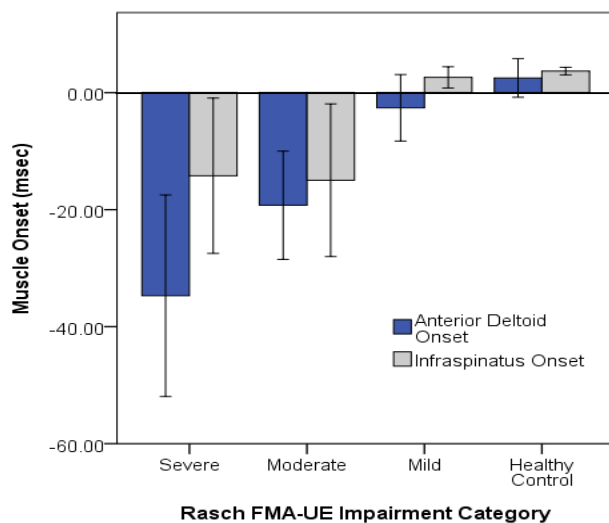


Figure 7: Muscle onset

(msec) was defined as occurring prior to (positive value) or after (negative value) the beginning of a forward reaching movement for the anterior deltoid (AD) and infraspinalis (IS) muscles. The AD is an agonist, and the IS is a synergist for the movement. The threshold of muscle onset was defined as 4 standard deviations above resting muscle activity. Movement onset (represented by the line at 0.00) was defined as the time point at which the linear velocity of the lateral wrist marker exceeded 5% peak velocity. A negative value indicates delayed activation; a positive value indicates anticipatory activation. The figure shows that the activation of the AD and IS are delayed for individuals in the severe and moderate categories. People in the mild category exhibit delayed AD, but are able to activate IS in an anticipatory manner, similar to healthy individuals. Post-hoc pairwise comparisons indicated significant differences between severe and mild ($p = 0.001$) individuals, but all other comparisons were not significant.

3f. Pilot tested targeted vs. non-targeted rehabilitation for one UE impairment category

In published research³² we conducted a pilot study to establish feasibility of our patient-targeted UE rehabilitation approach. We enrolled 12 individuals with stroke, 6 to each of two UE rehabilitation interventions. One intervention was targeted at the movement deficits of people with moderate stroke, the other intervention did not specifically target movement deficits but instead promoted overall arm-use.

We first utilized the Rasch FMA-UE to describe specific motor abilities of the sample and documented that individuals with moderate UE motor impairment fluctuate between partial ability and near normal ability to perform movements requiring simultaneous control of two joints. For this group of individuals, a key motor behavior



marking an expected next step in the recovery process is the ability to simultaneously control two joints while moving a third. Therefore, we designed an intervention to match the ability level of this category.

The targeted-training group performed all task-practice sessions behind a trunk restraint that prevented anterior trunk motion (see photo to left). Tasks for this group were located to afford repeated use of a shoulder flexion-elbow extension reaching pattern. The non-targeted treatment, constraint induced movement therapy delivered in its signature dose, was intended to provide high-dose repetitive task practice but was not aimed at altering any specific movement pattern.

Results from the study are presented in **Figure 1** above and also **Figure 8** which presents angle-angle plots for 2 representative individuals from this pilot study. The angle-angle diagrams for two representative individuals illustrate the treatment results. Specifically, Subject 1 (top row), a participant in the targeted training group, increased his ability to make a smooth transition from elbow flexion to elbow extension in mid-reach. In contrast the diagram of Subject 8 (bottom row), did not alter his movement pattern following non-targeted training.

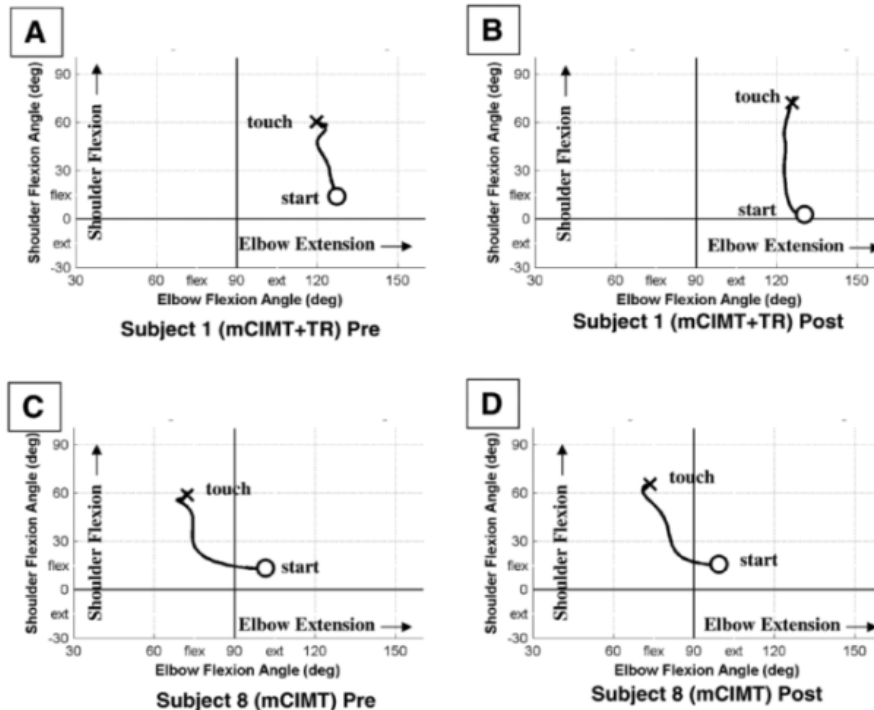


Figure 8: Angle – angle plots

Group data (not presented) suggested that participants demonstrated expected UE movement patterns prior to the intervention in that while attempting to reach forward they had difficulty extending the elbow while flexing the shoulder. Participants who underwent an intervention specifically aimed at altering this movement pattern demonstrated a statistically significant Pre to Post gain in voluntary elbow extension ranges of motion whereas those who underwent an intervention that was not aimed at altering the compensatory movement pattern showed very little gain in voluntary elbow extension. For example 4 out of 5 participants in the targeted treatment group showed increased elbow extension angular excursion, while 4 out

of 5 participants in the non-targeted treatment group showed little change in elbow extension angular excursion, or surprisingly increased elbow flexion angular excursion after training.

D. RESEARCH DESIGN AND METHODS

Methods and Procedures for All Aims:

Study Design: This is a prospective double-blind randomized trial with parallel arm design. 130 individuals with post-stroke UE hemiparesis will be enrolled. Each participant will be assigned a treatment group based on their Rasch analysis-derived FMA-UE score and classification system described in this proposal. That is, participants will be stratified into 1 of 3 levels of post-stroke UE motor impairment severity (mild, moderate, severe) based on our classification system. There will be two treatment groups for each severity level; a targeted-treatment group and a non-targeted treatment group. Subjects within each severity level will be randomized to either targeted or non-targeted rehabilitation therapy for their severity level. Thus, there will be a total of 6 treatment groups.

Sample size was calculated based on FMA-UE data obtained from our pilot study (see Preliminary Studies) to determine whether there is a statistical difference in people receiving targeted rehabilitation vs. a comparison non-targeted intervention in the present parallel arm design with 6 treatment groups. Specifically, we will test $H_0: \mu_{\text{targeted}} = \mu_{\text{non-targeted}}$, versus the two tailed alternative $H_a: \mu_{\text{targeted}} \neq \mu_{\text{non-targeted}}$. The pilot study demonstrated that the targeted (trunk restraint) group exhibited a post-training Rasch-derived FMA-UE person ability measure of 2.30 (± 1.00) logits, while the non-targeted intervention (mCIMT) group exhibited a post-training Rasch FMA-UE score of 1.42 (± 0.45) logits which yields a Cohen's d effect size of 1.13. With an alpha level = 0.05, for a two-tailed hypothesis test at a 90% power level, the sample size calculation specified that 18 individuals are needed in each group to answer the research hypothesis confidently. With 6 treatment groups,

N=108. Based on the stroke rehabilitation literature we anticipate a 20% drop out rate and therefore will enroll **N=130** subjects.

Project Timeline:

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
Yr1	Preparation and Recruitment						Enroll 20 patients					
Yr2	Enroll 48 patients											
Yr3	Enroll 40 patients											
Yr4	Complete follow-up tests				Data analysis and manuscript preparation							

Recruitment: This is a VA funded study (VA Merit Award) that will enroll Veterans and non-Veterans. Therefore, subjects will be recruited in collaboration with two stroke clinics: (1) the Ralph H. Johnson VAMC Physical Medicine and Rehabilitation (PM&R) stroke services and (2) the Medical University of South Carolina (MUSC) Comprehensive Stroke Center.

The Ralph H. Johnson VAMC PM&R Service coordinated the care of the 3500 veterans with stroke who were treated in 2007-2010 in the Charleston Veterans Affairs catchment area along the South Carolina and Georgia coast. There are 4 neurology follow up clinics occurring each week in which Veterans with stroke are seen. Investigators from the Department of Health Science and Research (the Department of Drs. Woodbury and Kautz) attend monthly grand-rounds at the VAMC PM&R department and therefore have developed a close working relationship with the neurorehabilitation therapy team. Recruitment for this study will be accomplished by advertisements at each VA facility in the catchment area, consultations with the PM&R staff, and presentations to the VA rehabilitation teams.

The MUSC Stroke Center sees over 50 new stroke patients per month and routinely screens all patients for eligibility to various research studies. Their database currently contains several hundred persons with stroke who have agreed to be contacted for participation in research studies. Investigators from the Department of Health Science and Research (the Department of Drs. Woodbury and Kautz) meet weekly with the MUSC Stroke Center medical and research teams to discuss and plan recruitment for research studies.

Of the 130 subjects that we will enroll, 20 of them will be asked to participate with TMS. Once 20 subjects have completed all testing with TMS, subject participation with this device will be concluded.

Inclusion criteria: 1) experienced ischemic stroke at least 3 mo. prior. The lesion type and location will be confirmed with medical records and past MRI or CT scan. This criteria is based on evidence suggesting lesions located in brainstem or cerebellum⁶⁴ and hemorrhagic⁶⁵ stroke may affect neural reorganization and observable patterns of UE motor recovery differently than lesion in the MCA distribution or ischemic etiology; 2) passive range of motion in affected shoulder, elbow and wrist within functional limits; 3) 20-90 years of age. Exclusion criteria: 1) pain in the affected UE that would interfere with movement; 2) unable to understand 3-step directions; 3) orthopedic condition or impaired corrected vision that would alter kinematics of reaching; 4) Any implanted ferromagnetic object that could be displaced by a magnetic field.⁶⁶; 5) a history of seizures. The study sample shall be inclusive of the general population of adults with stroke-related UE motor impairment without restriction in regard to gender, race, age, and socioeconomic status. Every effort will be made to include women, minorities and indigenous populations.

Procedure: Informed consent and all other procedures will occur in accordance with approval from the MUSC IRB and VAMC RR&D committee.

Study Flow: **Figure 9** illustrates the study flow.

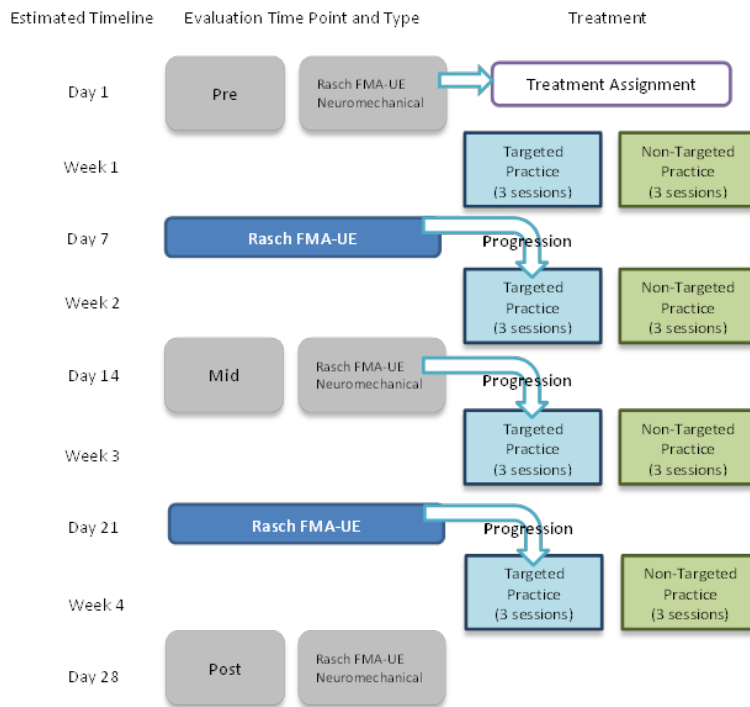


Figure 9: Study Flow

Evaluation Sessions: Participants will undergo a total of 3 full-evaluation sessions; pre-treatment, mid-treatment, and post-treatment. Each full-evaluation session will consist of administration of the FMA-UE according to standardized procedures.⁶⁷ and neuromechanical analyses (kinematic and EMG) of unconstrained 3D reaching movements. In addition, the FMA-UE will be administered at the end of weeks 1 and 3. The FMA-UE Rasch score will be used to progress treatment.

Blinding: All evaluations will be scored by an evaluator who is blind to treatment group assignment. Subjects will also be blinded to treatment group assignment. That is, they will not be told whether their treatment sessions are “targeted” or “non-targeted.”

Procedure for Administration of the FMA-UE: The FMA-UE will be administered to participants at all evaluation time points according to standardized procedures. Administration of the assessment will be videotaped and scored by a blinded

evaluator. The 3 reflex items will not be administered because our previous work showed that these items do not contribute to measurement of the construct “voluntary” UE motor function. FMA-UE item ratings will be converted to a person-measure using Rasch analysis (Winsteps⁶⁸) with item-difficulty calibrations anchored to published values⁴⁴ which will assure stable person-measure estimates.

Procedure for Neuromechanical Evaluation: Kinematic and EMG analyses will be conducted at three time points (pre, mid and post).

We have previously published our standardized procedures for neuromechanical evaluation.³² Subjects will be seated on a backless stool with the start posture standardized. Using their affected UE, subjects will perform 10 trials of reach-to-grasp (or touch) a soda can which will be placed at a location equal to 80% of arm’s length at midline, a location affording maximum shoulder flexion and elbow extension.⁵⁴ *No trunk constraint or arm support will occur during testing.* Kinematic data will be recorded with a 10-camera motion analysis system (PhaseSpace Inc) at a sampling frequency of 480 Hz using a marker set defined in our previous work.³² Kinematic data will be filtered with a 4th-order Butterworth low-pass filter (cutoff frequency of 12 Hz) then processed through a Visual 3D kinematic model using custom Matlab functions. Surface EMG electrodes will be applied to the center of the muscle bellies of the biceps (BI) and triceps (TRI) according to SENIAM procedures. The muscles are chosen because of their important roles as agonist (TRI) and antagonist (BI) for forward reach. Baseline EMG (16-channel wireless system, Motion Lab Systems) values will be collected (2000 Hz) with the limb at rest in order to identify the ambient noise and isoelectric muscle activity signal level, then collected during reach-to-grasp movement. EMG data will be bandpass filtered (5 Hz – 1 kHz), demeaned, rectified and low-pass filtered with a fourth-order, zero-lag digital Butterworth filter (cutoff 20 Hz).

We will use Transcranial Magnetic Stimulation (TMS) to measure Neural Excitability: TMS analysis will be conducted at five time points (pre-intervention, end of weeks 1,2, and 3, and post-intervention)

Transcranial Magnetic Stimulation (TMS) is a means measuring the excitability of brain activity by generating a magnetic field that induces an electrical impulse into specific regions of the brain. The handheld TMS device that will be used in this study are two coils positioned side by side in a figure eight fashion. These coils, encased in plastic housing, produce a magnetic field that is only able to penetrate the outer layers of the cortex of the brain without causing pain or discomfort to the patient⁶⁹.

We will use TMS to measure Neural Excitability: Control of motor activity in the paretic hand is influenced by interhemispheric interactions between the motor cortices of the LH and NLH.⁷⁰ Further, the degree of inter-hemispheric inhibition (IHI) exerted from the Non-Lesioned Hemisphere (NLH) M1 to the Lesioned Hemisphere (LH) M1 is associated with the degree of motor skill using the paretic hand. The extent of transcallosal IHI has also been suggested as a mechanism underlying movement recovery or the potential for recovery. In healthy individuals, transcallosal input from the M1 ipsilateral to movement turns from inhibitory to excitatory as movement onset is approached.⁷⁰ This does not happen in individuals who are post-stroke, i.e. transcallosal input from the NLH continues to inhibit the LH M1 as movement onset is approached.⁷⁰ Furthermore, those with greater IHI tend to have poorer motor performance. From a behavioral standpoint, the extent of baseline motor deficit is also related to the response to rehabilitation, i.e. those with more severe deficits in UE movement tend to experience smaller gains in motor capacity, use, and quality of movement than those with milder baseline deficits.⁷⁰ Thus, our primary outcome variable for neural excitability will be IHI.⁷⁰


Method to measure IHI: We will assess IHI in a manner similar to the paradigm used by Murase et al.⁷⁰ UsingBrainsight Neuronavigation, two figure-of-eight shaped TMS coils connected to two yoked Magstim 200 stimulators will be positioned over the M1 region corresponding to the hand knob in the LH and NLH hemisphere. A conditioning stimulus (CS) will be delivered to the NLH M1 followed 10ms later by a test stimulus (TS) delivered to the LH M1. Trials using paired-pulse TMS (CS→TS) will be intermixed with trials of TS only. IHI will be calculated as the MEP amplitude during CS→TS trials relative to MEP amplitude during TS-only trials: (CS→TS)/TS. Ten trials of each CS→TS and TS will be collected. *TMS measurements will be obtained at 5 time points; Pre-, end of week 1, end of week 2, end of week 3 and Post- treatment.*Treatment: The Baseline Rasch FMA-UE person measure will be the basis for assignment to a treatment group (Targeted or Non Targeted) based on clients' UE motor ability/impairment level. Within each impairment level, subjects will be randomized to a treatment group.

Self-Guided Home Treatment: Each day, the therapist will help the subject identify several daily activities that he/she can perform in his/her own home environment that integrate movement skills practiced during therapy sessions. The therapist will, in consultation with the subject, prepare and adapt instructions for the subject to accomplish these activities in their own home. This allows the therapist to integrate activities that are consistent with the study treatments and goals into the subject's home environment. Participating in the self-guided home treatment will reinforce the activities practiced during the study treatment sessions. The therapist will make periodic phone contact with all subjects during the course of the study allowing ongoing collaboration with the subject for suggestions and modifications to the self-guided home treatment. Subjects will therefore have better access to the therapist for questions about the study, modifications to the self-guided home treatment, and study retention efforts.

Dose: All subjects in all groups will engage in 12 rehabilitation sessions (3x/week over 4 weeks).. Recent data suggest that the dose of practice, e.g., number of movement repetitions, is important to produce neural reorganization and motor learning.⁷¹ We therefore will provide approximately 200 reach-to-grasp/touch repetitions per session which previous research has shown to be safe for people with stroke and feasible to accomplish in 2-

3 hours.⁷² **Treatment Groups:** Targeted practice is defined as an evidence-based intervention targeted to specific UE motor deficits characteristic of persons in each UE impairment level. Non-targeted task practice is defined as a “standard of care” intervention that consists of task practice with no guidance from measurement to choose appropriate tasks to address specific underlying deficits. **Table 4** presents a summary of the treatments.

Table 4: Summary of treatments

<i>Rasch FMA-UE Impairment Level</i>	<i>Rasch FMA-UE Person Measure</i>	<i>Targeted Treatment</i>	<i>Non-Targeted Treatment</i>
Mild	>2.44 logits	Forced-use task practice	Functional Upper Extremity Training
Moderate	- 0.22 to 2.44 logits	Task practice with trunk restraint	
Severe	<-0.22 logits	Task practice with trunk restraint and faded arm support	

Targeted Practice Treatment: A person with mild UE motor impairment has a 50% probability of accomplishing FMA-UE items requiring fine motor coordination and dexterity, i.e., items well-matched to his/her ability described in Table 1. For people with this level of UE motor impairment *Forced use task practice* is an optimal evidence-based intervention.⁷³ Forced use therapy, like Constraint-Induced Movement Therapy²⁸ although not delivered in its “signature” dose, restrains participants’ less affected UE in a glove to prevent its use thereby “forcing” exclusive use of the affected UE. The premise of the strategy is that repetitive object grasp, manipulation reduces “learned non-use”.⁷⁴ The intervention is shown to improve fine motor dexterity, movement speed, and smoothness.^{31,32}

A person with moderate UE motor impairment has a 50% probability of accomplishing FMA-UE items requiring simultaneous control of two joints (e.g., pronate/supinate forearm with elbow extended, shoulder flexion to 90° with elbow extended). *Task practice with trunk restraint* may improve these skills. This strategy is identical to forced use practice except that all tasks are performed with the trunk restrained to prevent compensatory recruitment of trunk range of motion. Limiting anterior trunk movement enables a permissive environment (by reducing number of body segments requiring control) in which to practice forward reach.^{32,56}

A person with severe UE motor impairment has a 50% probability of accomplishing FMA-UE items requiring arm movement away from the body (e.g., extend elbow, flex the shoulder to 90°). *Task Practice with trunk restraint and faded arm support* requires that participants perform tasks using a trunk restraint as described above, with the arm supported by an overhead sling. Arm support lessens the gravitational load on the limb thereby reducing the “difficulty” of a reaching task and is associated with increased reach distance.^{75,76}

Non-targeted Standard of Care Treatment: The non-targeted intervention will be Functional Upper Extremity Training⁷⁷, a published and standardized rehabilitation program popular among neurorehabilitation therapists and considered the current “standard of care.” The approach evolved from the Bobath concept but stresses the importance of functional activities. The approach assumes that provision of “normal” sensorimotor experiences will promote recovery of more normal movement patterns. Unlike contemporary motor learning approaches, patients are not challenged to engage in task practice independently. Instead, patients practice functional tasks only with the hand-over-hand guidance of the therapist. For example, if the patient is attempting to butter toast, the therapist wraps his/her hand over the patients hand as patient and therapist together perform the task. Throughout the task the therapist provides verbal feedback to continually motivate task performance (“keep

trying!”) but does not provide specific feedback about movement quality such as joint angle or posture. Tasks are performed in their entirety with therapist assistance throughout.

We will follow implementation of the therapy as per the published manual, online videos and available implementation guidelines. In addition, the PI recently attended an 8 hour workshop to develop competence in providing the therapy. We argue that Functional Upper Extremity Training⁷⁷ is not a “targeted” intervention according to our definition. That is, the approach does not specifically target a person-ability level because there will be no guidance from a measurement framework from which to choose appropriate tasks to ameliorate underlying specific deficits.

Specific to Aim 1: Compare the effects of targeted rehabilitation versus *non*-targeted rehabilitation on UE motor function.

Hypothesis: Targeted intervention will result in a greater pre- to post-intervention reduction of UE motor impairment when compared to *non*-targeted intervention.

Rationale: The Rasch-based FMA-UE classification defines levels of UE motor ability by describing UE movement tasks (FMA-UE items) which patients in each level can easily perform, cannot perform (too hard), and are well-matched to ability level. This information is the basis for designing task-practice sessions to specifically target the patient movement abilities. Because treatment is likely to induce changes in these variables, it is reasonable to expect changes in participants’ Rasch FMA-UE measure.

Approach: *Dependent Variable*: The dependent variable will be change in UE motor impairment as measured by the percent change in the Rasch FMA-UE occurring from pre- to post-intervention. The Rasch FMA-UE percent change will be calculated as Post minus Pre divided by Pre.

Independent Variables: The independent variable is Group. The independent variable has two levels; targeted-therapy and non-targeted therapy.

Data Analysis: ANOVA will be used to compare the mean values of the Rasch FMA-UE change scores for each targeted vs. non-targeted treatment group across each impairment level (mild, moderate, severe). We will correct for multiple comparisons, therefore, significance for all comparisons will be $\alpha = 0.05/3 = 0.02$.

Specific to Aim 2: Determine critical neuromechanical factors that influence response to targeted or non-targeted therapy

Hypothesis: Response to targeted therapy will be associated with recovery of “normal” UE movement and muscle activity patterns.

Rationale: Very little is known about the neural and biomechanical mechanisms contributing to post-stroke UE motor impairment. Identification of the critical kinematic and neural aspects of reach contributing to changes in UE motor impairment occurring with therapy will permit refinement of existing and development of new interventions specifically targeted at improving these motor control process.

Approach: As described in the procedures above, we will collect kinematic and electromyographic (EMG) data to provide information about motor control strategies (kinematic) neural influences on motor output (EMG) responding to therapy.

Dependent Variable: The dependent variable will be change in UE motor impairment as measured by the percent change in the Rasch FMA-UE occurring from pre- to post-intervention as calculated above.

Independent Variables: We hypothesize that 3 independent variables will explain changes in UE motor impairment expected to occur with rehabilitation. These variables will be measured as the percent change in each variable occurring from pre- to post-intervention (post minus pre divided by pre). The variables were chosen because they are reasonable measures of “normal” movement based on the literature, motor control theory and clinical interpretation. Two kinematic variables (trunk movements, elbow extension range of motion) provide information about the strategy utilized to execute the movement. Trunk movement will be calculated as the cumulative distance a marker placed at T-10 travels during the reach. Voluntary elbow extension is calculated as difference between elbow joint angle at start and the joint angle at touch. One EMG variables (Biceps-Triceps co-

contraction index) provide information regarding neural influences on motor output. The mean amplitude obtained during 5 sec. resting EMG activity will be used as baseline EMG values. For each trial, “time-to-EMG” is calculated as the difference between muscle onset and movement onset. Muscle onset is defined as a rise in EMG exceeding 4 standard deviations above resting EMG. Muscle offset is defined as a decrease in EMG below this value. Movement onset is defined as the time-point when velocity of the wrist marker exceeded 5% peak velocity. Positive time-to-EMG values indicate anticipatory muscle activation (occurred prior to movement onset); negative time-to-EMG values indicate delayed muscle activation (occurred after movement onset). The EMG activity occurring between onset and offset is defined as burst duration. A co-contraction index variable will be defined as Biceps Burst Duration divided by Triceps Burst Duration so that a value equal to 1 reflects simultaneous activity of the agonist and antagonist.

Data analysis: Two multiple regression models will examine the relationships between the dependent and independent variables. One regression model will include variables from all patients involved in targeted-therapy (i.e., pooled data from across UE impairment levels). The second model will include variables from all patients involved in non-targeted therapy.

We will first investigate assumptions of normality for all variables via visual inspection of probability plots and statistically verified with the Kolmogorov-Smirnov f test. If the data are not normally distributed, they will be logarithmically transformed. Although we expect that all variables will be associated with the FMA-UE person-measure, we do not expect that a simple linear trend will best describe this relationship. It is likely that the response variables have a different impact on the FMA-UE person-measure according the level of UE motor impairment. Thus it is likely that that a polynomial relationship exists between the response variables and the dependent variable. To determine whether a linear or polynomial regression model best fits our data we will first cross-plot each response variable against the dependent variable. Visual inspection of the scatterplot will help to facilitate the appropriate model and identify outliers which may affect the model. Outlier data points beyond 3 standard deviations of the mean value of that variable will be inspected to determine if the data was entered correctly. If not, the data point will be considered an aberrant rating and dropped from analysis. When it is determined that a quadratic trend likely best fits the data, we will transform the variable to its quadratic term via its unstandardized residual to compensate for multicollinearity. We will then apply a general linear model regression procedure to the data using SAS. A forced-entry procedure will be employed in which all variables will be examined for each model. Adjusted R-square values, p-values and 95 percent confidence intervals will be calculated.

We will test significance of the coefficient of determination (adjusted R-square value) for each response variable. The null hypothesis tested is that there is no significant association between each response variable and the dependent variable, meaning that the response variable does not contribute to UE motor ability (FMA-UE person measure). The alternative hypothesis is that the association is significant meaning that the response variable is associated with UE motor ability (FMA-UE person measure). We will reject the null hypothesis if $p < 0.05$ which will lead to the conclusion that the response variable does not contribute to the FMA-UE score at a 0.05 significance level.

Specific to Aim 3: Determine critical predictors of the time-course of response to targeted rehabilitation.

Hypothesis: People with stroke have different patterns of response to therapy, some respond slowly, some respond more quickly. Key neuromechanical variables (baseline measurements of elbow extension, amount of trunk movement, and biceps-triceps muscle co-activity) predict these response patterns.

Rationale: Individuals with different levels of post-stroke UE motor impairment likely follow distinct trajectories of UE recovery. It is possible that patients receiving intensive therapy make large improvements within the first few days of therapy, and it is also possible that some patients require days until therapy has an effect. However, little is known about patterns of recovery over time in response to rehabilitation. Identifying different patterns of recovery during therapy is critical to determine which patients may need the most extensive intervention to promote functional recovery, and which patients may not require intensive intervention. In addition, it is important to identify behavioral markers that predict gains in order to improve a-priori assessments and planning for the population that is most likely to benefit from an intervention after stroke.

Approach: Growth mixture modeling (GMM) offers a robust method of identifying sub groups of people with stroke who follow distinct trajectories of UE recovery. In contrast to analyses that focus on mean-level change in a

sample, GMM elucidates how different people recover in different ways. GMM separates repeated measurements of a sample into groups of individuals showing similar patterns of change over time.

Dependent Variable: A categorical latent variable representing unobserved groupings of stroke-patients with similar patterns of change in the Rasch FMA-UE scores over repeated measurements.

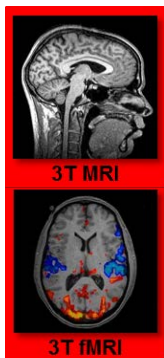
Observed Variables: The Rasch FMA-UE will be administered at 5 time periods (pre-intervention, end of weeks 1, 2 and 3 and post-intervention). The GMM calculates an intercept and slope of a line representing the mean and variance of the linear rate of change in Rasch FMA-UE over time. Sub-populations (or growth classes) will be displayed graphically. Each class will represent a percentage of the sample and demonstrate how the baseline Rasch FMA-UE measurement changed over time.

Data analysis: Data from participants in targeted-rehabilitation protocols will be pooled and analyzed. Three models will be tested in accordance with our a-priori hypothesis that each level of impairment (mild, moderate, severe) should show distinct patterns of recovery, i.e., we expect 3 classes of recovery. Specifically, we will test whether there is one overall pattern of recovery that describes the entire sample (1-class), whether there are two patterns of recovery within the sample (2-class) or whether there are three patterns of recovery in the sample (3-class). The models are not nested (a 1-class model is not a subset of the 2-class model) because different individuals make up each class. Therefore the chi-square model comparison test is not appropriate. Instead, we will define the best fitting model as the one having the lowest Bayesian Information Criteria (BIC) and an entropy value closest to 1.0.

To determine the best predictors of recovery patterns we will use logistic regression to relate recovery pattern (growth class membership) to kinematic and EMG variables hypothesized to be important predictors of recovery. The predictors hypothesized to be important are baseline elbow extension AROM, amount of trunk movement, and muscle co-activity. The predictor variables entered into analysis will be collected pre-intervention. Predictors will be examined to determine those which significantly discriminate class membership. Because the predictors are allowed to vary across classes, the analysis will provide a means of examining whether predictors of one trajectory differ across each trajectory. For example, loss of elbow extension AROM may be the most significant predictor of membership in one class, while inability to activate agonist muscles may be the most significant predictor of another recovery pattern.

Methods specific to the SUBSTUDY

Additionally, a group of 10 individuals with stroke will have an MRI on two visits. In order to be considered for this SUBSTUDY, participants will first be enrolled in the above study. The purpose of this SUBSTUDY is to gather preliminary data on patterns of neural activity that are associated with better performance outcomes in the rehabilitation intervention. We also seek to determine if the intervention is able to change baseline functional brain connectivity. This is a critical piece of knowledge to have in order to accurately understand and interpret the primary goals of the Main study. With this knowledge we can more effectively analyze and interpret the data gathered from the main study. This SUBSTUDY is non-significant risk.



Anatomical image acquisition. High-resolution structural scans will be obtained using an inversion recovery 3D spoiled gradient echo (3DSPGR) sequence using a matrix size of 256 x 256, field of view of 24 cm, section thickness of 1.5 mm with no gap between sections, and 128 slices, giving an in-plane resolution of 0.94 mm. This sequence will be used for anatomic overlays of the functional data and for spatial normalization to a standard atlas.

Functional MRI task and acquisition. Each participant will be asked watch a movie of hand movements on a monitor and mimic the ongoing actions with their own hands. Participants will be asked to do two, 6 min runs of the task. Each functional run consists of movement blocks interspersed with rest blocks. Following each rest block there will be a preparation block in which the participant will receive a preparation cue which counts down the number of seconds remaining before the motor task begins again. This preparation block will be modeled separately in the statistical analysis and used to eliminate the effects of attentional set-shifting to the visuo-motor performance data acquired in the task block. All participants performed a practice session before the functional MRI scan in order to limit the contribution of learning to the data acquired.

Experiments will be conducted on a 3T MR scanner with twin-speed gradients and a birdcage head coil (3T

Siemens Trio). Whole-brain activation will be assessed by examining the blood-oxygenation-level-dependent (BOLD) signal by measuring changes in the T2*-relaxation rate that accompany changes in blood oxygenation associated with cortical activation. The images will be collected parallel to the anterior commissure-posterior commissure (AC-PC) line with one slice overlying the AC-PC line. Functional imaging will be performed using multislice gradient-echo echo planar imaging (TR=2500, TE=40 msec) with a field of view of 24 cm (frequency) x15 cm (phase), and an acquisition matrix of 64x40 (28 slices, 5 mm thickness, no skip). This sequence delivers an effective voxel resolution of 3.75 x 3.75 x 5 mm.

Functional image analysis. Statistical parametric maps (SPMs) will be generated using SPM12 from the Wellcome Department of Cognitive Neurology, London, UK implemented in Matlab (The Mathworks Inc. Natick, MA, USA). Prior to generating SPMs, data will be preprocessed based on standard techniques. The raw data will be reconstructed and corrected for image distortion and alternate k-space line errors will be performed on each image on the basis of data acquired during phase-encoded reference imaging. The functional data sets will be motion corrected (intra-run realignment) within SPM12 using the first image as the reference. The functional data sets will be normalized to Montreal Neurological Institute (MNI) space and smoothed using an 8 x 8 x 10 mm Full Width at Half Maximum Gaussian smoothing kernel. The data will be modeled with a boxcar design including an explicit baseline model convolved with the hemodynamic response function. All data will be globally normalized with proportional scaling of the image means. Temporal smoothing and de-trending will be performed as part of the SPM analysis. SPMs will be generated using the general linear model within SPM12 for each subject. Group analyses will be performed using a random effects model. The random effects analysis will use the 'contrast image' generated for each subject by applying the appropriate weights to the multiple regression. The random effects analyses will utilize two sample t-tests available in SPM12 to compare activation patterns between groups. To make comparisons within groups to identify the effect of conditions, paired t-tests will be used. Secondary analyses will be performed on the fMRI data using a multiple regression technique. A variable, such as age, can be entered into the regression analysis to control for unanticipated population differences. Anatomic regions of interest will be defined automatically using an atlas-based program WFU_Pick Atlas, which runs in Matlab. All data will be thresholded at $p < 0.05$ corrected for multiple comparisons using the false discovery rate. E.

PROTECTION OF HUMAN SUBJECTS

a. Human Subjects Involvement and Characteristics

Human Subjects Involvement and Characteristics: 130 individuals with post-stroke UE hemiparesis will participate in this rehabilitation research study.

Participants with stroke will be recruited from three sources:

(1) The Ralph H. Johnson VAMC Physical Medicine and Rehabilitation (PM&R) Service: The Ralph H. Johnson VAMC PM&R Service coordinated the care of the 3500 veterans with stroke who were treated in 2007-2010 in the Charleston Veterans Affairs catchment area along the South Carolina and Georgia coast. There are 4 neurology follow up clinics occurring each week in which Veterans with stroke are seen. Investigators from the Department of Health Science and Research (the Department of Drs. Woodbury and Kautz) attend monthly grand-rounds at the VAMC PM&R department and therefore have developed a close working relationship with the neurorehabilitation therapy team. Recruitment for this study will be accomplished by advertisements at each VA facility in the catchment area, consultations with the PM&R staff, and presentations to the VA rehabilitation teams.

(2) The MUSC Stroke Center: The Stroke Center sees over 50 new stroke patients per month and routinely screens all patients for eligibility to various research studies. Their database currently contains several hundred persons with stroke who have agreed to be contacted for participation in research studies. Investigators from the Department of Health Science and Research (the Department of Drs. Woodbury and Kautz) attend weekly meetings with the MUSC Stroke Center medical and research teams. Therefore the two departments have a collaborative working relationship. We will provide our inclusion/exclusion criteria to the Stroke Center research team who will then pass on this information to care providers who may then refer potentially eligible patients to the study's research coordinator if the patient agrees.

(3) This study will recruit from the Registry for Stroke Recovery (RESTORE-Pro#00037803), which is a registry with subjects consented for future contact. RESTORE staff will query the registry for potential subjects and provide the Principal Investigator (PI) with the contact information of subjects who meet their criteria. The PI or research staff will contact subject to further screen for potential enrollment.

Sharing Data

If the subject agrees, the data collected and generated from this study will be shared and linked to RESTORE by the subject's registry ID. Sharing data from this study with the registry will allow for more targeted recruitment efforts in the future and allow researchers at MUSC to have a more complete registry with key stroke recovery elements including common data and physical function characteristics that are applicable to multiple studies.

Targeted/Planned Enrollment Table

Total Planned Enrollment - 130

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	3	4	7
Not Hispanic or Latino	48	75	123
Ethnic Category: Total of All Subjects*	130		
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	16	25	41
White	34	54	88
Racial Categories: Total of All Subjects*	51	79	130

**The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects".*

Inclusion criteria for the proposed study:

1. Experienced a stroke at least 3 months prior that has resulted in unilateral hemiparesis.
2. Passive range of motion in affected shoulder, elbow and wrist within functional limits;
3. 20-80 years of age.

Exclusion criteria for the proposed study:

1. Pain in the affected upper extremity that would limit participation in the study intervention.
2. Unable to understand 3-step directions;
3. Unable to attend the study-related treatment or evaluation sessions
4. Orthopedic condition in back or UE or impaired corrected vision that would alter kinematics of reaching.

We expect that our sample will have demographic characteristics similar to that of the general population in this region of South Carolina. These percentages, based on the 2010 census, reveal that the Charleston county area has a population that is 64% white, 30% African-American, 1% Asian, and 5% Hispanic and Latino and 39% female. There will be a total of 130 individuals with post-stroke UE hemiparesis enrolled in the overall study, and 10 subjects enrolled in this substudy..

No children will be included in this study.

This project will be conducted in the Upper Extremity Motor Function Laboratory which is designated as shared MUSC-VA space through a formal Memorandum of Understanding between MUSC and the VA. The laboratory is located in the same building as the offices of the PI, Co-I, engineer and research therapy staff.

Data for this study will consist of a clinical rating-scale assessment of upper extremity movement, the Fugl-Meyer Upper Extremity Assessment, kinematic analysis of upper extremity (UE) motion, and electromyographic (EMG) assessment of UE muscle activity. These data will be collected exclusively for research purposes.

b. Sources of Materials

The following information will be obtained from human subjects: Name, age, contact information, date of stroke, time since stroke, ethnicity, brief post-stroke medical history. Data that will be recorded from human subjects will include rating-scale assessments of upper extremity motor ability, kinematic motion analysis of upper extremity movement, measurements of upper extremity strength, and upper extremity electromyography. Identifiable information will be stored in password-protected files on a secure MUSC network (MUSC patients) or on the VA-network (VA patients). All data will be coded with a unique study identifier. The only people having access to this identifiable information will be Dr. Woodbury and her research study staff (named on this protocol). No other person will have access to PHI for study participants. All data will be de-identified with all personal identifiers removed for data analysis. That is, the PHI will be stripped of its identifiers for data analysis. Data analysis will incorporate only aggregate data that does not contain any participant-specific identifies. There will be no way to link the data being analyzed back to the individual. Hard copy data will be coded by unique study identifier and stored in a locked file cabinet which is located along the east wall of the secured office of the principal investigator which is located in room #307 of the College of Health Professions Research Building at 77 President Street in Charleston SC. This space is designated as a VA research space in a VA approved memorandum of understanding. Once the study is completed data (described below) will be de-identified. Potential participants will be identified through recruiting mechanisms described above associated with the MUSC Stroke Center and VA PM&R service. The PI and/or study coordinator for the present study will provide the MUSC Stroke Center and VA PM&R service with inclusion/exclusion criteria. Personnel associated with either of these places will then provide our contact information to participants. Participants will then initiate contact with either the PI or Study Coordinator of the present study. If potential participants meet inclusion criteria they will be asked by the study coordinator if they would like to participate in the current study. If they do wish to participate, they will be scheduled for a time to obtain written informed consent to participate in the study.

c. Potential Risks

Potential discomforts or risks for participation in this study are minimal. This is a prospective study with parallel arm design. Subjects will undergo 4 evaluation sessions (Pre-treatment, Mid-Treatment, Post-Treatment, 30 day Follow Up). Assessments will consist of (1) clinical rating scale assessments and (2) motion and EMG analysis. During both types of assessment sessions, subjects will be seated comfortably. They will be asked to perform UE movements commonly performed in everyday life (e.g., lift arm to eye level while keeping elbow straight, pick up a soda can). Sensors for motion and EMG analysis are attached to the participants' skin. There may be a temporary skin reaction to the adhesive used to secure the motion analysis markers or EMG sensors to the skin. To minimize this, the skin will be cleaned before and after the markers or sensors are placed on the skin and hypoallergenic gel and tape will be used on the skin. A skin reaction is a rare occurrence and resolves within 1-2 days. All participants will be asked if they have had any previous experience of allergic reaction to specific gel or tape types. If they answer yes, then we will avoid placing markers or sensors directly on the skin. Instead we will wrap the limb in non-sticky "pre-wrap" and attach motion sensors to it. Pre-wrap is a soft wrap often used under casts or braces.

Subjects will be randomized to two stroke rehabilitation treatment groups; "targeted" vs. "non-targeted" and will engage in 12 rehabilitation treatment sessions. The only difference between the treatments is that the "targeted" group will receive specific instructions from the therapist regarding the participants' quality of movement during rehabilitation treatment (e.g., straighten elbow, sit tall). During rehabilitation treatment, participants will be asked to practice using the arm most affected by stroke. They will perform 200 movement repetitions during rehabilitation treatment. They will include reaching, grasping and lifting common everyday objects. Participants may be seated or standing for these activities. While standing, all participants will be closely guarded by study personnel to monitor and maintain balance. In previous studies, 200 repetitions of reaching movement using the hemiparetic UE required approximately 2 hours with no reports of increased pain or fatigue although subjects will be offered a rest break after every set of 10 movements.

There is a very low risk of a seizure after TMS (7 reported cases in almost 7000 studies). The risk of seizure induction by this protocol has been thoroughly assessed and our TMS parameters will be well within published safety guidelines. Of these 7 cases, none has required external intervention in the form of medications to stop the seizure, and no patient has had any post-seizure sequelae, nor have they developed recurrent seizures. To minimize risk, we only use single pulse TMS, as the majority of adverse events have occurred after repetitive TMS and we will follow published safety guidelines. Anyone with a history of seizure will not be allowed to participate in this portion of the study.

Headaches are the most common complaint from patients following treatment with TMS. In one study conducted by George and Belmaker (2007)⁷⁸, 19% of healthy subjects reported having headaches after treatment with TMS. However, 17% receiving sham TMS also reported headaches after the session. These are generally self-limiting and respond to common analgesics like aspirin.

Potential Risks of MRI: MRI is considered minimal risk.

1. Although the risks from magnetic resonance imaging (MRI) are low, it is critical that you do not have **metal** in the skull, metal implants, a cardiac or brain pacemaker, or old metal fragments in the eye or retina. If you/your child have a question about metal in your body, inform the researchers and they will determine whether it is safe in a MRI scan.
2. Some discomfort may occur from having **to remain still** while you are in the MRI scanner. During the scanning you will be given an emergency ball to squeeze at any time you are feeling discomfort and desire to be pulled out of the scanner.
3. The MRI scanner is noisy, and there is a risk of **hearing damage** if you do not wear earplugs. As stated above, to eliminate this risk, you will be given earplugs to wear during each scan.
4. Although the MRI scanner is open on both ends, some people become anxious or claustrophobic when entering the MRI scanner due to the **feeling of being enclosed**. If this has happened to you in the past, inform the study personnel, as you/your child may be ineligible for the study. The researchers will work with you to keep this from happening by allowing you to view relaxing pictures on a screen prior to the start of the research procedure (until any anxiety has passed). Also, the researchers can talk with you during the procedure through a microphone in the scanner to reduce your concern.
5. If you are female and of child-bearing potential, you must have a **pregnancy** test performed prior to the scanning procedures. This test must be negative for you to participate in the study. If pregnant you will not be eligible to continue in the study.
6. Unknown Risks: The experimental procedures may have unknown side effects. The researchers will let you know if they learn anything that might make you change your mind about participation

A licensed occupational or physical therapist will oversee all evaluation and treatment sessions. The therapist will monitor the participant for safety and offer rest breaks when he/she determines that the patient needs one.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent

Subjects will be recruited in collaboration with two stroke clinics: (1) the Ralph H. Johnson VAMC Physical Medicine and Rehabilitation (PM&R) stroke services and (2) the Medical University of South Carolina (MUSC) Comprehensive Stroke Center. Recruitment and Informed Consent: The PI (Michelle L. Woodbury) and Co-I (Steve Kautz) are both fully funded VA researchers. They have a collaborative relationship with the Ralph H. Johnson VAMC PM&R Service for patient recruitment. In addition they are both appointed in the Department of Health Sciences and Rehabilitation Research at MUSC. They have a strong collaborative relationship with the MUSC Stroke Center. The Department of Health Science and Research recruitment coordinator will be informed of the inclusion criteria for the present proposal.

The recruitment coordinator will interface with the VAMC and MUSC for recruitment. If potential participants are identified that meet inclusion criteria the PI or Co-I will contact participants by phone to determine if they want to participate in the current study. If they wish to participate they will be scheduled for a time for the PI to obtain informed consent for the study proposed.

Consent will be obtained by the PI after reviewing the protocol and consent form with each potential subject. If a potential subject is deemed unable to participate in informed consent, consent will be obtained from a relative with the patient present. For patients consenting themselves, every attempt will be made to have a relative present during the informed consent. The MUSC IRB will approve the informed consent form, and the Ralph H. Johnson VAMC R&D committee will also approve the protocol.

b. Protection against Risk

Potential discomforts or risks for participation in this study are minimal. Each participant will be asked to perform a series of upper extremity movements that may include reaching, grasping and lifting a series of common every day objects. Participants may be seated or standing for these activities. While standing, all participants will be closely guarded by study personnel to monitor and maintain balance.

There may be a temporary skin reaction to the adhesive used to secure the motion analysis markers or EMG sensors to the skin. To minimize this, the skin will be cleaned before and after the markers or sensors are placed on the skin and hypoallergenic electrode gel and tape will be used on the skin. A skin reaction is a rare occurrence and resolves within 1-2 days. All participants will be asked if they have had any previous experience of allergic reaction to specific gel or tape types. If the participant has a history of reaction to gels/tapes then the limb will be wrapped in non-sticky pre-wrap and motion sensors will be attached to it. Pre-wrap is a soft wrap often used under casts or braces.

During rehabilitation treatment, participants will be asked to practice using the arm most affected by stroke. They will perform 200 movement repetitions during rehabilitation treatment. They will include reaching, grasping and lifting common everyday objects. Participants may be seated or standing for these activities. While standing, all participants will be closely guarded by study personnel to monitor and maintain balance. In previous studies, 200 repetitions of reaching movement using the hemiparetic UE required approximately 2 hours with no reports of increased pain or fatigue although subjects will be offered a rest break after every set of 10 movements.

A licensed occupational or physical therapist will oversee all evaluation and treatment sessions. The therapist will monitor the participant for safety and offer rest breaks when he/she determines that the patient needs one.

Participants will undergo screening before the MRI. The screening form has been uploaded. This screening form asks questions such as “do you have any metal in your body?”, “are you claustrophobic?” If the participant answers “yes” to any of these screening questions, we will not obtain the MRI. While in the MRI scanner, the participant will be given an emergency ball to squeeze at any time that he/she is feeling discomfort and desire to be pulled out of the scanner. The participant can stop the scanning protocol at any time. All participants will wear earplugs to protect against possible hearing damage. A member of the research team will accompany the participants to the scanner and remain outside the MRI but will remain in voice contact with the subject while he/she is in the scanner (via a microphone). The research team member will provide reassurance, answer questions and coach the subject as needed. If subject is pregnant, they will not be enrolled in this substudy.

All data and documents associated with this study will be coded with a unique study identifier and securely stored in either a password protected dedicated computer network drive or a locked cabinet in the secured office of the Principal Investigator. The master list linking the study identifiers to the individuals and any PHI will be stored separately from the study data and kept in a password protected file on the MUSC secure network (MUSC patients) or VA network (VA patients).

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

Subjects are hypothesized to benefit from the short intervention. Benefits could include more “normalized” reaching and muscle activity patterns in the arm most affected by stroke. However, because rehabilitation interventions are sometimes not effective, it is possible that there will be no long term benefits. The findings in this study may assist therapists in decision-making to optimize post-stroke rehabilitative therapy and enhance beneficial outcomes for persons with neurological injury and upper extremity impairment. The results of this study will be used to develop or refine rehabilitation treatments to promote more recovery of function. In addition, the study will provide critical information about how best to match a rehabilitation therapy to a patient given his/her specific upper extremity impairments. Our ultimate aim is to generate a scientific-based model for rehabilitation of post-stroke upper extremity motor impairment that is effective and efficient in accomplishing patient goals for arm and hand use.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

The present proposal seeks to systematically investigate the effects of an UE therapy strategy that is designed according to clinical and laboratory-based measurements of post-stroke UE motor function. This Merit Review award, if funded, will enable a more comprehensive understanding of how to link the measurement of specific

motor processes that are impaired with injury to interventions targeted at these motor processes. It will also permit a greater understanding of how intervention affects specific motor processes.

The risks to the subjects are minimal because the rehabilitation testing and programs are similar to those provided to persons with stroke in inpatient and outpatient rehabilitation settings. The PI and study coordinator are both licensed occupational therapists with extensive experience providing rehabilitation programs to persons with stroke. There are no drugs, devices or biologicals in this study. This study is comprised only of post-stroke rehabilitation aimed at improving arm movement through task-practice.

5. SUBJECT SAFETY AND MINIMIZING RISKS (Data and Safety Monitoring Plan)

Any adverse events will be recorded and monitored as required by our Institutional Review Board. On-campus medical services will be available in the event of adverse events to the subjects. Subjects will be able to terminate the movement analysis and/or task-practice protocol at their request at any time without prejudice. All documents with PHI (e.g., the ICF) will be stored in locked cabinets in the PI's office in the MUSC College of Health Professions Research Building which is also a VA designated research space.

All electronic files containing PHI will be stored on the VA network (VA patients) or MUSC network (MUSC patients) in password protected files which will be encrypted at the highest level of encryption available at the time of data storage.

A licensed occupational or physical therapist will oversee all evaluation and treatment sessions. The therapist will monitor the participant for safety and offer rest breaks when he/she determines that the patient needs one.

F. REFERENCES/LITERATURE CITATIONS

1. American-Heart-Association. *Heart Disease and Stroke Statistics — 2010 Update*. Dallas, Texas: American Heart Association.
2. Scott SH, Norman KE. Computational approaches to motor control and their potential role for interpreting motor dysfunction. *Curr Opin Neurol*. Dec 2003;16(6):693-698.
3. Kwakkel G, Kollen BJ, van der Grond J, Prevo AJ. Probability of regaining dexterity in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke. *Stroke*. Sep 2003;34(9):2181-2186.
4. Broeks JG, Lankhorst GJ, Rumping K, Prevo AJ. The long-term outcome of arm function after stroke: results of a follow-up study. *Disability & Rehabilitation*. Aug 1999;21(8):357-364.
5. Warraich Z, Kleim JA. Neural plasticity: the biological substrate for neurorehabilitation. *Pm R*. Dec 2010;2(12 Suppl 2):S208-219.
6. Merzenich MM, Nelson RJ, Stryker MP, Cynader MS, Schoppmann A, Zook JM. Somatosensory cortical map changes following digit amputation in adult monkeys. *J Comp Neurol*. Apr 20 1984;224(4):591-605.
7. Nudo RJ, Milliken GW, Jenkins WM, Merzenich MM. Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. *J Neurosci*. Jan 15 1996;16(2):785-807.
8. Nudo R. Adaptive plasticity in motor cortex: implications for rehabilitation after brain injury. *J Rehabil Med*. 2003;41:7-10.
9. Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *J Speech Lang Hear Res*. Feb 2008;51(1):S225-239.
10. Wolf SL, Blanton S, Baer H, Breshears J, Butler AJ. Repetitive task practice: a critical review of constraint-induced movement therapy in stroke. *Neurology*. Nov 2002;8(6):325-338.
11. Plautz EJ, Milliken GW, Nudo RJ. Effects of repetitive motor training on movement representations in adult squirrel monkeys: role of use versus learning. *Neurobiology of Learning and Memory*. 2000/7 2000;74(1):27-55.
12. Jones TA, Kleim JA, Greenough WT. Synaptogenesis and dendritic growth in the cortex opposite unilateral sensorimotor cortex damage in adult rats: a quantitative electron microscopic examination. *Brain Res*. Sep 9 1996;733(1):142-148.

13. Kleim JA, Swain RA, Czerlanis CM, Kelly JL, Pipitone MA, Greenough WT. Learning-dependent dendritic hypertrophy of cerebellar stellate cells: plasticity of local circuit neurons. *Neurobiol Learn Mem*. Jan 1997;67(1):29-33.
14. Cohen LG, Brasil-Neto JP, Pascual-Leone A, Hallett M. Plasticity of cortical motor output organization following deafferentation, cerebral lesions, and skill acquisition. *Adv Neurol*. 1993;63:187-200.
15. Liepert J, Bauder H, Wolfgang HR, Miltner WH, Taub E, Weiller C. Treatment-induced cortical reorganization after stroke in humans. *Stroke*. Jun 2000;31(6):1210-1216.
16. Nudo RJ, Plautz EJ, Frost SB. Role of adaptive plasticity in recovery of function after damage to motor cortex. *Muscle Nerve*. Aug 2001;24(8):1000-1019.
17. Kleim JA, Jones TA, Schallert T. Motor enrichment and the induction of plasticity before or after brain injury. *Neurochem Res*. Nov 2003;28(11):1757-1769.
18. Harris-Love ML, Morton SM, Perez MA, Cohen LG. Mechanisms of Short-Term Training-Induced Reaching Improvement in Severely Hemiparetic Stroke Patients: A TMS Study. *Neurorehabil Neural Repair*. Feb 22 2011.
19. Nudo RJ, Milliken GW. Reorganization of movement representations in primary motor cortex following focal ischemic infarcts in adult squirrel monkeys. *J Neurophysiol*. May 1996;75(5):2144-2149.
20. Kleim JA, Barbay S, Nudo RJ. Functional reorganization of the rat motor cortex following motor skill learning. *J Neurophysiol*. Dec 1998;80(6):3321-3325.
21. Kleim JA, Cooper NR, VandenBerg PM. Exercise induces angiogenesis but does not alter movement representations within rat motor cortex. *Brain Res*. Apr 26 2002;934(1):1-6.
22. Remple MS, Bruneau RM, VandenBerg PM, Goertzen C, Kleim JA. Sensitivity of cortical movement representations to motor experience: evidence that skill learning but not strength training induces cortical reorganization. *Behav Brain Res*. Sep 14 2001;123(2):133-141.
23. Shumway-Cook A, Woollacott MH. *Motor Control: Translating Research into Clinical Practice*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2011.
24. Guadagnoli MA, Lee TD. Challenge point: a framework for conceptualizing the effects of various practice conditions in motor learning. *J Mot Behav*. Jun 2004;36(2):212-224.
25. Wolpert DM, Kawato M. Multiple paired forward and inverse models for motor control. *Neural Netw*. Oct 1998;11(7-8):1317-1329.
26. Dromerick AW, Lang CE, Birkenmeier RL, et al. Very Early Constraint-Induced Movement during Stroke Rehabilitation (VECTORS): A single-center RCT. *Neurology*. Jul 21 2009;73(3):195-201.
27. Lo AC, Guarino PD, Richards LG, et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. *N Engl J Med*. May 13 2010;362(19):1772-1783.
28. Wolf SL, Winstein CJ, Miller JP, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. *JAMA*. 2006;296(17):2095-2104.
29. Caimmi M, Carda S, Giovanzana C, et al. Using kinematic analysis to evaluate constraint-induced movement therapy in chronic stroke patients. *Neurorehabil Neural Repair*. Jan-Feb 2008;22(1):31-39.
30. Wu CY, Lin KC, Chen HC, Chen IH, Hong WH. Effects of modified constraint-induced movement therapy on movement kinematics and daily function in patients with stroke: a kinematic study of motor control mechanisms. *Neurorehabil Neural Repair*. Sep-Oct 2007;21(5):460-466.
31. Massie C, Malcolm MP, Greene D, Thaut M. The effects of constraint-induced therapy on kinematic outcomes and compensatory movement patterns: an exploratory study. *Arch Phys Med Rehabil*. Apr 2009;90(4):571-579.
32. Woodbury ML, Howland DR, McGuirk TE, et al. Effects of trunk restraint combined with intensive task practice on poststroke upper extremity reach and function: a pilot study. *Neurorehabil Neural Repair*. Jan 2009;23(1):78-91.
33. Alaverdashvili M, Foroud A, Lim DH, Whishaw IQ. "Learned baduse" limits recovery of skilled reaching for food after forelimb motor cortex stroke in rats: a new analysis of the effect of gestures on success. *Behav Brain Res*. Apr 9 2008;188(2):281-290.
34. Levin MF, Kleim JA, Wolf SL. What do motor "recovery" and "compensation" mean in patients following stroke? *Neurorehabil Neural Repair*. May 2009;23(4):313-319.
35. American Physical Therapy Association. Guide to Physical Therapist Practice. . *Phys Ther*. Jan 2003;81(1):9-746.
36. American Occupational Therapy Association. Occupational Therapy Practice Framework: Domain and Process (2nd edition). *American Journal of Occupational Therapy*. 2008;62:625-683.
37. Woodbury M, Velozo CA, Thompson PA, et al. Measurement Structure of the Wolf Motor Function Test: Implications for Motor Control Theory. *Neurorehabil Neural Repair*. Jul 8 2010.

38. Van Wijck FM, Pandyan AD, Johnson GR, Barnes MP. Assessing motor deficits in neurological rehabilitation: patterns of instrument usage. *Neurorehabilitation Neural Repair*. 2001;15(1):23-30.
39. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient: a method for evaluation of physical performance. *Scandinavian Journal of Rehabilitation Medicine*. 1975;7(1):13-31.
40. Duncan PW, Lai SM, Keighley J. Defining post-stroke recovery: implications for design and interpretation of drug trials. *Neuropharmacology*. Mar 3 2000;39(5):835-841.
41. Wright BD, Stone MH. *Best test design*. Chicago: Mesa Press; 1979.
42. Wright BD, Stone MH. *Measurement Essentials*. Wilmington, DE: Wide Range, Inc.; 1999.
43. Andrich D. A rating formulation for ordered response categories. *Psychometrika*. 1978;43:561-573.
44. Woodbury ML, Velozo CA, Richards LG, Duncan PW, Studenski S, Lai SM. Dimensionality and construct validity of the Fugl-Meyer Assessment of the upper extremity. *Archives of Physical Medicine & Rehabilitation*. Jun 2007;88(6):715-723.
45. Jette AM, Tao W, Norweg A, Haley S. Interpreting rehabilitation outcome measurements. *J Rehabil Med*. Oct 2007;39(8):585-590.
46. Brunnstrom S. Motor testing procedures in hemiplegia: based on sequential recovery stages. *Phys Ther*. Apr 1966;46(4):357-375.
47. Beer RF, Dewald JP, Rymer WZ. Deficits in the coordination of multijoint arm movements in patients with hemiparesis: evidence for disturbed control of limb dynamics. *Exp Brain Res*. Apr 2000;131(3):305-319.
48. Lang CE, Beebe JA. Relating movement control at 9 upper extremity segments to loss of hand function in people with chronic hemiparesis. *Neurorehabil Neural Repair*. May-Jun 2007;21(3):279-291.
49. Twitchell TE. The restoration of motor function following hemiplegia in man. *Brain*. 1951;74:443-480.
50. Wolpert DM. Computational approaches to motor control. *Trends in Cognitive Science*. 1997(1):209-216.
51. Newell KM, Liu YT, Mayer-Kress G. Time scales, difficulty/skill duality, and the dynamics of motor learning. *Adv Exp Med Biol*. 2009;629:457-476.
52. Massie CL, Fritz S, Malcolm MP. Elbow extension predicts motor impairment and performance after stroke. *Rehabilitation Research and Practice*. 2011;2011:1-7.
53. Ellis MD, Holubar BG, Acosta AM, Beer RF, Dewald JP. Modifiability of abnormal isometric elbow and shoulder joint torque coupling after stroke. *Muscle Nerve*. Aug 2005;32(2):170-178.
54. Cirstea MC, Levin MF. Compensatory strategies for reaching in stroke. *Brain*. May 2000;123:940-953.
55. Mirbagheri MM, Rymer WZ. Time-course of changes in arm impairment after stroke: variables predicting motor recovery over 12 months. *Arch Phys Med Rehabil*. Aug 2008;89(8):1507-1513.
56. Michaelsen SM, Dannenbaum R, Levin MF. Task-specific training with trunk restraint on arm recovery in stroke: randomized control trial. *Stroke*. Jan 2006;37(1):186-192.
57. Wagner JM, Lang CE, Sahrman SA, et al. Relationships between sensorimotor impairments and reaching deficits in acute hemiparesis. *Neurorehabil Neural Repair*. 2006;20(3):406-416.
58. Mirbagheri MM, Lilaonitkul T, Rymer WZ. Prediction of natural history of neuromuscular properties after stroke using fugl-meyer scores at 1 month. *Neurorehabil Neural Repair*. Jun 2011;25(5):458-468.
59. Mirbagheri MM, Rymer WZ. Predication of reflex recovery after stroke using quantitative assessments of motor impairment at 1 month. *Conf Proc IEEE Eng Med Biol Soc*. 2009;2009:7252-7255.
60. Woodbury ML, Velozo CA, Richards LG, Duncan PW, Studenski S, Lai SM. Longitudinal stability of the Fugl-Meyer Assessment of the upper extremity. *Archives of Physical Medicine & Rehabilitation*. Aug 2008;89(8):1563-1569.
61. Velozo CA, Woodbury ML. Translating measurement findings into rehabilitation practice: An example using the Fugl-Meyer Assessment of the Upper Extremity with clients following stroke. *Journal of Rehabilitation Research and Development*. 2011;in press.
62. Wang YC, Hart DL, Stratford PW, Mioduski JE. Clinical interpretation of a lower-extremity functional scale-derived computerized adaptive test. *Phys Ther*. Sep 2009;89(9):957-968.
63. Tao W, Haley SM, Coster WJ, Ni P, Jette AM. An exploratory analysis of functional staging using an item response theory approach. *Arch Phys Med Rehabil*. Jun 2008;89(6):1046-1053.
64. Luft AR, Waller S, Forrester L, et al. Lesion location alters brain activation in chronically impaired stroke survivors. *Neuroimage*. Mar 2004;21(3):924-935.
65. Kleim JA, Boychuk JA, Adkins DL. Rat models of upper extremity impairment in stroke. *Ilar J*. 2007;48(4):374-384.

66. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*. 2009;120(12):2008-2039.
67. *Administration of the Fugl-Meyer Assessment* [unpublished videotape]: Duke University; 1983.
68. *WINSTEPS Rasch measurement computer program* [computer program]. Version 3.61.2. Chicago: Winsteps.com; 2006.
69. Higgins E GM. *Brain Stimulation Therapies for Clinicians*. 1st ed. Arlington, VA American Psychiatric Publishing Inc.; 2009.
70. Murase N DJ, Mazzocchio R, Cohen LG. Influence of interhemispheric interactions on motor function in chronic stroke. *Annals Neurol*. 2004;55(400-409).
71. Lang CE, Macdonald JR, Reisman DS, et al. Observation of amounts of movement practice provided during stroke rehabilitation. *Arch Phys Med Rehabil*. Oct 2009;90(10):1692-1698.
72. Birkenmeier RL, Prager EM, Lang CE. Translating animal doses of task-specific training to people with chronic stroke in 1-hour therapy sessions: a proof-of-concept study. *Neurorehabil Neural Repair*. Sep 2010;24(7):620-635.
73. Corbetta D, Sirtori V, Moja L, Gatti R. Constraint-induced movement therapy in stroke patients: systematic review and meta-analysis. *Eur J Phys Rehabil Med*. Dec 2010;46(4):537-544.
74. Taub E, Wolf SL. Constraint induced movement techniques to facilitate upper extremity use in stroke patients. *Topics in Rehabil*. 1997;3(4):38-61.
75. Beer RF, Ellis MD, Holubar BG, Dewald JP. Impact of gravity loading on post-stroke reaching and its relationship to weakness. *Muscle Nerve*. Aug 2007;36(2):242-250.
76. Ellis MD, Sukal-Moulton T, Dewald JP. Progressive shoulder abduction loading is a crucial element of arm rehabilitation in chronic stroke. *Neurorehabil Neural Repair*. Oct 2009;23(8):862-869.
77. Davis JZ. Task selection and enriched environments: a functional upper extremity training program for stroke survivors. *Top Stroke Rehabil*. Summer 2006;13(3):1-11.
78. George MS BR. Transcranial Magnetic Stimulation in Clinical Psychiatry. *American Psychiatric Publishing* 2007:l.

G. CONSULTANTS

No Consultants

H. FACILITIES AVAILABLE

RESOURCES

Scientific Environment

The Ralph H. Johnson VA Medical Center and its partner academic affiliate, the Medical University of South Carolina (MUSC) offer a wealth of intellectual support and substantial institutional support for establishing a research program in neurorehabilitation with an emphasis in stroke rehabilitation, which is the goal of the PI. Together, the two institutions provide a superb scientific environment that will greatly increase the probability of success of the proposed study.

The Ralph H. Johnson VA Medical Center and the MUSC are located in close proximity to one another on a shared campus with a majority of the staff having dual appointments (VA+MUSC). For example, the PI has an appointment as Assistant Professor in the Department of Health Sciences and Research in the MUSC College of Health Professions. There is a close, open working relationship between the local VA Medical Center's PENTAD and ACOS for Research and counterparts at MUSC. This is especially evident within MUSC's Strom Thurmond Biomedical Research Institute Building, half of which is leased by the VA to support VA ORD's bench research and animal research activities. The distinction between MUSC and VA faculty is almost non-existent with investigators working side-by-side in an atmosphere that promotes intellectual sharing of scientific knowledge and expertise that has led to the development of new collaborations between VA and MUSC investigators. This has allowed VA and MUSC investigators to propose and carryout a large number of innovative and intriguing investigations. Several of these collaborations have resulted in the discovery and use of new methodology not readily considered for use in a particular area of investigation that has added a whole new dimension to many of our investigators' protocols. The VA Research Office provides excellent administrative support to investigators in

all areas. Of significant note is the level of support they provide in the preparation of applications in response to VA initiatives. They take the lead in coordinating and preparing all non-scientific aspects, including biosketches/other support forms, budgets and justifications, letters of support, intramural reviews, etc. which allows investigators to focus all their energies on the scientific aspects of the application. MUSC is a research intensive university, with an academic medical center, and is the state's largest medical complex and the only tertiary/quaternary care referral center in the state. In FY 2009, MUSC faculty received grants and contracts totaling more than \$217 million, with funding from NIH totaling \$103.3 million. The College of Health Professions was ranked #9 in the country in total funding for similar colleges; the Department of Neurosciences, an integrated department of clinical and research neuroscientists that contains several nationally renowned senior investigators in stroke-research, ranks # 5 in the nation in NIH funding. MUSC is home to the JCAHO-certified SC Comprehensive Stroke and Cerebrovascular program, MUSC Stroke Center of Excellence and the REACH Stroke Network. The Stroke Center directed by Robert Adams, M.D. conducts innovative clinical trials throughout the state as well as through national networks, and offers remote urgent consultations through a new Web-based system that allows virtual examination of patients and CAT scans at community medical centers across the state.

Center for Biomedical Imaging (CBI): The CBI provides state-of-the-art imaging resources to support clinical and research activities, provide opportunities to advance the imaging field, disseminate new technologies and approaches to the larger community, and train and mentor young investigators interested in developing and applying biomedical imaging to clinical and research problems. The CBI includes approximately 4500 square feet of space at 30 Bee Street, as well as approximately 9000 square feet in the new Bioengineering Building. This proposal will utilize the brain imaging and stimulation facilities available at the 30 Bee St. location of the CBI. The 30 Bee Street location is the main facility for human imaging research and houses a Siemens 3T TIM Trio MRI scanner equipped with integrated fMRI paradigm presentation equipment. It is located directly across the street from the main hospital and is 1 block from the Institute of Psychiatry. The scanner operates with a 100% mandate for research use and is covered by a master research agreement with Siemens Medical. The site also contains an image analysis laboratory, a brain stimulation laboratory, and bioengineering facility along with subject interview and changing rooms. Research access is coordinated and billed through CBI and a web-based signup system. Researchers also have access to clinical Siemens 1.5T and 3T Verio MR scanners, located within the Radiology Department in the Clinical Sciences Building.

Laboratory

Upper Extremity Motor Function Laboratory: The Upper Extremity Motor Function Laboratory is a 900 square foot VA/MUSC laboratory located with the College of Health Professions Research Building (77 President Street, Room 207) on the campus of Medical University of South Carolina. This laboratory is designated as VA space through a formal Memorandum of Understanding between MUSC and the VA. The laboratory is located in the same building as the offices of the PI, Co-I, engineer and research therapy staff. It features equipment capable of collecting kinematic, kinetic, electromyographic, strength, and metabolic data. The motion analysis laboratory is adjacent to a small workshop available for the construction, repair, and alteration of simple mechanical devices. This space is located in close proximity to the VA Medical Center (within 2 blocks). The laboratory is a shared resource of the college and is supported in part by the Department of Health Sciences and Research, of which the Co-PI is Chairman. The College enthusiastically supports the integration of VA research within its research portfolio.

Clinical

One avenue for recruitment of hemiparetic subjects for this project is the MUSC JCAHO-certified Stroke Center is directed by Robert Adams, M.D. The Stroke Center at MUSC includes highly trained neuroscience nurses, a neuroscience service line administrator, stroke neurologists, neurointensivists, interventional neuroradiologists, diagnostic neuroradiologists, cerebrovascular neurosurgeons, medical intensivists, neurosonology technologists, dedicated neurosciences critical care pharmacists, comprehensive rehabilitation services, dedicated case managers and social workers, and a hospital-based ground transport system. The program holds Joint Commission's Certificate of Distinction for Primary Stroke Centers which recognizes centers that make exceptional efforts to foster better outcomes for stroke care. The MUSC Stroke Center sees over 50 new stroke patients per month and routinely screens all patients for eligibility to research studies. Their database currently contains information on several hundred persons who have given consent to be contacted for stroke research studies. The Stroke Center research team will assist with recruitment by reviewing the patient rosters to identify potential participants. Potential participants will be given information while inpatient and again when they are seen

for follow up in the outpatient clinic. The Stroke Center research team will establish communication with the potential participants and act as a liaison with the PI to facilitate recruitment. In addition to facilitating subject recruitment, these facilities offer the PI opportunities to gain exposure to clinical problems by attending grand rounds, observing inpatient rehabilitation, and interacting with clinicians.

In addition, investigators within the Department of Health Sciences and Research have established collaboration with Vanessa Hinson, M.D., Chief of Neurology at VAMC Charleston. In the last 5 year period, over 3500 veterans with stroke were seen throughout the Charleston Veterans Affairs catchment area along the South Carolina and Georgia coast. The Charleston VAMC conducts 4 neurology follow-up clinics per week in which Veterans with stroke are seen.

Computer

All staff have personal computers in their office that are linked together on a network. All office computers are equipped with necessary software for professional productivity (e.g., Microsoft Office, Internet Explorer, Adobe Acrobat, Matlab, etc.). The office computers are all on automated backup systems and linked for file sharing. Laboratory computers are also on the network, so that data are readily available to investigators. The PI has software available for conducting (a) item response theory data analyses (Winsteps Rasch Analysis, Rasch Unidimensional Modeling, Multilog Item Response Theory Modeling); (b) mathematical data analysis (Matlab) and (c) statistical data analysis (SPSS, SAS).

Office

Project investigators and staff have dedicated offices, telephones, and up-to-date office technology software. The PI and Co-I have offices in the College of Health Professions Research Building (with an approved VA off-site waiver). Project staff will have office space in the building. Conference telephones and videoconferencing capabilities are readily available. Well-appointed conference rooms with teleconferencing capabilities are readily available on a scheduled basis for conference calls and collaborator meetings. Support staff and standard office services are available to facilitate the project.

I. INVESTIGATOR BROCHURE

No Investigator Brochure

J. APPENDIX

Patient-Targeted Upper Extremity Rehabilitation After Stroke – Recruitment Questionnaire

Patient-Targeted Upper Extremity Rehabilitation After Stroke – Recruitment Questionnaire

Inclusion criteria:

1. Experienced an ischemic stroke at least 3 months prior
2. Passive range of motion in affected shoulder, elbow, and wrist within functional limits
3. 20-80 years of age

Exclusion criteria:

1. Pain in the affected upper extremity that would interfere with movement
2. Unable to understand 3-step directions
3. Unable to attend the study-related treatment or evaluation sessions
4. Orthopedic condition in back, UE, or impaired corrected vision that would alter kinematics of reaching.

1. Date of stroke _____

2. Medical records and MRI or CT available for review before participation yes no

3. Adult age 20 – 80? Current age _____

4. Gender: Male Female

5. Affected side: left right

6. Do you have passive ROM

a. Shoulder yes no

Motions _____

Limitations _____

Pain with PROM yes no scale: 1 2 3 4 5 6 7 8 9 10

Does your pain interfere with movement: yes no

b. Elbow yes no

Motions _____

Limitations _____

Pain with PROM yes no scale: 1 2 3 4 5 6 7 8 9 10

Does your pain interfere with movement: yes no

c. Wrist yes no

Motions _____

Limitations _____

Pain with PROM yes no scale: 1 2 3 4 5 6 7 8 9 10

Does your pain interfere with movement: yes no

