# Predicting Ipsilesional Motor Deficits in Stroke With Dynamic Dominance Model

Protocol and Statistical Analysis Plan

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# HRP-591 - Protocol for Human Subject Research

## Protocol Title:

Predicting Ipsilesional Motor Deficits in Stroke with Dynamic Dominance Model

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## Clinicaltrials.gov Registration #:

NCT03634397

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# 1.0 Objectives

## 1.1 Study Objectives

In the previous cycle of this grant, we characterized hemisphere specific motor control deficits in the non-paretic arm of unilaterally lesioned stroke survivors. Our preliminary data indicate that functional performance in the non-paretic arm, measured by the Jebsen-Taylor Hand Function Test (JTHFT), is diminished in patients with **severe paresis** by on average, 66% following right-hemisphere damage and 115% following left hemisphere damage. We hypothesize that such large deficits in the non-paretic arm interfere with the performance of functional activities in patients with severe paresis, who also cannot use the paretic arm for prehension and manipulation.

We have specifically designed an intervention to remediate the hemisphere-specific deficits in the non-paretic arm, using a virtual-reality platform. We then facilitate generalization and transfer to functional behaviors encountered in the natural environment by training speed and accuracy of manipulation using a variety of real objects. This intervention protocol is grounded in the premise that targeted remediation of fundamental control deficits exhibited by the non-paretic arm will generalize beyond practiced tasks to functional activities and functional independence. This intervention contrasts with the more typical approaches focused on paretic arm improvements, and the more pragmatic task-specific training therapies of essential ADL's which we argue is limited in scope, more cumbersome and ignores known fundamental motor control deficits. The impact of the proposed research is that we address persistent functional performance deficits in chronic stroke patients with severe paresis, who's non-paretic arm impairments are generally ignored in most current rehabilitation protocols. We propose a 2-site, two-group randomized intervention with a treatment group, which will receive unilateral training of the non-paretic arm, through our **V**irtual **R**eality and **M**anipulation **T**raining (**VRMT**) protocol. The control group will receive a comparison intervention, designed to match the experimental intervention in duration and frequency, but employs conventional therapies according to recently released practice guidelines for upper limb intervention in adult stroke. This proposal combines the research and recruiting strengths of two active laboratories, each with a history of studying hemisphere specific motor deficits in stroke survivors (Sainburg and Winstein), and stroke clinical trial intervention research (Winstein). We have already integrated our laboratories to conduct the pilot research that provides support for the predictions of the first two aims, detailed below.

**Aim 1: To determine whether non-paretic arm VRMT in chronic stroke survivors with severe paresis will produce durable improvements in non-paretic arm motor performance that will generalize to improve functional activities and functional independence to a greater extent than conventional therapy focused on the paretic arm.** We predict that: 1a) Unilateral **VRMT** training of the non-paretic arm will produce functional improvements in non-paretic arm motor performance (JTHFT), 1b) Conventional therapy focused on the paretic arm should decrease paretic arm impairment (Fugl-Meyer) to a greater or equal extent than non-paretic arm VRMT. We will assess paretic arm impairment level using the upper extremity component of the Fugl-Meyer Assessment (UEFM) as our primary measure, and "work area" using kinematic analysis, as detailed by Dewald and Co-workers [5] as our secondary measure. 1c) The effects of non-paretic arm VRMT will generalize to functional activities (Abilhand) and functional independence (FIM-motor/Barthel) to a greater extent than conventional paretic arm therapy. This aim provides a strong test of our hypothesis that non-paretic arm motor training will have a greater impact on functional independence than conventional paretic arm training in patients who lack paretic hand function, a prediction supported by our pilot data (see Figure 8).

**Aim 2: To determine whether intervention-induced improvements in non-paretic arm performance are associated with improvements in hemisphere-specific reaching kinematics.** We predict that **VRMT** -induced improvements in performance will be correlated with reductions in hemisphere-specific motor deficits [6-9], which are targeted by the VR component of our intervention. We will test this using a planar reaching paradigm that we developed and employed in the previous cycle of this grant for

quantifying hemisphere-specific non-paretic arm kinematics [6]. We predict that improvements in functional performance (JTHFT) will correlate better with *early trajectory variance* in LHD patients, but with *late trajectory variance* in RHD patients. These variables have previously been associated with left and right hemisphere processes, respectively.

**Aim 3: To determine whether our experimental intervention (non-paretic arm VRMT) might have detrimental effects on paretic arm impairment (Fugl-Meyer, Kinematics).** We predict that VRMT dependent improvements in non-paretic arm motor performance ***will not*** *decrement* paretic arm impairment level, a prediction supported by our pilot data (Figure 7) and the findings of Urbin et al [10]. This aim is important to ensure that VRMT of the non-paretic arm does not have a negative effect on paretic arm function. *Our pilot data from 15 severely paretic patients supports this hypothesis, indicating that VRMT remediation of the non-paretic arm leads to modest reductions in paretic arm impairment.*

### 1.2 Primary Study Endpoints

Non-Paretic Arm Evaluation: Jebsen-Taylor Hand Function Test
Paretic Arm Evaluation: Upper-Extremity Fugl-Meyer Assessment
Upper Extremity Functional Activity: Abilhand Assessment
Functional Independence: Barthel Index

### 1.3 Secondary Study Endpoints

Functional Independence Measure (FIM)-motor component

*Kinematic Outcomes:*
Positional Variance (Early and Late):

- Peak Velocity,
- End point of movement (tangential velocity minimum, after peak velocity that has an amplitude of less than 15% of maximum velocity)

Work Area (Paretic Arm)

## 2.0 Background

### 2.1 Scientific Background and Gaps

Stroke is a major health problem in the United States that leaves many survivors with chronic motor impairment, including hemiparesis in the limbs that are on the opposite side of the body to the damaged brain hemisphere. A substantial body of research has now established that the non-paretic arm often has motor deficits that limit performance of activities of daily living and thus functional independence [6, 8, 11-22]. The significance of the proposed research is that we developed a targeted remediation protocol to ameliorate persistent functional performance deficits in chronic stroke patients with severe paresis, who's non-paretic arm impairments are generally ignored in most current rehabilitation protocols. Our intervention protocol is grounded in the premise that targeted remediation of fundamental control deficits exhibited by the non-paretic arm will generalize and transfer beyond practiced tasks to functional activities and functional independence. The previous cycle of this grant detailed the mechanistic underpinnings of non-paretic arm motor deficits. The scientific premise of this proposal is based on the finding that non-paretic arm motor deficits become functionally limiting in patients with severe paresis, who are unable to use the paretic arm for manipulation [23]. This group of patients is identified by an upper extremity Fugl-Meyer (FM) score between 0-28 and a score of 0 (inability to perform) in the mass extension and prehension components of the Fugl-Meyer Assessment.

Woytowicz et al [1] recently reported a cluster analysis of 247 stroke patients, and identified a severely paretic group in the FM score range of 0-28. With the exception of mass finger flexion, 95-100%

of the patients scored 0 (unable to perform) for each item of the wrist movement, mass finger extension, and each prehension item of the FM. Thus, this severely paretic group of stroke patients is unable to use the paretic arm for manipulation purposes in activities of daily living. Deficits in coordination of the non-paretic arm can thus produce substantial limitations in the speed and efficacy of functional activities in this population. In fact, our preliminary findings (see Figure 2) indicate that unilateral tasks with the non-paretic arm take, on average, twice as long to complete as the comparable arm of age-matched control participants, indicating labored and inefficient movement that can interfere with patient's participation in activities. Unfortunately, clinical rehabilitation has yet to recognize the need to address non-paretic arm motor deficits, largely because scientific evidence has not yet been translated into clinical practice, nor has the best practice for this translation been specified through innovative intervention studies. This proposal will directly address these shortcomings, in order to provide a model for understanding how to incorporate non-paretic arm motor training into clinical rehabilitation practice for patients with severe paresis. It should be noted, however, that in animal models, training of the non-paretic arm in the acute phase of stroke recovery has been shown to interfere with subsequent paretic arm recovery [24, 25]. In addition, constraining the use of the non-paretic arm can facilitate functional recovery in those stroke survivors with mild to moderate paresis who are capable of distal manipulation in the contralesional hand, but who avoid using that arm due to learned non-use [26, 27].

Importantly, our proposed intervention focuses on patients with severe paresis who are in the chronic phase of stroke, and who do not have the sensorimotor requisites for paretic hand dexterity or manipulation. In this group of patients, recent findings indicate that intense resistance training of the non-paretic arm can reduce impairment measured in the paretic arm [10]. Consistent with this finding, our pilot data shows that intense non-paretic arm dexterity training also leads to a modest reduction in paretic arm impairment. Thus, we expect that the unilateral non-paretic arm VRMT training proposed here will improve functional independence without jeopardizing paretic arm function in patients with severe paresis (Aim 3). Our ultimate goal is to determine whether non-paretic arm remediation should be part of a package of rehabilitation that assesses and remediates fundamental control deficits in each arm of severely paretic stroke patients [4].

### 2.2 Previous Data

Preliminary Studies: Our findings from the previous grant cycle showed that the nature of non-paretic arm motor deficits can be explained by a model of hemispheric lateralization for motor control [64]. Thus, damage to each hemisphere produces specific and unique motor deficits in the non-paretic arm [7, 9]. *Figure 1A* shows reaching movements in the non-paretic arm of patients with left and right hemisphere damage. While patients with left hemisphere damage (LHD) made highly curved movements with accurate final positions, patients with right hemisphere damage (RHD) made straight movements with poor final position accuracies. *Figure 1B* shows the variance in hand positions during the initial trajectory phase (bottom ellipses) and in the final position (top ellipses) of the movement. This demonstrates the double dissociation between hemisphere of damage and motor control process effected by the lesion: RHD patients had deficits in stabilizing accurate final positions across trials, while LHD patients had deficits in stabilizing accurate initial trajectories across trials. We characterized these hemisphere-dependent movement deficits in studies that restricted motion to the horizontal plane; this was necessary to better control experimental variables, such as the joint displacements associated with a particular target. To achieve Aim 2, we will use this well-established horizontal reaching paradigm that yields initial positional variance (at peak velocity) and final position variance (at movement end) to assess potential training-related changes in hemisphere-specific motor deficits.

As an important foundation for the proposed research, we tested whether non-paretic arm motor function depends on the severity of paresis in the contralesional arm, and on the side of the brain that is damaged [23]. All patients were right-handed, prior to stroke. Figure 2 shows data from 54 right-handed, age and gender matched control participants, 48 right-handed LHD survivors, and 62 right-handed RHD survivors. The y-axis represents the time to complete the Jebsen-Taylor Hand Function Test (raw score). The JTHFT is a clinical assessment of unilateral arm function [65] that includes a range of

tasks that simulate the coordination requirements of functional daily activities [66, 67]. The left column in Figure 2 (control) shows the difference between healthy participants performing with the non-dominant left arm (Black) and the dominant right arm (Grey). The data are stratified on the x-axis by hand, and severity of contralesional paresis, as measured by the upper extremity component of the Fugl-Meyer Assessment of motor impairment [68] (mild [43-66], moderate [29-42], Severe [0-28]). In stroke survivors, JTHFT scores are only for the non-paretic arm (ie. Gray = non-paretic right arm of RHD participants; Black = non-paretic left arm of LHD participants). Note that the 'severe' classification in this plot reflects the level of impairment we target in this proposal.

In stroke survivors, JTHFT performance with the non-paretic arm was impacted substantially by both the severity of paresis and the side of brain damage. Participants with the most severe paresis in the contralesional arm had the greatest motor deficit in the non-paretic arm. Furthermore, the magnitude of the deficit depended on the side of the lesion, such that left hemisphere damage was associated with a 115% increase in JTFT score, while right hemisphere damage increased the time to complete the JTFT by 66%. These comparisons are relative to performance of the same arm (right or left) of age-matched control participants. However, it should be stressed that in LHD patients, the non-dominant arm must now function as a dominant controller, indicating an even larger deficit relative to age-matched dominant arm performance. Thus, stroke survivors who are forced to rely most extensively on the non-paretic arm for performance of ADL have the greatest deficits in coordination in the non-paretic arm. These stroke survivors were tested, on average, 1.8 years (±0.3 SE) after stroke, which suggests that these deficits do not spontaneously improve over time. To provide a reference, imagine using only your non-dominant arm to carry out all your activities of daily living, such as preparing food, dressing including buttoning, putting on socks, and shoes, etc. This would be somewhat frustrating. Now imagine that your non-dominant arm has become 115% slower and less coordinated than it was-the case for our severely impaired LHD patients. RHD patients get to use the previously dominant arm, but with a 66% decrement in function. Overall, these impairments are substantially functionally limiting.

### 2.3 Study Rationale

While motor deficits in the non-paretic arm of patients with unilateral stroke have been documented as early as 1967 [42], more recent research has shown that these deficits are functionally limiting and that they persist throughout the chronic phase of stroke [6-9, 11, 17, 19-22, 29, 31, 33, 43-51]. In fact, studies of non-paretic arm function in chronic stroke patients have reported performance deficiencies on a number of clinical tests, including the Purdue Pegboard Test [52], the Jebsen-Taylor Hand Function Test [8], and a variety of tests that directly assess or simulate activities of daily living [11, 53, 54]. Furthermore, significant deficits in movement coordination and accuracy have been shown through studies that use motion analysis [7-9, 17, 28-30, 33, 43, 46, 48, 55-62]. Winstein's laboratory published some of the earliest research characterizing the hemisphere specificity of ipsilesional movement deficits in stroke [50, 59] while in the previous grant cycle, Sainburg systematically detailed the hemisphere specificity, neural foundations, and functional implications of non-paretic arm motor deficits [9, 17, 28-30, 32, 33, 43, 60]. Together, our findings have demonstrated that stroke-related non-paretic arm motor deficits result from a loss of the contributions of the ipsilateral hemisphere to motor control, and that right- and left-hemisphere damage lead to deficits in different aspects of motor control [9, 29, 36, 59, 63]. Most relevant to the current proposal is the finding that hemisphere specific motor deficits in the non-paretic arm produce deficits in functional performance [8]. Our findings have demonstrated that stroke-related non-paretic arm motor deficits result from a loss of the contributions of the ipsilateral hemisphere to motor control, and that right- and left-hemisphere damage lead to deficits in different aspects of motor control [9, 29, 36, 59, 63]. Most relevant to the current proposal is the finding that hemisphere specific motor deficits in the non-paretic arm produce deficits in functional performance.

## 3.0 Inclusion and Exclusion Criteria

### 3.1 Inclusion Criteria

1. Right handed (pre-stroke)
2. Neurological confirmation of unilateral stroke
3. Ipsilesional deficits (JTHFT > 70 seconds or 40 (RHD)/45 seconds (LHD) seconds without writing time), contralesional deficits (upper extremity) (UEFM mass extension and prehension components score of 0)
4. Over the age of 18
5. Chronic stage of stroke

### 3.2 Exclusion Criteria

1. Neuroradiological confirmation of extensive periventricular white matter changes (based on consultation with neuroradiology)

A history of:
1) neurological disease other than stroke (e.g., head trauma),
2) a major psychiatric diagnosis (e.g., schizophrenia, major affective disorder),
3) hospital admission for substance abuse
4) peripheral disorders affecting sensation or movement of the arms, including pain or arthritis
5) currently taking prescription drugs with known sedative properties that might interfere with sensory-motor function
6) significant joint pain that is activity limiting.

### 3.3 Early Withdrawal of Subjects

#### 3.3.1 Criteria for removal from study

- failure of subject to adhere to protocol requirements (attending sessions)
- subject consent withdrawal
- new stroke or disabling disorder

#### 3.3.2 Follow-up for withdrawn subjects

Following withdraw from the study investigators will call participants 1 week later to follow up. Data will be used if enough has been collected for analysis. If not, subject will be replaced by additional recruitment.

## 4.0 Recruitment Methods

### 4.1 Identification of subjects

Participants will be recruited from Penn State Hershey Medical Center (PSHMC) and University of Southern California (USC) local stroke network. At Penn State, recruitment will include the Sainburg Laboratory's current database consisting of a large number of current and previous stroke participants, and by Penn State Hershey Medical Center's neurologists including Dr. David Good, and local stroke support groups/hospitals. At USC, recruitment will include the Winstein Laboratory's current database, a database of current and previous stroke survivors at USC, USC's Neurology Department, and local stroke support groups/hospitals. We will also use StudyFinder for recruitment. Participants may also contact researchers directly. Flyers may also be placed in local locations.

### 4.2 Recruitment process

After identifying potential subject, they will be sent a letter to notify them of the study, unless the participant contacts the lab first. They will be contacted be a study team member by telephone within 2 weeks of sending the letter.

### 4.3 Recruitment materials

Letter to patient, Flyers
(See StudyFinder page)

### 4.4 Eligibility/screening of subjects

See StudyFinder page for telephone script.

## 5.0 Consent Process and Documentation

### 5.1 Consent Process

#### 5.1.1 Obtaining Informed Consent

##### 5.1.1.1 Timing and Location of Consent

Informed consent will be obtained from all participants at the beginning of the first session at either Hershey Medical Center (Room C2852) or USC, Biophysical Therapy Dept.

##### 5.1.1.2 Coercion or Undue Influence during Consent

To minimize the possibility of coercion or undue influences, each participant will be thoroughly explained the purpose and expectations of the study. The participants will also be made aware that the study is completely voluntary and they can withdraw themselves at any time. In addition, consent will be explained to the patient by a member of the research team who doesn't have any prior relationship with the potential participants.

#### 5.1.2 Waiver or alteration of the informed consent requirement

The study team is requesting a waiver of informed consent to allow for recruitment from clinical schedules and curated databases.

### 5.2 Consent Documentation

#### 5.2.1 Written Documentation of Consent

Consent will be documented in writing by having the participant sign the informed consent form at the beginning of the first research session, and documents will be kept in a locked filing cabinet (please see consent documents). Participants will receive a paper copy of the signed informed consent document at their first session.

#### 5.2.2 Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)

The study team is requesting this waiver to allow for telephone screening and scheduling.

### 5.3 Consent – Other Considerations

#### 5.3.1 Non-English Speaking Subjects

not applicable

**5.3.2 Cognitively Impaired Adults**

not applicable

**5.3.2.1 Capability of Providing Consent**

not applicable

**5.3.2.2 Adults Unable To Consent**

not applicable

**5.3.2.3 Assent of Adults Unable to Consent**

not applicable

**5.3.3 Subjects who are not yet adults (infants, children, teenagers)**

not applicable

**5.3.3.1 Parental Permission**

not applicable

**5.3.3.2 Assent of subjects who are not yet adults**

not applicable

# 6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

**6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI**

**Check all that apply:**

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☒ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

**6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI**

**6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual**

**6.2.1.1 Plan to protect PHI from improper use or disclosure**

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

**6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers**

The list linking subject numbers to their PHI will be deleted following publications of study within 2 years of study closing. Any paper copies will be shredded.

#### 6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

In order to identify potential participants, stroke patients' charts must be accessed to screen for inclusion criteria. Because we exclude hundreds of subjects from the stroke database due to exclusion criteria, it would not be practical to contact patients unless they are an appropriate fit for the study. In addition, contact information needs to be obtained.

#### 6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

Given the number of subjects and the possibility that subjects may no longer be living this research would not be practical without waiver. No clinical information which would be pertinent to the care of individual subjects is expected to result from this study.

### 6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

## 7.0 Study Design and Procedures

### 7.1 Study Design

- Two 20-40-minute components comprise each session, one consists of virtual reality (VR) 'games' that separately target right- and left-hemisphere specific motor deficits, and the next component consists of dexterity training. The order of these sessions will be counterbalanced between subjects.
- The VR component is designed to focus on specific aspects of control that we have previously shown to be deficient in the non-paretic arm of right or left hemisphere damaged stroke patients. For the first 20-30 minutes of training, patients with LHD and RHD will practice tasks adapted to the motor control deficits associated with the damaged hemisphere. LHD patients will practice virtual shuffleboard, which focuses on predictive aspects of trajectory control, while RHD patients will play tracing games that focus on feedback mediated control.
- We then follow this with 30-40 minutes of hemisphere-independent speed and accuracy training of manipulation using a variety of real objects, designed to facilitate generalization and transfer to functional behaviors encountered in the natural environment. In this phase of the session, participants will first engage in mild resistive exercises, using theraputty and theraband, elastic substances designed for resistive exercises of the hand and arm, respectively. After 6 minutes of preparation, all participants will engage in a series of 6 tasks. The order that the tasks are presented will be randomized between sessions for each participant. Each task will be practiced for 4 minutes. The number of items successfully completed in each task will be counted and recorded as a 'target' to beat in the next session, providing motivation for improvement within and between sessions. While most of these tasks are self-explanatory, the

cup-stacking task uses 100 16-ounce disposable plastic cups, which are stacked in rapid sequence. The nuts and bolts task uses 5 varied diameter inverted bolts attached to a wooden base. The participants must pick up and screw on as many nuts as possible in 4 minutes. These tasks were chosen to have no overlap with the components of the JTHFT.

- While our pilot data indicates the effectiveness of this intervention package, it is beyond the scope of this proposal to assess the relative efficacy of its individual components. However, in aim 2, we will determine whether this package of training specifically ameliorated hemisphere-specific movement deficits in RHD and LHD patients. If so, this would suggest that the hemisphere-specificity of the VR training may be important in reducing such deficits.

**Comparison Intervention:**

- Our comparison intervention is designed to match our experimental intervention in duration and frequency (3X/week for 1 hour over 5 weeks), but using conventional therapeutic activities, based on the best-practices framework for arm recovery post stroke that was developed by an international group of clinicians and researchers in post-stroke rehabilitation [3]. This group, which included occupational therapists, physical therapists, physiatrists, neurologists, and scientists, developed an algorithm for a clinical decision tree which was implemented through a smartphone app, ViaTherapy. In short, recommended therapies are stratified based on research evidence for efficacy, take into account chronicity, potential for reported shoulder pain, and are filtered by co-morbidities such as neglect, cognitive impairment, aphasia, and apraxia.
- To avoid any confounds with the experimental intervention, we exclude any interventions requiring technology that might not be found in a typical community-based rehabilitation clinic, such as robotic rehabilitation, functional electric stimulation, or computer based interfaces. For a typical patient in our study (> 6 months chronicity, no activity limiting shoulder pain, able to partially abduct the shoulder against gravity and partially extend the elbow without gravity, but cannot initiate finger and thumb extension three times within a minute), recommendations include 1) Proximal strength training, 2) Motor imagery and mental practice, 3) Mirror Therapy, using a midsagittal mirror reflecting the non-paretic arm, while the patient attempts bilateral symmetrical forward reaching, and 4) Task specific training, involving reaching toward meaningful objects, with manual assistance as required. The first ten minutes of the 60-minute session will begin with passive range of motion, gentle stretching, and proximal weight bearing, which will help relax spasticity (if present) and prepare the proximal muscles for activity. This will be followed by two of the first 3 recommended therapies (10 minutes each), and then will be followed by 30 minutes of active assisted task-specific reach training. While the specific recommendations may vary slightly based on the decision algorithm, all therapies will begin with 10 minutes of proximal preparation, and all sessions will end with 30 minutes of assisted task-specific reaching of the paretic arm in various directions.
- This study is after the standard care of treatment has been finished or in addition to standard care of treatment, not in place of standard care.

## 7.2 Study Procedures

### 7.2.1 Visit 1 (pre-test 1):

Visit 1 (pre-test/screening): subjects will be consented, and then tested using standardized tests including the primary and secondary measures. In addition, the Edinburgh handedness inventory, Confidence in Arm and Hand Movement (CAHM), Multidimensional Scale of Perceived Social Support, NIH stroke scale, tests for comorbidities including testing of grip strength, visual neglect, and apraxia. If they meet criteria for the study, they will be randomly assigned to either the intervention or comparison condition. Tests may be videotaped for scoring and standardization purposes. Participant's names will not be associated with the videotapes. A data safety monitoring board will monitor the study for safety and to minimize risk.

### 7.2.2 Visit 2 (pre-test 2):

Visit 2 will include the same assessments as visit 1 to establish stability in baseline measures. Participants will also receive an MRI of the brain, which will take about one hour, as long as they are able to have one. The research grade MRI is used for data analysis regarding lesion location and volume. It is standard for studies of this nature to collect this information.

### 7.2.3 Visit 3-17:

**Intervention condition:** Two 20-40-minute components comprise each session, one consists of virtual reality (VR) 'games' that separately target right- and left-hemisphere specific motor deficits, and the next component consists of dexterity training. The order of these sessions will be counterbalanced between subjects. The VR component is designed to focus on specific aspects of control that we have previously shown to be deficient in the non-paretic arm of right or left hemisphere damaged stroke patients. For the first 20-30 minutes of training, patients with LHD and RHD will practice tasks adapted to the motor control deficits associated with the damaged hemisphere. LHD patients will practice virtual shuffleboard, which focuses on predictive aspects of trajectory control, while RHD patients will play tracing games that focus on feedback mediated control. We then follow this with 30-40 minutes of hemisphere-independent speed and accuracy training of manipulation using a variety of real objects, designed to facilitate generalization and transfer to functional behaviors encountered in the natural environment. In this phase of the session, participants will first engage in mild resistive exercises, using theraputty and theraband, elastic substances designed for resistive exercises of the hand and arm, respectively. After 6 minutes of preparation, all participants will engage in a series of 6 tasks. The order that the tasks are presented will be randomized between sessions for each participant. Each task will be practiced for 4 minutes. The number of items successfully completed in each task will be counted and recorded as a 'target' to beat in the next session, providing motivation for improvement within and between sessions. These tasks are shown in the flow chart in Figure 5. While most are self-explanatory, the cup-stacking task uses 100 16-ounce disposable plastic cups, which are stacked in rapid sequence. The nuts and bolts task uses 5 varied diameter inverted bolts attached to a wooden base. The participants must pick up and screw on as many nuts as possible in 4 minutes. These tasks were chosen to have no overlap with the components of the JTHFT. While our pilot data indicates the effectiveness of this intervention package, it is beyond the scope of this proposal to assess the relative efficacy of its individual components. However, in aim 2, we will determine whether this package of training specifically ameliorated hemisphere-specific movement deficits in RHD and LHD patients. If so, this would suggest that the hemisphere-specificity of the VR training may be important in reducing such deficits.

**Comparison (sham) Intervention:** Our comparison intervention is designed to match our experimental intervention in duration and frequency (3X/week for 1 hour over 5 weeks), but using conventional therapeutic activities, based on the best-practices framework for arm recovery post stroke that was developed by an international group of clinicians and researchers in post-stroke rehabilitation [3]. This group, which included occupational therapists, physical therapists, physiatrists, neurologists, and scientists, developed an algorithm for a clinical decision tree which was implemented through a smartphone app, ViaTherapy. In short, recommended therapies are stratified based on research evidence for efficacy, take into account chronicity, potential for reported shoulder pain, and are filtered by co-morbidities such as neglect, cognitive impairment, aphasia, and apraxia. To avoid any confounds with the experimental intervention, we exclude any interventions requiring technology that might not be found in a typical community-based rehabilitation clinic, such as robotic rehabilitation, functional electric stimulation, or computer based interfaces. For a typical patient in our study (> 6 months chronicity, no activity limiting shoulder pain, able to partially abduct the shoulder against gravity and partially extend the elbow without gravity, but cannot initiate finger and thumb extension three times within a minute), recommendations include 1) Proximal strength training, 2) Motor imagery and mental

practice, 3) Mirror Therapy, using a midsagittal mirror reflecting the non-paretic arm, while the patient attempts bilateral symmetrical forward reaching, and 4) Task specific training, involving reaching toward meaningful objects, with manual assistance as required. The first ten minutes of the 60-minute session will begin with passive range of motion, gentle stretching, and proximal weight bearing, which will help relax spasticity (if present) and prepare the proximal muscles for activity. This will be followed by two of the first 3 recommended therapies (10 minutes each), and then will be followed by 30 minutes of active assisted task-specific reach training. While the specific recommendations may vary slightly based on the decision algorithm, all therapies will begin with 10 minutes of proximal preparation, and all sessions will end with 30 minutes of assisted task-specific reaching of the paretic arm in various directions.

Note: sessions may be videotaped for standardization purposes.

#### 7.2.4 Visit 18: Post test

Visit will include the same assessments as visit 1

#### 7.2.5 Visit 19: Post test 2 (short term retention)

Visits will include the same assessments as visit 1, 2 weeks following completion of training sessions

#### 7.2.6 Visit 20: Post test 3 (long term retention)

Visits will include the same assessments as visit 1 six months following completion of training sessions

### 7.3 Duration of Participation

This study will require each participant to attend three 60-minute sessions per week for 5 weeks, as well as 5 separate test (pre and post) sessions, for a total of 20 sessions. If participant misses a session, it will be made up the following week, or by adding it to the end of training sessions. The first two separate pretests take place at visit 1 and 2, one to two weeks apart. The other additional testing sessions take place the visit after the conclusion of therapy sessions, 2 weeks later, and a 6 months following conclusion of therapy sessions.

## 8.0 Subject Numbers and Statistical Plan

### 8.1 Number of Subjects

We seek to recruit a total of 30 participants for the study per year between sites, and after screening and attrition rate, have 20 subjects a year complete the research procedures, for a total of 120 participants.

### 8.2 Sample size determination

Based on our primary outcome measures (Barthel, FIM-motor, Abilhand, UEFM, JTHFT) the proposed sample size of 60 participants per group provides adequate power (>=0.80) to assess each prediction when the effect size (Cohen's f) is 0.35 or greater. Cohen suggested that researchers consider f=0.1 as a small effect, f=0.25 as a medium effect, and f=0.4 as a large effect. To determine sample size, we used a power analysis program, SOLO [81], and computer simulation. SOLO permitted us to vary effect sizes and determine the test's power for a fixed group size. The simulation permitted us to use our pilot data to generate multivariate normal data; fit a model with fixed effects for group, test, and group by test interaction; conduct tests to include those for the linear contrasts; and record the p-value and associated effect size. The pilot data was particularly useful because the participants had been chosen so that they would span the expected impairment levels, and included right- and left-hemisphere-damaged participants. We will go through the major measures and analyses for each aim below. We have collected pilot data for 15 participants, using a cross-over design, for Aims 1 and 2, which provide preliminary support for our predictions.

### 8.3 Statistical methods

To assess our intervention, we will fit linear mixed models (LMMs) with single-degree-of-freedom linear contrasts [80] to determine if the data support our predictions (see next section). We will use a linear mixed model with main effects for group (experimental, control) and time (Test) and the group by time interaction simply provides a more flexible approach to the typical analysis of variance (ANOVA) model for a randomized pretest-posttest design. Specifically, LMMs will permit us to account for participant matching with a random cluster effect; and they permit each participant to have her or his initial value (random intercept) and different change patterns across the tests (random coefficients for an underlying piecewise regression). LMMs allow us to use covariates to adjust for any potential confounders. Finally, these models can tolerate missing data on the response, which is not true of the standard ANOVA-based model.

Lesion Reconstruction Methods: Winstein's laboratory personnel will reconstruct stroke lesions from the research grade MRI scans. They will superimpose lesions on each axial slice to identify common areas of lesion overlap associated with damage to the right or left hemisphere and to assess comparability of intrahemispheric lesion location in our two tracks. This grant will not specifically examine intrahemispheric lesion location, but these data will provide pilot data for future studies. To calculate the CST lesion load, we will use the tractography based atlas of human brain connections from the natbrain lab [72]. We will use the MRIcron descriptive tool for the calculation of the CST-lesion overlap volume. The binary lesion mask file will be overlaid onto either the left or right binary template CST atlas, and the percentage of CST which overlaps with the lesion is calculated.

## 9.0 Confidentiality, Privacy and Data Management

### 9.1 Confidentiality

#### 9.1.1 Identifiers associated with data and/or specimens

##### 9.1.1.1 Use of Codes, Master List

Each site will have a code linked to subject's identifiable information in a locked document. The list will not be shared between sites or with members that are not part of the research group.

#### 9.1.2 Storage of Data and/or Specimens

Data will be kept electronically on password-protected computers and backed up on external hard-drives locked in filing cabinets in room C2852 at the COM or Carolee Winstein's Laboratory at USC. Hardcopies of the data will be kept as well, also locked in room C2852 at the COM or locked in Carolee Winstein's laboratory at USC.

#### 9.1.3 Access to Data and/or Specimens

Electronic key card access is required to enter room C2852. A list of approved personnel is kept by the neurology dept. USC also has locks on the door and a list of approved personnel.

#### 9.1.4 Transferring Data and/or Specimens

De-identified data will be collected at both sites (PSU, USC) and managed using REDCap (Research Electronic Data Capture) at Penn State. REDCap is a secure web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). The system was developed by a multi-institutional consortium which includes The Pennsylvania State University and was initiated at Vanderbilt University. The database is hosted at the Penn State Hershey Medical Center and College of Medicine data center, which will be used as a central location for data processing and management. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team. This iterative development and testing process results in a well-planned data

collection strategy for individual studies. REDCap is flexible enough to be used for a variety of types of research and provides an intuitive user interface for database design and data entry. Deidentified data can be sent via password protected files. Videotapes will be shared for standardization and scoring purposes. They will be shared on a secure server, hosted by USC. https://uscbknpt.sharepoint.com/sites/IPSI/default.aspx
There is a password protected account for PSU members and a separate account for USC members. A list is available documenting team members that have access to the site. Participants are coded with a label and names are not used, however their faces are visible in the videotapes.

### 9.2 Subject Privacy

Research team can access medical records of stroke patients after completing HIPPA training. Participants can choose to not interact with specific team members if requested, and may decline to provide any personal information. The personal identifiable information will be previously collected from medical record. However, if the participant does not want to answer any questions on the questionnaires, they may choose not to. Researchers will be through in response to participant questions and assure participants that their answers are confidential.

## 10.0 Data and Safety Monitoring Plan

Not Applicable/minimal risk

### 10.1 Periodic evaluation of data

### 10.2 Data that are reviewed

### 10.3 Method of collection of safety information

### 10.4 Frequency of data collection

### 10.5 Individuals reviewing the data

### 10.6 Frequency of review of cumulative data

### 10.7 Statistical tests

### 10.8 Suspension of research

## 11.0 Risks

Loss of confidentiality is a risk for data analysis and/or chart review research. The techniques employed in this study are non-threatening, non-invasive, and pose no risk beyond that experienced during normal daily activities. In general, subjects may experience fatigue or discomfort due to the two 30 minute increments of sitting.

Because the MRI scanner contains a very strong magnet, participants will not be able to have the MRI if they have certain kinds of metal in your body (for example, a heart pacemaker, a metal plate, certain types of heart valves or brain aneurysm clips). Someone will ask them questions about this before they have the MRI. Having a MRI may mean some added discomfort to the participant. In particular, they may be uncomfortable inside the MRI scanner if they do not like to be in closed spaces (“claustrophobia”). They may also be bothered by the loud banging noise during the study. Temporary hearing loss has been reported from the loud noise. This is why they

will be asked to wear earplugs. During the procedure, they will be able to talk with the MRI staff through a speaker system. They can tell them to stop the scan at any time.

It is possible that the study procedures (brain MRI scan) could detect a possible unknown medical problem that is unrelated to the purpose of this study. If the research procedures uncover findings that may be important for the participant to know about, such as the possibility of a previously unknown medical condition, a member of the study team may contact them to find out if they would like to learn more. These findings may require additional testing or treatment. The cost of any additional tests or related treatment will be their responsibility.

## 12.0 Potential Benefits to Subjects and Others

### 12.1 Potential Benefits to Subjects

There is no guaranteed direct benefit to the research subjects. However, they may increase non-paretic arm function. There is minimal risk to the study participants, so the risk/benefit ratio is quite favorable.

### 12.2 Potential Benefits to Others

This study addresses important questions regarding motor training in stroke patients. If, as hypothesized, these techniques demonstrate potential as therapeutic agents, this research may lead to clinical intervention research, and ultimately to the development of more effective rehabilitation techniques.

## 13.0 Sharing Results with Subjects

Not applicable

## 14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

Subjects will be paid $50 per visit. Additional travel reimbursement will be given if traveling more than 25 miles from study site, up to $50 per visit.

## 15.0 Economic Burden to Subjects

### 15.1 Costs

not applicable

### 15.2 Compensation for research-related injury

not applicable

## 16.0 Resources Available

### 16.1 Facilities and locations

Hershey Medical Center & University of Southern California

### 16.2 Feasibility of recruiting the required number of subjects

Previous experience indicates that we can recruit a minimum of 20 eligible participants each year, from each site. This, in combination with the current databases at each site, makes the recruitment goal of 30 participants per year (15 per site), over the four-year course of recruitment (120 total), realistic. The HMC database has every stroke patient that is a patient in the hospital, which is over 100 per month. However, we have selective criteria, therefore we aim to recruit less than 5% of them.

### 16.3 PI Time devoted to conducting the research

PI will reduce teaching load to less than one class per semester in order to devote more time to this study.

### 16.4 Availability of medical or psychological resources

Both sites have qualified medical personnel available at each location

### 16.5 Process for informing Study Team

Personnel will be trained prior to the start of the study. Twice a year researchers will fly between sites to provide refresher training. Meetings will be Skyped between the two sites.

## 17.0 Other Approvals

### 17.1 Other Approvals from External Entities

USC's IRB has agreed to let COM IRB be the IRB of record for this study (letter uploaded)

### 17.2 Internal PSU Committee Approvals

**Check all that apply:**

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of HRP-902 - Human Tissue For Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – Hershey only – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes, but are no longer needed for clinical use. Upload a copy of HRP-901 - Human Body Fluids for Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Clinical Research Center (CRC) Advisory Committee – All campuses – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of HRP-903 - Radiation Review Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☐ Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/investigator

# 18.0 Multi-Site Research

## 18.1 Communication Plans

In order to facilitate communication and interaction, Drs. Winstein and Sainburg will communicate weekly and via conference call formally once a month that will include all members of the research teams at both sites. As mentioned, Drs. Sainburg and Winstein have an ongoing collaboration and have an established foundation of communication. Dr. Sainburg and Dr. Winstein, as well as one main representative from each research team, will travel to the other laboratory one time per year, to review methods and materials, prevent drift and to insure consistent procedures between laboratories.

## 18.2 Data Submission and Security Plan

- De-identified data will be collected at both sites (PSU, USC) and managed using REDCap (Research Electronic Data Capture) at Penn State. REDCap is a secure web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus).
- The database is hosted at the Penn State Hershey Medical Center and College of Medicine data center, which will be used as a central location for data processing and management. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team. This iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap is flexible enough to be used for a variety of types of research and provides an intuitive user interface for database design and data entry.
- De-identified research data generated by the project will be shared through ScholarSphere (https://scholarsphere.psu.edu/), the repository service that both the University Libraries and Information Technology Services administer at Penn State. Researchers will be able to access the data via ScholarSphere, which ensures persistent access to deposited content. The data will be discoverable via Google and other major search engines, as well as by request to Dr. Sainburg or Dr. Winstein.
- A master list for data will be kept at each site, locked in filing cabinets in a locked room (previously described).
- Videotapes will be shared for standardization and scoring purposes. They will be shared on a secure server, hosted by USC. https://uscbknpt.sharepoint.com/sites/IPSI/default.aspx There is a password protected account for PSU members and a separate account for USC members. A list is available documenting team members that have access to the site. Participants are coded with a label and names are not used, however their faces are visible in the videotapes.

## 18.3 Subject Enrollment

One statistician will be responsible for randomizing all subjects across both sites and will have communication with researchers weekly.

### 18.4 Reporting of Adverse Events and New Information

We appreciate the importance of accurately monitoring patient accrual and data collection as well as the possibility of the occurrence of any serious adverse event (expected and unexpected). To deal with these issues we have included a data and safety monitoring board (DSMB), which consists of a Chair and 3 members all external to the study and including two medical monitors, one from each of the two sites. The DSMB will be established to monitor the well-being of the study participants, ensure scientific integrity of the study, and assure timely patient accrual. See the Table (section 3.3 of grant, uploaded). The site IRB will review and approve all study protocols, require annual updates of the study and monitor for adverse events. The DSMB will assist the IRB's and the study personnel in the careful monitoring of the risk / benefit ratio of the implementation of this study. The DSMB will meet regularly (determined by the Chair) to ensure the safety of the participants during the course of the study and the validity and integrity of the data. They will monitor patient safety, recruitment, adherence to inclusion and exclusion criteria, retention, deviations from assigned treatments, quality control, and interim analyses of primary and main secondary outcomes as well as the occurrence of adverse events and other indicators of patient safety. All adverse events and participant drop outs will be reported to the PIs immediately so the case can be examined in detail with the on-site Medical Monitor to determine the reason for drop out and/or circumstances behind the adverse event. Should any adverse events deemed to increase risks to participants be identified, the study will stop immediately and an investigation will be conducted. The local Medical Monitor at each site (who is not part of the investigative team) will be responsible for reviewing the activities of the clinical trial including the incidence and type of adverse events. The Medical Monitor at each site will consult with the local Site PI (Sainburg, Hershey; Winstein, USC) relative to complications and any questions regarding inclusion, and progression through the protocol. All serious adverse events will be reported immediately to the Medical Monitor, as well as the IRB, and DSMB.

The investigative team has established definitions for adverse events, criteria for causally related and an adverse event protocol. These definitions and protocols will be used for reporting all adverse events from each site for this study. Any adverse events from either of the two sites will be recorded and monitored as required by the respective Institutional Review Boards and the Study Data Safety and Monitoring Board (DSMB). A composite report will be generated by each site coordinator and submitted to the DSMB every 6 months. Each site PI will submit a signed report to their local IRB in compliance with their standard policies and procedures. The DSMB will provide on-going monitoring of adverse events for a pattern of events that would indicate increased risk or potential harm. This information could indicate a need to change the protocol or cease the trial. During the course of the study all severe adverse events will be immediately entered into a Redcap database, and at the same time, an adverse event report will be sent to the Chair of the Data Safety Monitoring Board, and each site PI. All serious events will be reported to each site IRB within five days. A cumulative adverse event-reporting table will be completed for annual continuing review.

### 18.5 Audit and Monitoring Plans

The PIs and the site study coordinators will monitor ongoing data collection, perform quality checks on the actual participant files for recording accuracy, and monitor data entry into Redcap for accuracy, including random checks throughout the duration of the study.

## 19.0 Adverse Event Reporting

### 19.1 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

## 20.0 Study Monitoring, Auditing and Inspecting

### 20.1 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Penn State quality assurance program office(s), IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

## 21.0 Future Undetermined Research: Data and Specimen Banking

### 21.1 Data and/or specimens being stored

Name, birthday, address, phone number

### 21.2 Location of storage

Room C2852 (COM), Dr. Carolee Winstein's laboratory, USC

### 21.3 Duration of storage

Deidentified data will be made available through online data sharing resources for reproducibility. Identifiable data will be discarded within 2 years following final publications of study.

### 21.4 Access to data and/or specimens

Only members of the research team will have access to data.

### 21.5 Procedures to release data or specimens

De-identified data will be collected and managed using REDCap (Research Electronic Data Capture) at Penn State with access granted to study team members at both locations (COM, USC). REDCap is a secure web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). The system was developed by a multi-institutional consortium which includes The Pennsylvania State University and was initiated at Vanderbilt University. The database is hosted at the Penn State Hershey Medical Center and College of Medicine data center, which will be used as a central

location for data processing and management. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team. This iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap is flexible enough to be used for a variety of types of research and provides an intuitive user interface for database design and data entry. De-identified research data generated by the project will be shared through ScholarSphere (https://scholarsphere.psu.edu/), the repository service that both the University Libraries and Information Technology Services administer at Penn State. Researchers will be able to access the data via ScholarSphere, which ensures persistent access to deposited content. The data will be discoverable via Google and other major search engines, as well as by request to the PI.

### 21.6 Process for returning results

Others may use data when it is uploaded through above procedures.

## 22.0 References


1. Woytowicz, E.J., J.C. Rietschel, R.N. Goodman, S.S. Conroy, J.D. Sorkin, J. Whitall, and S. McCombe Waller, Determining Levels of Upper Extremity Movement Impairment by Applying a Cluster Analysis to the Fugl-Meyer Assessment of the Upper Extremity in Chronic Stroke. Arch Phys Med Rehabil, 2017. 98(3): p. 456-462.
2. Woodbury, M.L., C.A. Velozo, L.G. Richards, P.W. Duncan, S. Studenski, and S.M. Lai, Dimensionality and construct validity of the Fugl-Meyer Assessment of the upper extremity. Arch Phys Med Rehabil, 2007. 88(6): p. 715-23.
3. Wolf, S.L., G. Kwakkel, M. Bayley, M.N. McDonnell, and G. Upper Extremity Stroke Algorithm Working, Best practice for arm recovery post stroke: an international application. Physiotherapy, 2016. 102(1): p. 1-4.
4. Rose, D.K. and C.J. Winstein, The co-ordination of bimanual rapid aiming movements following stroke. Clin Rehabil, 2005. 19(4): p. 452-62.
5. Sukal, T.M., M.D. Ellis, and J.P. Dewald, Shoulder abduction-induced reductions in reaching work area following hemiparetic stroke: neuroscientific implications. Exp Brain Res, 2007.
6. Schaefer, S.Y., K.Y. Haaland, and R.L. Sainburg, Ipsilesional motor deficits following stroke reflect hemispheric specializations for movement control. Brain, 2007. 130(Pt 8): p. 2146-58. PMCID: PMC3769213
7. Schaefer, S.Y., K.Y. Haaland, and R.L. Sainburg, Dissociation of initial trajectory and final position errors during visuomotor adaptation following unilateral stroke. Brain Res, 2009. 1298: p. 78-91. PMCID: PMC3151492
8. Schaefer, S.Y., K.Y. Haaland, and R.L. Sainburg, Hemispheric specialization and functional impact of ipsilesional deficits in movement coordination and accuracy. Neuropsychologia, 2009. 47(13): p. 2953-66. PMCID: PMC2752301
9. Schaefer, S.Y., P.K. Mutha, K.Y. Haaland, and R.L. Sainburg, Hemispheric specialization for movement control produces dissociable differences in online corrections after stroke. Cereb Cortex, 2012. 22(6): p. 1407-19. PMCID: PMC3357180
10. Urbin, M.A., M.L. Harris-Love, A.R. Carter, and C.E. Lang, High-Intensity, Unilateral Resistance Training of a Non-Paretic Muscle Group Increases Active Range of Motion in a Severely Paretic Upper Extremity Muscle Group after Stroke. Front Neurol, 2015. 6: p. 119.
11. Wetter, S., J.L. Poole, and K.Y. Haaland, Functional implications of ipsilesional motor deficits after unilateral stroke. Arch Phys Med Rehabil, 2005. 86(4): p. 776-81.
12. Swinnen, S.P., F. Debaere, V. Puttemans, S. Vangheluwe, and C. Kiekens, Coordination deficits on the ipsilesional side after unilateral stroke: the effect of practice on nonisodirectional ipsilateral coordination. Acta Psychol (Amst), 2002. 110(2-3): p. 305-20.

13. Quaney, B.M., J. He, G. Timberlake, K. Dodd, and C. Carr, Visuomotor training improves stroke-related ipsilesional upper extremity impairments. Neurorehabil Neural Repair, 2010. 24(1): p. 52-61.
14. Hermsdorfer, J., S. Ulrich, C. Marquardt, G. Goldenberg, and N. Mai, Prehension with the ipsilesional hand after unilateral brain damage. Cortex, 1999b. 35(2): p. 139-61.Page 122
15. Hermsdorfer, J., K. Laimgruber, G. Kerkhoff, N. Mai, and G. Goldenberg, Effects of unilateral brain damage on grip selection, coordination, and kinematics of ipsilesional prehension. Exp Brain Res, 1999a. 128(1-2): p. 41-51.
16. Hanlon, C.A., A.L.H. Buffington, and M.J. McKeown, New brain networks are active after right MCA stroke when moving the ipsilesional arm. Neurology, 2005. 64: p. 114-120.
17. Haaland, K.Y., S.Y. Schaefer, R.T. Knight, J. Adair, A. Magalhaes, J. Sadek, and R.L. Sainburg, Ipsilesional trajectory control is related to contralesional arm paralysis after left hemisphere damage. Exp Brain Res, 2009. 196(2): p. 195-204.
18. Debaere, F., D. Van Assche, C. Kiekens, S.M. Verschueren, and S.P. Swinnen, Coordination of upper and lower limb segments: deficits on the ipsilesional side after unilateral stroke. Exp Brain Res, 2001. 141(4): p. 519-29.
19. Chestnut, C. and K.Y. Haaland, Functional significance of ipsilesional motor deficits after unilateral stroke. Arch Phys Med Rehabil, 2008. 89(1): p. 62-8.
20. Arya, K.N., S. Pandian, and D. Kumar, Task-based mirror therapy enhances ipsilesional motor functions in stroke: A pilot study. J Bodyw Mov Ther, 2017. 21(2): p. 334-341.
21. Bustren, E.L., K.S. Sunnerhagen, and M. Alt Murphy, Movement Kinematics of the Ipsilesional Upper Extremity in PersonsWith Moderate or Mild Stroke. Neurorehabil Neural Repair, 2017. 31(4): p. 376-386.
22. Semrau, J.A., T.M. Herter, J.M. Kenzie, S.E. Findlater, S.H. Scott, and S.P. Dukelow, Robotic Characterization of Ipsilesional Motor Function in Subacute Stroke. Neurorehabil Neural Repair, 2017. 31(6): p. 571-582.
23. Sainburg, R.L., C. Maenza, C. Winstein, and D. Good, Motor Lateralization Provides a Foundation for Predicting and Treating Non-paretic Arm Motor Deficits in Stroke. Adv Exp Med Biol, 2016. 957: p. 257-272. PMCID: PMC5364330
24. Allred, R.P., C.H. Cappellini, and T.A. Jones, The "good" limb makes the "bad" limb worse: experiencedependent interhemispheric disruption of functional outcome after cortical infarcts in rats. Behav Neurosci, 2010. 124(1): p. 124-32.
25. Allred, R.P., M.A. Maldonado, J.E. Hsu And, and T.A. Jones, Training the "less-affected" forelimb after unilateral cortical infarcts interferes with functional recovery of the impaired forelimb in rats. Restor Neurol Neurosci, 2005. 23(5-6): p. 297-302.
26. Taub, E., G. Uswatte, V.W. Mark, and D.M. Morris, The learned nonuse phenomenon: implications for rehabilitation. Eura Medicophys, 2006. 42(3): p. 241-56.
27. Wolf, S.L., D.E. Lecraw, L.A. Barton, and B.B. Jann, Forced use of hemiplegic upper extremities to reverse the effect of learned nonuse among chronic stroke and head-injured patients. Exp Neurol, 1989. 104(2): p. 125-32.
28. Mani, S., A. Przybyla, D.C. Good, K.Y. Haaland, and R.L. Sainburg, Contralesional Arm Preference Depends on Hemisphere of Damage and Target Location in Unilateral Stroke Patients. Neurorehabil Neural Repair, 2014. 28(6): p. 584-593. PMCID: PMC4128911
29. Mutha, P.K., K.Y. Haaland, and R.L. Sainburg, Rethinking motor lateralization: specialized but complementary mechanisms for motor control of each arm. PLoS One, 2013. 8(3): p. e58582. PMCID: PMC3589347
30. Mutha, P.K., K.Y. Haaland, and R.L. Sainburg, The effects of brain lateralization on motor control and adaptation. J Mot Behav, 2012. 44(6): p. 455-69. PMCID: PMC3549328

31. Mutha, P.K., R.L. Sainburg, and K.Y. Haaland, Coordination deficits in ideomotor apraxia during visually targeted reaching reflect impaired visuomotor transformations. Neuropsychologia, 2010. 48(13): p. 3855-67. PMCID: PMC3712783
32. Mutha, P.K., L.H. Stapp, R.L. Sainburg, and K.Y. Haaland, Frontal and parietal cortex contributions to

action modification. Cortex, 2014. 57: p. 38-50.
33. Mutha, P.K., R.L. Sainburg, and K.Y. Haaland, Left parietal regions are critical for adaptive visuomotor control. J Neurosci, 2011. 31(19): p. 6972-81. PMCID: PMC3107546
34. Sainburg, R.L., Laterality of basic motor control mechanisms: Different roles of the right and left brain hemispheres, in Laterality in Sports, F. Loffing, et al., Editors. 2016, Academic Press: San Diego. p. 155-177.
35. Yadav, V. and R.L. Sainburg, Handedness can be explained by a serial hybrid control scheme. Neuroscience, 2014. 278: p. 385-96. PMCID: PMC4263961
36. Sainburg, R.L., Convergent models of handedness and brain lateralization. Front Psychol, 2014. 5: p. 1092. PMCID: PMC4189332
37. Coelho, C.J., A. Przybyla, V. Yadav, and R.L. Sainburg, Hemispheric differences in the control of limb dynamics: a link between arm performance asymmetries and arm selection patterns. J Neurophysiol, 2013. 109(3): p. 825-38. PMCID: PMC3567394
38. Przybyla, A., D.C. Good, and R.L. Sainburg, Dynamic dominance varies with handedness: reduced interlimb asymmetries in left-handers. Exp Brain Res, 2012. 216(3): p. 419-31. PMCID: PMC3709262
39. Yadav, V. and R.L. Sainburg, Motor lateralization is characterized by a serial hybrid control scheme. Neuroscience, 2011. 196: p. 153-67. PMCID: PMC3199140.
40. Mani, S., P.K. Mutha, A. Przybyla, K.Y. Haaland, D.C. Good, and R.L. Sainburg, Contralesional motor deficits after unilateral stroke reflect hemisphere-specific control mechanisms. Brain, 2013. 136(Pt 4): p. 1288-303. PMCID: PMC3613707
41. Sainburg, R., D. Good, and A. Przybyla, Bilateral Synergy: A Framework for Post-Stroke Rehabilitation. J Neurol Transl Neurosci, 2013. 1(3). PMCID: PMC3984050
42. Wyke, M., Effect of brain lesions on the rapidity of arm movement. Neurology, 1967. 17(11): p.1113-20.
43. Mutha, P.K., R.L. Sainburg, and K.Y. Haaland, Critical neural substrates for correcting unexpected trajectory errors and learning from them. Brain, 2011. 134(Pt 12): p. 3647-61. PMCID: PMC3235559
44. Poole, J.L., J. Sadek, and K.Y. Haaland, Ipsilateral deficits in 1-handed shoe tying after left or right hemisphere stroke. Arch Phys Med Rehabil, 2009. 90(10): p. 1800-5.
45. Haaland, K.Y., Left hemisphere dominance for movement. Clin Neuropsychol, 2006. 20(4): p. 609-22.
46. Haaland, K.Y., J.L. Prestopnik, R.T. Knight, and R.R. Lee, Hemispheric asymmetries for kinematic and positional aspects of reaching. Brain, 2004. 127(Pt 5): p. 1145-58.
47. Prestopnik, J., K. Haaland, R. Knight, and R. Lee, Hemispheric dominance in the parietal lobe for open and closed loop movements. J. Int. Neuropsychol. Soc., 2003. 9: p. 1-2.
48. Prestopnik, J., K. Haaland, R. Knight, and R. Lee, Hemispheric dominance for open and closed loop movements. Soc. Neuroscience Abstr., 2003. 30(1).

49. Haaland, K.Y., D.L. Harrington, and R.T. Knight, Neural representations of skilled movement. Brain, 2000. 123 ( Pt 11): p. 2306-13.
50. Pohl, P.S. and C.J.Winstein, Practice effects on the less-affected upper extremity after stroke. Arch Phys Med Rehabil, 1999. 80(6): p. 668-75.
51. Winstein, C.J., A.S. Merians, and K.J. Sullivan, Motor learning after unilateral brain damage. Neuropsychologia, 1999. 37(8): p. 975-87.
52. Rapin, I., L.M. Tourk, and L.D. Costa, Evaluation of the Purdue Pegboard as a screening test for brain damage. Dev Med Child Neurol, 1966. 8(1): p. 45-54.
53. Desrosiers, J., D. Bourbonnais, G. Bravo, P.M. Roy, and M. Guay, Performance of the 'unaffected' upper extremity of elderly stroke patients. Stroke, 1996. 27(9): p. 1564-70.
54. Haaland, K.Y., P.K. Mutha, J.K. Rinehart, M. Daniels, B. Cushnyr, and J.C. Adair, Relationship between arm usage and instrumental activities of daily living after unilateral stroke. Arch Phys Med Rehabil, 2012. 93(11): p. 1957-62.
55. Haaland, K.Y. and D.L. Harrington, Hemispheric asymmetry of movement. Curr Opin Neurobiol, 1996. 6(6): p. 796-800.
56. Haaland, K.Y. and D. Harrington, The role of the hemispheres in closed loop movements. Brain & Cognition, 1989. 9(2): p. 158-80.

57. Haaland, K.Y. and D.L. Harrington, Hemispheric control of the initial and corrective components of aiming movements. Neuropsychologia, 1989. 27(7): p. 961-9.
58. Winstein, C.J., P.S. Pohl, C. Cardinale, A. Green, L. Scholtz, and C.S. Waters, Learning a partial-weightbearing skill: effectiveness of two forms of feedback [published erratum appears in Phys Ther 1997 Mar;77(3):328]. Physical Therapy, 1996. 76(9): p. 985-93.
59. Winstein, C.J. and P.S. Pohl, Effects of unilateral brain damage on the control of goal-directed hand movements. Exp Brain Res, 1995. 105(1): p. 163-74.
60. Mutha, P.K., R.L. Sainburg, and K.Y. Haaland, Coordination Deficits in Ideomotor Apraxia during Visually-Targeted Reaching Reflect Impaired Visuomotor Transformations. Neuropsychologia, 2010. PMCID: PMC3712783
61. Esparza, D.Y., P.S. Archambault, C.J. Winstein, and M.F. Levin, Hemispheric specialization in the coordination of arm and trunk movements during pointing in patients with unilateral brain damage. Exp Brain Res, 2003. 148(4): p. 488-97.
62. Pohl, P.S., C.J. Winstein, and S. Onla-Or, Sensory-motor control in the ipsilesional upper extremity after stroke. NeuroRehabilitation, 1997. 9(1): p. 57-69.
63. Tretriluxana, J., J. Gordon, B.E. Fisher, and C.J. Winstein, Hemisphere specific impairments in reach-tograsp control after stroke: effects of object size. Neurorehabil Neural Repair, 2009. 23(7): p. 679-91.
64. Sainburg, R.L., Evidence for a dynamic-dominance hypothesis of handedness. Experimental Brain Research, 2002. 142(2): p. 241-58.
65. Beebe, J.A. and C.E. Lang, Relationships and responsiveness of six upper extremity function tests during the first six months of recovery after stroke. J Neurol Phys Ther, 2009. 33(2): p. 96-103.
66. Jebsen, R.H., E.R. Griffith, E.W. Long, and R. Fowler, Function of "normal" hand in stroke patients. Arch Phys Med Rehabil, 1971. 52(4): p. 170-4 passim. Page 125
67. Jebsen, R.H., N. Taylor, R.B. Trieschmann, M.J. Trotter, and L.A. Howard, An objective and standardized test of hand function. Archives of Physical Medicine & Rehabilitation, 1969. 50(6): p. 311-9.
68. Fugl-Meyer, A.R., L. Jaasko, I. Leyman, S. Olsson, and S. Steglind, The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. Scand J Rehabil Med, 1975. 7(1): p.13-31.
69. Austin, P.C., A comparison of 12 algorithms for matching on the propensity score. Statistics in Medicine, 2014. 33(6): p. 1057-1069.
70. Lanza, S.T., J.E. Moore, and N.M. Butera, Drawing causal inferences using propensity scores: a practical guide for community psychologists. Am J Community Psychol, 2013. 52(3-4): p. 380-92.
71. Spreen, O. and E. Strauss, A Compendium of Neuropsychological tests: Administration, norms, and commentary. 2nd ed. 1988, NY: Oxford University Press.
72. Dell'Acqua, F. and M. Catani, Structural human brain networks: hot topics in diffusion tractography. Curr Opin Neurol, 2012. 25(4): p. 375-83.
73. Oldfield, R.C., The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia, 1971. 9(1): p. 97-113.
74. Kim, S.G., J. Ashe, K. Hendrich, J.M. Ellermann, H. Merkle, K. Ugurbil, and A.P. Georgopoulos, Functional magnetic resonance imaging of motor cortex: hemispheric asymmetry and handedness. Science, 1993. 261(5121): p. 615-7.
75. Perelle, I.B. and L. Ehrman, An international study of human handedness: the data. Behav Genet, 1994. 24(3): p. 217-27.
76. Wang, T.N., K.C. Lin, C.Y. Wu, C.Y. Chung, Y.C. Pei, and Y.K. Teng, Validity, responsiveness, and clinically important difference of the ABILHAND questionnaire in patients with stroke. Arch Phys Med Rehabil, 2011. 92(7): p. 1086-91.
77. Hsueh, I.P., M.M. Lee, and C.L. Hsieh, Psychometric characteristics of the Barthel activities of daily living index in stroke patients. J Formos Med Assoc, 2001. 100(8): p. 526-32.
78. Hsueh, I.P., J.H. Lin, J.S. Jeng, and C.L. Hsieh, Comparison of the psychometric characteristics of the functional independence measure, 5 item Barthel index, and 10 item Barthel index in patients with stroke. J Neurol Neurosurg Psychiatry, 2002. 73(2): p. 188-90.
79. Lin, J.H., M.J. Hsu, C.F. Sheu, T.S. Wu, R.T. Lin, C.H. Chen, and C.L. Hsieh, Psychometric comparisons of 4 measures for assessing upper-extremity function in people with stroke. Phys Ther, 2009. 89(8): p.

840-50.
80. Brown, M.B. and A.B. Forsythe, Robust Tests for Equality of Variances. Journal of the American Statistical Association, 1974. 69: p. 364-367.
81. Hintze, J.L., SOLO Statistical System: Power Analysis. Los Angeles, CA: BMDP Statistical Software, Inc. 1991.