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PROTOCOL TITLE:

Effects of device-assisted practice of activities of daily living in a close-to-normal pattern on upper extremity motor recovery in individuals with moderate to severe stroke

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STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	Devices: 1, ReIn-Hand device; 2, ACT3D robot; 3, PACT3D robot
IND / IDE / HDE #	Since both of them are NSR devices, IDE or IND numbers are not available for either of them.
Indicate Special Population(s)	☐ Children ☐ Children who are wards of the state ☐ Adults Unable to Consent ☐ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☐ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Employees
Sample Size	60
Funding Source	National Institute of Health
Indicate the type of consent to be obtained	☒Written ☐Verbal/Waiver of Documentation of Informed Consent ☐Waiver of HIPAA Authorization ☐Waiver/Alteration of Consent Process
Site	☐ Lead Site (For A Multiple Site Research Study) ☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☐Yes ☒ No
DSMB / DMC / IDMC	☒Yes ☐No

OBJECTIVES:

Up to 85% of stroke survivors have hemiparesis that affects the upper extremity (UE) on one side[1] and usually impacts the hand more than shoulder and elbow[2]. Currently, for mildly impaired stroke survivors (about 20-25%)[3], constraint-induced movement therapy (CIMT) and modified CIMT have been reported to produce significantly greater gains in hand/arm function compared to conventional therapy[4,5]. However, intervention options for a large percent of stroke survivors, who have moderate to severe impairment, are lacking, since these individuals do not meet the inclusion criteria for CIMT[6,7].

Device use has been studied to assist arm/hand function for individuals with moderate to severe stroke. Positive clinical outcomes have been reported[8-10], but the quality of the evidence is low[11]. One of the factors that impact the effects of device-assisted interventions is how the device is used. We suggest that devices should assist the practice of Activities of Daily Living (ADLs) in a way that enhances the neural activities related to 'normal' motor patterns, and minimizes undesired activities related to suboptimal compensatory movements. Most of these compensatory movements are obligatory, due to the loss of independent joint control, which is clinically called 'synergy'.

The importance of practicing ADLs has been demonstrated by previous hand/arm interventions in mildly impaired individuals[6]. However, when success in ADL tasks becomes the primary goal, individuals frequently develop compensatory movements[12] and evoke neural activities unrelated to the required movements. As demonstrated in animal models, compensatory neural activities negatively impact neuroplasticity and motor recovery[13-18]. Conversely, trainings that restrict compensation heightened ipsilesional plasticity and enhanced motor recovery[20-22], which is defined as the restoration of a back to pre-injured state at the levels of function, performance, and neural acvitivites[16,19]. This has prompted the opinion that interventions should focus on maximizing motor recovery versus task accomplishment via compensation[19].

We aim to investigate the feasibility of maximizing hand motor recovery and minimizing compensation via practicing ADLs in an anti-synergy environment in the more severely impaired chronic post-stroke population. Specifically, we propose to use devices to address 2 major issues that are commonly presented in this population: 1) inability to open the paretic hand[23,24], and 2) abnormal UE synergic movement patterns, defined as the abnormal coupling between shoulder, elbow, wrist, and fingers[23,25,26]. Recently, we developed and tested an EMG-triggered functional electrical stimulator (named ReIn-Hand) to assist voluntary hand use during the practice of ADLs and found promising preliminary results in gaining finger extension ability and UE motor function[27-30]. We also have evidence demonstrating that ACT3D robotic modulation of shoulder abduction (SABD) loading during active reaching can reduce the UE synergy both acutely and long-term[31-34]. By combining ReIn-Hand with a robot, we propose a reaching-grasping-retrieving-releasing (GR3) intervention in individuals with moderate to severe chronic stroke. This design aims to practice ADLs in an 'anti-synergy' pattern, via augmenting hand opening by ReIn-Hand and minimizing the effects of the UE synergy by the robot, to maximize potential motor recovery. We will measure not only the intervention-induced changes in clinical outcomes, but also in UE kinematics and functional and morphologic neuroplasticity to disentangle motor compensation versus recovery.

Aim 1: We will measure the intervention-induced changes in clinical outcomes. We will recruit 60 individuals with moderate to severe (10≤Fugl-Meyer≤40, and Chedoke≤4) chronic (>1 year) hemiparetic stroke, who will be randomly assigned to 2 different groups. The experimental group will receive a ReIn-Hand+robot assisted GR3 intervention, and the control group will receive a dose-matched ReIn-Hand assisted GR3 intervention without robot mediation of SABD load. All stroke participants will be examined using validated clinical assessments twice pre-intervention, post-intervention (within one week immediately after the end of the intervention, and at 3-months follow-up. We hypothesize that the experimental group will have greater improvements than those in the control group, as primarily measured by the Box and Blocks Test.

Aim 2: We will measure the intervention-induced changes in UE kinematics while performing hand opening with and without SABD load at pre- and post-intervention tests to attempt to disentangle motor compensation from recovery. We hypothesize that at post-intervention, 1) the maximal hand opening area will be increased, and less coupled with compensatory forces at the shoulder and elbow; and 2) the above

improvements will be significantly larger in the experimental group. These motor performance changes will suggest motor recovery at the performance level.

Aim 3: We will measure the intervention-induced changes in neuroplasticity. We will measure intervention-induced functional and structural changes in gray matter density (GMD) and white matter integrity (WMI) at pre- and post-intervention. We hypothesize that after the intervention both groups will have: 1) hand-opening related cortical activity shift from the contralesional to the ipsilesional hemisphere, 2) increased GMD in ipsilesional and decreased GMD in contralesional sensorimotor cortices; and 3) increased WMI in ipsilesional cortico-fugal tracks and decreased WMI in the contralesional cortico-fugal tracks, with larger changes in the experimental group compared to that in the control group. These neuroplastic changes will suggest motor recovery at the neural level.

This will be the first effort to investigate the effects of device-assisted practice of ADLs in an anti-synergic pattern, and thus close-to-normal, on UE motor recovery in individuals with moderate to severe stroke by evaluating clinical outcomes, kinematics, and neuroplasticity. If hypotheses are supported, the results may impact current clinical practice by pushing towards implementing device-assisted practice of ADLs in an anti-synergy pattern and potentially benefit a large population.

BACKGROUND:

A. Significance

A large post-stroke population exhibits poor or no voluntary control of the paretic hand[1]. In our recent survey on arm/hand function in 94 post-stroke individuals, participants reported the biggest gap between the desired and available function for the paretic hand compared to shoulder/elbow function[35]. Furthermore, from the stroke survivors' perspective, the most important factor impacting UE recovery is 'the use of the arm in everyday tasks'[36]. Unfortunately, hand interventions currently largely ignore individuals with moderate to severe stroke. Re-engaging this large population in arm/hand interventions via device assistance is of great significance.

We propose to use ReIn-Hand, a smart EMG-driven FES device, and a robot to assist this more severely impaired population to practice reaching-grasping-retrieving-releasing (GR3) training in an anti-synergy pattern. Results will be used to answer the following 3 questions with increased power:

1. Is a device-assisted intervention that targets performing ADLs in an anti-synergy pattern feasible to improve hand and arm function in individuals with moderate to severe chronic stroke? Due to practical reasons, this question has not been well studied yet. Currently, one opinion is that patients who cannot develop finger extension within the first couple of days after a stroke have limited hope for the return of hand dexterity[37-40]. However, such prediction is largely based on conventional and spontaneous recovery, which may not apply to new therapeutic methods. As we know, an initial severe neural injury usually results in motor compensation in the early phase[41], which in turn causes persistence of 'learned nonuse.' In a rat model, when this maladaptive compensation was enhanced by training the rat's non-paretic forelimb, such training not only resulted in exacerbated impairments and disuse of the paretic forelimb[14,15], but also diminished performance improvements in subsequent rehabilitative training of the paretic forelimb compared with rats that did not received 'maladaptive compensation' training[14,42,43]. These behaviors were found to be the result of increased aberrant formation of synapses by multisynaptic boutons[17], which reflects ongoing competition for survival between synapses[18,44] (i.e., 'synaptic competition'). On the contrary, restricting the non-paretic forelimb and training the paretic one leads to increased perforated synapses in peri-lesion areas, reflecting mature and efficacious excitatory synapses[45]. These previous results imply that synapses generated by increased use of paretic limb competes with the compensation-induced synapses, probably even in more severely impaired individuals. Furthermore, in order to maximize the ability to compete with compensation-induced synapsis, we need to assist practices of motor activities in an anti-synergy pattern, rather than compensatory strategies. It has been shown that behavioral manipulation impacts the neural and vascular repair (e.g., axonal sprouting[46-50], synaptogenesis[17], dentritic growth[51], astrocytic reactions[52-54],

and vascular remodeling responses[55]). Therefore, practice ADLs in an anti-synergy pattern can be critical for creating desired neural activities while minimizing undesired neural activities. Although the chronic phase is not optimum for neural repair, it diminishes the confounding factors caused by participating in various therapies as well as the spontaneous recovery. Ability for neural repair may still exist even during chronic phase, as previous results and our own preliminary results showed that even long after stroke new movement patterns can be developed in response to motor training[19, 29] and associated with the neuroplasticity similar to that was reported in mildly impaired subacute individuals following CIMT[29]. As an initial feasibility study, we choose the chronic phase that guarantees a 'worst' case situation. Answers to this question, if positive, are expected to push future related research to sub-acute or acute phase, and open a door for this large population back to intervention targeted hand function recovery.

2. Is progressively modulating shoulder abduction (SABD) load important for implementing device-assisted ADL-related intervention in more severely impaired individuals? Our lab demonstrated that increased SABD load introduced 1) increased involuntary flexion forces at elbow[25,32-34], wrist and fingers[24], 2) decreased voluntary finger extension ability[23], and 3) decreased FES-mediated hand opening[30] on the paretic UE. On the contrary, by providing appropriate SABD-load support while a subject actively lifts and reaches, even a severely impaired stroke survivor can reach in a comparable way as a healthy control subject does[34]. Furthermore, when training moderate to severe impaired chronic individuals reaching with subject- and need-specific SABD-load, they gained significant range of motion[33]. Practically, although our inclusion criteria require a minimal FES-mediated thumb-index finger distance of 4cm on the tabletop, once the subjects lift the paretic arm above tabletop, the FES assistance may not result in sufficient hand opening anymore[30], and thus may hinder the intervention progress. Furthermore, even if the ReIn-Hand can successfully open the paretic hand in the context of SABD-induced synergy, such synergy itself can cause abnormal movement patterns at shoulder and elbow, and the associated neural activities may result in non-desired synaptic competition. In short, without appropriate SABD-load supporting, an intervention can be restricted to a tabletop until a subject gains his/her ability to lifting the paretic arm against gravity without maladaptive compensation. However, restricted training on tabletop will impact the ability to transfer training to real ADL performances that usually require arm lifting. Mechanistically, the primary means to increase hand opening is via using contralateral corticospinal tracks (CST)[56]. With robotic support, we can initially lower the neural demands for driving shoulder and elbow, and reserve more residual CST resources (which are limited in stroke) for driving the hand. Therefore, implementing SABD control via robot during GR3 is anticipated to be especially important for individuals who cannot lift the paretic arm above table without compensation, which is prevalent in individuals with moderate to severe stroke[25]. For these participants, robot will create a haptic environment that allows them for the lifting and reaching in an anti-synergy pattern and enhances its associated neural/vascular activities. Specifically, we will progressively modulate SABD load in a manner where subjects are able to demonstrate 70%-80% FES-mediated opening ability in the experimental group. By comparing the intervention-induced changes resulted by practicing GR3 with and without SABD modulation, we will be able to shed a light on this question.

3. Are the intervention-induced changes in individuals with moderate to severe chronic stroke motor compensation or recovery? Both previous results from other groups and our preliminary results demonstrated intervention-induced changes in this more severely impaired chronic population[8,29,33,57]. However, whether these changes are motor compensation or recovery is still unknown. Although compensation is easier to occur, rehabilitation should urge the use of effective ways to maximize motor recovery, which refers to the restoration of a function back to a more-normal, pre-injured state[16,19] (see table 1 for the definition of 'recovery' and 'compensation' at functional, performance, and neuronal levels, respectively). Previous evidence from clinical assessments usually suggests pure compensation during the chronic phase[58]. However, post-intervention increase in the functional use of ipsilesional sensorimotor cortices and back-to-normal structural changes were also reported[29,59,60]. This discrepancy between measures at performance and neural levels may be due to the limited resolution of impairment measures, like Fugl-Meyer Stroke Assessment[61,62] (FMA), the Chedoke-McMaster Stroke Assessment[63] (CMSA),

etc. Detailed kinematic analysis of motor patterns together with non-invasive neural imaging methods are desired to quantify 'recovery' versus 'compensation'[64]. Up to now, such efforts in more severely impaired individuals are very limited. We propose to measure changes in kinematics with high resolutions (a position accuracy of 1mm and an angular accuracy at 0.02 degrees for hand opening area, and an accuracy of 0.1N for shoulder/elbow force generation), and in functional and structural neuroplasticity to shed a light on this question.

Table 1. Definitions of recovery and compensation at 3 different levels[19]

Level	Recovery	Compensation
Functional	Successful task accomplishment using limbs or end-effectors typically used by nondisabled individuals	Successful task accomplishment using alternate limbs or end-effectors.
Performance	Restoring the ability to perform a movement in the same manner as it was performed before injury.	Performing an old movement in a new manner.
Neuronal	Restoring function in neural tissue that was initially lost after injury.	Neural tissues acquire a function that it did not have prior to injury.

B. Innovation

The combined use of ReIn-Hand and robotic devices will facilitate hand opening and reduce abnormal SABD-induced synergy when practicing ADL-related activities. For facilitating hand opening, various devices have been used in interventions, including both non-EMG-driven and EMG-driven ones. Non-EMG-driven devices, like The Ness H200 (Bioness, Inc, Valencia, CA), require pushing a button (usually by the unaffected hand) to trigger the assistance[8]. This type of devices cannot provide the synchronized proprioceptive and somatosensory feedback with motor tasks. Such synchronization is preferred since it increases Hebbian learning by strengthening the involved synapses[65], and acts as a signal for axonal sprouting after cortical lesions[62]. EMG-triggered devices provide this desired synchronization. However, current available devices commonly use EMG amplitude to control repeated hand opening and/or closing at a fixed sequence, usually with the arm resting on a table. Due to the UE synergies, when a stroke user activates proximal muscles during reaching and lifting, EMG-amplitude from both finger/wrist flexors and extensors could significantly increase[24]. Therefore, amplitude based approaches cannot reliably control the hand in the context of non-tabletop activities in individuals with abnormal UE synergies[66]. Innovatively, we have designed algorithms to reduce the impact of synergic muscle activation[67], thus guaranteeing a <1% error rate in the detection of a hand close instead of an open, while keeping a >90% accuracy rate of detecting hand opening during a functional arm movement.

Although ReIn-Hand can detect hand opening in the context of synergic muscle activities, its resulted hand opening area is usually reduced with a lifted the arm[30]. Furthermore, it cannot reduce the expression of SABD-induced synergy at shoulder or elbow either. Due to these 2 issues, interventions without appropriate SABD-support will either be restricted to a tabletop, thus becoming less ADL-related, or be performed with the abnormal movement patterns caused by SABD-induced synergy. We therefore innovatively propose to combine ReIn-Hand and robot to allow individuals with moderate to severe stroke for the practice of some of ADLs in an anti-synergy movement pattern. By providing the dose-matched control group who will only get assistance from ReIn-Hand for hand opening, we will be able to investigate the importance of practicing in 'close-to-normal' pattern vs. non-controlled way.

The use of robotic-controlled kinematic measures at multiple joints will provide high resolution and accurate data to disentangle motor recovery versus compensation. Using an effective ACT3D robotic modulation of shoulder load, we have developed and validated a set of methods to reliably quantify elbow and hand control abilities under various conditions with high resolution and accuracy[31]. In order to disentangle motor recovery versus compensation for hand control, we propose to use these validated methods to quantify intervention-induced changes simultaneously in at multiple joints when maximally opening the paretic hand with or without lifting the arm in moderate to severe stroke individuals. As suggested, reduced synergy is one of the important signs of motor recovery[68]. In the proposed study, we will measure both hand-opening-induced UE synergies as quantified by coupling torques generated

at shoulder and elbow, and the impact of SABD-induced synergy on hand opening ability. When performing hand opening without lifting the arm, an intervention-induced increase or decrease in the coupling shoulder and elbow torques (i.e., hand-opening-induced UE synergy) will indicate motor compensation or recovery, respectively. Furthermore, we will quantify the impact of SABD-induced flexion synergy on the hand opening ability. A better maintaining of maximal hand opening area while lifting the arm compared to without lifting will indicate motor recovery. Otherwise, a significantly reduced hand opening when lifting will indicate motor compensation, since it reflects that when restricting the compensation from shoulder by requiring an arm lifting, an individual cannot open the hand anymore.

The use of multi-modality imaging methods will provide quantitative measures of intervention-induced neuroplasticity. Motor recovery is not only defined at functional and motor performance levels (see table 1), but also at the neural level. Up to now, cortical activities related to hand opening with and without lifting the arm following a hand related intervention have not been widely investigated yet. We have established validated methods in using high density EEG approach together with subject-specific MRI-based brain model in estimating the cortical activities with a time resolution of 1 ms and a spatial resolution of 3-5 mm[69-73]. Using this method, we have previously demonstrated abnormal cortical activities that were associated with abnormal synergies[71]. We expect that a post-intervention shift of cortical activity back to ipsilesional sensorimotor cortices will indicate motor recovery since it mimics "normal" hand-related cortical activity.

At neuronal level, motor recovery is defined as restoring function in neural tissue that was initially lost after injury[19]. If strictly following this definition, then structural repair has to occur to support it. In animal models, evidence for structural changes, such as axonal sprouting, synaptogenesis, dendritic growth, and so on, has been reported[46-54]. In human model, several groups have shown increases in gray matter (GM) density in ipsilesional sensorimotor cortices[74], along with increases in fractional anisotropy (FA) in ipsilesional corticospinal tract (CST)[75] in acute and chronic stroke individuals with mild impairments. However, since individuals with moderate to severe stroke are largely ignored in current arm/hand interventions, it is still unknown whether an arm/hand intervention for these more severely impaired post-stroke individuals will result in structural changes. Using advanced anatomical and structural magnetic resonance imaging (MRI) methods we will measure morphological changes in GM density and descending WM integrity. Different from the previous work that focused on the ipsilesional side in mildly impaired subjects, we will also innovatively quantify these structural changes in the contralesional side. This is based on our recent results that separately evaluated reticulospinal and rubrospinal tract microstructure in chronic stroke individuals with UE motor impairment for the first time[76]. Our results demonstrated that individuals with the greatest UE synergy severity and hand impairments post-stroke have the highest FA in the contralesional reticulospinal tract, a pattern consistent with increased myelination and suggestive of neuroplastic reorganization following stroke-induced compensation[76]. Using a multi-modal MRI approach, the proposed study will provide evidence for morphological neuroplasticity in this more severely impaired large population. We anticipate simultaneous structural changes in the form of a decrease in the contralesional GM density and FA, and an increase in these structural measures in the ipsilesional side. This will agree with 'synaptic competition' theory and support the motor recovery.

C. Relevant prior experience and gaps, as well as preliminary data

Aim 1: to measure the device-assisted intervention-induced changes in clinical outcomes

Both electronic and robotic devices have been used to assist arm/hand therapy in individuals with moderate-severe stroke. As a systemic review summarized, robotic-assisted interventions improved ADL scores, arm function and arm muscle strength, but the quality of the evidence was low to very low[11]. Many factors may impact the effects of device-assisted interventions. One of them may be the way to use devices. For example, although various devices have been used to facilitate the training of different joints, they have never been used in a way to assist both proximal and distal joints during the performance of an ADL. A recent large trial used 3 robots to assist 127 participants with moderate-to-severe chronic

stroke to practice horizontal reaching (the 1st 3 weeks), grasping without arm lifting (the 2nd 3 weeks), and integrating proximal and distal joints (the 3rd 3 weeks)[77]. At the end of a 12-week intervention, results of this device-assisted training was not different from usual care[77] or intensive therapy[77]. Although this intervention involved 3 robots and integrated shoulder, elbow and wrist in the last session, the intervention did not target any ADL.

The importance of practicing ADLs has been demonstrated by CIMT in mildly impaired individuals, where beneficial effects usually included motor function, arm-hand activities, and self-reported arm-hand functioning, immediately after treatment and at long-term follow-up[6]. When taking the ADL practice out of CIMT as used in forced use therapy[78-80], there is no evidence for the efficacy of constraint alone[78-80]. In more severely impaired individuals, devices have assisted the practice of ADLs. For example, Bioness H-200, a FES device, was used to assist removing items from a dishwasher in moderate chronic indiviudals[8]; and a hand robot was used for reaching and grasping objects in sub-acute mild-severe individuals[60]. These ADL-targeted interventions, all with relatively small size (N is about 10), reported better outcomes than the large size study without targeting ADL[77], and supported the importance of ADL practice in this more severely impaired population.

It is worth noting that none of previous ADL-targeted interventions support shoulder load to reduce the remarkable impact of SABD-induced synergy on function and motor patterns at distal joints[23-25,34]. When success in the ADL task becomes the dominant goal without efforts to reduce synergy, individuals frequently develop compensatory movements. One study found that CIMT improved efficiency of paretic arm movements by increasing the reliance on trunk movements[12], suggesting that CIMT promotes the refinement of compensatory movement strategies. While realizing the importance of being able to progressively use the paretic UE during ADLs, we also strive for motor recovery with the hope of breaking the bottleneck that may be caused by compensation. We propose to combine ReIn-Hand and robot to allow participants to repetitively practice reaching, grasping, retrieving, and releasing (GR3) with progressively increased challenge. We expect that this intervention will improve motor function (as we practice ADLs) and decrease impairment (as we enhance the hand opening[29] and reduce the SABD-induced synergy[33] simultaneously).

Preliminary results: Eight participants with chronic (>1-year post, mean: 11.2 years) severe stroke (UE FMA scores 10-24/66) were recruited to participate in a 20-session intervention (3 sessions/week). During each session, participants performed 20-25 trials of Reaching, Grasping, Retrieving, and Releasing (GR3) a 3cm jar with the assistance of the ReIn-Hand device. Pre, post and 3-month follow-up clinical assessments, including UE FMA[61,62], Chedoke McMaster Stroke Assessment Hand Subscale[63] (CMSA_H), grip dynamometry, the BBT[81,82], active and passive goniometrics for wrist and metacarpal phalangeal (MCP) flexion and extension (II, V fingers), the Nottingham Stereognosis Assessment[83,84] (NSA), and sensory touch thresholds using monofilaments were performed. Non-parametric Friedman tests of differences between pre- and post-intervention measures found significant changes in the BBT (λ^2=10.38 $p < .05$), passive and active range of motion (λ^2=11.31 $p < .05$ and λ^2=12.45, $p < .01$, respectively), and NSA (λ^2=6.42, $p < .05$). These results suggest that the ReIn-Hand assisted GR3 intervention may improve voluntary hand control in individuals with severe impairment following stroke.

Other considerations: 1) Dropout rate: The dropout rate for robot-assisted arm/hand training has been reported to be 45 per 1000, which is comparable to that for conventional interventions (42 per 1000)[11]. As adverse events were seldom described, assistive devices are concluded to be safe as a rehabilitation tool[11]. 2) Dosage: A home-based study used the Bioness H-200 to assist 8 moderately impaired individuals to repetitively practice a subject-selected ADL (e.g., open jar) every weekday for 8 weeks. It reported significant increases on motor function in the group who practiced 120min/session but not in the group of 60 or 30min/session[85]. Furthermore, our own preliminary results using ReIn-Hand to assist 8 severely impaired individuals to practice GR3 suggested that a dose of 60min/day, 3 weekdays for 6-7 weeks produced a significant change on the Box and Block Test (BBT), however it was not maintained on 3-month follow up[27]. Our ACT3D-mediated reaching intervention in 13 moderate-severe individuals reported significant outcomes at post-intervention test with a dose of 60min/day, 3 weekdays for 8

weeks[32]. In order to balance fatigue and intensity, we choose a dose of 90min/day, 3 weekdays for 8 weeks. This dose is stronger than that used in our preliminary interventions, but weaker than 120min/session for 40 sessions.

Aim 2: to measure the intervention-induced changes in biomechanics

To disentangle intervention-induced improvements due to motor recovery or motor compensation, quantitative measures that simultaneously quantify multi-joint kinematics with high resolution and accuracy have advantages compared to clinical assessments[19]. These kinematic measures also closely follow the validated clinical assessments such as FMA[86]. Using kinematic measures a few previous studies reported that reduced synergy was one of the important signs of motor recovery[68,87,88]. Therefore, we propose to quantify maximal hand opening area with and without lifting the paretic arm. Simultaneously, we will also measure the coupling force/distance in X, Y, Z directions generated by shoulder and elbow (see figure 1C). This will allow us to quantify the impact of SABD-induced synergy on hand opening, and impact of hand-opening-induced synergy on proximal joints. Measuring these UE kinematics before and after the two interventions have potential to provide information about underlying mechanisms that drive any potential improvements achieved by the proposed interventions.

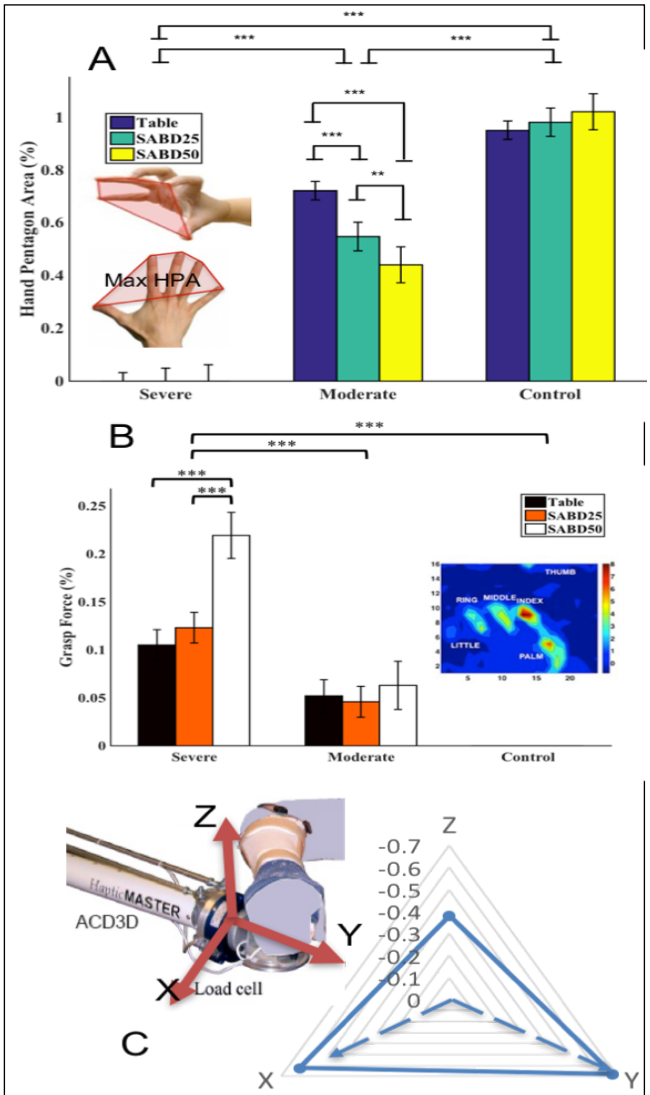

Figure 1. A) Hand pentagon area (HPA) during hand opening task in severe, moderate and control groups at table, SABD25 and SABD50 conditions. The severe group was not able to generate any measurable HPA. The subplots illustrated the HPA definition and the HPA that was used for normalization that was measured when the non-paretic hand was maximally stretched on a tabletop. B) Grasping force under thumb and fingers during opening task. When asked to perform hand opening, the severe group was actually generated flexion force, which was increased with the increased SABD load. The subplot showed an example of force measure. C) Intervention-induced relative changes in the coupling force in the X, Y, Z directions, calculated as (post-pre)/pre, during hand opening with (dashed line) and without arm lifting (solid line). All the results are negative, reflecting a reduction in coupling force after intervention.

Preliminary results

Kinematics: 36 individuals (moderate stroke: FM=26~40 N=13, severe stroke: FM=10~25 N=13, healthy control: N=10) were recruited for this study. Each participant was instructed to perform following sequent movements: 1) moving the hand to the home position; 2) resting for 1s; 3) lifting the arm off the table with a shoulder load equal to 25% or 50% of the participant's shoulder abduction maximum voluntary torque (MVT) or staying at table for 2s; 4) maximal hand opening while keeping the arm position. More details of the experimental setup and protocol can be found in our publication[23]. Hand pentagon area (HPA), defined as the area formed by the tips of thumb and fingers (see figure 1A subplot), was used to quantify hand opening ability. Forces under thumb

and fingers were recorded to quantify grasping force (see figure 1B subplot). We found that 1) in individuals with moderate stroke, increasing shoulder abduction loading reduced the ability to maximally open the hand; and 2), in individuals with severe stroke, who were not able to open the hand, involuntary grasping forces were generated and increased with shoulder abduction loading[23] (see figure 1A and 1B). Furthermore, coupling forces generated at shoulder and elbow while performing maximal hand opening with and without SABD load were recorded by the 3D load cell that was attached to the forearm orthosis. In 3 severe stroke individuals, we compared such coupling forces before and after the preliminary GR3 intervention as stated in aim 1. As shown in figure 1C, when these individuals performing maximal hand opening without SABD, the overall post-intervention coupling forces at X, Y, and Z directions (solid lines) were reduced to about 50% of that before intervention. When performing the hand opening while lifting up again 50% of a subject's SABD maximal voluntary torque, coupling forces at X and Y directions (dashed lines) also reduced about 50%. Please note for the hand opening with SABD load, the force in the Z direction was controlled by the ACT3D robot, and thus was not compared. These preliminary results demonstrated the feasibility of quantifying hand opening ability and coupling forces at shoulder and elbow with high resolution. Furthermore, results in figure 1C supported feasibility of motor recovery after the preliminary GR3 intervention in chronic stroke individuals with moderate to severe impairments.

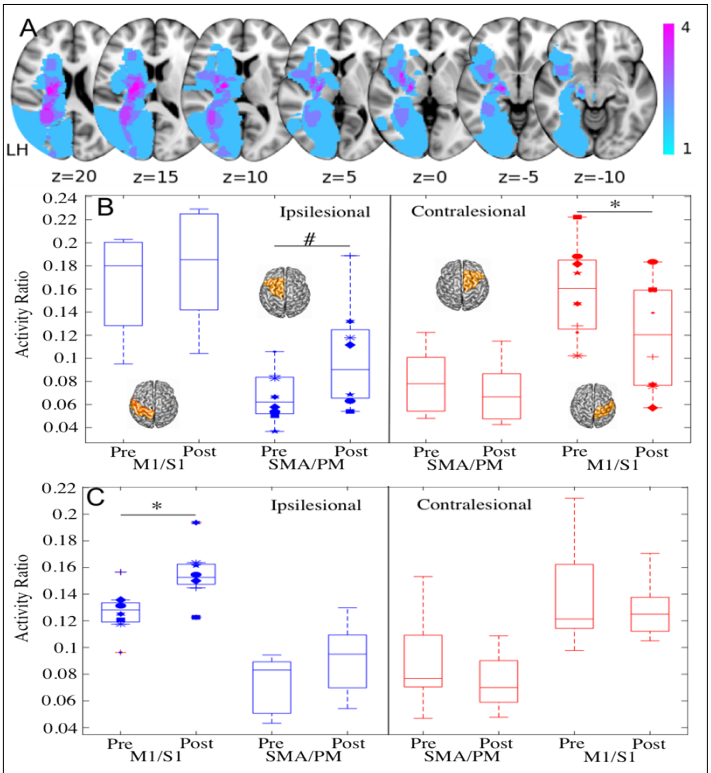

Figure 2. A) Lesion locations for the 8 subjects overlaid on axial MNI T1 slices. The color bar indicates the number of subjects with lesioned tissue in a particular voxel. LH indicates the lesioned hemisphere. B) Box plots depicting cortical activity ratio prior to and following the intervention for Hand Opening without lifting the arm; C) and with lifting the arm against 50% of SABD MVT. *p < .05, #p = .06. Individual data was plotted when p< 0.1.

Aim 3: to measure the intervention-induced changes in neuroplasticity

Aim 3A: neuroplasticity at functional level

Motor recovery is also demonstrated at the neural level. Intervention-induced neural changes have been investigated widely using animal models[89]. For instance, monkeys or rodents trained on a skilled 'reaching to grasping' task express enlarged representation of the digits of the hand or forelimb in ipsilesional primary motor cortex (M1) following training as measured by intracortical microstimulation[90,91]. The cortical reorganization underlying effective task-specific arm/hand interventions in acute and chronic stroke subjects with mild impairments support those seen in the animal literature described above. Several variations of arm/hand interventions, including CIMT, bilateral task-specific training, and hand-specific robot-assisted practice have shown cortical reorganization such as increased sensorimotor activity and enlarged motor maps in the ipsilesional hemisphere related to the paretic arm/hand[92-95]. These results suggest increased recruitment of residual resources from the ipsilesional hemisphere following training. In moderate to severe chronic stroke, hand task related cortical activity has been reported to involve contralesional or secondary motor areas[96-101], reflecting compensatory mechanisms at neural level. In these individuals, increased contralesional activity when moving their paretic arm

correlates with impairment[102,103]. Intervention-induced cortical reorganization in individuals with moderate to severe stroke was less investigated before, and thus largely remaining unknown. We propose to simultaneously measure the changes in cortical activities related to hand opening with and without SABD load while measuring the UE kinematics. We expect that hand-opening related cortical activities will shift from contralesional sensorimotor cortices back to ipsilesional side. This back to normal change will suggest motor recovery at neural level.

Aim 3B: neuroplasticity at structural level

It is widely accepted that neuroplasticity is a key factor for determining outcome[104-106]. Besides functional cortical reorganization that is proposed to study in aim 2, structural changes may also occur. In animal models, it has been reported that cortical activity changes significantly influence the targets for both local and distant sprouting axons[89,107], and thus guide structural changes. For example, in monkeys or rodents trained on a skilled reach to grasp task, in addition to functional cortical activity changes mentioned above, rapid local structural changes in the form of dendritic growth, axonal sprouting, myelination, and synaptogenesis also occur[21,108-110]. Importantly, these neural changes correspond to motor recovery following rehabilitative training in these animals[111,112]. In human model, rapid acquisitions of high-resolution anatomical 3D imaging (MPRAGE) allow for the detection of changes in gray matter (GM) density using techniques such as voxel-based morphometery[113,114]. Furthermore, the inception of diffusion tensor imaging (DTI) has allowed for researchers to identify neural tissue connectivity and is particularly sensitive to white matter (WM) morphology[115]. Together, MPRAGE and DTI measures can be implemented to detect gray and white matter changes in health, disease, and injury[115]. Using these methods, intervention-induced structural changes in subacute mildly impaired stroke individuals have been reported[74,75]. These results are largely in agreement with findings in animal models, suggesting increased synaptogenesis and/or dendritic complexity in GM, along with increased integrity of WM tissue[74,75]. However, since individuals with moderate to severe stroke are largely ignored in current arm/hand interventions, it is unknown whether an arm/hand intervention for these more severely impaired post-stroke individuals will result in structural changes. If yes, whether structural changes restore the function in neural tissue that was initially lost after injury is also a question.

To answer above questions, we will use anatomic T1 and Diffusion weighted scans to quantify GM density, a measure of dendritic complexity, and WM Fractional Anisotropy (FA), a measure of white matter integrity, before and after intervention. We hypothesize that following device-assisted GR3 interventions, moderate to severe chronic stroke individuals will show similar structural changes as observed in mildly impaired individuals, demonstrated by 1) an increase in GM density in ipsilesional sensorimotor cortices and decreased GM density in contralesional sensorimotor cortices; and 2) increased WM integrity in ipsilesional cortico-fugal tracks and decreased WM integrity in the contralesional cortico-fugal tracks. Furthermore, above changes will be at a higher level in the experimental group as compared to that of the control group.

Preliminary results

At cortical level: For the 8 individuals that participated the preliminary GR3 intervention as stated in the aim 1 preliminary result part, we also quantified the intervention-induced changes in functional cortical activity. Surface EEG data related to hand opening with and without lifting the arm were measured before and after the intervention; We then reconstructed the cortical activity (see method part for details). Reconstructed sources in the regions of interest (ROIs), including bilateral primary sensorimotor cortices (primary motor cortex (M1) + primary sensory cortex (S1)) and secondary motor cortices (supplementary motor area (SMA) + premotor area (PM)), were used to calculate the 1) cortical activity ratio (CAR), which was defined as the total current strength of one ROI normalized by the total combined strength of the 4 ROIs; and 2) a Laterality Index (LI) that reflects the relative contributions of each cerebral hemisphere to the source activity (definitions for both CAR and LI can be found in the method part). Individuals demonstrated a shift in cortical activity related to hand opening from the contralesional to the ipsilesional hemisphere following the intervention ($p<0.05$, not depicted). For the table condition, this was driven by

decreased contralesional M1+S1 activity and increased ipsilesional secondary motor cortices' activity ($p<0.05$, see figure 2B); and for the lifting condition, this back-to-normal shift was driven by increased ipsilesional M1+S1 activity ($p<0.05$, see figure 2C). The increased use of ipsilesional resources and decreased use of contralesional resources support the motor recovery after the preliminary GR3 intervention.

At the structure level: On 19 moderate to severely impaired chronic stroke individuals and 15 healthy age-matched controls, we used high-resolution DTI to quantify WM fractional anisotropy (FA) in relation to severity of arm synergy (as measured by UE FMA) and hand related motor impairments (FMA hand portion). We found that post-stroke the contralesional reticulospinal tract FA correlated significantly with both UE synergy severity ($r=-0.606$, $p=0.003$) and hand impairment ($r=-0.609$, $p=0.003$)[76] (see Figure 3). This supports the hypothesis that more severely impaired chronic stroke individuals depend more on contralesional corticobulbar pathways to compensate for the stroke-induced damage, and that these contralesional pathways lack the ability to allow further significant recovery. Furthermore, we examined structural GM changes in the 8 individuals who participated in the preliminary study as stated in aim 1 preliminary results section. Subjects displayed increased GM density in ipsilesional primary sensorimotor cortex and decreased GM density in contralesional primary sensorimotor cortex at the level of $p<0.001$[29]. These findings suggest that despite moderate to severe chronic impairments, post-stroke participants maintain ability to show GM structural changes following a ReIn-Hand assisted GR3 intervention. The ipsilesional GM density changes are similar as those reported in post-stroke individuals with mild impairment. The intervention-induced decrease in contralesional GM density has not reported before. This discrepancy may be because compensatory structural changes in contralesional side in mildly impaired individuals is not as significant as that in more severely impaired individuals. Overall, our preliminary results suggest that residual neuroplasticity in more severely impaired individuals may have the potential to support improved hand motor recovery, and such neuroplasticity may include structural changes corresponding to both inhibiting the compensatory expression and facilitating motor recovery.

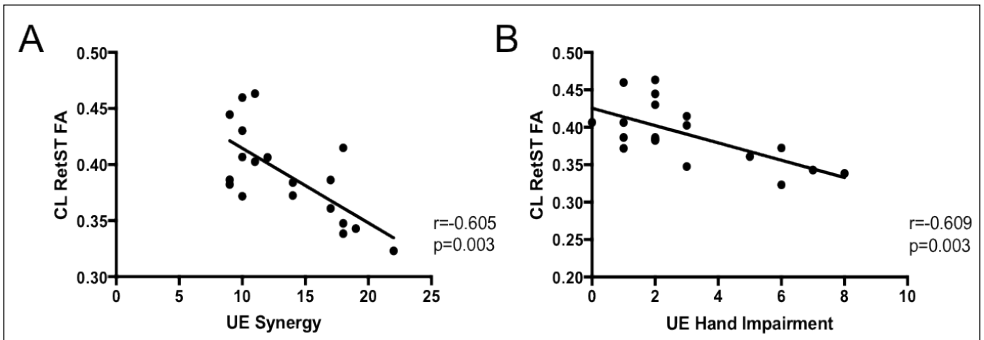

Figure 3. The correlation of contralesional reticulospinal tract FA with UE synergy (A) and hand impairment (B) on 19 moderate to severely impaired chronic stroke individuals.

STUDY ENDPOINTS:

Aim 1: to measure the device-assisted intervention-induced changes in clinical outcomes

The primary outcome measures will be the Box and Blocks Test (BBT)[82-83]. The secondary outcomes will be the Action Research Arm Test[116,117] (ARAT), Quantitative Measure of Hand Opening Area and Closing Force (QMHOC), Cutaneous Sensory Touch Threshold (CSTT) Test using Semmes-Weinstein Monofilaments, Upper Extremity Fugl-Meyer Assessment[61,62] (UE FMA), Chedoke–McMaster Stroke Assessment – Hand portion (CMSA-Hand), Sensory Assessment (Stereognosis), Motor Activity Log[122-124] (MAL), the Stroke Impact Scale (hand function domain, SIS_H)[125,126] and Revised Nottingham Sensory Assessment: Kinaesthesia Subscale (NSA)[83,84].

Aim 2: to measure the intervention-induced changes in biomechanics

The primary measure will be overall coupling in X, Y, Z directions generated by shoulder and elbow, defined as:

$$\left|\frac{\vec{Z}_{open}}{\vec{Z}_{max}}\right| + \left|\frac{x_{open}}{x_{max}}\right| + \left|\frac{y_{open}}{y_{max}}\right|,$$

where $\vec{z}_{open}$ and $\vec{z}_{max}$ are the forces measured in Z (vertically down to the floor) direction when a subject performs the maximal hand opening on the virtual table provided by the robot, and when a subject the maximally pushes down to the virtual table, respectively. Similarly, x_{open} and x_{max}, as well as y_{open} and y_{max} are the moving distances in X and Y directions, respectively, when a subject performs the maximal hand opening on the virtual table, and when a subject the maximally moving in X and Y directions, respectively.

The secondary outcome measure will be hand opening ability, defined as the ratio between (hand-open-aperture with 50% subject's maximal shoulder abduction ability) and (hand-open-aperture with table support). When hand opening is not available even with the arm resting on the table, the hand opening ability will be defined as -1x$\frac{Gripping\ force_{SABD50}}{Gripping\ force_{table}}$.

Aim 3: to measure the intervention-induced changes in neuroplasticity
Aim 3a: **at functional level**
The primary measure will be Laterality Index (LI = (I-C)/(I+C)), where 'I' and 'C' are the current density strengths from the ipsilesional and contralesional sensorimotor cortices (i.e., combined primary sensorimotor and secondary motor cortices).

The secondary measure will be cortical activity ratio $CAR = \sum_1^n S_n / \sum_1^m S_m$ for each of the 4 regions of interest (ROIs), where 'S' represents the current density strength of one of the nodes, and n and m represent the number of nodes in one of the ROIs and whole sensorimotor cortices, respectively. Specific regions of interest (ROIs) include bilateral primary sensorimotor cortices (primary motor cortex (M1) + primary sensory cortex (S1)) and secondary motor cortices (supplementary motor area (SMA) + premotor area (PM)). The cortical activity ratio reflects the relative strength from one ROI as normalized by the total combined strength of the 4 ROIs.

Aim 3b: **at structural level**
The primary measure will be voxel-based changes in gray matter density (GM density) caused by intervention.

The secondary measures will be fractional anisotropy of the corticospinal and corticobulbar tracts from the both hemispheres.

STUDY INTERVENTION(S) / INVESTIGATIONAL AGENT(S):

This study investigates the feasibility of regaining hand opening ability in individuals with moderate to severe stroke using device-assisted intervention. Three devices will be used during intervention:

1), The ReIn-Hand device: it combines intelligent detection software, “the ReIn-HAND platform”, and an FDA approved (510(k)# K021100) electrical stimulator (Empi 300 PV, Vista, CA, or E-Wave Zynex Medical, Inc, Englewood, CO). The ReIn-Hand platform wirelessly and simultaneously records surface EMG activities from up to 8 upper limb muscles, including: deltoid, biceps brachii, triceps, extensor communis digitorum, extensor carpi radialis, flexor digitorum profundus, flexor carpi radialis, and abductor pollicis. The device then uses novel signal processing methods to detect hand opening with or without arm movements based on EMG features[118]. Once hand opening is detected, a signal is sent to trigger ES to assist with paretic hand opening (see the supplementary material for a video of the use of this device). The stimulation electrodes will be placed over finger/wrist extensors; and the stimulation will have following parameters: amplitude sufficient for maximal hand opening without discomfort, biphasic waveform, frequency 50Hz±20% and 300us pulse width, ‘ON’ duration=3s.

2), The arm coordination training 3D robot (ACT3D): ACT3D is a customized research equipment. It comprises a modified force-controlled HapticMASTER (HM) robot (MOOG, The Netherlands) integrated with a Biodex experimental chair (Biodex Medical Systems, Shirley, NY). The ACT3D allows for low inertia movements in three dimensions and can provide a virtual effect of gravity that can be enhanced or reduced by imposing forces along its vertical axis (i.e., Z-axis). ACT3D robot will be used to measure the forces and moments during the performance of required motor tasks for quantifying the intervention -induced changes in biomechanics (i.e., experiments for aim 2), and for providing controlled Z-force during determining the intervention parameters when PACT3D is not available. Please note that both PACT and ACT3D provide the same control of force in the Z-direction.

3) The passive arm coordination training 3D robot (PACT3D): The PACT-3D generates the required endpoint forces using a novel spring system that is passive in nature but can be controlled using an actuator to set the desired force. Same as ACT3D, it also allows for low inertia movements in three dimensions and can provide a virtual effect of gravity that can be enhanced or reduced by imposing forces along its vertical axis (i.e., Z-axis). However, PACT3D is portable, lighter, and with even lower inertia as compared to ACT3D robot. PACT3D robot will be used to providing controlled Z-force during interventions for the experimental group.

***Device Handling*:** The above three devices will be stored in the laboratories in the Department of Physical Therapy and Human Movement Sciences at 645 N Michigan Ave, Chicago, IL 60611. Use of one or two of these devices will be only on consented participants by authorized investigators that are approved by IRB.

PROCEDURES INVOLVED:

Introduction

The general hypothesis is that the ReIn-hand and robot assisted GR3 intervention will result in improved hand/arm motor recovery in individuals with moderate to severe stroke, as measured by clinical outcomes, UE kinematics, and neuroplasticity, and such improvement will be larger in the experimental group (trained with ‘ReIn-Hand + robot’) as compared to the control group (trained with ‘ReIn-Hand only’). The control factors are time (3 levels: pre, post, and 3-month follow up intervention) and group (2 levels).

Aim 1: to measure the device-assisted intervention-induced changes in clinical outcomes

Experimental Design

A double-blinded, 2-baseline, randomized experimental design will be used (see Figure 4).

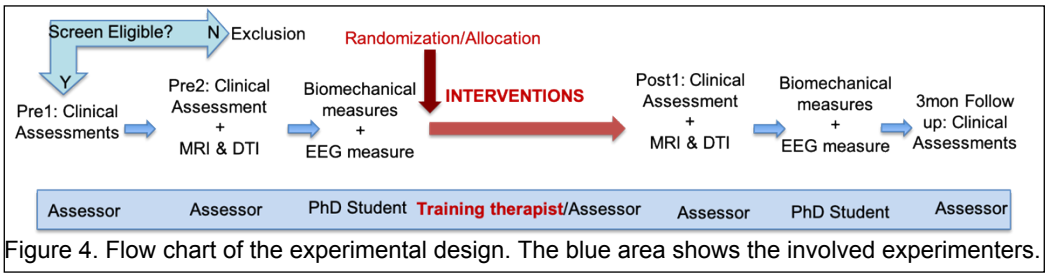

Figure 4. Flow chart of the experimental design. The blue area shows the involved experimenters.

Power analysis and Subjects: Using our preliminary results, we will power the study to detect differences in the BBT of a minimum effect size of 0.9 at a significance level of 0.01. Based on our power analysis with consideration of dropout rate at 7%, we will recruit 60 (with 56 valid data in the end) adults (age: 21-81 years) with chronic (>1 year since stroke) UE hemiparesis resulting from unilateral stroke to participate in this study. Main inclusion criteria include: 1) moderate to severe UE impairments with UE FMA 10-40[119]; 2) moderate to severe hand impairment with CMSA_H scores between 0 and 4[120]; 3) ability for the ReIn-Hand device to generate an opening of ≥4 cm between thumb and the index finger. Exclusions include: 1) inability to follow 3 step commands[121]; 2) difficulty in sitting for 3 hours by self-report; 3) Chemodenervation: Botox injection within the last 6 months; 4) incompatible with MRI scan, and 5) any contraindications to electrical stimulation (e.g. pregnancy, seizure in the past 6 months, implanted pacemaker). More detailed inclusion/exclusion criteria can be found in the inclusion and exclusion criteria section.

Randomization: Following consent, the blinded assessor will determine the eligibility using the inclusion and exclusion criteria. Participants who satisfy study criteria will undergo baseline assessments 2 times prior to randomization/allocation. The training therapist, who will not be blinded, will assign participants to the experimental or control group via a computer-generated random, permuted, randomization sequence, with consideration of the balance in FMA scores of the 2 groups.

Interventions:

Research participants will participate in a 24-session intervention, ~2 hours per session, 3 sessions per week, for 8 weeks in total. The individuals involved with the administration of the intervention are two training physical therapists (Training PT) and two training technicians. Research participants, training PTs, and clinical evaluators will be blind to group assignment.

For all sessions and both groups, research participants will be seated in a seating system with straps across the chest and waist to prevent unwanted trunk movement. The training technicians will stretch the paretic UE for up to 15 minutes. The ReIn-Hand device will be attached to the paretic upper extremity (UE) and then positioned at a home position in 75° shoulder abduction (SABD), 30° shoulder flexion, and 60° elbow flexion.

The first session will be a 'parameter adjusting session', during which the training PT will determine training parameters, including: 1) SABD load, 2) target(jar) distance, 3) jar width, 4) jar weight, 5) jar height, and 6) jar orientation. These training parameters will be established both on the table condition and using a robot. The robot modulates the supporting force in Z-direction applied to the arm while participants are required to lift the arm, thus changing the shoulder abduction (SABD) load. The SABD load will be set as the maximum load that allows the participant to: actively reach the target distance, and achieve a ReIn-Hand mediated hand opening no less than 4 cm between the tips of the thumb and index fingers. After establishing SABD load, all the additional parameters (#2-6) will be set, first with the established SABD load as following: 2) Target distance is 70% of the distance of the max reach of the paretic UE when fully supported on a frictionless table created by the robot; 3) Jar width will be increased in 0.5 cm increments, by adding padding around the jar, to the max width the participant can achieve with the ReIn-Hand; 4) Jar height (i.e., distance from the lowest part of the jar to the surface of the table) will be set as 2 cm increments to the max height the participant can successfully (and painlessly) reach the jar; 5) Jar orientation (i.e., the relation of the long axis of the jar to the table surface) will be set as 2° increments to the maximum amount that allows the participant to successfully grasp the jar; and 6) Jar weight will be increased in 100 g increments, stopping if the participant

experiences pain or cannot lift the jar. The Training PT will then repeat the steps 2-6 to determine these parameters (#2-6) under table condition; i.e., this time without robot support and thus using a height-adjustable table.
Once the intervention parameters are set, the training technician will guide the participant to perform the GR3 activities using these parameters. Participants in the experimental group will be trained using the robot. Their forearm of a participant will be attached to an orthosis, which will be firmly attached to the robot. Participants in the control group will be trained on a regular height-adjustable table. All training sessions will consist of 40 trials (about 1 hour) of 'reaching-grasping-retrieving-and- releasing' (GR3) activities, which include: 1) Reaching towards a plastic jar (diameter=3cm, weight=30g when empty); 2) Activating finger/wrist extensor muscles to trigger the ReIn-Hand device, which in turn assists the opening of the paretic hand while reaching; 3) Grasping the jar; 4) Retrieving the jar to the home position and placing it on the table; and 5) Releasing the jar. In order to avoid fatigue, a resting time of 20-30 seconds will be provided between trials.
Participants in the control group will be encouraged to perform GR3 activities with the arm above the table. The experimental group will get the necessary SABD support via the PACT3D and thus be required to reach above the table. Both groups will be provided with the same verbal cues. A successful trial requires the completion of all five tasks required during one trial: Reaching towards a plastic jar, triggering the ReIn-Hand device, grasping the jar, retrieving the jar to the home position and placing it on the table, and releasing the jar. An unsuccessful trial is defined as the failure to complete one of the five tasks during one trial. The result of each of the 40 trials will be recorded by the training technician. The Training PT will review the training performance after each session to determine if adjustment of parameters is necessary for the next session. If a participant successfully completes 30/40 trials in 2 successive sessions, the training PT will re-adjust all the parameters at the following session in order to progressively challenge the participant. New parameters then will be implemented by the training technician during the following session.

Outcomes: Clinical assessments will be completed by the blinded assessor at baseline (2 times), within one week of the end of treatment, and 3 months after completion of treatment. The primary outcome measures will be the Box and Blocks Test (BBT)[82-83]. The secondary outcomes will be the Action Research Arm Test[116,117] (ARAT), Quantitative Measure of Hand Opening Area and Closing Force (QMHOC), Cutaneous Sensory Touch Threshold (CSTT) Test using Semmes-Weinstein Monofilaments, Upper Extremity Fugl-Meyer Assessment[61,62] (UE FMA), Chedoke–McMaster Stroke Assessment – Hand portion (CMSA-Hand), Sensory Assessment (Stereognosis) (SAS), Motor Activity Log[122-124] (MAL), the Stroke Impact Scale (hand function domain, SIS_H)[125,126] and Revised Nottingham Sensory Assessment: Kinaesthesia Subscale[83,84] (NSA).

In addition, the blinded assessor will also perform the following outcome measures weekly: BBT (about 5 mins), QMHOC (~10 mins), and CSTT Test (~15 mins).

Aim 2: to measure the intervention-induced changes in biomechanics
Experimental Design
Before and after one week of the intervention, we will measure UE kinematics and surface EEG data during maximal hand opening with and without SABD load. All the participants will be seated in a Biodex seating system with straps across the chest and waist to prevent unwanted trunk movement (Figure 7). The arm will be

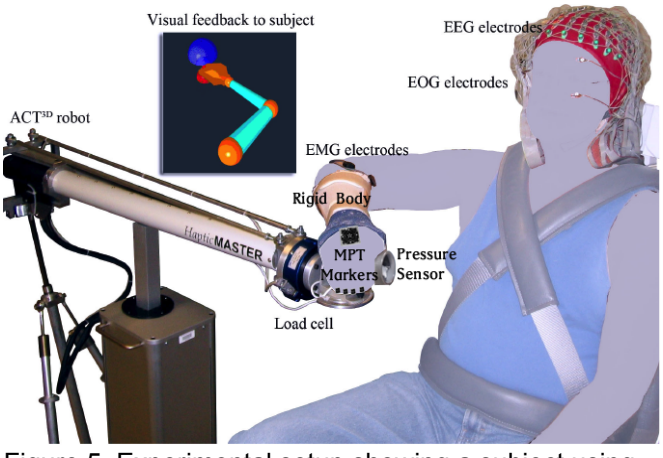

Figure 5. Experimental setup showing a subject using the robot while high-density EEG and surface EMG signals will be simultaneously recorded. Visual feedback will be displayed on a computer screen.

positioned at a home position in 85° shoulder abduction and 40° shoulder flexion, and 90° elbow flexion with the forearm in mid pronation-supination. The hand will rest on a cylinder, attached to forearm orthosis that is covered with an array of pressure sensors (Pressure Profile Systems, Inc., Los Angeles, CA 90045). Furthermore, a six-axis load cell (JR3, model 45E15A) will be used to measure forces generated by shoulder and elbow. These forces will also be used by our admittance controlled robot (Moog-FCR B.V., the Netherlands) and to measure the weight of the arm. Subsequently, 160 EEG active electrodes (Biosemi, Inc, Active II, Amsterdam, The Netherlands) will be mounted on a stretchable fabric cap based on a 10/20 system. Skin under each of the electrodes will be prepared to keep the impedance below 5 kΩ for the duration of the experiment. Additionally, the positions of EEG electrodes on the subject's scalp will be recorded with respect to a coordinate system defined by the nasion and pre-auricular notches using a Polaris Krios handheld scanner and reflective markers (NDI, Ontario, Canada). This will allow for coregistration of EEG electrodes with each subject's anatomical MRI data. EMG signals of the intermediate head of deltoid (IDL), flexor digitorum profundus (FDP) and extensor digitorum communis (EDC) will be recorded using surface electrodes. Furthermore, 5 markers at the size of (9x9 mm) with unique optical features will be placed on the tip of the thumb and the 4 fingers, with another marker on the back of the hand for reference purposes. Position (with an accuracy of 1mm) and angular (with an accuracy at 0.02 degrees) information of fingertips will then be captured by 2 registered portable Moire Phase Tracking cameras (Metria Innovation, Inc., Wauwatosa, WI). This will allow for the kinematic tracking of the hand pentagon area during the various motor tasks. The total setup time will be about 2 hours. A lunch break (0.5-1 hour) will follow setup to avoid fatigue.

Before implementation of the main protocol, we will first measure a subject's maximal voluntary torque (MVT) in the direction of SABD, maximum finger grasping forces of the paretic UE, and maximum HPA of the non-paretic hand when the hand is maximally stretched on a table top (see figure 4A subplot) for normalization purposes. During the main protocol, participants will be instructed to move to the home position (the blue ball in figure 7) first, which will trigger the home position to change to a green ball. This sign will indicate the experimenter to inform the subject the start of a trial. Participants will then be asked to relax in the home position for 5-7s and then to self-initiate the required motor task for 2s, with the eyes looking at the paretic hand without blinking or eye moving. Maximal hand opening will be performed in 2 conditions, including table condition where the arm will rest on the haptic table, and a SABD load condition where the arm will be lifted above table against 50% of his/her SABD MVT. Real time visual feedback of the participant's SABD torque will be provided to the experimenter only to control the performance of the task. A set of 60-70 trials will be collected for each condition. These trials will be collected in blocks of 20-30 trials in a random order. Rest periods of at least 15 seconds between trials and ~10 min between blocks will be included to avoid fatigue. The total duration of data collection is about 3 hours.

We will simultaneously collect EEG, EOG and EMG data (all at 1KHz, Active II, Biosemi, Inc., Amsterdam, The Netherlands, or), forces generated by shoulder/elbow (at 256 Hz, ACT3D robot, Moog-FCS, The Netherlands, or PACT3D robot, Hankamp Rehab BV, Enschede, The Netherlands), 3D-position of fingertips (at 180Hz, MPT Series 2, Metria Innovation Inc. Milwaukee, WI 53213, Or at 250 Hz, trakSTAR, Northern Digital Inc. Waterloo, Canada) and the pressures under the thumb and fingers (at 512Hz, Pressure Profile Systems, Inc., Los Angeles, CA 90045). We will also measure subject's upper- and forearm lengths.

Aim 3: to measure the intervention-induced changes in neuroplasticity

Aim 3A: Experimental Design

We will use the EEG data collected during aim 2 to investigate the neuroplasticity at functional level.

Aim 3B: Experimental Design

Within two weeks prior to and following the intervention, scans will be performed at Northwestern University's Center for Translation Imaging on a 3 T Siemens Prisma scanner with a 64-channel head coil. Structural T1-weighted scans will use an MPRAGE sequence (TR=2.3s, TE=2.94ms, FOV

Visit #	Experimental Sessions	Duration (hours)
1	Pre-clinical Assessment 1	1.5
	Pre-intervention MRI + DTI	1
2	Pre-clinical Assessment 2	2
	3D Scanning	1
3	Pre-intervention biomechanical + EEG	6
4-27	Intervention (24 sessions) Weekly Measures	1.5-2
28	Post-clinical Assessment 1	1.5
	Post-intervention MRI + DTI	1
29	Post-intervention biomechanical + EEG	6
30	1-month post-intervention	1.5

256x256mm^2) producing an isotropic voxel resolution of 1x1x1 mm^3. DTI will use spin-echo echo-planar imaging (TR=5s, TW=85ms, matrix size=150x150, FOV=225x225mm, number of slices=120) producing an isotropic voxel resolution of 1.5x1.5x1.5 mm^3. The sequence will consist of diffusion weighting of 1000s/mm^2 in 60 different directions, and 8 scans with no diffusion weighting (b=0 s/mm^2).

Statistical Analysis, expected outcomes, Potential Problems and Alternative Strategies

A voxel-wise General Linear Model will be applied using permutation-based non-parametric testing with Threshold-Free Cluster Enhancement[127] to detect changes in GM density and FA integrity following the intervention and any group differences. Voxel-based threshold of changes in GM density and FA integrity will be set at $p < .05$ Family-wise error corrected.

Alternative methods

We expect that about 50% of our participants will have severe impairment, and thus cannot open hand voluntarily. In this case, we will measure the pressure under thumb and fingers before and after intervention.

Other methods, such as functional MRI, can also measure the functional cortical reorganization. We choose to use high-density EEG approach, since robotic control of SABD loading will be used. This will allow us to measure both SABD-induced and hand-opening-induced synergies simultaneously at multiple joints and at cortical level. Furthermore, the EEG method is robust to the head movements that are commonly associated with the shoulder abduction. We have more than 15-year experience in using high-density EEG with robot and thus confidant that this approach can give us reliable measures.

Alternative diffusion analysis methods such as probabilistic and deterministic tractography allow the recreation of WM tracts through user-specified regions of interest. We choose to instead use TBSS since tractography methods may lose validity when passing through lesioned tissue, whereas we can mask out lesioned tissue and restrict our analysis to healthy tissue in TBSS while using a whole-brain analytical approach. Additionally, it solves the issues of non-ideal registration and the arbitrary nature of choosing spatial smoothing extent in analyzing white matter connectivity by using fine-tuned nonlinear registration and subsequent projection onto a static white matter tract representation (i.e. mean FA skeleton).

STUDY TIMELINES

Table 2 lists the duration of an individual's participation in the various study sessions.

	clinical session follow-up	
31	3-month post-intervention clinical session follow-up	1.5

Table 2. The expected duration of participation for study sessions

We will actively recruit subjects from the Clinical Neuroscience Research Registry (N=700+). We will conduct interventions for 7-8 subjects per year. Considering a dropout rate of 7%, we expect that we will recruit and collect data on 60 subjects. This will result in 56 (with 28 for each of the groups) valid data by the end year of the proposed study. We will keep making enrollment effort, until we successfully collected data on 56 participants.

INCLUSION AND EXCLUSION CRITERIA

The target age range of stroke participants is 21-80 years old. We plan to recruit 60 individuals with chronic hemiparetic stroke who have some shoulder and elbow control, but lack basic hand function, to participate in the cross-sessional experiments of this study (Upper Extremity (UE) FMA[61,62] in the range of 10-40/66, Chedoke McMaster Stroke Assessment Hand Subscale[63] (CMSA_H) stage of the hand section <=4).

Subjects who have had a stroke will be selected from the Clinical Neuroscience Research Registry, maintained by the Physical Therapy and Human Movement Sciences department at Northwestern University and the Shirley Ryan AbilityLab (Former Rehabilitation Institute of Chicago - RIC), containing more than 700 members. Stroke survivors residing in the Chicago area who wish to participate in the study will be considered as well. Tests of the ReIn-Hand system will be performed on the paretic arm of individuals with stroke. Clinical assessments will be performed on both the paretic and non-paretic arm. The following inclusion criteria will be applied to the stroke participants: 1) Age between 21-80; 2) Paresis confined to one side, with substantial motor impairment of the upper limb and some residual voluntary movement (UE FMA in the range of 10-40/66, CMSA_H stage of the hand section <=4); 3) Capacity to provide informed consent; 4) Ability to elevate their limb against gravity up to at least 75 degrees of shoulder flexion and to generate some active elbow extension; 5) Ability to achieve ReIn-Hand device assisted hand-open at the level of thumb-to-index finger distance ≥4 cm; 6) MRI compatible; 7) Discharged from all forms of physical rehabilitation, 8) Intact skin on the hemiparetic arm, 9) Ability to tolerate sitting for no less than one hour, and 10) Montreal Cognitive Assessment (MoCA) score >=23.

Exclusion criteria are: 1) Motor or sensory impairment in the non-affected limb; 2) Any brainstem and/or cerebellar lesion; 3) Severe concurrent medical problems (e.g. cardiorespiratory impairment, uncontrolled hypertension, inflammatory joint disease); 4) History of neurologic disorder other than stroke (PD, ALS, MS, TBI, peripheral neuropathy); 5) Any acute or chronic painful condition in the upper extremities or spine, indicated by a score ≥5 on a 10-point visual analog scale; 6) Using cardiac pacemaker, implanted cardioverter defibrillator, neurostimulation system inside brain or spinal cord, bone growth box fusion stimulation; 7) Seizure in the past 6 months; 8) Severe upper extremity sensory impairment indicated by absent sensation on the tactile sensation subscale (light touch and pressure items) of the Revised Nottingham Assessment of Somato-Sensations[84,85] (score<4); 9) Chemodenervation: botulinum toxin, Myobloc, phenol block, or dysport injection to any portion of the paretic UE within the last 6 months, or phenol/alcohol injections <12 months before participation; 10) Unable to passively attain 90 degrees of shoulder flexion and abduction, measured using a goniometer based on adapted methods; 11) Flexion contractures larger than 45 degrees in the elbow, wrist, metacarpophalangeal joints (MCP) and interphalangeal joints (IP); 12) Pregnant or planning to become pregnant; and 13) Participating in any experimental rehabilitation or drug studies; 14) Inability to attend intervention sessions 3 times a week during 8 weeks, as well as assessments/evaluations and follow up; 15) UE musculoskeletal impairment limiting function prior to stroke, 16) currently using oxygen, and 17) upper limb amputation.

While most inclusion criteria will not rule out the potential participation of Registry Members, the greatest impacting criteria is the FMA and the ability of opening hand with the aid of the electric stimulation

device. We anticipate that a minimum of 40% of Registry members (n=700) will be of the moderate to severe levels described above and appropriate for participation.

PARTICIPANT POPULATION(S)

Accrual Number:	Category/Group: (Adults/Children Special/Vulnerable Populations)	Consented: Maximum Number to be Consented or Reviewed/Collected/Screened	Enrolled: Number to Complete the Study or Needed to Address the Research Question
Local	60/0/0	200/60/80	56
	0		
Study-wide	0	0	0
	0		
Total:	60/0/0	200/60/80	56

RECRUITMENT METHODS

Once funded, we will immediately start to work on the proposed study. Subjects who have had a stroke will be selected from the Clinical Neuroscience Research Registry, maintained by the Physical Therapy and Human Movement Sciences department at Northwestern University and the Shirley Ryan AbilityLab (Former Rehabilitation Institute of Chicago - RIC), containing more than 700 members. In the registry, basic information, like phone number, address, contact email, onset time of stroke, and so on, is listed. Stroke survivors residing in the Chicago area and have other available information satisfying our inclusion/exclusion criteria will be contacted by phone or email for recruitment (wording of the phone and email has been attached).

In addition to the Clinical Neuroscience Research Registry, the study will be listed on The New Normal (TNN) Match and ResearchMatch. Both are web-based recruitment portals offered by the Center for Clinical Research, a center in the Northwestern University Clinical and Translational Sciences Institute.

Stroke survivors residing in the Chicago area who wish to participate in the study will be considered as well. Flyers will be distributed in rehabilitation centers. In most cases, these subjects are referred by participants who are already recruited.

COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES

Participants will be paid $20 per hour for participation in this study, with $10 from NIH support and the other $10 from Physical Therapy and Human Movement Sciences departmental funds. If your session lasts less than 1 hour, your participation time will be compensated as 1 full hour. If you are here for more than one hour, your participation time will be compensated as the nearest half or full hour, whichever is closer. If the experiment continues through lunch time, we will provide a quick lunch at the laboratory.

Participants will be given reimbursement for public transportation expenses or parking fee in Northwestern Medical School parking lots (located at 321 E. Erie St. or 222 E. Huron St.) where a parking voucher will be provided for your free parking when you drive here. If a cab or rideshare car (Uber or Lyft) is needed, we request the participant to contact lab staff to confirm that the fare can be covered before scheduling pickup. If using the rideshare program Lyft, the Lyft trip will be booked by a research team member through the Lyft application on your behalf. Since it will be booked through a Lyft Concierge

account that has been set up by the Department of Physical Therapy and Human Movement Sciences, there is no cost to the participant. If using a cab or Uber, reimbursement will be paid by check and a receipt is required.

Reimbursement and payment will be submitted to the accounting department on a weekly basis. Typically, the accounting department will mail you a check 4 weeks after receiving the payment request.

The Accounting Services at Northwestern University will be given your name, address, and Social Security Number in order to issue a check for your study participation. Study payments are considered taxable income and reportable to the IRS. A Form 1099 will be sent to you if your total payments are $600 or more in a calendar year.

WITHDRAWAL OF PARTICIPANTS

Possible reasons for removal include changes in participant health conditions, changes in experimental inclusion/exclusion criteria, or other unpredictable conditions.

Participants are free to choose to stop being in the study at any time. Already collected data may not be removed from the study database. An investigator may review study data related to the participant collected prior to the participant's withdrawal from the study, and may consult public records, such as those establishing survival status. If a participant wants to withdraw their data for the further use in our research, we will request they write a letter with signature to the PI of this study Dr. Yao.

RISKS TO PARTICIPANTS

Performing different movements using the arm: The repeated movements may result in minor muscle soreness, fatigue and muscle spasms. However, our protocols include many rest periods that should significantly reduce the risk of these adverse effects.

Surface electrodes: The self-adhesive surface electrodes used to record muscle activity may produce minor irritation of the skin. The possibility of irritation will be minimized by cleaning the skin with alcohol before and after application of the electrodes.

Using Electrical stimulator: If the intensity progressively increases during the contraction period, then risk of muscle tear or injury is minimal. If a high intensity is applied, participants will experience high levels of soreness. We will use the 300 PV Complete Electrotherapy System or E-Wave, both are FDA approved, clinically safe device. The stimulation configuration, expect the stimulation intensity, will be pre-set up by clinicians. The clinician will also determine a suggested range of intensities, and setup the maximal stimulation intensity to protect users. When using at home, the individual with stroke will adjust and determine the required stimulation intensity on daily based on the suggested range of intensities from the clinician, with the maximal stimulation intensity pre-set by the clinician.

Taking MRI: This study uses structural and diffusion-weighted magnetic resonance imaging (MRI) to look at the brain. These structural and diffusion-weighted MRI are types of scans that use magnetic fields and radio waves to make a picture of the brain and will allow us to look at the anatomy and structure of the brain, including lesioned tissue and tracts. Some people cannot have an MRI because they have some type of metal in their body. For instance, if a participant has a heart pacemaker, artificial heart valves, metal implants such as metal ear implants, bullet pieces, chemotherapy or insulin pumps or any other metal such as metal clips or rings, they cannot have an MRI. During this test, the subject will lie in a small closed area inside a large magnetic tube. Some people are scared or anxious in small places (claustrophobic). The MRI scanner makes loud banging noises while taking a measurement, so either ear plugs or specially designed headphones will be used to reduce the noise.

POTENTIAL BENEFITS TO PARTICIPANTS

We cannot promise any benefits to participants from taking part in this research. However, the literature supports the use of an EMG-driven electrical stimulator (ES) device, which ReIn-hand is in this category, in the treatment of the hemiplegic wrist and forearm. Please note, such benefits are based on statistical data, may not apply to all the participants, and may not continue after the research has ended.

DATA MANAGEMENT AND CONFIDENTIALITY

Efforts will be made to limit the use and disclosure of personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete secrecy. Organizations that may inspect and copy information including the IRB and other representatives of this institution.

Involvement in this research study may result in a loss of privacy, since persons other than the investigator and research team might view study records. Unless required by law, only the following people can review study records and they are required to keep personal information confidential:

- Authorized members of the Northwestern University workforce, who may need to see information, such as administrative staff members from the Office for Research, Office for Research Integrity and members of the Institutional Review Board (a committee which is responsible for the ethical oversight of the study),
- Representatives of the study sponsor, the National Institute of Health
- Representatives of Food and Drug Administration (FDA), and Office for Human Research Protections (OHRP)
- Registries or other research-related databases: the results of your examinations will be kept in a central computer or data registry at the NU Department of Physical Therapy and Human Movement Sciences. These results will be stored by research identifier code for privacy of records and your records will only be accessed by the investigators listed for this study.

The results of this study may also be used for local and regional scientific and healthcare conference presentations, as well as peer-reviewed scientific and medical journal papers. If individual results are discussed, participant identities will be protected by using a study code number rather than a name or other identifying information

The sponsor, monitors, auditors, the IRB, the Northwestern University Office for Research Integrity, the US Office of Research Integrity (ORI), the US Office for the Protection of Human Research Protections (OHRP), the US Food and Drug Administration (FDA) may be granted direct access to medical records to conduct and oversee the research.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS

Data analysis plan

Aim 1: to measure the device-assisted intervention-induced changes in clinical outcomes

We will first compare the 2 baseline scores in each of the subjects. If no significant differences were found on baseline scores, they will be averaged and taken as pre-intervention measures. Otherwise, a 3rd baseline assessment will be conducted. In the case that no stable baseline scores can be found, the subject will be excluded. Then, a two-way (time points: pre, post, 3-month, and groups: experimental and control) mixed-effects model will be conducted on ARAT, FMA, BBT, CMSA_H, MAL, SIS_H and NSA scores. If any significant effect is found, a post-hoc Bonferroni test will be used to compare the means with correction of type II error of multiple comparisons. We expect to see post-intervention improved

scores on ARAT, FMA, BBT, CMSA_H, MAL, SIS_H and NSA in both groups, with the experimental group having greater improvements than that in the control group.

Aim 2: to measure the intervention-induced changes in biomechanics

Hand opening ability: An HPA is defined as the sum of the areas of three triangular areas, formed by the thumb and two fingertips, $HPA = S_{\Delta TIM} + S_{\Delta TMR} + S_{\Delta TRL}$, where S_{Δ} denotes the triangular area, T, I, M, R, L are abbreviations for thumb, index, middle, ring and little fingers (Figure 1A). HPA is shown to be an effective measure in evaluating hand opening ability[30], and will be used as the primary measure in the present study to quantify hand opening. All participants will be asked to rest their hand on the cylinder prior to the trial and the resting HPA formed by the initial hand posture on the cylinder will serve as baseline. The HPA will be baseline corrected to zero while the hand is relaxed on the cylinder and then normalized to the maximal HPA. Maximal HPA will be measured when the non-paretic hand is placed on a flat surface with maximal finger abduction (see figure 1A subplot). Peak HPA value will first be identified during the hand opening period, and then an averaged HPA over a 100ms time window, centered at the peak value, will be calculated as the HPA for one trial during a certain abduction condition. In the case of generating closing force when opening (as shown in our previous publication[23]), the grasping forces will be calculated as the sum of the forces generated by the thumb and fingers (Figure 1B subplot). To quantify the grasping forces, the peak value during the hand grasping period will be first identified, and then an averaged grasping force over a 100ms time window centered over the peak value will be calculated as the grasping force for one trial. The maximal grasping forces of the paretic hand will normalize the grasping force measured during opening.

Coupling forces generated by shoulder and elbow: Forces/moments generated by shoulder and elbow in the Z directions, as well as the distance in X and Y directions will be measured. Measurements in each direction within each of the conditions (i.e., table and SABD50 conditions) will then be averaged cross trials, separately. We are interested in the intervention-induced changes in coupling movements, defined as $(Mpost - Mpre)/Mpre$.

A three-way repeated measure of ANOVA with mixed model will be used to determine whether SABD load, time (pre, midtreatment, post, 3m and 6m followup), group, and/or their interaction explains the measured changes in HPA, the grasping forces, coupling movements, separately. Data will be first examined to determine the presence of outliers (if found, will be removed) and to test for normal distribution (if found, will be corrected) using Shapiro-wilk test. Post hoc comparisons with the Bonferroni adjustment will be adopted to compare within-subject differences. Statistical significance will be set at $p<0.05$.

We expect that 1) the GR3 intervention will increase the post-intervention HPA (or reduce the grasping force if no HPA can be detected); 2) the post-intervention coupling movements at shoulder and elbow during hand opening will be decreased; 3) the impact of SABD-induced synergy on HPA will be reduced in the posttest. Result #1 will reflect the gained hand opening ability and #2-3 will imply the improved motor recovery, while results in an opposite trend will imply motor compensation. Furthermore, we expect that greater improvement will be found in the experimental group as compared to that in the control group, suggesting the importance of practicing ADLs in 'close-to-normal' pattern.

Aim 3: to measure the intervention-induced changes in neuroplasticity

Aim 3A: at the cortical level

For the EEG data, trials beyond 95% confidence intervals for maximum velocities, maximum accelerations, and trajectory path position or with eye/muscle movement artifacts in the EEGs will first be removed. For the remaining trials, the onset of EMG activity will be detected off-line to align EEG signals in individual trials for ensemble averaging across trials for each of the conditions, separately. Averaged EEG signals from -2000 ms to +200 ms, with 0 denoting the onset of EMG, will be imported into the CURRY software environment (Compumedics Neuroscan Ltd., Charlotte, NC) for low-pass

filtering with a cutoff frequency of 70 Hz and baseline correction. Cortical activity from -700 to +50 ms will then be reconstructed using an inverse method (Low Resolution Electromagnetic Tomography[128-133]) based on a subject-specific boundary element method model. Possible sources will be located on a cortical layer with 3 mm distance between each node. Although the inverse calculation will be performed over the whole cortex, only the activity in bilateral sensorimotor cortices will be further analyzed. Specific regions of interest (ROIs) include bilateral primary sensorimotor cortices (primary motor cortex (M1) + primary sensory cortex (S1)) and secondary motor cortices (supplementary motor area (SMA) + premotor area (PM)).

Our primary interest is to investigate the shift of cortical activity. Therefore, we will use the estimated current density strengths to calculate a Laterality Index (LI = (I-C)/(I+C)), where 'I' and 'C' are the current density strengths from the ipsilesional and contralesional sensorimotor cortices (i.e., combined primary sensorimotor and secondary motor cortices). LI reflects the relative contributions of each cerebral hemisphere to the source activity, with a value close to +1 for an ipsilesional source distribution and -1 for a contralesional source distribution. As the secondary measure, we will quantify a cortical activity ratio $CAR = \sum_1^n S_n / \sum_1^m S_m$ for each of the 4 ROIs, where 'S' represents the current density strength of one of the nodes, and n and m represent the number of nodes in one of the ROIs and whole sensorimotor cortices, respectively. The CAR reflects the relative strength from one ROI as normalized by the total combined strength of the 4 ROIs.

Statistical analysis: A three-way mixed model will be used to determine whether SABD load, time (pre, post), group, and/or their interaction explains the measured changes in LI, and CAR, respectively.

We expect that the post-intervention LI will be more positive with increased CAR in the ipsilesional activity and decreased CAR in the contralesional activity. Furthermore, we expect that greater improvement will be found in the experimental group as compared to that in the control group, suggesting the importance of practicing ADLs in 'close-to-normal' pattern.

Aim 3B: At the structure level

To calculate GM density, anatomical T1 data will be analyzed with FSL-Voxel Based Morphometry (VBM) 1.1 (http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html; Oxford University, Oxford, United Kingdom)[134] using FSL tools[135]. First, T1 images for participants who have left hemisphere lesions will be flipped to ensure the lesions of all subjects are in the right hemisphere. The T1 images will then be brain-extracted using the Brain Extraction Tool and segmented into GM using FAST4. The resulted GM partial volume images will be aligned to Montreal Neurological Institute (MNI) 152 standard space using the affine registration tool FLIRT and averaged to create a study-specific gray matter template. Subsequently, individual GM partial volume images in native space will be nonlinearly registered to this template using FNIRT, modulated to correct for local expansion or contraction due to the non-linear component of the spatial transformation, and then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm.

To calculate the integrity of the white matter, the FSL software library[136] will be used for processing of raw diffusion imaging data. The images will be skull-stripped, each diffusion weighted condition will be linearly registered to the b=0 s/mm^2 to minimize subject motion artifacts, and all data will be subsequently corrected for eddy current distortions for preprocessing. The diffusion tensor parameters will be calculated from the preprocessed diffusion data to generate fractional anisotropy (FA) maps that will be used to perform tract-based spatial statistics (TBSS). All FA maps will be linearly and then non-linearly registered to the FMRIB58_FA in Montreal Neurological Institute's (MNI) standard space using FNIRT. A mean FA image will be created from all individual FA images and thinned to generate a common group WM skeleton which represents the centers of all tracts common to the group. A FA threshold will be applied at 0.2 to minimize potential WM / GM partial volume effects. All FA images will be projected onto the common group skeleton for subsequent statistical analysis.

Plan for securing the data

All of the collected data are for research purposes only, and data will be kept in strict confidence. With the exception of the form needed to collect participant contact information required for the success of the study, all remaining data collection forms are designed so that only the study identification number appears as an identifier. Data collection paper forms will be kept in a locked, secure file cabinet at the PI's office at Northwestern University. Electronic data collection forms will be secured in an encrypted study folder stored on the server provided by the Feinberg School of Medicine at Northwestern University. Access to the server is regulated and monitored by the PI and only qualified study personnel authorized by IRB. The PI, with support from the project manager, will monitor compliance with IRB and HIPAA regulations. No identifiable information will be given to any unauthorized person without permission from the subject. The consent form will include statements required by the Northwestern IRB regarding information disclosure requirements (e.g. NIH, FDA audits, etc).

All data will be merged and stored on the server provided by the Medical School of Northwestern University. The database will be secured with password protection. The informatics manager will receive only coded information that is entered into the database under those identification numbers. Electronic communication with outside collaborators will involve only unidentifiable information. All information published on papers or presented at conferences will be identified as a number without identification of subject personal information.

The link between the study identification numbers and identifying information (e.g., name, address, age, telephone numbers and email addresses) will be kept separate from the dataset. Only the research study staff has need (and necessary access) to cross-reference files such as when it is necessary to contact a participant for monthly check-ins, scheduling follow-up appointments and/or clarification of survey answers (e.g., interpreting hand-written comments).

Data Quality Control

All study staff will be trained on all aspects of the study – including data monitoring, quality and security. The PI or study staff will review all data collection form on an ongoing basis for data completeness and accuracy as well as protocol compliance.

Data monitoring efforts will include monitoring and review of all self-reports and clinical measures data collection forms for completeness. We will contact participants for clarification if returned paper or electronic self-reports are incomplete or if handwriting is illegible.

We will also use this contact opportunity to schedule follow-up appointments and remind participants about upcoming study appointments. We will closely monitor all data and conversations with participants for any reporting of adverse events as noted above. Dr. Yao will regularly create and review reports on eligibility, screening, recruitment, retention, reasons for ineligibility, declining participation and withdrawals. Information from these reports and monitoring activities will allow for effective and efficient identification of protocol deviations and troubleshooting that may or may not require modification to the produce, testing protocol or standard operating procedures.

Data quality will be safeguarded by careful review of all incoming data for completeness. All data in paper format will be double-entered in the data set. All online captured data will be reviewed by two different research team members.

Dr. Yao will check data quality reports to describe missing, erroneous, and inconsistent data to ensure that the protocol is followed, protocol deviations are tracked, and a high quality of data is maintained. Further, double entry of data will be conducted.

Data quality will also be guaranteed by the creation of and adherence to standard operating procedures such as key operating procedures, protocol review and administration, IRB approval and continuing review processes, adverse event reporting procedures, data storage and management, and emergency procedures in our Lab. The operations manual for our Lab includes policies and standard operating procedures for data, lab and clinical security, handling of hazardous materials and emergencies, and how to use shared core resources such as NUCATS, the Quantitative Data Sciences Core, and all software required for the study.

Each study undertaken at our Lab has a unique study protocol manual, which will be checked and approved by IRB at Northwestern University before recruiting subjects. All the protocols have data collection forms for each of the designed experiments/surveys, which list all the steps that will be checked while conducting the study. Research staff members undergoing training will have the chance to observe an experienced team member in the clinic for a data collection session. The research staff trainee will then be observed by the experienced team member to ensure their eligibility for participating.

Finally, in accordance with Northwestern University IRB requirements, all research team members are required to complete training certification in human subjects' research ethics through the online CITI (Collaborative Institutional Training Initiative) certification program - a leading provider of research education content. Northwestern University also requires certification from the National Health Institute's online "Protecting Human Research Participants" (which can be accessed at the following url: http://phrp.nihtraining.com/users/login.php). Northwestern University's IRB requires staff orientation on all safety and standard operating procedures to conduct research in the clinical environment. All of these elements will ensure a high quality of the study data as well as a consistent and comprehensive approach practiced by all research team members.

Data security will be ensured by adherence to all operating procedures, study protocol, and research training requirements as noted above. The data will be secured in paper and/or electronic format as described above. Data required to review for eligibility screening will be kept in the locked storage cabinet in the PI's office. The link between the study identification numbers and identifying information (e.g., name, address, age, telephone numbers and email addresses) will be kept separate from the dataset. Only the research study staff has need (and necessary access) to cross-reference files such as when it is necessary to contact a participant for scheduling follow-up appointments and/or clarification of survey answers (e.g., interpreting hand-written comments).

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS

To ensure the safety of participants, the data monitoring committee (DMC) will periodically evaluated the data collected regarding both harms and benefits. The data monitoring committee (DMC) will composed of the PI of this study and 2-3 independent monitors. The DMC will review safety data, such as adverse events (AE) reported by telephone calls or written case reports via letter or email, either by participants or by the experimenters. The DMC will also review efficacy data, such as the clinical assessments before and after the intervention.

The frequency of data review for this study differs according to the type of data and can be summarized in the following Data Review Table:

Table 2. Data Review Table

Data type	Frequency of review	Reviewer
Subject accrual (including compliance with protocol	When N=4*n; N is the total number of finished subjects, and n=1~15 which is expecting	DMC

enrollment criteria)	resulting in a Quarterly frequency.	
Status of enrolled subjects, as of date of reporting	Quarterly,	DMC
Adherence data regarding study visits and intervention	Quarterly,	DMC
AEs and rates (including out of range values)	Quarterly,	DMC
Severe AEs	Per occurrence	DMC, NICHD

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into questions the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial. The PI will include an assessment of futility in the annual progress report to NIH and will consult with the study monitors to assess the impact of significant data loss due to problems in recruitment, retention, or data collection.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

Steps that will be taken to protect participants' privacy interests

During this study, medical history and clinical assessments will be performed at baseline, middle of the intervention, post the intervention, and 3 months after the end of the intervention, i.e., follow up test. However, all of the materials collected are for research purposes only, and data will be kept in strict confidence. Access to these files will be limited to authorized research team members. All data generated in this study will be identified with an identification code unique to the subject. Confidentiality will be ensured by use of these identification codes. No information will be given to any unauthorized person without permission from the subject, except: 1) if necessary to protect participant's rights or welfare (for example, if they are injured and need emergency care or when the Institutional Review Board monitors the research or consent process); or 2) if required by law.

A database will be used to store/manage all the electronic data. This database will be secured with password protection. The informatics manager will receive only coded information that is entered into the database under those identification numbers. Electronic communication with outside collaborators will involve only unidentifiable information. All information published on papers or presented at conferences will be identified as a number without identification of subject personal information.

Subject's feeling at ease

Subjects who choose to be in this study will be informed that they have the right to be treated with respect, including respect for the decision whether or not to continue or stop participating in the study. All examinations and procedures will be thoroughly explained to each subject to ensure subjects feel at ease with the questions, examinations, and procedures involved. Subjects will be informed that if at any point they feel uncomfortable about answering any questions on any questionnaires or surveys, they will not be required to answer that question. Subjects will be informed that they are free to choose to stop being in the study at any time, and that choosing not to be in this study or to stop being in this study will not result in any penalty or loss of benefit to which they are entitled. Specifically, the choice not to be in this study will not negatively affect the right to any present or future medical treatment.

Subject's medical record access

The research staff from Northwestern University will obtain a release from the patient, if we need to access medical records of the subject.

COMPENSATION FOR RESEARCH-RELATED INJURY

Minimal risk is when the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. The proposed research is greater than minimal risk. In the event of research-related injury, subjects will not be compensated for medical care required because of an untoward outcome resulting from participation in the research study. Subjects should seek medical treatment through his or her doctor or treatment center of choice.

As stated in the consent form: “If you become ill or get injured as a result of this study (medications, devices or procedures), you should seek medical treatment through your doctor or treatment center of choice. You should promptly tell the study doctor about any illness or injury. The researchers will not pay for medical care required because of a bad outcome resulting from your participation in this research study. This does not keep you from seeking to be paid back for care required because of a bad outcome.”

ECONOMIC BURDEN TO PARTICIPANTS

Taking part in this research study will not lead to any costs to participants.

CONSENT PROCESS

We will obtain Written Documentation of Consent (HRP-592), a copy of consent has been attached, from all subjects.

During phone/email recruiting, basic information of the consent will be already explained to the subjects. Upon request, a copy of consent form will be emailed or mailed to the subjects. If not heard from the potential subjects, a follow up phone or email may be provided.

All of the involved studies will be conducted at Department of Physical Therapy and Human Movement Science (PTHMS), Northwestern University (address: 645 N Michigan Ave, Suite 1100, Chicago, IL 60611). On arrival to PTHMS for data collection, subjects will undergo a more detailed orientation to learn about the study protocol. One of the research team members will answer questions related to the study. Once subjects confirm his/her full understanding of the consent form, he or she will sign the informed consent. A copy of signed consent will be given to subject.

If there is a significant change to the research protocol or if there is new information that may alter an individual’s willingness to participate in the research, subjects will be provided an updated informed consent document and consent will be reobtained.

Non-English Speaking Subjects, minors, and cognitively impaired subjects will not be enrolled.

PROTECTED HEALTH INFORMATION (PHI AND HIPAA)

When choosing to take part in this study, subjects are giving us the permission to use his/her personal health information that includes health information in the medical records and information that can identify him/her. Health information we may collect and use for this research includes:

- Name
- Street Address
- Telephone number
- Date of Birth
- Information from a physical examination including only: blood pressure reading, upper extremity range of motion, strength, and functional movement assessment.
- Medical record related to stroke, and any potential conditions that may impact eligibility for MRI scan.
- Social Security Number - needed for the Accounts Payable Department at Northwestern University in order to issue the study stipend and for the medical records department of

most hospitals to identify the medical record file.
- 3D movement analysis of the arm during reaching/grasping tasks.

QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE

The feasibility of recruiting

Subjects who have had a stroke will be selected from the Clinical Neuroscience Research Registry, maintained by the Physical Therapy and Human Movement Sciences department at Northwestern University and the Shirley Ryan AbilityLab (Former Rehabilitation Institute of Chicago - RIC), containing more than 700 members. Stroke survivors residing in the Chicago area who wish to participate in the study will be considered as well.

While most inclusion criteria will not rule out the potential participation of Registry Members, the greatest impacting criteria is the upper limb motor impairment level (evaluated by Upper Extremity (UE) Fugl-Meyer Stroke Assessment [61,62] in the range of 10-40/66, Chedoke McMaster Stroke Assessment Hand Subscale[63] (CMSA_H) stage of the hand section <=4) and the ability of opening hand with the aid of the electrical stimulator device. We anticipate that a minimum of 40% of Registry members (n=700) will be of the moderate to severe levels described above and appropriate for participation.

Two experienced research physical therapists (RPTs), each using 5% of their efforts, will supervise research staff actively recruit subjects during the first 4 years of this project. This will guarantee an enrollment of 15 subjects per year.

The time that you will devote to conducting and completing the research

Dr. Yao, the PI, will spend 20% of her effort on conducting and completing the research. Drs. Dewald, Sullivan and Ingo will each spend 5% effort. Drs. Carmona and Drogos will spend 35% of their effort on this study.

Facilities and resources

The facilities and other resources available at Northwestern University include everything needed to undertake and complete the proposed research successfully. The appropriate personnel, laboratories, and existing equipment are in place.

Laboratory: The Department of Physical Therapy and Human Movement Sciences (PTHMS) includes eight laboratories, each approximately 500 sq. ft. in size. We will be using three of these laboratories to perform our research. One of the laboratories contains height-adjustable tables, comfortable chairs and cabinets to conduct the proposed tests. The other 2 labs, which are shielded rooms, contain the latest in robotic technology, 3 surface EMG recording systems, 1 active portable EEG/EMG system, and 2 wireless EEG/EMG systems.

Clinical: The NU PTHMS is affiliated with the Shirley Ryan AbilityLab and Northwestern Memorial Hospital (NMH). Both hospitals have stroke, spinal cord injury, and head trauma wards as well as a large outpatient facility. Subjects chosen for the research component of this proposal belong to our 700+ outpatient participant database and the Clinical Research Registry (CRR) maintained through Shirley Ryan AbilityLab. The proximity to the Shirley Ryan AbilityLab and NMH, as well as access to the CRR, contributes substantially to the recruitment of research participants and, thus, the potential success of the proposed study.

Computer: The NU PTHMS maintains a large computer simulation laboratory including the latest PCs, a 100 core PSSC labs cluster computer, as well as installed analysis software (Matlab, CURRY, Analyzor, Cortech, FMRIB Software Library (FSL)) for EEG/EMG/MRI/DTI data processing, source reconstruction and musculoskeletal modeling purposes. Furthermore, Northwestern University, Feinberg IT department provides a minimum one Terabyte of desktop mountable storage for research purpose to

guarantee the safety of the research data. The combination of these information technologies contributes to the potential for success by assuring both efficient data handling and optimal communication among members of the research team.

Office: The PTHMS investigators working on this project have their own offices at NU. Furthermore, the PTHMS department will provide administrative support. These facilities assure that the PI and the immediate research team will have the necessary space in which to formulate experiments, analyze results, and prepare manuscripts for publication.

Other Resources:

Machine Shop: The NU PTHMS also maintains a machine and electronics shop (800 sq. ft.) that is available to construct and build custom equipment under the direction of the department engineer. The machine shop has been expanded to include the latest in computer-controlled milling devices, a large electronic bench, aluminum welding equipment, and a brand-new lathe. This equipment allows us to manufacture new parts for ReIn-Hand device as needed and repair/upgrade broken parts or electronics. The availability of this machine shop provides a valuable resource for on-demand fabrication, alteration, and repair of hardware used in our experiments.

HD Video-conferencing facilities: NU-PTHMS has 3 HD videoconference rooms (400 sq. ft.) that house brand new HD conference systems with an 80-inch touch screen TVs, which allows for effective communication with external collaborators.

Quality of research team members:

The PI, Dr. Yao has more than 15-year experience in exploring the neuromechanisms underlying the dysfunction of the upper extremity (UE) following stroke, evaluating the feasibility of restoring UE function using various novel rehabilitation techniques. She has led the pilot study using brain computer interface for detecting the intention of grasp and release in individuals following stroke (NIH UL1 RR025741 subproject), as well as the development of an EMG-driven functional electronic stimulation for reliable and intuitive control of the paretic hand (ReIn-Hand) during functional arm activities following stroke (HHS grant 90IF0090-01-00, formerly DOE NIDRR H133G120287). Dr. Yao is an expert in EEG-based neural imaging. She has also accumulated experience in experimental design for collecting and processing biomechanical data.

The Co-investigators are well-established investigators in their fields. Dr. Dewald has more than 20 years of experience in the quantification of abnormal synergies (i.e. loss of independent joint control) and developing new quantitative robotic intervention methods in acute and chronic hemiparetic stroke subjects. Dr. Sullivan has been involved in the clinical care of stroke survivors for 30+ years. She has been engaged in research focusing on testing rehabilitation interventions using appropriate standardized measurement tools. She has also been involved in using electrical stimulation to treat stroke since 1988; and participated in several clinical trials. Dr. Ingo has a strong background in biophysics and MR imaging. He is well versed in structural MR imaging and sequence development in this field. Dr. Ingo will lead the analysis, as well as the design of the MR sequences for Aim 3 of this study.

The two research physical therapists Drs. Carmona and Drogos are both licensed Physical Therapists, and have been previously involved in the preliminary interventions using both ReIn-Hand and/or ACT3D for 15 years. All the members in the research team have valid CITI training certificates. They have all read the IRB. We have weekly meetings to make sure everyone knows their specific duties.

STUDY-WIDE RECRUITMENT METHODS

Once funded, we will immediately start to work on the proposed study. Subjects who have had a stroke will be selected from the Clinical Research Registry (CRR), maintained by the Physical Therapy and

Human Movement Sciences department at Northwestern University and the Shirley Ryan AbilityLab (Former Rehabilitation Institute of Chicago - RIC), containing more than 700 members. In the registry, basic information, like phone number, address, contact email, onset time of stroke, and so on, is listed. Stroke survivors residing in the Chicago area and have other available information satisfying our inclusion/exclusion criteria will be contacted by phone or email for recruitment (wording of the phone and email has been attached).

In addition to the Clinical Research Registry, the study will be listed on The New Normal (TNN) Match and ResearchMatch. Both are web-based recruitment portals offered by the Center for Clinical Research, a center in the Northwestern University Clinical and Translational Sciences Institute. Stroke survivors residing in the Chicago area who wish to participate in the study will be considered as well. Most of cases, these subjects are referred by participants who are already recruited.

Flyers will also be used in recruitment. These flyers will be disseminated in person or via email or through social media to resource organizations and stroke support groups in the Chicagoland area.

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