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Development of a Portable Synergy Resistant EMG-driven FES Device for Intuitive Control of Grasp And Release During Functional Arm Activities Following Stroke

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A. Importance of the Problem

A.1. Target population and need

A.1.1. Target population

The target population of this development is individuals impaired by moderate to severe stroke. Stroke, which affects approximately 795,000 people annually, is currently the third ranking cause of death and one of the leading causes of disability in adults[2].

Since innovative scientific research and improved medical techniques have increased the life span of stroke survivors, the incidence and mortality rates of stroke have decreased. However, the number of individuals permanently disabled by stroke continues to increase. Sensorimotor deficits and restricted mobility are among the more common problems following stroke. Studies of stroke survivors six months post-stroke and greater than 65 years of age indicate that 50% experience persistent hemiparesis and 26% were dependent in activities of daily living[3]. The majority of stroke survivors report that impaired upper extremity (UE) function, especially the hand, is a major problem[4]. At 3 months post-stroke **only** 20% have normal arm function[5]. The trend toward increasing numbers of stroke survivors living with disability suggests that more attention needs to be directed towards investigating methods to regain the lost function by reducing the residual impairments and secondary complications associated with stroke.

Years of research results suggest that the intensity and functionality of practice appear to be critical elements of successful interventions to improve hand function[6-14]. Distal arm function seems critical to successful integration of the arm into routine daily activities. Individuals with moderate to severe arm impairment often lack hand function; and despite proximal arm movement they typically do not incorporate the affected arm in function. The evidence for critical rehabilitation parameters of intensive task-based functional practice and the reality of that a large number of stroke survivors lack sufficient arm movement to engage in this type of practice creates a clear gap and unique challenge to rehabilitation professionals. Therefore, hemiparetic stroke survivors who have some shoulder and elbow control but lack of basic hand function, i.e., the paretic hand cannot even perform the most basic function like grasp and release, are the targets of this development proposal (Fugl-Meyer Motor Assessment Scores for UE of 10-40/66).

A.1.2. The need

The need is to fill the identified gap, and thus creating a chance for our target population regaining their UE function. Unfortunately, for the severely affected UE, the evidence for conventional therapy on regaining meaningful hand function is poor. Furthermore, due to the shortened inpatient rehabilitation stays and reduced funding for outpatient rehabilitation, therapists may be forced to focus less on the use of the UE[15]. All these requirements and realities point out that we need an assistive device that allows our target population to Reliably and Intuitively use their HAND (ReIn-HAND) during therapy and at home during daily functional arm activities. However, currently there is no such an assistive device available, mainly due to the lack of a real time platform that can reliably detect a user's intention (see the review of current assistive devices

in section 1.1.2). The development of such a platform combining with a right assistive device would regain basic hand function and be highly beneficial to this population.

We have identified four specific requirements (needs) for this real time platform: 1) a non-invasive interface providing control for the most basic hand function, i.e., grasp and release; 2) an intuitive control meaning that the control signal comes from intent of the subject for moving the paretic hand; 3) a safe and reliable detection allowing the usage of the paretic hand during functional arm activities; and 4) clinical utility including portability, individualized configuration, easy setup and low-cost.

In addition, due to shortened inpatient rehabilitation stays and reduced funding for outpatient rehabilitation, therapists have been forced to focus less on the use of the upper extremity[15]. It is not uncommon for stroke survivors to find that once they are ready to work on arm recovery, there is no service available or they are no longer eligible[16]. Barriers like limited resources, transportation, assistance, etc. make a compelling argument for a device that is easy-to-use, low-cost, and thus employable at home.

Finally, although commonly we believe that recovery plateaus at ~12 months post-stroke, there are cases reporting arm/hand function recovery after intensive task-specific intervention in chronic stroke survivors[17,18]. It is therefore proposed that a plateau in motor performance should be re-interpreted as a cue to implement new therapy, such as using home-based task-specific device-mediated therapy, rather than cease it[19]. The proposed device will enable us to test whether such a therapy can improve basic hand and as a consequence upper extremity function in individuals with moderate to severe stroke. If positive, the results can benefit large population of stroke survivors.

A.2. Beneficial impact for stroke survivors

The majority of stroke survivors report that impaired UE function, especially the hand, is a major problem that results in significant functional deficits, often leading to total disuse[4]. Currently there is no effective intervention that can restore basic hand function for individuals with moderate to severe stroke. The current proposal seeks to demonstrate that the combination of an intelligent detection, the ReIn-HAND platform, and an artificial control device, 'RECLIAM' electrical stimulator, will allow for possibility of using the paretic hand and arm during activities of daily life for this population. Although many different hand-movement aid devices are available on the market now, none of them meets all the requirements identified previously (see the next chapter for review for the currently available devices). If successful, this proposal will provide a much-needed scientifically-based rehabilitation platform, accessible for use in the clinic and home, both for assistive and therapeutic purposes to regain hand/arm function following stroke. Such a platform will have a great impact on current neuro-rehabilitation patient management by providing the ability to deliver effective interventions.

Given that the concepts embedded in the proposed ReIn-HAND real time platform have been shown to be effective to increase arm/hand function, the commercial viability of this development proposal is substantial. Improvement in functional usage of the impaired upper limb in stroke survivors, through the use of an assistive device incorporating ReIn-HAND,

may have a direct positive impact on their self-image, life satisfaction, interaction with family and environment, and re-integration into society.

B. Design Of Development Activities

B.1. Development Plan

B.1.1. Background and Literature Review

The loss of basic hand function control following stroke --- physiological reasons, rehabilitation and possible solutions

Hand impairment is one of the leading causes of major, long-term disability following stroke. A number of factors contribute to the hand impairment, including abnormalities of muscle tone (identified as spastic hypertonia or spasticity), muscle weakness, and disturbances of muscular coordination (abnormal muscle and torque synergies). An individual with moderate to severe stroke usually experiences difficulty in activating hand muscles, especially wrist/finger extensors[20-22]. Another commonly observed change in EMG activation following stroke is an increased coactivation between antagonist and agonist muscles[23-25]. Reflex coupling between proximal and distal muscles of the upper limb has also been well reported[26-29]. More prominently, studies in both primates[30-32] and human subjects[22,33] indicate wrist/finger flexors are usually overly activated followed stroke, causing hand release to be even more difficult than grasp.

Although the pathophysiology behind all above features is not fully understood, we believe it is primarily due to the loss of corticospinal tract (CST) innervation of relevant motoneurons, and an increased reliance on brainstem pathways. Among the different brainstem pathways, the reticulospinal tract (RST) is the only tract that has been found to innervate distal muscles. In monkeys, RST has been shown to innervate both proximal and distal muscles[30-32] particularly facilitating shoulder abductors and arm flexors and suppressing extensors ipsilaterally[34-37]. This innervation pattern is equivalent to the aforementioned abnormal flexion synergy, which is expressed as obligatory coupling between shoulder abductors and elbow/wrist/finger flexors in the paretic upper limb following stroke. Because of this, the reticulospinal tract (RST) is NOT able to provide adequate hand control, which makes the CST the main descending pathway that provides reliable and adequate hand control.

Following moderate to severe stroke, the amount of CST innervation is limited. Furthermore, the residual CST may not be available for hand-control due to the increased inhibition from the non-lesioned hemisphere[38-40] and possibly also from the adjacent motor areas[41] that control other parts of the paretic arm, such as the shoulder and elbow. We believe the intensive functional usage is one of the key issues for a joint to win the competition for the residual CST resources. Therefore, the loss of the access to remaining CST resources from the hand may be further amplified by 'learned non-use,' a phenomena wherein an individual with stroke virtually learns to function without (not use) the paretic limb. Over time, the individual "learns not to use" the paretic hand, which may further exacerbate the loss of residual resources, such as the CST, for hand function.

Based on our understanding of the underlying neuromechanisms, two possible solutions for regaining hand function are: 1), to use a neuroprosthesis if there are not enough CST fibers left to provide distal innervation, and 2) to reallocate/re-enable the remaining CST fibers for controlling hand function such that the neuroprothesis over time becomes not necessary. With the new imaging techniques, like diffusion tensor imaging, we now can quantify the amount of residual CST with reasonable accuracy[42,43]. However, we still do not know what loss of CST will result in a poor prognosis for regaining hand control. Therefore, in this proposed development, the goal is to optimize the chance of reallocating/re-enabling the remaining CST for the hand control. To make this feasible, two conditions are required: 1) the potential for neural plasticity, and 2) the implementation of an approach that effectively stimulates the use of residual CST resources.

One of the most exciting findings during the past 20 years is that neural plasticity remains even in chronic stroke. This opens the possibility for the reallocation of residual brain resources. The remaining question is: what is the right way to trigger the optimal use of remaining neural resources? Currently, there is little evidence that any of the exercise interventions that have been studied is the best for an individual with stroke[8,44-47]. Instead, numerous studies have identified the intensive practice as the critical element of successful interventions to improve function in the hemiparetic UE[6-14]. Furthermore, the benefits of training in a functional context (task-specific training) have been demonstrated as well[13,48-55]. Most of all above results were obtained in mild and moderately impaired stroke individuals, with whom there is assumed to be more preservation of the CST. Currently, the recovery of hand function in more severely impaired individuals is poor. We believe that this is at least partially because the loss of hand function (despite the preservation of some proximal arm movements) makes use of the affected UE non functional, and thus the individual learns not to use the arm. On the other hand, new evidence is keeping emerging. These results demonstrate that even in severely impaired stroke survivors, recovery of proximal arm function can still be obtained if a science-based right intervention is used[56,57], and thus suggesting preserved neural plasticity of this population. An effective assistive device would allow for further investigation of improved use and associated recovery of the paretic arm.

B.1.2. Currently available devices for hand-function rehabilitation following stroke

We can classify the commercially available devices for enhancing movement of the paretic hand into 2 broad categories: mechanical devices and electrical devices.

Mechanical devices

Mechanical devices range from "not actuated" to "active robotic devices". Typical non-actuated devices included theraband (The Hygienic Corporation, Akron, OH), digi-web (cando-web™, HOSPEQ International, Miami, FL), and power web (HandHealth Unlimited). These devices all contain some elastic material, which is used to provide external resistance during exercise. The goal of use of these non-actuated devices is mainly strengthening. In order to utilize these devices, individuals require the ability to actively contract muscles against an external load. More recently, the

Figure 1. Saeboflex

Saeboflex™ (Saebo, Inc, Charlotte, NC, see figure 1) device and Hand Spring Operated Movement Enhancer (the National Rehabilitation Hospital, Washington DC, USA) uses adjustable springs to open the hand of more severely impaired individuals with hemiparetic stroke. Although the Saeboflex™ has been reported to be useful in enabling subjects to participate in intensive functional training [58,59,60], the system is difficult to set up and only overpowers the finger and thumb flexion bias to open the hand and requires an active grasp by the subject. It therefore necessitates volitional control of grasp, something many individuals with sever stroke no longer have. Given the difficulty to get the paretic hand in, and the lack of required control, the system is unlikely to become a prosthetic device that can be used on a daily basis.

The second tier of devices are termed "active robotic devices"[61]. These devices can impose actuated position-controlled movements of the hand, such as passive motion devices (CPM). CPM devices utilize an external motor to passively cycle joints through available range of motion (ROM). A review of arm interventions following stroke suggested that CPM combined with elevation may have a beneficial effect on hand edema[62]; however, there is no evidence that this intervention conveys a positive effect on regaining active movement since movement is not encouraged in this type of a device.

Other active robotic devices[61], varying from devices that specifically target forearm and hand motion to exoskeletons and gloves for thumb and finger exercise, etc., designed to assist or guide patients in one of the pre-set movements while encouraging the user to actively use his/her UE. Three recent systematic reviews of robotic therapy in the arm following stroke concluded that there are improvements in the proximal arm in both sub acute and chronic stroke[63]; but no consistent influence on function[63,64,65]. After an extensive review of characteristics of 15 devices ranging from non-actuated to robotic, Dovat and colleague concluded that current active mechanical devices for hand rehabilitation are often too large to be used at home, have too limited range of force or do not offer the possibility for training fingers individually[61].

Electrical Stimulation Devices

Electrical stimulation devices can be subdivided into 4 categories, (1) simple surface electrical stimulation, (2) surface electrical stimulation coupled with a wrist hand orthosis, (3) electromyographic (EMG) triggered surface electrical stimulation, and (4) invasive electrical stimulation. Since our target population desires a non-invasive device, our review only focuses on the first 3 categories.

Surface electrical stimulation was first used to enhance arm function in the hand following stroke in the early 1960's[66]. Numerous studies describe positive effects on decreasing impairment and enhancing arm function post stroke[8,67-77]. The Veterans Administration/Department of Defense clinical practice guideline recommends electrical stimulation for patients who have impaired "UE muscle contraction, specifically with patients with elbow/wrist motor impairment"[78]. Many of the subjects for whom electrical stimulation has proven beneficial are those with mild-moderate motor impairment following stroke. The challenges to widespread use of surface stimulation systems include electrode placement, cumbersome equipment, the

complexity of achieving consistent distal control, and lack of intuitive control. In addition, many systems are not easy for stroke survivors to apply without assistance, limiting use outside of the clinic.

Electrical stimulation has been coupled with a wrist hand orthosis (WFO). The Ness H200 (Bioness, Inc, Valencia, CA, see figure 2) combines a WFO, 5 surface electrodes that can be individually positioned, and an external control system. Studies using either the Ness H200 or an earlier version the "Ness Handmaster" report improved grip strength, motor scores (Fugl-Meyer Assessment) and better arm function[79-83]. Combined WHO/ES systems are portable and easy for users to manage. Difficulties with reliable precision control, and lack of intuitive control limit their widespread use.

Figure 2. NESS H200

Devices have been developed to allow for triggering electrical stimulation using the user's EMG signal (EMG-triggered ES). When using these devices, the patient is asked to voluntarily contract the paretic muscles. When EMG activity exceeds a preset level, external electrical stimulation of the muscle takes place, which increases or triggers muscle contractions. Numerous devices for EMG-triggered ES, like Biomove (Israel), Combistim (Galway, Ireland), and etc., are available in the market now. The underlying thought behind intention-dependent, EMG triggered functional electrical stimulation is a positive influence on neuronal plasticity due to proprioceptive and somatosensory feedback from the electrically stimulated, active muscle contraction. Meta-Analyses of Clinical Studies have demonstrated that triggered functional electrical stimulation appears to be superior to non-triggered electrical stimulation on motor control of the upper extremities (see figure 3). The total number of hours of stimulation and the stimulation frequency were not found to be significant. The same was true for the various recovery stages after the stroke (acute, subacute, chronic). The literature supports the use of EMG-triggered ES in the treatment of the hemiplegic wrist and forearm (Level 1 evidence) [84]. Commercially available EMG-triggered ES devices all allow for pre-set movements without intuitive control to switch between these movements. Portability, ease of use, lack of intuitive control, and cost are also barriers of these type devices to widespread use.

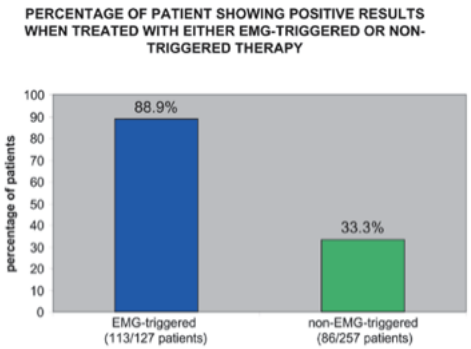

Figure 3. EMG triggered ES is superior in motor control recovery than non-triggered ES. Meta-analysis involved a total of 588 acute, subacute and chronic patients [1].

If a simple EMG-triggered electrical stimulation of fixed muscles with pre-programed amplitudes can achieve superior recovery than a non-triggered ES, we expect that functional practice using the appropriate muscles to implement grasp and release activities during different arm activities will be even more successful. The development of the proposed ReIn-HAND real time platform will allow us to move one step closer to this idea.

B.1.3. Pros and cons for mechanical and NMES devices

Each of the mechanical and electrical devices has pros and cons. A mechanical robotic device can provide more complex control to both hand and fingers; however, these usually are big and complex. Furthermore, these devices do not have the benefit of adding electrical stimulation, which directly activates a person's own neuromuscular system to generate the assistive force. Conversely, ES devices have limited ability in control of fine movements, due to difficulties in controlling for contraction speed of individual muscles, or desired kinematic qualities, such as speed, trajectory, and motion smoothness[85]. Furthermore, ES devices can cause muscle fatigue, since stimulated contractions are inherently fatiguing due to synchronous muscle firing and motoneuron recruitment reversals [86-89], limiting the duration of use. However, many ES are battery powered, can be programed, are portable and have been demonstrated to be safe.

B.1.4. Gap in the development of the next generation assistive devices

In summary, current commercially available devices cannot meet the need as identified above. The proposed EMG-ES device will fill this significant technical gap. In the long-term, we aim to investigate whether individuals with moderate to severe stroke can regain upper extremity function by participating intensive task-specific paretic hand practice together with the rest of arm.

C. Novelty of the proposed ReIn-HAND platform

C.1. A safe, reliable, intuitive detection of the intention of hand movements during functional arm activities

The resulted ReIn-HAND platform of this proposal will be novel in its detection algorithms that can provide non-invasive, safe, reliable, intuitive and continuous detection of a subject's intention for hand grasp, release and relaxation during different functional arm activities. This will be achieved by strictly designed robot-mediated experiments, simulating different environments when using the entire UE during various hand activities. These experiments have been designed to reflect special characteristics of individuals with stroke, such as muscle weakness, abnormal co-contraction, and abnormal muscle synergies. Furthermore, we have chosen to only implement the detection of grasp, release and relaxation of the paretic hand to optimize the required reliability. The developed platform will be implemented using a portable device, the RECLAIM ES designed by Simple Systems Inc (Simple Systems Inc, Toronto, Canada). The implemented platform will convert a user's intention to timely assistance of usage of the paretic hand during different functional arm activities.

C.2. Portable, subject-dependent configuration, easy-to-setup and low-cost

The ReIn-HAND platform is envisioned to be portable and customized based on subject specific features and desires. The device that incorporates the ReIn-HAND platform will also be easy to setup and low cost. Therefore, we propose to test its performance in an ES device (i.e., the RECLAIM). Although an ES device can cause muscle fatigue more easily than a mechanical

device, it can easily provide assistance to hand movements for at least 15 minutes without fatigue. Users can practice in short bouts, multiple times daily.

The device will allow for position-dependent selection of elements from the electrode-array: Another challenge for an EMG-driven FES device with surface recording and stimulation electrodes is that the relative position of the skin and muscle changes during a functional task. To account for this problem, we innovatively propose to add an inertial measurement unit (IMU) to the forearm orthosis to detect forearm pro/supination. This information will be used to auto-select elements from the electrode-array.

The device will translate the use of ReIn-Hand device outside the laboratory/clinic: Home-based practice can be beneficial to our targeted population[90,91]. Due to the large variation in movement ability following stroke, the configuration of recording/stimulation electrodes requires it to be subject-specific. We therefore propose to perform a 3D scan of the subject's forearm/hand followed by a 3D-printing of a subject-specific orthosis with recording and stimulation electrodes embedded to fit individual user's needs. Together with the ReIn-Hand detecting platform on a smart phone, the proposed device will be portable, individualized, easy-to-use, and low-cost, thus having potential for widespread home-based practice.

D. Specific Objectives

The realization of this novel EMG-driven FES device that can be used both in the clinic and at home will be through the following specific aims:

Objectives 1: Develop a real-time ReIn-Hand opening platform as a portable device for home use
We will design a proof of concept FES device that is portable and user-friendly, incorporates graphical user-interfaces, and provides Reliable and Intuitive hand (ReIn-Hand) opening during functional use of the shoulder/elbow. The control algorithms of ReIn-Hand have already been developed on a laptop system for 4 different functional hand tasks. Preliminary results in 8 participants with moderate to severe chronic hand paresis are promising. All subjects learned to use this platform within one 3-hour session, which demonstrates the efficacy of our current algorithms and the intuitiveness of our current control. After a 7-week laboratory-based intervention using the ReIn-Hand, all subjects demonstrated improvements in sensory/motor assessments, and showed changes in related cortical activities and integrity of white matter (see preliminary results). These results provide mechanistic evidence of the efficacy of the current system, and suggest that it is worthy to improve the ease-of-use utilities of ReIn-Hand system to make it suitable for a home-based intervention. The necessity of this aim is therefore to transfer the current algorithms to a portable device (i.e., smart phone), to enable automatic parameter adjustment based on user feedback, and to make this platform sufficiently user-friendly, such that ReIn-Hand assisted functional intervention can be safely and easily implemented both in the clinic and at home.

Objectives 2: Develop a subject-specific forearm/hand orthosis with embedded electromyographic (EMG)-recording and stimulation electrodes

Besides detecting and controlling hand opening in the context of abnormal synergies, several other practical difficulties limit the ease of use of most current EMG-driven FES devices for assisting hand opening. This includes the challenge of identifying recording/stimulation sites and a lengthy setup time. To resolve this problem, we plan to develop a subject-specific 3D-printed forearm-hand-orthosis (FHO) that has EMG recording/ stimulation electrode-array embedded (aim 2A). Furthermore, we will also address the changes in the relative positions between the EMG recording/stimulation electrodes and the corresponding muscles that occur when moving the forearm between a pronation and a supination position. We plan to add an inertial measurement unit (IMU) with a 3D accelerometer and a 3D gyroscope with Kalman sensor fusion algorithm to the system. This IMU will detect the amount of forearm rotation, which will be used to auto-select the recording/stimulation elements in the electrode-array (aim 2B). The FHO will allow the device to be user-friendly by providing easy and reproducible electrodes placement.

E. Selection of Subjects

We plan to recruit about 100 moderately to severely impaired stroke subjects who have some shoulder and elbow control, but lack hand function (UE FMA Scores of 10-40/66, CMcM<=4) to participate in the cross-sessional experiments. Individuals with stroke will be selected from the Clinical Research Registry (CRR) housed at the ShirleyRyan AbilityLab which contains more than 700 members, as well as from stroke survivors residing in the Chicagoland area who wish to participate in the study. Recruitment of subjects who are currently enrolled in the Clinical Research Registry will be done via phone call and email. Recruitment of stroke survivors residing in the Chicagoland will be done via flyer or on-clinical-site survey for willingness of participation. In addition, in order to facilitate recruitment, we will post this study on the The New Normal (TNN[1]) Match matchmaking portal, a National Institutes of Health (NIH) funded collaborative project to give communities access to information about healthy research opportunities. These stroke subjects will go through 1 or 2 stages (i.e., the 1st stage as remote prescreening which is optional and the 2nd one as on-site screening for eligibility test which is required) of eligibility tests. Recruitment for stroke participants will be ended when 20 individuals with moderate to severe impairment post-stroke are enrolled and finished the data collection.

Once confirmed their desire and willingness to participante, the potential participant will be asked to sign an online e-Consent form, or a hard copy consent form. For individuals who signed the e-Consent form and passed the remote pre-screen, a hard copy of consent form will still be signed on the first on-campus visit.

We will recruit 10 healthy individuals at least 45 years old. These individuals will participate in one session of the EEG experiment, and will provide control data to compare against the stroke individuals who partake in the home-based practice.

[1] https://www.nucats.northwestern.edu/news/2020/northwestern-new-normal-launch.html.

Also, 10 independent physical therapists (PTs) or senior physical therapy students (SPTs), who have experience working with stroke subjects and using FES, will be recruited for setting up the ReIn-Hand device for stroke users, and then teaching stroke users to use the device. Stroke, PT and SPT users will provide feedback from clinicians and stroke users' angles, respectively.

After the eConsent or Consent form is obtained either online or as a hard copy, a qualified team member will call the stroke participant to conduct a phone survey to screen their current medical status and history and willingness to participate in the study. If a stroke participant agrees to have a remote section using video call, like zoom, FaceTime, WhatsApp etc., a video call will be scheduled to assess three short-version clinical assessments (MOCA, FMA and Chedoke). These remote sections will allow the team members to pre-screen the eligibility of a stroke participant without requiring an in-person visit. These two remote sessions (phone survey and video call) may be combined, with a total of about 30 minutes.

E.1. Inclusion and Exclusion criteria

Stroke participants should have sustained a unilateral lesion at least 6 weeks prior to participation in this project. The following inclusion criteria will be applied to the participants: 1) Paresis confined to one side, with substantial motor impairment of the upper limb; 2) Absence of motor impairment in the unimpaired limb; 3) Absence of a brainstem and/or cerebellar lesion; 4) Absence of severe concurrent medical problems (e.g. cardiorespiratory impairment, changes in management of hypertension); 5) Absence of any acute or chronic painful condition in the upper extremities or spine; 6) Absence of cardiac pacemaker; 7) seizure free; 8) no Botox within the last 6 months; 9) Capacity to provide informed consent; 10) Ability to elevate their limb against gravity up to horizontal and to generate some active elbow extension; 11) Ability to achieve functional grasp and release with the assistance of an ES device with the help of an experience professional physical therapist; and 12) Not in pregnant or planning to become pregnant. Overpressure at the end of the range of motion will be used as a medical screening measure to verify the absence of inflammatory condition at the shoulder, elbow, wrist, and fingers. The shoulder passive range of motion of the affected upper extremity will be measured using a goniometer based on adapted methods. Maximum grip and key pinch forces for each participant will also be measured using a hand dynamometer and a pinch gauge. The impairment level of the upper extremity and the wrist/hand will be evaluated by a research physical therapist using Fugl-Meyer score.

While most inclusion criteria will not rule out the potential participation of registry members, the greatest impacting criteria are the Fugl-Meyer score and the ability of release with the aid of the RECLAIM ES device. We anticipate that a minimum of 50% of registry members will be moderately to severely impaired and will be appropriate for participation in this study.

Participating Physical therapists (PTs) should have a valid Illinois PT license and should have worked with individuals with stroke. Senior physical therapy students (SPTs) should be currently

enrolled in the third year and have successfully completed all the course work and clinical experiences required for the first and second year of their program. Students or employees who directly work with the investigators (for example, students who currently work with the investigator as part of their coursework or research projects, employees who are listed as part of the research team in this IRB or are paid by the research grants led by the investigators) will be excluded. No penalties will be applied to students or employees who fail to show up for scheduled research-related appointments. No extra credit, besides the participation fee listed in this IRB, will be offered. During the recruitment based on an IRB-approved consent form, we will thoroughly explain the potential risks and protection that will be used to reduce these risks. Participation in the research is entirely voluntary, and after that decision is made, participants have the right to withdraw at any time for any reason.

E.2. Pre-training Clinical assessments

All participants will undergo a series of impairment-level and functional clinical assessments that will be performed by a research physical therapist. The Impairment-level assessments will include the Upper Extremity Subscale of the Fugl-Meyer Motor Assessment (UE FMA)[92], Chedoke-McMaster Stroke Assessment hand portion (CMcM), the Nottingham Stereognosis Assessment (NSA)[93,94], the Action Research Arm Test (ARAT)[95], Box and Blocks test (BBT)[96], the Stroke Impact Scale (SIS) [99-101], **Cutaneous Sensory Touch Threshold using Semmes-Weinstein Monofilaments (CSTT) [102-103],** Montreal Cognitive Assessment (MoCA) [104-105]**.**

In addition, quantitative measure of hand opening area and closing force (QMHOC) will be conducted during the whole course of 12-week home-based practice, using pressure sensors (Pressure Profile Systems, Inc., Los Angeles, CA 90045) in conjuction with portable Moire Phase Tracking cameras (Metria Innovation, Inc., Wauwatosa, WI) (~1 hour).

F. Study Design and Methods

F.1. Lab-based testing

Each PT will be trained for the use of ReIn-Hand by watching a 20-min video, and practice the use of ReIn-Hand under the supervision of the research PT, Dr. Carmona, who is experienced in using ReIn-Hand device.

F.1.1. A. Pre-training non-EEG Experimental protocols

Once confirmed, a stroke participant will be randomly assigned to one of 11 physical therapists (10 clinical PTs+1 research PT (i.e., Dr. Carmona)) who will participate this study. The assigned PT will determine 1) the electrode positions for recording the muscle activities during performing different arm/hand function, and 2) the stimulation electrode positions and stimulation intensities for

achieving the best hand opening with the forearm at 0º and 90º positions (~1-1.5 hour). Then, the corresponding electrode positions will be marked, and the forearm/hand with these markers will be scanned (~0.5-1 hour). This visit is expected to last approximately 3 hours. The scanned results will be used to develop a subject-specific forearm-hand orthosis (FHO) that fits to the paretic forearm and hand.

B. Pre-training EEG Experimental protocols

Before and after this 12-week home-based practice, these stroke individuals will participate in an electroencephalography (EEG) experiment. Additionally, 10 control subjects will be recruited to participate in one session of this EEG experiment to provide healthy neuroimaging data for comparison.

At the start of the experiment, we will measure maximum grasping forces (requiring 3 trials within a 10% range of each other). During this experiment, we will use the ACT-3D, a robot developed by Dewald Rehab Tech, LLC, to simulate the situation of performing different hand movements against different loads against gravity. The tested forearm (paretic for stroke, dominant for control) will be attached to an orthosis that is linked to the ACT-3D. The subject's hand will be placed around a cylinder on the orthosis with a custom pressure sensor mat (Pressure Profile System Inc., CA) to measure grasping forces. A 9x9 mm marker will be placed on the tip of each finger, with another on the back of the hand as reference. The position and angle of the fingers/hand will be captured by 2 portable Moire Phase Tracking cameras and these markers (180 Hz; Metria Innovation Inc. Milwaukee, WI). The subject's upper limb and forearm lengths will then be measured and entered into the computer. A "home" position will then be defined as the position in which the arm is placed with 85° shoulder abduction, 40° shoulder flexion, and 90° elbow flexion. During the experiment, the subject will be instructed to perform 1 of 2 movements: 1) hand opening while resting on a haptic table, or 2) hand opening while lifting against 50% of their maximum shoulder abduction (SABD) force. A monitor will continuously display the position with a cursor indicating where the subject's arm is relative to the home position. For each trial, subjects will first move to the home position, then relax for 5-7 seconds, and then initiate the movement. Subjects will perform 60 trials for each movement, broken up into randomized blocks of 20 trials. Subjects will be given 30 seconds of rest between trials, and 10 minute rests between blocks to avoid fatigue. Additionally, a 3-minute resting-state block will be recorded in which subjects are instructed to fixate on a fixation cross on the screen. The whole experiment will last approximately 6 hours.

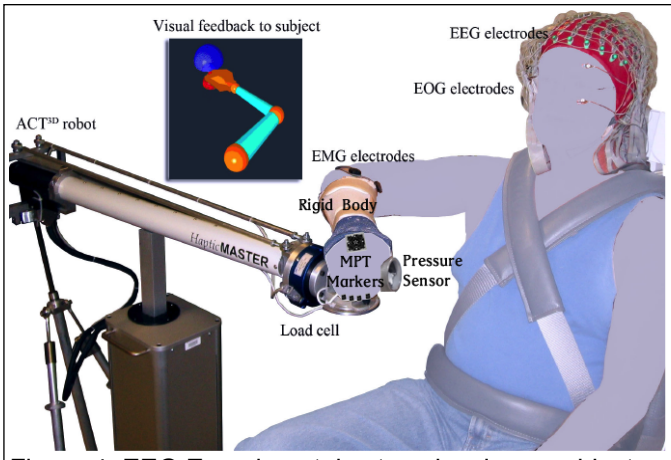

Figure 4. EEG Experimental setup showing a subject using the ACT3D robot while high-density EEG and surface EMG signals will be simultaneously recorded. Visual feedback will be displayed on a computer screen.

Throughout the experiment, we will measure scalp recordings using a 160-channel EEG system using active electrodes (Biosemi, Inc., Active II, Amsterdam, The Netherlands). Surface EEG electrodes will be mounted on a stretchable fabric cap based on the 10/20 system. The cap will be fitted on the head of the subject with the Cz electrode aligning with the intersection of the planes defined by the nasion, inion, and pre-auricular points. Eye movement detection electrodes will also be placed on the supra- and infra-orbital margins for detection of vertical eye movement. The skin under each electrode site will be prepared by clearing away any hair, and conductive gel will be injected to achieve electrode impedances lower than 5kΩ throughout the experiment. EEG data will be collected at 2048 Hz sampling rate and anti-aliasing filter (100 Hz) will be provided before data acquisition. The Biosemi system is equipped with active electrodes that provide a first amplification stage, allowing detection of EEG signals with a higher SNR and quicker preparation. A Polaris Krios handheld scanner and reflective markers (NDI, Ontario, Canada) will be used to record the EEG electrode positions compared to the coordinate system defined by the nasion, inion, and pre-auricular notches. EMG will be recorded from the extensor carpi radialis, flexor carpi radialis, and deltoid of the arm. The EEG and EMG data will be collected and stored on a computer.

These sessions will allow us to compare the cortical activity related to these movements pre- and post-intervention for the stroke individuals and how these compare to healthy controls to investigate any intervention-induced cortical reorganization.

F.1.2. <u>The 1st and 2nd lab-based training with ReIn-Hand (2 visits)</u>

After the subject-specific FHO is ready, the stroke participant and his/her paired PT will be called to participate the 1st and 2nd lab-based training with ReIn-hand device. During these 2 visits, the assigned PT (1st test) or the research PT (2nd test) will train the stroke participant to use his/her FHO and the ReIn-Hand software on a mobile phone, until the stroke participant demonstrates the ability in using the device independently twice in a row. On the 2nd test, the research PT will also re-test partial of the clinical assessments, however, this time with the assistance of ReIn-Hand device. Each of these 2 visits is expected to last about 3 hours. During these 2 visits, we will measure the time for a stroke participant to learn the use of ReIn-Hand device. Within 0-3 days after the 1st (for PTs) or the 2nd lab-based training (for individuals with stroke), a 5min user survey to report the level of ease-of-use of the ReIn-Hand device will be conducted.

F.2. Home-based practice

After the 3 lab-based visits as listed above, 4 out of 20 stroke participants will further participate the home-based practice. They will take the ReIn-Hand device, including his/her FHO, the mobile phone with ReIn-Hand software, and the electronic stimulator (300 PV, Empi, Minnesota, USA, a FDA approved clinical device) back to home. At home, they will perform 20 trials of pre-set tasks, like reaching and grasping, per session (1 hour), 1 session per day, 7 days per week for 12 weeks. During these 12 weeks. During these 12 weeks, they will visit the lab once per week to make necessary device changes, update the partial of the clinical assessments, all without ReIn-hand. These clinical tests will also be re-measured at 1 and 3-month after the home-based practice, again without ReIn-hand.

Both electrodes and electrical stimulator are commercially available devices (300 PV Complete Electrotherapy System, Empi, Inc., St. Paul, MN). Each subject will be assigned task-specific, functional exercises targeted to their individual abilities, deficits, and personal preferences. Stimulation will be provided with the following characteristics:

Amplitude – at motor threshold with the maximum intensity lower than 100 mA
Frequency – 50±20% Hz
Pulse Duration – 300-400 microseconds
Ramp/Fall Times and Duty Cycle – adjusted to the task

F.3. Data collection and procession

Main data collection is listed in table 2.

Day 1	#1, Demographic data, #2, Clinical assessments as listed above, #3, Time for a) determining the stimulation /recording electrode positions, b) for scanning,
Day 2	#1, EEG data, #2, EMG data, #3, finger position during hand-opening and graping force data during closing
Day 3	#1, Time for the stroke subject to a) to attach the FHO, b) use the software, including connecting all the cables following the instructions, c) set up the detection rule, and d) clean up. #2, The accuracy in detecting grasping and releasing; and #3, EMG data while performing task, sampled at 1K Hz.
Day 4	Measures #1-3 on Day 2, #4, ARAT and BBT with the assistance of ReIn-Hand.
Home-based test	Measures #1-4 on Day 3 and MAL-14, NSA, and hand opening and closing ability weekly during the 12-week home-based practice, then again at 1 and 3-month after. To the end of the 12-week home-based practice, we will use a GLOC scale (one question survey) to collect user overall satisficaory level of the ReIn-Hand supported home practice.

Data analysis for evaluating the engineering aspects is listed on Table 3.

Primary measures	**Measured by**	**Expectation**
Time for learn-to-use the device	#1 on Day 3 and Day 4	<3 hours in each of the 2 days, and no difference between 2 days[1].
Time for setup and cleanup	#1 a) and d) on Days 3 & 4, and during the home-based test	<5 min for each, and significantly less than the

		measure #3 (a) on Day 1
Successful rate on controlling grasping and releasing during reaching	#2 on Days 3, 4, and during the home-based test	a false 'transfer' < 10%
Time delay caused by the device	We will detect the onset of EMG at the extensor measured on days 3 &4, and the onset of stimulation artifact. The latency between them will be calculated.	<350 ms
Difference in Clinical assessments with and without ReIn-Hand	Difference between measure #4 on Day 4 & measure #2 on Day 1	ARAT and BBT with ReIn-Hand will outperform that without ReIn-Hand.
Willingness to use ReIn-Hand at home	#1-3 during the home-based test	Continuous use on daily base.
Cortical activity related to hand open with and without lifting	We will use EEG data to estimate the cortical activity related to the 2 motor tasks pre- and post-home-practice	Post-intervention cortical activity related to these 2 motor tasks become 'closer to' that in healthy control subjects.

[1]Ease-of-use feature of the device will be reflected by the <3 hours learning time. We will further study effects of 1) PT's experience with ReIn-Hand, and 2) the number of experimental sessions on the time to learn to use the device. For PT's experience, since Dr. Carmona already has 4-year experience in using current ReIn-Hand device in stroke participants, we will compare 1) the learning time on day 2 of the group 1 (N=10) working with the 10 PTs versus the time of the group 2 (N=10) working with Dr. Carmona; and 2) the learning time of group 1 on day 2 with the 10 PTs versus the time of the same group on day 3 with Dr. Carmona. A non-significant difference for both comparison will suggest non-significance for PT's experience in using the device. For the number of sessions needed to learn to use the device, we will compare the learning time of both groups on day 2 versus that on day 3. A non-significant difference will suggest sufficiency of one session in learning the device.

Evaluation of the usability of the ReIn-Hand: Within 0-3 days after Day 3, the 10 PTs and the 20 stroke participants will finish a 5min user survey to report the level of ease-of-use of the ReIn-Hand device. Items that will be rated (on ordinal scale 0-5, with the easiest use at 5) include: 1) determination of the stimulation/recording electrode positions (PT only), 2) setting up the initial detection rule (PT only), 3) fine adjustment of the detection rule (both), 4) placement of the FHO (both), 5) using the mobile phone software (both), 6) performance of the trained functional task (both). We expect to observe users' grades ≥4/5, with grades ≤3/5 will be queried for explanation and compiled for future design modifications.

Transportation: Participants will be given reimbursement for transportation expenses. Participants are encouraged to take public transportation, or to drive and park in Northwestern Medical School parking lots (located at 321 E. Erie St. or 222 E. Huron St.) where a parking sticker

will be provided. If a cab or rideshare car (Uber or Lyft) is needed, it is requested that the participant contact lab staff to confirm that the fare can be reimbursed before scheduling pickup.

Reimbursement and payment will be submitted to the NU accounting department on a weekly basis. Alternatively, participants may also be compensated using a pre-stored value card.

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