# Cognitive-based Rehabilitation Platform of Hand Grasp after Spinal Cord Injury using Virtual Reality and Instrumented Wearables

NCT04577573

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Study Protocol and Statistical Analysis Plan

# PROTOCOL

## (a) Background and Significance

The VA provides care to 27,000 veterans with SCI-related issues each year. The most frequent neurological category of SCI is **incomplete tetraplegia** (40.8%), which involves sensory loss and motor paralysis of the arms [1]. For persons with cervical level SCI, restoration of hand function is the top priority [2]. Physical therapy at rehabilitation centers is still the most effective approach to recover significant function for this population [3]. **Advanced modes of rehabilitation** are increasingly used and include computerized interfaces (e.g., **virtual reality** (VR) [4]) and powered devices (e.g., **prosthetics, exoskeletons**) [5-8]. In any case, *physical therapy requires intense participant commitment during and in between sessions. Methods that cognitively motivate and engage the person are critical to maximize rehabilitation outcomes.* **Cognitive agency** refers to the perception of control during voluntary action [9]. Cognition of movement implies better physical function, but agency has not been prioritized as a primary rehabilitation goal compared to increased strength or practiced skill. Incorporating cognitive-based features, such as agency, into rehabilitation platforms may be the key to unlock the promise of advanced rehabilitation using VR and powered devices. *In this project, we propose rehabilitation platforms for grasping and reaching that leverage cognitive factors of (1) agency and (2) sensory-driven learning using virtual reality and instrumented wearables.*

By the concept of intentional binding [10], agency is reinforced when one performs an action and perceives, or expects, sensory consequences sooner in time. A growing body of evidence indicates that greater cognitive engagement [4, 11] and sensory guides (visual, auditory, and haptic) [12-14] can accelerate neuromotor learning. Powered devices such as exoskeletons and prostheses inject mechanical energy to physically assist the user. But the user must cognitively integrate their own intention against observed movements for better performance. More 'natural' interfaces involve the recording of user biosignals such as muscle electromyography (EMG) [15] or brain electroencephalography (EEG) to command devices. We seek to create a rehabilitation platform for both grasp and reach that leverages cognitive agency and sensory feedback to improve user abilities for both independent function and potential EMG-control of powered devices. **The expected outcome of this research** is to provide accessible, cognitive-based platforms that are entertaining and more effective in rehabilitating hand grasp and reach for persons with cervical SCI. Within the scope of this SPiRE, we will establish cognitive approaches for immediate (post-training) improvement in performance of grasp and reach after SCI. These methods will then be adapted to train better user control of powered assistive devices (e.g., exoskeletons [16-18] with functional neuromuscular stimulation [6, 19-21]) for reach and grasp in a subsequent MERIT award.

## (b) Preliminary Studies

Prior to 2017, our team developed and deployed feedback control systems for neuroprostheses and exoskeletons to assist movement function for persons with SCI [6, 16, 17, 22]. The laboratory at Stevens (est. 2017) has been investigating the roles of control perception and sensory feedback in further improving performance of reaching and grasping tasks [5, 23, 24]. Virtual reality, motion capture, force and flex instrumentation, and physiological signals (EMG, EEG) have been utilized to determine the links across visual feedback, agency, and performance of hand grasp tasks. The three major results from these studies include:

### Result #1: Agency and performance of reach and grasp are co-modulated through sensory feedback

Experiments were conducted to investigate modulation of agency and computerized performance by varying control modes observed *visually* during reach-to-grasp in VR (**Fig 1A**), and grasp-only on a force-sensitive pinch apparatus (**Fig 1B**). The reach-to-grasp task involved controlling a virtual hand (Modular Prosthetic Limb, [25]) in a physics-based computer environment (MuJoCo, [26]). The subject controlled the virtual hand, viewed in an Oculus headset, from marker-based motion tracking (Optitrack) of their own hand. Evaluation of performance was based on minimizing the reaching pathlength to a target sphere. The grasp-only task involved applying precision pinch (thumb and index finger loads) onto the apparatus. Pinch force magnitude was projected as a force trace intended to track a displayed ramp that rose constantly with time. Performance was based on minimizing the error between the force trace and target ramp. For both tasks, control of either the virtual hand or the force trace was modified across modes typical for tuning assistive devices. These modes included variations in speed [27, 28], noise mitigation [29, 30], and automation [31, 32] from a 'baseline' mode best representing the subject's intentions for control. For both tasks, agency was measured using time-interval estimation methods for intentional binding [33]. Following task completion (e.g., contacting sphere, end of ramp), a sound beep would be delay-activated at a variable time-interval the subject would estimate. Relative underestimation of intervals indicated greater agency due to intentional binding [9]. We identified significant positive relationships (linear regression, slope>0, p<0.05) between performance and agency for both reaching (**Fig 2A**) [23, 34, 35] and grasping either rigid or compliant surfaces (**Fig 2B**) [23, 24]. We also observed patterns of increased neuromuscular coupling (**Fig 2C**) during states of high agency. These results suggest *for reach and grasp, agency (perception of control) and performance are positively related and modulated across varied control modes perceived by visual feedback*. This finding motivates the design of devices that utilize sensory feedback to enhance perception of control and improve functional performance.

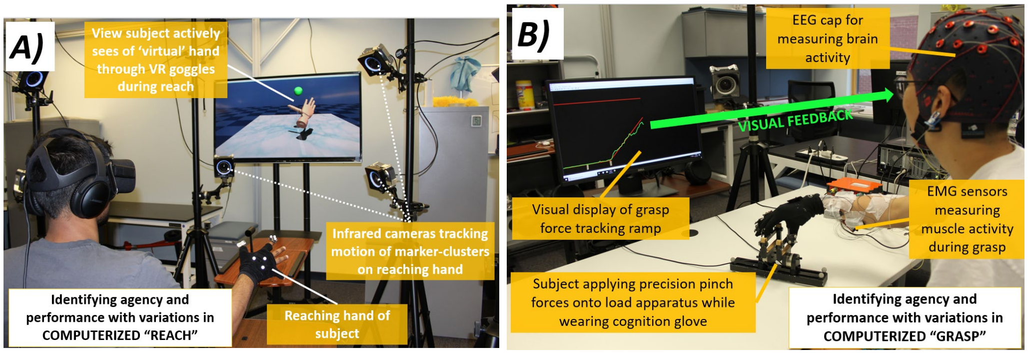


**Fig 1:** Experiments to demonstrate links between agency and performance of reach-to-grasp (**A**) and grasp-only (**B**).

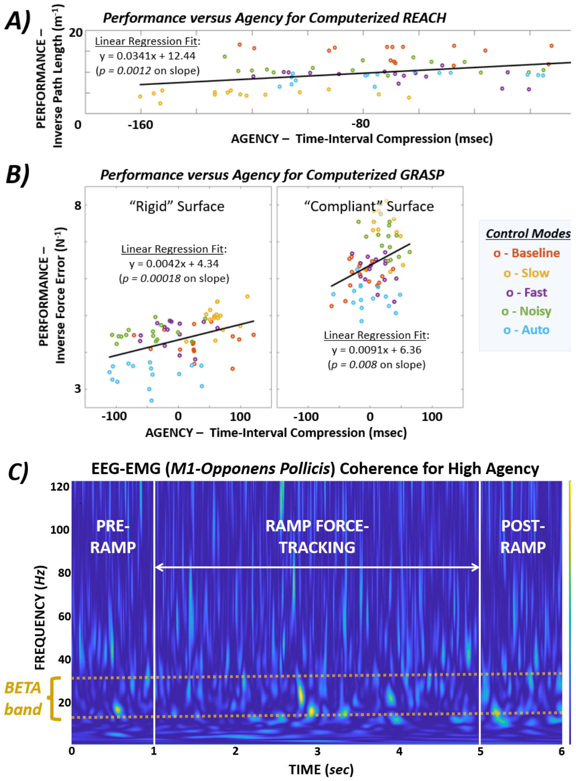


**Fig 2:** Experimental results for positively relating performance and agency during reach (**A**) and grasp (**B**). For grasp, high states of agency demonstrate spectral spiking (**C**) in the beta band for neuromuscular coupling (coherence between EEG and EMG).

## Result #2: Instrumented "cognition" glove to compute secure grasp and provide sensory feedback improves functional grasp

Our lab has developed and tested a functional prototype of an instrumented glove to alert the user about secure grasp [36] of objects. Onboard force and flex sensors provide inputs to a machine learning algorithm (artificial neural network, ANN) to estimate secure grasp based on previously collected training data. The glove enhances agency by alerting the user to secure grasp through sensory feedback modules (*visual* – LED, *audio* – beeper, *tactile* – vibrator) (**Fig 3A**). Each user undergoes a simple calibration procedure to use the glove (**Fig 3B**). We have demonstrated reliable ANN prediction of secure grasp from signal pattern recognition compared to analytical methods assuming force vectors [37] (**Fig 3C**). For an able-bodied study (n = 15), the glove provided visual and audio feedback during training blocks for a precision grasp task to pick-up and place a small cubic object (**Fig 4**). Vibration feedback was omitted in this study but expected to assist sensation for persons with neuromuscular deficits [38]. Feedback from the glove was provided *either* 'instantly' after secure grasp *or* at time-intervals 'decaying' from 1 to 0 seconds after secure grasp. We hypothesized that decaying feedback would progressively induce agency-based performance by priming the person to perceive shorter intervals. Compared to no feedback, decay feedback improved immediate post-training performance with reduced time for task completion and minimized pathlength of object motion. This preliminary study suggests that *training with the cognition glove can generate immediate increases in performance of functional precision pinch.* Our next step is to investigate if sensory feedback from the glove, and from VR, will improve grasp performance for persons with SCI.

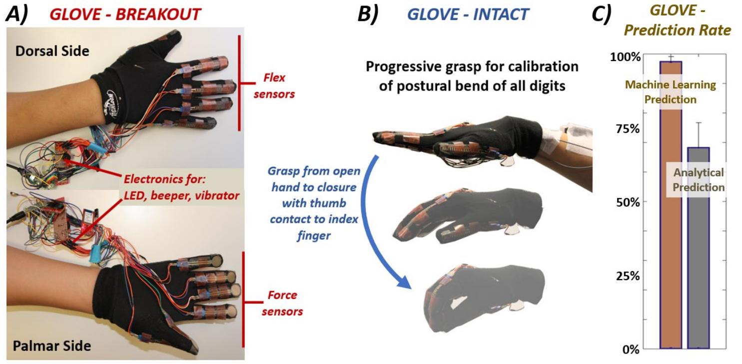


**Fig 3:** Instrumented glove with onboard sensors and modules providing sensory feedback (**A**). Glove accommodates each user hand after 10 repetitions of simple calibration procedure (**B**). Machine learning for sensor signal pattern recognition improved prediction rate of secure grasp (**C**).

## <u>Result #3</u>: Electromyography patterns can be regulated with sensory feedback training

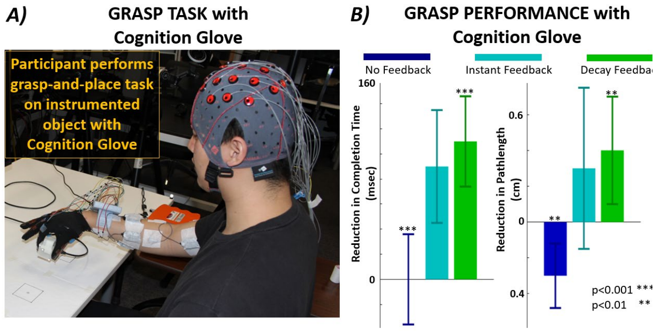


**Fig 4:** Using cognition glove to train better performance of functional grasp-and-place task (**A**). Following provision of sensory feedback from the cognition glove, there was significant reduction in time to complete the task and in pathlength of object movement (**B**).

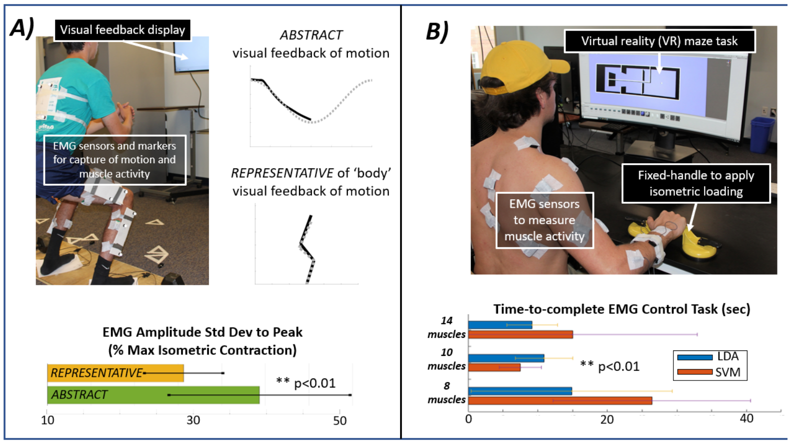


**Fig 5:** Visual feedback paradigms for modulating EMG patterns for better performance (**A**) or monitoring EMG patterns to drive movement performance in a virtual environment (**B**).

In creating a multi-sensory platform to train better muscle control for potentially improving independent function and command of myoelectric devices, we have <u>accomplished the following</u>: 1) established a method using systematic forms of visual feedback to mold EMG patterns during movement, and 2) progress in developing a virtual arm training platform with sensory feedback modalities. *For accomplishment 1,* we investigated the consistency to peak EMG magnitude across all measured muscle groups during squat with visual feedback. The squat exercise produces large bursts in muscle activations that are sensitive to small variations in technique [39]. Electromyography was measured (Delsys Trigno wireless system) for major flexor-extensor muscle groups of the ankles, knees, hips, and lower torso. The various forms of visual feedback included *abstract* (sinusoid) versus *representative* (stick-figure represents 'body'). Increased consistency in EMG, indicated by lower standard deviations to the peak, were observed with representative feedback (**Fig 5A**). Other variations of feedback were examined based on complexity and intermittency (results not shown here) [23, 40]. From these squat studies, we have directives to present virtual reality feedback to train greater consistency in EMG movement. Specifically, *our results indicate that complex body-representative visual cues presented more intermittently with progressively improved performance has the greatest potential for acutely shaping EMG patterns during movement.* We plan to employ this approach for VR movement training in Aim 2. *For accomplishment 2*, we have completed utilization of EMG pattern classifiers to control a cursor in a 3D virtual reality environment (**Fig 5B**) for completing a maze task from isometric force loading of the upper-arm and torso. Several classifiers were trained, but only results for the support vector machine (SVM) and linear discriminant analysis (LDA) are shown. The SVM represents a traditional computational technique for controlling myoelectric devices [41] while LDA has markedly higher potential for reducing training times [42]. In our pilot study [43], we limited computational time to <10 minutes and observed better performance with LDA three muscle sets (ANOVA, $p<0.01$), but peak performance was achieved by SVM on an intermediate muscle set. This result suggests *a unique and effective set of muscle inputs for myoelectric control can be identified for our platform within practical time constraints.* This is a promising result for real-world SCI rehabilitation settings that must consider various degrees of muscle impairment and limited time to train users.

## (c) Research Design and Methods

The Research Design for this two-year SPiRE proposal to RR&D will comprise of testing for two cognitive-based training platforms for functional grasp and reach, respectively, on persons with cervical SCI (**Fig 6A**). The experimental set-ups developed at Stevens are modular and portable for conducting tests with Veterans having SCI at the James J. Peters VAMC. Testing of each platform represents a unique proposal aim. Execution of each aim will be done independently in each of the two years and similarly include: 1) adaptation of platforms for use with persons having SCI, 2) recruitment of five participants per year, 3) execution of a single 8-hour experimental session for each participant. Each session includes 3 hours for data collection, and the remaining time for preparation, rest, feeding, bathroom trips, and 90-minute washout of each experimental condition. Inclusion criteria for subjects include: 1) aged 18 to 65 years, post-SCI for more than 1 year, SCI between C1-T1 with hand weakness (2-4 out of 5 manual muscle test in intrinsic hand muscles of thumb or 5th digit).

The schedule for each 12-month aim: recruitment (months 1-6), refining protocols for SCI (months 1-6), SCI participant testing (months 6-9), data and statistical analysis (months 7-10) and dissemination via conference and paper writings and submissions (months 9-12). Recruitment will be done via IRB-approved flyers at local SCI clinics; study posting at clinicaltrials.gov; and communication with previous participants at our VAMC. Among the ten total subjects (five per aim), our enrollment plan includes at least three females, three Latinos, and three African Americans.

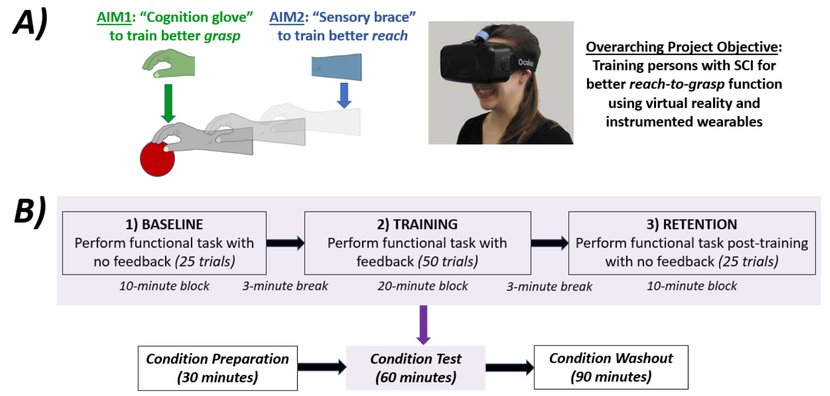


**Fig 6:** *Project overview* - objective of each Aim (**A**) and flow chart for testing a condition, three conditions per session, for each Aim (**B**). *Note*: the third (final) condition does not require washout.

For each aim, the data analysis will involve *within-subject* comparisons across three conditions: (1) control with minimal-to-no cognitive feedback, (2) intermediate level of cognitive feedback, and (3) enhanced cognitive feedback. *Enhanced feedback* refers to addition of VR to glove feedback in Aim 1, and addition of vibration to visual feedback in Aim 2. For each condition, there will be three consecutive trial blocks (**Fig 6B**): 1) *baseline* – performing real-world task 25 times with no feedback before training, 2) *training* – performing training task 50 times with feedback specific to condition, 3) *retention* – performing real-world task 25 times with no feedback after training. Repeated-measures MANOVA will be utilized given the three condition groups and two or more performance metrics specific to each aim. Our previous analyses for Result #1 with able-bodied persons suggest that n = 5 is sufficient to show significant difference ($p<0.05$) for MANOVA across three condition groups and two performance metrics (completion time, motion pathlength) at 90% power. ***The primary hypothesis for each aim is that performance after training is significantly greater with enhanced feedback***. Both aims of this study will also capture 32-channel EEG recordings for exploratory analysis of coherence computations with select recordings of muscle EMG as in **Fig 2C**.

### AIM 1: Investigate the effect of a "cognition" glove and virtual reality on grasp performance in SCI persons with partial hand paralysis.

The cognition glove protocol from Result #1 will be extended to include VR feedback to persons with SCI performing the grasp-and-place of a small cubic object.

<u>PROTOCOL</u> – Each trial involves: firstly, secure grasp of the cubic object placed in front of the dominant arm; secondly, pick-up the object and move towards target in front of non-dominant arm; thirdly, accurate placement onto target. The three condition groups for training task performance in Aim 1: *1) no feedback from glove as 'control', 2) 'decay' feedback from glove that includes audio, visual, and vibration feedback from onboard modules, and 3) enhanced feedback with the addition of mixed-mode virtual reality.* 'Instant' feedback is omitted given the observed improvement from baseline with 'decay' in persons without SCI (**Fig 4**). Enhanced feedback is 'mixed mode' since there still exists grasp onto a physical cubic object with the glove but interactions are viewed in VR. Subjects observe their own hand registered in VR using the LEAP® hand-tracker compatible with Oculus. The virtual cubic object is position-calibrated with the real object at the start of each trial. The glove communicates with the VR environment to cue real-time sensory feedback following detection of secure grasp. Enhanced VR feedback includes the small cubic object changing color to green and a view panel whose border also turns green. The panel also allows for posting of customized messages or images meaningful to the subject. The subject will pre-select a message, image, and sound to positively affirm achievement of secure grasp from a pool of options provided by the experimenters. Sample message and image include 'great job' and cartoon sunshine, respectively. At this stage, the novel VR feedback display is intended to be simple and evident 'reward' [44] to accelerate motor rehabilitation over the glove-only condition. **Functional performance metrics for Aim 1 include:** *1) time to achieve secure grasp upon initial contact, 2) time to complete pick-up and placement of object, 3) motion pathlength in moving object, 4) error in placing object onto target.* Higher performance is indicated by reduction in these metrics.

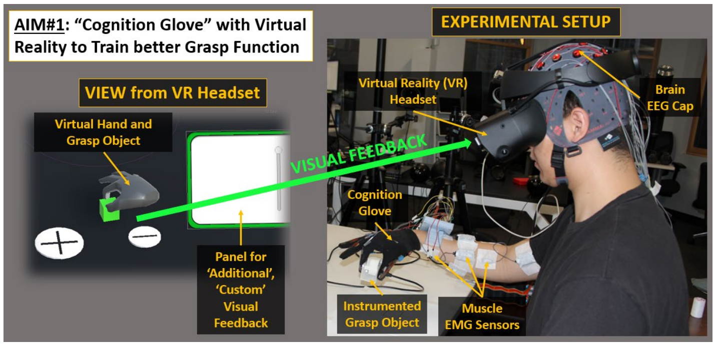


**Fig 7:** Experimental protocol for enhanced training feedback condition in Aim 1. Condition includes mixed-mode feedback with manipulation of real object while observing VR environment with enhanced visual and audio feedback.

## <u>AIM 2</u>: Investigate the effect of a "sensory" brace and virtual reality on <u>reach</u> performance in SCI persons with partial hand paralysis.

The broad objective of this platform is to train greater strength and muscle control while interacting in an engaging environment. The virtual reality environment from Result #2 has been extended to include successful communication between all electronic modules. Subjects have EMG control of a virtual arm prosthesis in Unity (**Fig 8**). We are currently developing a size- and position-adjustable arm brace with weight-support capability and housing for vibration motors and EMG sensors. Position adjustment allows for physical therapists to find and recommend arm postures that are clinically relevant to each person. The participant can then isometrically push/resist against the brace to strengthen target muscles while performing VR reach-to-touch. The person will receive visual feedback from the virtual environment to train movement performance and vibrotactile feedback at tendons to subconsciously adjust their muscle activation patterns. Tendon vibration is proven to elicit movement sensations affecting muscle activations [45-47].

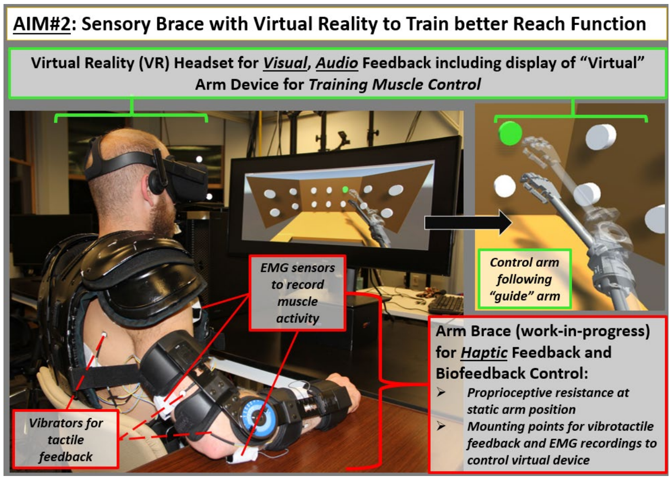
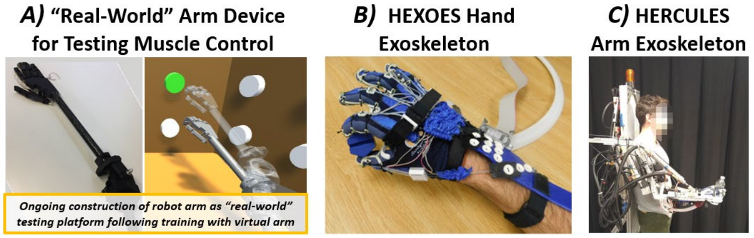


**Fig 8:** Pilot experimental set-up providing visual, audio, vibrational feedback to participant held in isometric (static) position in EMG-control of virtual arm in VR. *<u>Note</u>*: an arm brace is currently being constructed to replace ad hoc set-up shown and used for pilot testing.

PROTOCOL - The fundamental task for this aim is to reach-to-touch designated targets with a real arm (baseline, retention) or virtual arm (training). Each trial involves: firstly, moving the hand towards a specific target; secondly, minimizing pathlength of hand motion; thirdly, accurately touching the center of the target. For this Aim, prior to training across three conditions, data will be collected to train an LDA pattern classifier based on each subject's EMG patterns. This data collection involves 5 maximum isometric voluntary exertions within the brace in each of six command directions (front, back, right, left, up, and down). The three condition groups for training task performance in Aim 2: 1) no feedback and simply practicing the virtual arm task with the classifier, 2) visual feedback to control the virtual arm with complex-representative-intermittent visual feedback of a transparent guide arm to be followed, 3) visual and tactile feedback whereby vibro-tactile feedback will be added near tendon locations for muscles on the chest (pectoral), back (latissimus dorsi) and upper arm (biceps, triceps). Able-bodied subject experiments, conducted outside the scope of this proposal, will demonstrate how to provide vibration feedback that optimizes (maximizes) EMG inter-cluster distances [48] and augments isometric myoelectric control [49] with the trained classifier. Isometric training and distinct EMG activation patterns have demonstrated improved rehabilitation performance [50-52]. **Functional performance metrics for Aim 2 include:** *1) time to touch each target, 2) motion pathlength of reaching arm, 3) contact position error from center of each target.* Higher performance is indicated by reduction in these metrics.

Challenges/Alternatives – There are two primary challenges to this project: *1) For Aim 1, the ability of a person with SCI and compromised sensation to find and skillfully grasp the real object while viewing the virtual environment.* If the subject is overly challenged to grasp the real object, then virtual feedback will be provided in desktop mode. VR goggles will be removed, and the participant can see and grasp the real object directly while a virtual environment is projected onto a background monitor. We expect viewing the virtual environment peripherally will still have additive reinforcement effects [53]. *2) For Aim 2, subjects with various levels of SCI and conditioning may experience more fatigue than others given a total of 300 trials per session.* For each Aim, condition 1 allows us to re-calibrate our procedures based on participant behavior and apparent onset of fatigue. Re-calibration includes longer rest periods and fewer trials. A pilot analysis in persons without SCI for a reach-to-touch task done in our lab [54] suggests MANOVA significant differences in performance (pathlength and contact accuracy) across two feedback conditions (reward, punishment) could be observed with only 40 trials per condition. For both Aims, fatigue will also be monitored from EMG recordings [55].

Implications for MERIT award: Following the SPiRE, we will investigate these cognitive training approaches on three separate device testbeds (**Fig 9**). The first testbed would involve reach-to-touch with a physical robotic arm. We are developing a low-cost (<$1000) VR training toolkit which will include the cognition glove, sensory brace, and the real robot arm to be utilized at physical rehabilitation centers. The robotic arm provides a fun, real-world alternative to test muscle control after virtual arm training. The second testbed would be for training better user control of a powered hand exoskeleton (HEXOES, [18]) for grasp assistance. We would employ a hybrid approach to combine motor actuation from the glove with one-channel FES (g.tec FES stim) to elicit grasp from tenodesis [56, 57]. Our cognitive platform would be used to compute secure grasp and provide sensory feedback as with the cognition glove to enhance agency with this device. The third testbed would be incorporation of sensory brace training with use of an arm exoskeleton (HERCULES, in progress) driven by EMG signals. The same training approach from Aim 2 would be utilized to provide feedback and achieve better reach-to-touch performance with the arm exoskeleton from more distinct EMG commands.



***A)* "Real-World" Arm Device for Testing Muscle Control**

***B)* HEXOES Hand Exoskeleton**

***C)* HERCULES Arm Exoskeleton**

*Ongoing construction of robot arm as "real-world" testing platform following training with virtual arm*

**Fig 9:** Device testbeds with future MERIT proposal. Real-world robot arm serves as a 'fun' alternative for performance testing after training with virtual arm from Aim 2 (**A**). Powered hand exoskeleton would include FES and be adapted to provide sensory training feedback as the cognition glove with VR as in Aim 1 (**B**). Arm exoskeleton (in progress) training would incorporate a brace for sensory feedback as in Aim 2 (**C**).