Albert Einstein Healthcare Network

Annual Progress Report: 2012 Formula Grant

Reporting Period

July 1, 2013 – June 30, 2014

Formula Grant Overview

The Albert Einstein Healthcare Network received $61,734 in formula funds for the grant award period January 1, 2013 through June 30, 2014. Accomplishments for the reporting period are described below.

Research Project 1: Project Title and Purpose

Electrophysiologic and Behavioral Evidence of Consciousness: a Longitudinal Analysis – This project will collect preliminary longitudinal data from patients with Disorders of Consciousness (DoC) to investigate the reliability and sensitivity of electrophysiologic versus behavioral evidence of consciousness. The goal is to determine if evidence of covert command following exists in the absence of overt behavior and ultimately to generate sufficient data to power a larger, externally funded project on this topic. As an exploratory step, we will develop hypotheses about differences in both data domains using patients' physical exam findings and brain neuroimaging.

Duration of Project

1/1/2013 – 6/30/2014

Project Overview

Recent research suggests that certain individuals diagnosed in a vegetative state based on the inability to produce motor responses do indeed show evidence of covert command following when brain activity is measured by sources such as electroencephalography (EEG). Although evidence endorses EEG to locate previously undetected cognition at singular time points, the literature lacks evidence documenting its stability and sensitivity in the DoC population (i.e. those in vegetative or minimally conscious state). Thus, this project aims to collect preliminary data over several weeks from patients with DoC to examine both the reliability and sensitivity of EEG as well as of simultaneous overt behavioral data. Behavior will be assessed quantitatively via motion capture of the upper limbs. Given that this methodology is a new process for our laboratory, an initial aim will require debugging the EEG and motion equipment to ensure accurate data collection and then refining analyses to generate appropriate characterization of data. The long-term objective is to produce ample quality data to obtain extramural grant funding in this area.

Specific Aim #1: (Operational) Debug the data acquisition protocol, hardware, and software systems to ensure accurate collection of relevant data, and refine the machine learning data analysis algorithms that characterize the accuracy of both EEG and behavioral motion data.

Specific Aim #2: Obtain preliminary data on the test-retest reliability and pattern of longitudinal recovery of data in both domains to support power and sample size calculations for an externally funded project.

Specific Aim #3: (Exploratory) Using physical examination data about sensory and motor deficits and imaging data related to focal lesions, develop hypotheses about the source of discrepancies between EEG and behavioral evidence for consciousness.

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Other Participating Researchers

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Expected Research Outcomes and Benefits

This project will specifically address the reliability and sensitivity of EEG and movement data in persons with DoC. Once methodology is refined, we anticipate finding that the reliability of EEG and movement data will vary with each subject's functional and arousal level. We also expect that the accuracy scores from each data domain will increase weekly with some individuals demonstrating earlier and/or stronger evidence of consciousness on EEG than through movement. After reviewing neuroimaging and physical examination data, we suspect that patterns of focal lesions will emerge as potentially responsible for disruption of actual movement but not attempted movement (i.e. EEG-represented activity). Findings from this project will assist in generating an extramural grant proposal for a larger study investigating the utility of EEG as a diagnostic tool for DoC.

Summary of Research Completed

In the last year, we have completed the following research activities for this pilot project:

<u>Participant Recruitment</u>
All five healthy participants from the community completed up to three testing sessions to ensure we obtained adequate data for all four testing paradigms. The additional sessions allowed for either a repeat data collection of paradigms that were previously collected, but contained flaws

(e.g., lacking event markers due to technical disruptions), or collection of new paradigms. Additionally, since the Einstein IRB approved our protocol modification to acquire data from five higher functioning persons with brain injury who were fully conscious and able to follow simple commands, we initiated testing with these individuals on the inpatient brain injury unit at MossRehab. Finally, we started recruiting and testing inpatients admitted to the Responsiveness Program at MossRehab. All of these individuals were clinically diagnosed with Disorders of Consciousness (DoCs). By the end of the project period, four patients had been admitted to the program since beginning this phase of the study and three legally authorized representatives consented for their family member's participation.

Instrumentation Challenges

As the study progressed to assessment of persons with brain injury, we encountered a few technical challenges that are unique to this patient population in the early stages of recovery (versus in the chronic stages). Specifically, many individuals after a severe TBI undergo craniectomies, in which a portion of the cranium is removed to relieve pressure from cerebral edema. Although the "skull flap" is eventually replaced, the cranioplasty does not occur until months later. Many of our patients undergo inpatient rehabilitation prior to the cranioplasty. Although our EEG system uses the most advanced technology of caps with high density arrays of active pin-type electrodes, the application process is complicated when a portion of the cranium is missing because no solid surface remains to apply pressure when inserting electrodes. While this application can technically be performed, the duration is substantially increased and longer than we can afford in the rehabilitation setting (i.e., between tight therapy schedules). After consulting with another DoC researcher colleague at University of California Los Angeles and in the interest of patient safety and testing time, ultimately we made the decision to avoid instrumenting the craniectomy sites. Other challenges we encountered in some patients included excessive automatic or involuntary movements and diaphoresis. These conditions impacted the efficiency of the instrumentation process as well as data processing and analysis.

Data Processing and Analysis

The methodology we originally proposed used a machine classifier to determine accuracy of individual trials where the subject was asked to "move hands" or "hold still," based on both cerebral activity and accelerometry. The goal was to replicate EEG methods published in the literature. However, our consultants at Weill-Cornell Medical College performed a reanalysis of the published data using a statistical technique that they argued was more appropriate. Using this technique, the data from a number of the published subjects no longer demonstrated statistically significant evidence of consciousness. The results of this reanalysis made us seek alternative statistical methods using EEG spectral analysis, developed with the help of our consultants. The method that we implemented made many fewer assumptions than the method originally proposed. Given the heterogeneity in this patient population, minimizing statistical assumptions is a reasonable strategy. However, the new statistical technique weighs the EEG data from all trials to come up with an overall estimate of the statistical significance of the evidence for consciousness, but does not classify individual trials as "move hands" or "hold still" trials, thus allowing calculation of accuracy at the individual trial level. This is desirable if we want to examine continuous improvements in the strength of evidence for consciousness during the course of recovery.

Using Skype and Google + technologies, we worked with our consultants on learning the new data processing techniques and analyses and applied them to data from healthy individuals and patients with brain injury. The pre-processing steps included manual rejection of data segments with obvious motion artifacts, removal of 60Hz line noise, and removal of eye movement and electromyographic artifact with Independent Component Analysis. Next, a Laplacian montage and a multitaper Fourier transform were applied. Finally, a Two Group Test (TGT) was conducted for each channel of data from 4 to 24 Hz (frequencies within which we would anticipate differences between conditions) to determine if significant differences existed among electrical signals when patients were asked to "move hands" versus "hold still."

Currently this analysis can only be performed with paradigms that compare two conditions as dictated by the TGT. While we continued to collect the originally planned four paradigms with healthy individuals and persons with BI for possible future use, we elected to test patients with DoCs using the simplest paradigm that asks patients to differentiate between moving both hands and holding still (i.e., two conditions). As mentioned, the ability to assess accuracy of EEG response to individual trials is another goal of our research. For example, if a patient's arousal level is high during the first several trials and he responds accurately, but then arousal and attention decrease as the session continues such that the person is no longer responding, the aggregate analysis may not show significant evidence of consciousness even though a subset of trials may have resulted in accurate responses. Therefore, we recently recruited the expertise of a biostatistician from Thomas Jefferson University to assist us in generating an additional statistically-sound strategy for evaluating individual trials during testing sessions.

Furthermore, because we were no longer using the machine classifier, we developed an analysis for our hand accelerometry data that permitted trial-by-trial classification of overt behavioral responses. Accelerations were extracted into epochs and grouped by command type. The mean of 3D accelerations from each trial (excluding the first second after command delivery) within each command type was calculated and trials were sorted in descending order of acceleration magnitude. If the patient's accuracy were perfect, we would predict that the first 30 trials would be "move hands" trials and the last 30 trials would be "hold still" trials, with deviations from this ordering indicating errors on individual trials. The Mann-Whitney U test is performed to determine statistical significance of the difference between "move hands" and "hold still" trials overall.

<u>Results</u>

Given the heterogeneity in the patient population with BI and the fact that each case must be analyzed individually, the results presented below provide representative data from a healthy individual and a patient clinically diagnosed in vegetative state. Also, because we are exploring new, complementary analyses to look at each trial during a session (versus all trials averaged) and are continuing to collect data from persons with DoCs beyond the funded project in order to increase sample size, we are refraining from drawing definitive conclusions about the degree of consciousness for persons with DoCs studied thus far.

EEG: For all spectrograms below, data represent the difference between the average of all "move hands" and all "hold still" trials. The x-axis denotes time in seconds. The first second is the time in which the command was presented followed by the response interval. Along the y-axis are the individual electrodes (e.g., A1, B16) along the motor strip bilaterally as well as the frequency bands (5 to 25Hz). On the far right, the color spectra quantify power changes represented by color bands in the spectrogram (-10 to 10 dB). Non-significant power changes are translucent, while significant changes have prominent color bands (*p*<.05). Of those changes that are significant, the goal is to observe concentrated patterns of decreased power (blue bands) throughout several electrode channels during the response interval (e.g. Figure 1a) rather than bands scattered in a few channels for brief time periods (e.g. Figure 2a).

Accelerations: Accuracy of movement or lack of movement for command conditions is presented below in dot density graphs. The x-axes show acceleration values. We aimed to observe tight data clusters with true hand movement occurring when the “move hands” command was given (high values) and no hand movement when the “hold still” command was given (values around zero). Figure 1b for a control participant displays this separation with 100% accuracy.

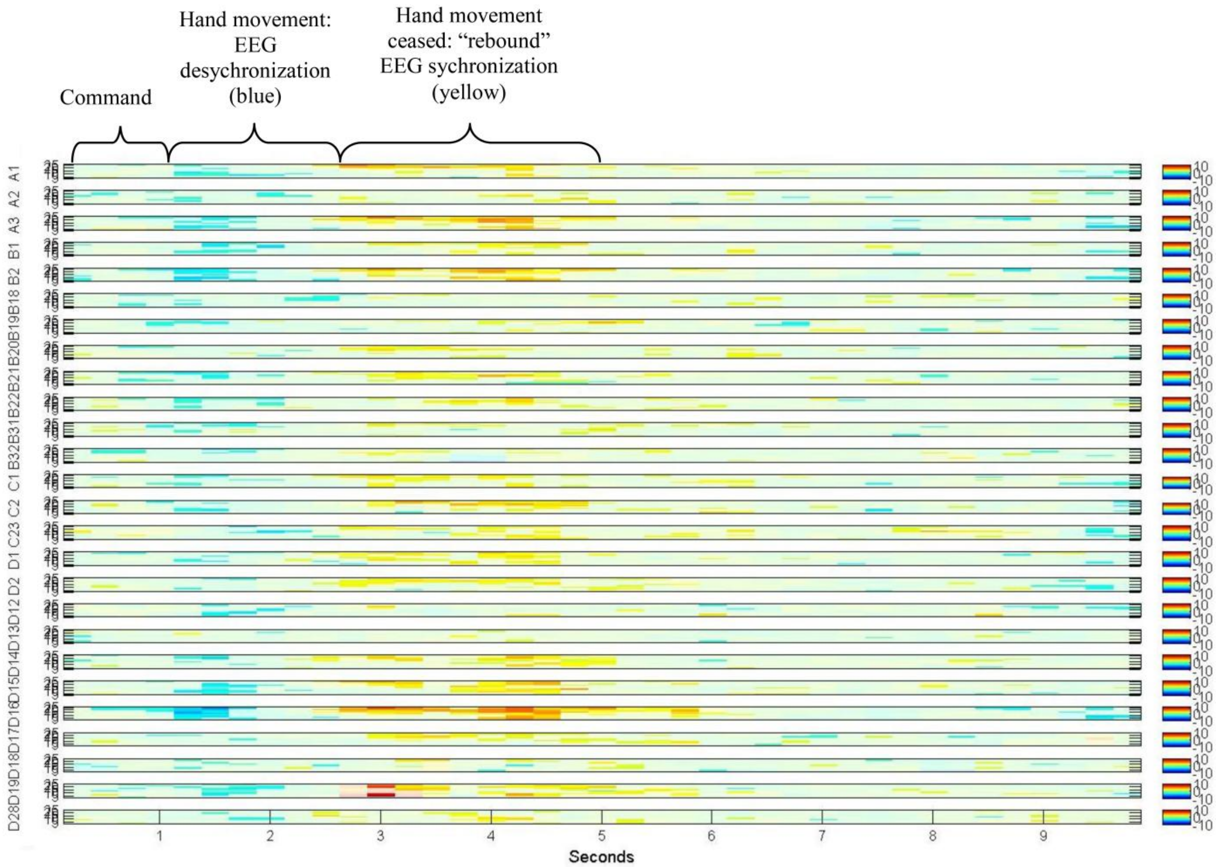

Figure 1a. Spectrogram for 23 year old female control participant. This individual moved bilateral hands briefly over 1-2 seconds immediately after the command.

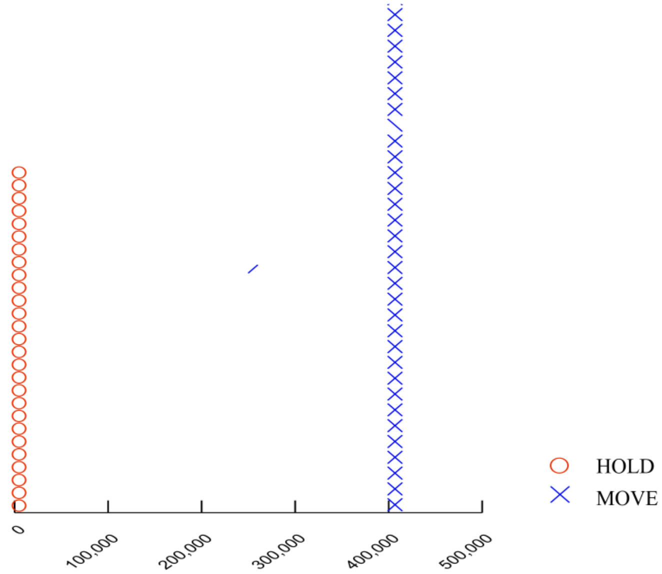

Figure 1b. Acceleration values for the control participant. Note the perfect separation of data for the two conditions (p<0.001).

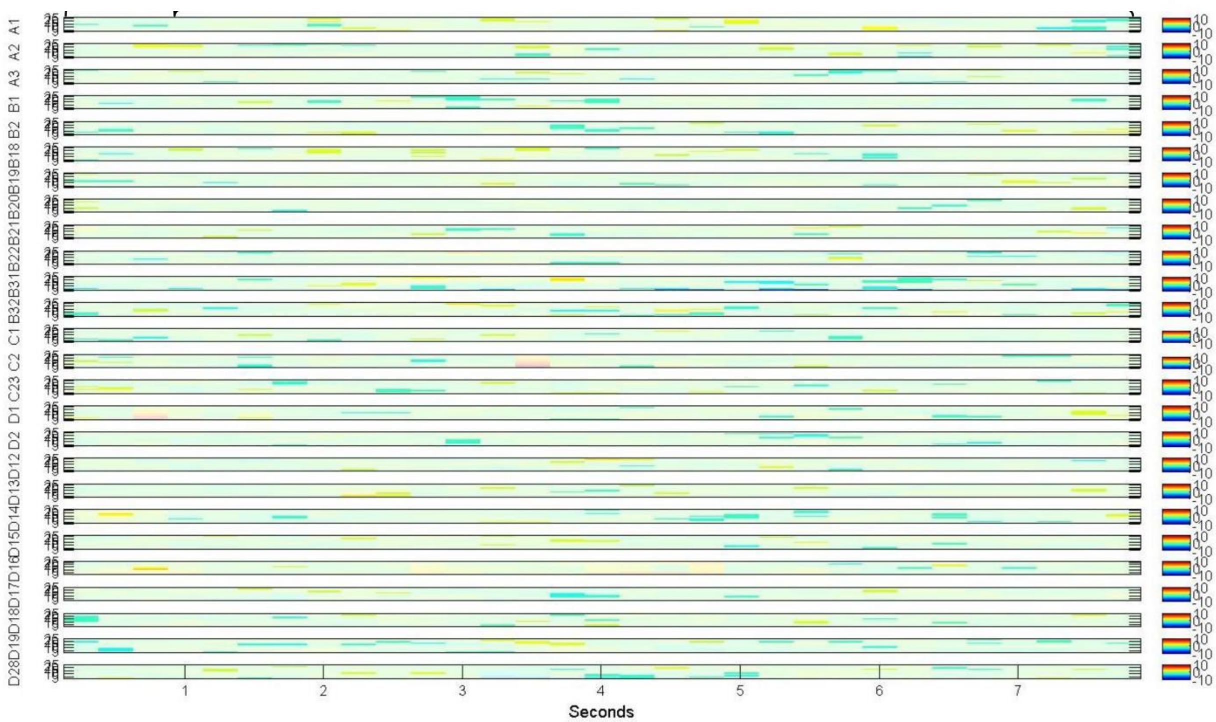

Figure 2a. Spectrogram for 34 year old female clinically diagnosed in vegetative state on CRS-R. No active hand movement.

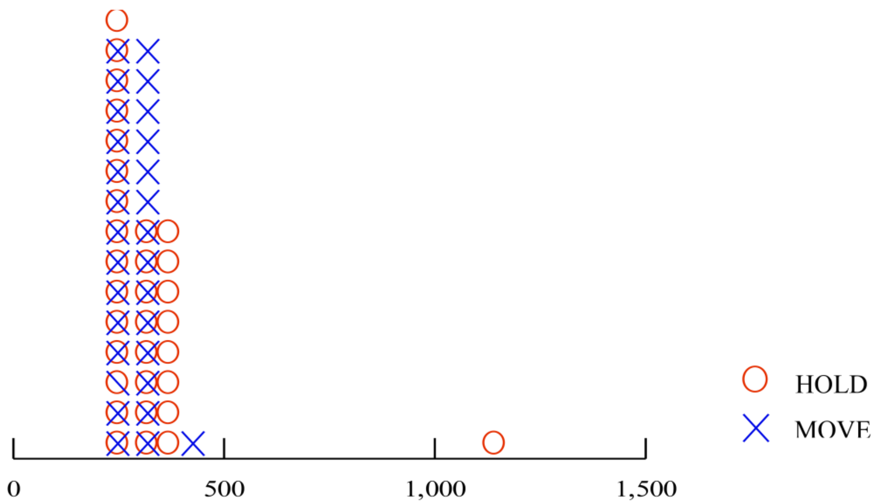

Figure 2b. Acceleration values for participant diagnosed in vegetative state. Zero separation of data is detected (*p*=0.942). Note the small scale on the x-axis relative to those for the control participant (Fig. 1b).

Research Project 2: Project Title and Purpose

Home-Based Mirror Therapy for Lower-Limb Rehabilitation Post-Stroke: A Pilot Study – Hemiparesis, or a weakness on one side of the body, is a frequent and disabling consequence of stroke. Lower limb hemiparesis can greatly limit the ability to walk and participate in activities of daily living. Mirror therapy (MT) is a relatively new therapeutic intervention that has been shown to improve the range of motion, speed, and accuracy of hemiparetic upper limb movements. MT uses a mirror to create an illusion where movements of the unimpaired limb appear as if they are being made by the impaired limb. The purpose of this study is to investigate whether a home-based form of MT is an effective treatment for lower limb hemiparesis.

Duration of Project

1/1/2013 – 6/30/2014

Project Overview

Stroke is a leading cause of long-term disability. Up to 60% of stroke survivors suffer significant and persistent neurologic deficits that limit participation in activities of daily living. When hemiparesis affects the lower limb, it impairs mobility and can be challenging to treat. Treatments that restore lower limb strength and control, and improve functional mobility could significantly impact stroke rehabilitation.

Mirror therapy (MT) is a relatively new therapeutic intervention for hemiparesis. MT involves performing movements with the unimpaired limb while watching its mirror reflection superimposed over the (unseen) impaired limb, thus creating a visual illusion of enhanced movement capability of the impaired limb. A growing body of clinical research indicates that upper limb MT benefits stroke patients to a degree comparable to or better than other therapies. Only one study has demonstrated efficacy of lower limb MT in a subacute, hospitalized stroke population, and potential benefits in a chronic population are unknown.

The primary aim of this study is to determine whether a home-based form of MT is an effective treatment of lower limb hemiparesis in chronic stroke survivors. The secondary aim is to evaluate the relationship between the amount of MT delivered (i.e., amount of practice) and improvement in key outcome measures, in order to identify the optimal dosage for this treatment. The therapy will consist of a standardized set of knee, ankle, and toe movements completed in two 30-minute sessions, 5 times per week for 4 weeks. Efficacy will be measured with a series of movement production tests measuring performance at the impairment and functional levels. If effective, MT will be one of very few treatments targeting the lower limb that is low-cost and can be administered in the home without therapist assistance. This is of tremendous importance to rehabilitation, particularly since we are targeting MT to a chronic stroke population which typically has limited access to physical therapy.

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Expected Research Outcomes and Benefits

We predict that people with stroke will show improvement in the strength and control of hemiparetic ankle movements following four weeks of home-based mirror therapy. This will be evaluated using standardized tests of muscle strength and an ankle tracking task, where participants are asked to track a moving target using ankle dorsiflexion and plantarflexion movements. We also predict that these improvements will be retained for up to three months post-treatment. Furthermore, we hypothesize that the improvement in ankle strength and control will be correlated with improvement in functional mobility, as assessed by gait speed and the Stroke Impact Scale, which evaluates the impact of stroke-related impairments on quality of life.

Importantly, this study will be the first to test whether a home-based mirror therapy training program can improve lower limb motor function people who have a stroke. The expected benefit of this project is to develop a new form of therapy that is effective, low-cost, and accessible to many stroke survivors who are currently not getting any treatment for gait disorders. Improving functional mobility in this population is of critical importance in terms of helping people recover the ability to perform activates of daily living and also for improving fitness and cardiovascular health, thus reducing the risk of a second stroke.

Summary of Research Completed

In the previous funding period (1/1/13-6/30/13), we designed and built equipment for home-based Mirror Therapy (MT). We also designed and built a device to quantitatively assess the ability to voluntarily control movement around the ankle joint. Pilot testing of these devices was completed in the prior funding period. Therefore, in the current period, we were able to focus our efforts on human subjects testing.

Our original aim was to recruit 8 participants. We recruited 11 participants, although only 7 of these individuals were included in the analysis. Two participants were withdrawn after consenting because they did not meet the inclusion criteria. An additional two withdrew shortly after baseline testing, but before training began, for personal reasons.

The 7 participants that were included underwent the testing paradigm shown in Figure 1. Unfortunately, 2/7 withdrew after completing mid-treatment session 3; both participants withdrew due to personal reasons (lack of time). The remaining 5/7 participants completed all training sessions and reported that the training was quite feasible. In fact, many responded positively to the training and reported that they were pleased to be trying these exercises at home. Nevertheless, our drop-out rate in the small pilot study was 2/7 or 29%. It is important that we have identified this high drop-out rate before pursuing a larger-scale study. Now that we know this, we will revisit our recruitment and communication strategies to help identify individuals who are likely to stick with training (i.e., those that have enough time) and to help motivate individuals who are undergoing training.

The primary aim of this study was to determine whether a home-based form of MT is an effective treatment of lower limb hemiparesis in chronic stroke survivors. MT consisted of a set lower limb movements involving the hip, knee, and ankle. Efficacy was measured with a series of tests measuring movement production ability and functional mobility, including tests of voluntary ankle control, lower limb Fugl-Meyer Assessment (FMA), preferred walking speed and maximal walking speed. Volitional ankle control was evaluated using an ankle tracking task, which was described in detail in the previous progress report (1/1/13-6/30/13). The participant's shank and foot were strapped into a modified orthotic that was hinged around the ankle joint. The participant was asked to dorsiflex and plantarflex the ankle, and output from a potentiometer measuring rotation around the ankle was shown to the participant on a computer screen. Participants were instructed to plantarflex and dorsiflex in order to track the movement of a sine wave that was also displayed on the screen. An accuracy index (AI) was calculated as $AI=(P-E)/P$, where E is the root-mean-square (rms) error between the target sine wave and the participant's response (i.e., potentiometer signal), and P is the rms value between the sine wave and the midline separating the upper and lower phases of the sine wave. The maximum possible score is 100%, indicating perfect accuracy.

We first examined whether there were significant changes in any of these tests from the beginning to the end of training in the 7 participants. The post-training measurement was taken after 4 weeks of training for 5 participants; for the 2 participants who only completed up to the 3rd mid-treatment assessment, post-training was taken after 3 weeks of training. We found that only the accuracy index on the more affected side improved significantly over the course of training ($p<0.05$) (Figure 2). Accuracy index on the less affected side and scores on the lower limb Fugl-Meyer Assessment also trended towards significance ($p = 0.07$), which is notable considering our small sample size and low power. There were no significant changes in preferred walking speed ($p=0.67$), or fastest walking speed ($p=0.30$).

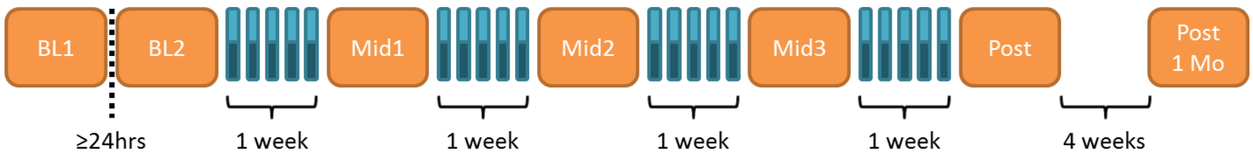
The secondary aim of this study was to evaluate the relationship between the amount of MT delivered (i.e., amount of practice) and improvement in key outcome measures, in order to identify the optimal dosage for this treatment. These changes are shown by box and whisker plots in Figure 3. Outcome measures during the second baseline period (BL2) were used as reference values. Changes from BL2 are shown for accuracy index (more affected & less affected legs), Fugl-Meyer Assessment scores, preferred walking speed, and fastest walking speed across MT training. Note that only five subjects were included in Post and Post 1Mo, since two withdrew after Mid3.

It is acknowledged that the data shown in Figure 3 are preliminary, but there are a couple of trends emerging that are worth noting. First, all subjects appear to be improving accuracy index on the more affected leg (Figure 3B) – this trend begins around Mid2 and persists up to 1 month post-training (Post 1Mo). This suggests that MT improved volitional control around the ankle joint on the more affected side. Many people with hemiparesis due to stroke have weak dorsiflexors and evertors, and rely on ankle-foot orthoses (AFO) to walk. It is possible that training the ankle muscles through a paradigm like MT could significantly improve functional gait in these people.

Second, all subjects show improvements in preferred walking speed at Post 1Mo, but these improvements are not evident earlier in training (Figure 3D). The minimally clinically important difference (MCID) in walking speed is 0.16 m/s in persons with stroke, and two out of the five participants who completed all sessions achieved this (all subjects mean = 0.14 m/s). This change from baseline does not occur until after MT has ended – it is not clear whether this is a delayed effect of MT and improved ankle control, or if the training encouraged individuals to be more active once the training ended. Regardless, such delayed effects of training have been reported in other gait training studies. In fact, Reisman and colleagues did not show walking speed improvements exceeding the MCID until 8 weeks post-training, whereas we only tested up to 4 weeks post-training. It is also important to note that we were able to achieve close-to MCID improvements in gait speed using a home-based treatment; to the best of our knowledge, this has not been previously reported.

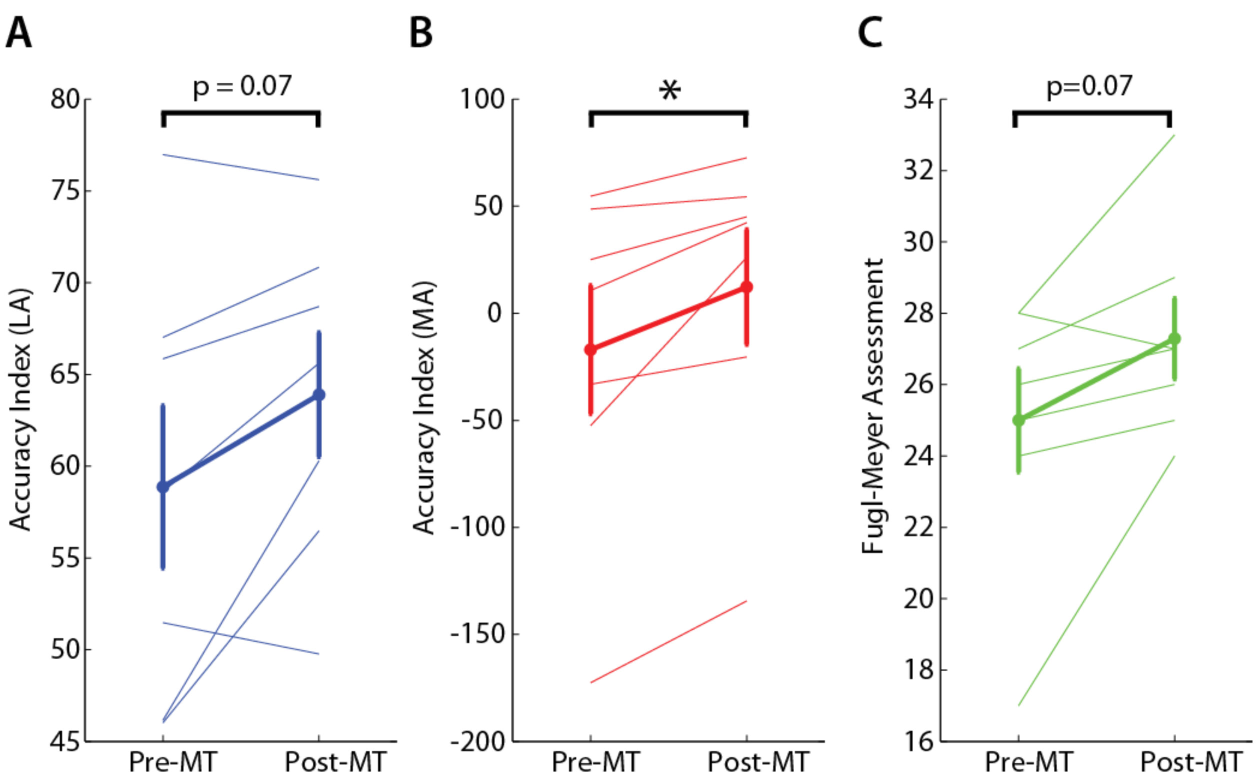
Overall, we have identified some positive effects of MT, particularly on volitional control of the more affected ankle. MT may also contribute to improved walking speed over time. The pilot study funded by this award is a first step towards establishing a home-based therapy for gait rehabilitation for stroke survivors who have limited access to other forms of rehabilitation.

Figure 1:



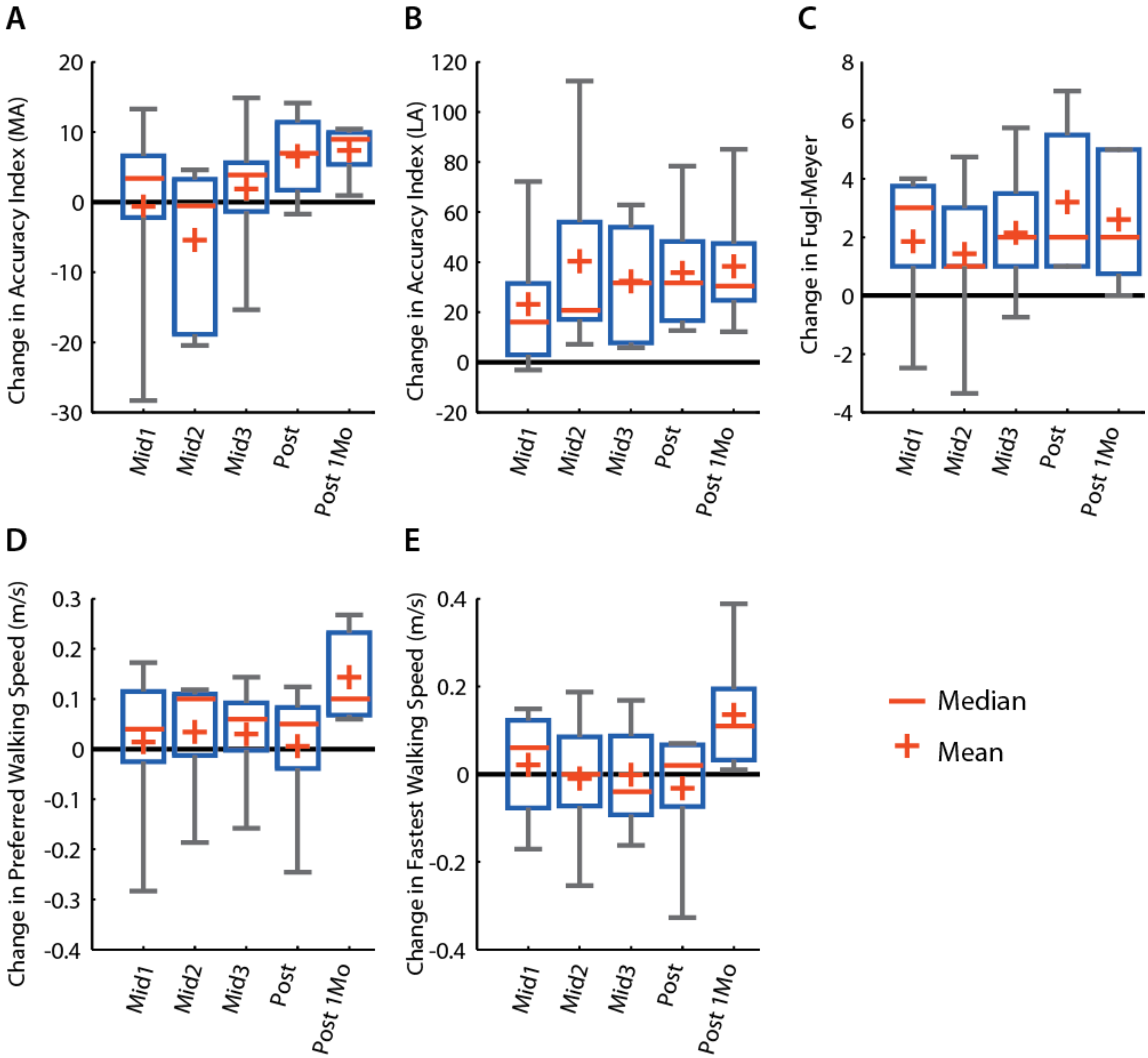
Mirror Therapy (MT) Experimental Paradigm: Orange blocks indicate sessions that were performed in the laboratory. During these sessions, we tested each participant's accuracy index (AI), preferred and fastest walking speeds, and lower limb Fugl-Meyer assessment. Teal blocks show MT practice sessions that were performed at home. During each practice week, participants did the mirror therapy home training DVD for five days, with two 30 min sessions per day. A follow-up test was performed at one month to measure retention. Abbreviations: BL, baseline assessment; Mid, mid-treatment assessment; Post, post-treatment assessment.

Figure 2:



Changes in Accuracy Index and Fugl-Meyer Assessment scores before and immediately following 3-4 weeks of MT. Accuracy index is shown for the less affected (LA) and more affected leg in (A) and (B), respectively. There were significant improvements in the accuracy index on the more affected side (B), suggesting that these participants made significant gains in volitional ankle control on this side. Fugl-Meyer Assessment (C) and Accuracy Index for the less affected side (B) trended towards significance.

Figure 3:



Changes from baseline in accuracy index (A & B), Fugl-Meyer Assessment scores (C), preferred walking speed (D) and fastest walking speed (E) during mirror therapy training. Values from the second baseline test (BL2) were subtracted from all subsequent values to quantify change. Therefore, performance at BL2 is equivalent to zero. Positive values indicate improvement. Mean and medians are shown in red; blue boxes indicate the 25th – 75th percentiles and whiskers (grey lines) show the range of all the data.