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14. ABSTRACT

This study evaluated Constraint-Induced Movement (CI) therapy for promoting motor recovery in veterans and civilians with traumatic brain injury (TBI). This form of physical rehabilitation has been shown to substantially improve motor function after brain injury not due to trauma and to provoke a widespread neuroplastic response in the brain. This single blind, randomized controlled trial (N = 40) compared CI therapy for improving use of the more-affected arm in adults with TBI to a holistic fitness program named Lakeshore Enriched Fitness Training (LEFT). In addition to assessing changes from pre-treatment in more-affected arm motor function at post-treatment and 1-year afterwards, changes were examined in white matter, grey matter, and functional brain activity. Products at the end of the four years of this blinded study were a manual of procedures, a method for generating synthetic neuroimaging data for the purpose of evaluating the sensitvity of the techniques proposed for quantifying changes in grey matter, and a manuscript on the study protocol.

15. SUBJECT TERMS
Constraint-Induced Movement therapy, neurorehabilitation, traumatic brain injury, upper-extremity, hemiparesis, neuroplasticity

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1. INTRODUCTION

The purpose of this study was to determine the value of Constraint-Induced Movement (CI) therapy for promoting motor recovery in veterans and civilians with traumatic brain injury (TBI). CI therapy is a family of physical rehabilitation interventions derived from basic research in behavioral neuroscience and behavioral psychology. Each of the members of the family has four main components: (a) extensive, intensive training; (b) organization of the training following shaping principles, a well-known method in psychology for teaching new behaviors; (c) constraint of compensatory behaviors; and (d) a package of behavioral techniques designed to transfer therapeutic gains from the treatment to everyday setting. CI therapy has been shown in controlled studies to produce substantial improvement in function in motor disorders produced by several types of damage to the central nervous system and to produce widespread plastic changes in the organization and structure of the brain. Preliminary data suggested that CI therapy has an equivalent positive effect for motor deficit produced by TBI in military and civilian populations. This rigorous, single blind, randomized controlled trial compared the efficacy of CI therapy for improving use of the more-affected arm in adults with TBI to a holistic fitness program named Lakeshore Enriched Fitness Training (LEFT). Half of this intervention consisted of meditation and relaxation exercises based on breathing; the other half consisted of physical fitness exercises. Forty adults with TBI, who were randomly assigned to each group, completed both pre- and post-treatment testing. Participants in each group received 35 hours of training over two weeks, although the type of training, i.e., CI therapy vs. LEFT, varied depending on group assignment. Assessment of more-affected arm motor function was conducted at pre- and post-treatment and 1-year afterwards. On the same occasions, magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), and functional MRI (fMRI) of the brain was carried out to determine changes in white matter, grey matter, and functional brain activity and their relation to any changes in motor function of the more-affected arm. A paper is attached that reports the study protocol, including a detailed description of the CI therapy and LEFT interventions and a comprehensive testing schedule.

2. KEYWORDS

Constraint-Induced Movement therapy
neurorehabilitation
occupational therapy
physical therapy
traumatic brain injury
arm
hand
upper extremity

hemiparesis
neuroplasticity
magnetic resonance imaging
diffusion tensor imaging
fMRI

3. ACCOMPLISHMENTS

3a. What were the major goals of the project?

1. To compare the effect of CI therapy and LEFT training on motor function in TBI patients.
2. To determine whether the initial clinical treatment effect, if any, persists over time.
3. To ascertain whether plastic brain changes accompany whatever clinical changes that may result from CI therapy and LEFT, and whether the magnitude of the clinical and plastic brain changes are correlated.
4. To evaluate the effects of CI therapy and LEFT on return to work and quality of life on a preliminary basis.

Table 1. Milestones

Milestones	*Date Completed or Percent of Task Completed*
Year 1	
IRB approval for UAB and Lakeshore Foundation sites	Pre-award (3/26/14)
HRPO approval for these two sites	Pre-award (9/8/15)
IRB approval for VA recruitment sites	
Birmingham VAMC	Month 1 (10/22/14)
Richmond VAMC	Month 2 (11/11/14)
Denver VAMC	Month 4 (1/9/15)
HRPO approval for VA recruitment sites	
Birmingham VAMC	Month 6 (3/31/15)
Richmond VAMC	Month 6 (3/31/15)
Denver VAMC	Month 7 (4/2/15)
All personnel on board	Month 1
Data system set-up	Month 2
Enroll 11 participants	11 enrolled (100%)
Treat & pre- and post-test first 11 participants	9 completed (81%)
Year 2	
Enroll 33 additional participants	33 enrolled (100%)
Treat & pre- and post-test 33 participants	13 completed (39%)
Conduct 1-year follow-up testing for 9 participants treated in Year 1	2 completed at least primary outcome (22%)
Year 3	

Enroll 32 additional participants	13 enrolled (41%, one of 13 enrolled in Year 4, Quarter 1)
Treat & pre- and post-test 32 participants	18 completed (56%, one of 18 completed in Year 4, Quarter 1)
Conduct testing for 20 participants treated in Years 1 & 2 with outstanding 1-year follow-ups	16 completed at least primary outcome (80%)
Year 4	
Conduct testing for 22 participants treated in previous years with outstanding 1-year follow-ups	13 completed (60%)
Process accelerometry and neuroimaging data	Month 48 (9/29/18)
Analyze data	Month 44 (major outcomes, 6/30/18)
Write-up and disseminate data	Month 51 (12/28/18, presentations made at 3 scientific conferences, protocol paper in press)
Note. The milestones, i.e., completion targets, for tasks are from the most recent version of the statement of work, which is dated October 26, 2015 and was approved by the DOD.	

A small number of changes to the methods were made since our application was submitted. All have already been described in our pre-award correspondence or quarterly progress reports and been reviewed with and approved by the Science Officer for this project or the HRPO or both. The changes, which are listed below, were all made in Year 1 except for the one described in the last bullet. All have been described in previous progress or annual reports.

- The original design for this RCT was a 2 x 2 factorial: Type of Therapy (CI therapy vs. LEFT) X Severity of Arm Motor Impairment (Mild-to-moderate vs. Moderate). A third factor was added after the award was made: Provision of Transfer Package (Standard vs. Enhanced). The Transfer Package is a set of behavioral techniques designed to facilitate transfer of gains from the treatment to everyday setting.
- Collection of data on the presence of variants of the gene that codes for BDNF was added. Animals with different variants of this gene have varying neuroplastic responses to training. We wanted to test whether the response to rehabilitation will vary among study participants with different variants of this gene.
- Housing of participants was split between the Lakeshore Foundation and our institution, the University of Alabama at Birmingham (UAB). All participants were originally to have been housed at the Lakeshore Foundation.
- The makeup of the VA recruitment sites was changed. Subcontracts were negotiated with the Birmingham VAMC, Denver VAMC, and Richmond VAMC.

- The option of collecting MRI data using a 1.5T scanner was added for participants for whom a 3T scanner is contraindicated but 1.5T is safe.
- The option of giving participants with anxiety about scanning a mild sedative agent was added.
- The collection of MRI scans was switched to a different set of scanners from the original instruments. This change was necessary because our University shut down the original scanners soon after the new scanners came on line. The new 3T scanner is a Siemens MAGNETOM Prisma 3T, which is considered state-of-the-art.

3b. What was accomplished under these goals?

The specific objectives in Year 1 were to obtain IRB and other regulatory approvals for the project, hire and train new personnel needed to round out the project team, refine and make final the study protocol, and recruit, enroll, treat, and test 11 participants. The specific objectives in Year 2 were to enroll, treat, and test an additional 33 participants and complete 1-year follow-up testing on the 11 participants planned for Year 1. The specific objectives in Year 3 were to enroll, treat, and test an additional 32 participants and complete 1-year follow-up testing on 20 participants treated in Year 1 and Year 2.

Major activities were largely in accord with these objectives. Table 1 shows that we obtained IRB and HRPO approval for study activities in Birmingham before the start of the award. Although applications for approval of recruitment activities at our VA recruitment sites were submitted to their respective IRBs two-three months before the start of the award, IRB and HRPO approval was not obtained for the last VA recruitment site until Month 7 of the project. The study was registered with clinicaltrials.gov in Month 4. All study personnel were on board before the end of Month 1. Training and verification that personnel had appropriate knowledge of and skill in the study procedures was completed by end-Month 3. In addition, the protocol for the LEFT intervention was refined and an enhanced version of the set of behavioral techniques used in CI therapy for transferring therapeutic gains from the therapeutic setting to everyday life was developed. The key aspects of the database that warehouses the study data were completed by end-Month 2. In Months 4-6, three practice participants were treated and tested to ensure that coordination of the complex array of treatment and testing procedures was in order. In addition, in this quarter, step-by-step instructions were written up for all the study procedures and assembled in a manual of procedures (MOP; see Section 6c.1). In Months 7-9, a method was developed for generating synthetic neuroimaging data to permit evaluation of the sensitivity of the different types of structural MRI analyses proposed on the study (see Section 6c.2). In Months 6-12, 11 participants were enrolled. Treatment and pre-and post-testing were completed with 9 participants. One participant withdrew after being randomized to the

LEFT intervention. The other was withdrawn by mutual consent of the project and the mother of the participant because the participant missed several treatment sessions.

In Year 2, 33 were enrolled. Treatment and pre- and post-testing were completed with 13 participants; 15 were scheduled for treatment and testing in Year 3. A total of 5 withdrew or were asked to withdraw. Three withdrew before pre-testing took place: one realized his work commitments did not permit participation in the project, one was a no show, and one had a spouse and psychiatrist who did not want him to take part in the study. One participant withdrew during pre-testing because he had to attend legal proceedings against him. Another was asked to withdraw during treatment because he missed or was very late for his treatment and testing sessions. One-year follow-up testing was completed with 2 of the 9 participants who completed treatment in Year 1.

In Year 3, 12 participants were enrolled. Treatment and pre- and post-testing were completed with 17. (The number treated was larger than the number enrolled because several participants who were enrolled in Year 2 were scheduled for treatment in Year 3.) One-year follow-up for at least the primary outcome was collected from 16 out of the 20 participants who were one-year or more after completion of treatment.

In Year 4, which was on a no-cost extension basis, one additional participant was enrolled, and treatment and pre- and post-testing were completed with that individual. One-year follow-up for at least the primary outcome was collected from 14 out of the 22 participants who were more than one year after completion of treatment. Since the inception of the project, 40 in total have completed pre-testing, treatment, and post-testing. One-year follow-up for at least the primary outcome has been collected from 32. In addition, in Year 4, processing of the accelerometry and neuroimaging data collected was completed, along with analysis of the major outcomes. The study procedures and findings were disseminated via three scientific conference presentations and acceptance for publication of a paper describing the study protocol. The study findings are discussed in **4. Impact**.

Recruitment of candidates for the study proceeded in parallel to these efforts. Since IRB and HRPO approval for recruitment of veterans with TBI at our VA sites was not yet granted, we initiated a major effort to recruit veterans in Alabama in Month 1 with the assistance of Admiral Clyde Marsh, Commissioner, Alabama Department of Veterans Affairs. Admiral Marsh directed his team to distribute this project's recruitment materials to all 67 county offices in Alabama of AlaVetNet. In Month 2, UAB did a press release in connection with Veterans Day, which was followed by interviews with two local television stations about the project and opportunities for veterans to take part in it. In Month 3, a brief recruitment interview was taped with Admiral Marsh for airing on TV in

Central Alabama on the program Veterans Affairs. We also placed color, 1/8 page ads in the Spring and Summer issues of US Veterans Magazine. In Year 2, the Brain Injury Association of American published a full page article in its newsletter describing the project, the inclusion and exclusion criteria, and the fact that the project would cover travel costs. Regrettably, these substantial efforts have yielded only a handful of contacts. It appears that outreach to the general community of veterans or civilians was too diffuse to reach our specific, target audience: veterans with TBI with motor impairment of one or both arms.

HRPO approval for recruitment activity at our three VA sites was received in Months 6 & 7. Recruitment efforts at these sites began shortly afterwards. The investigators at the three sites queried their electronic medical record system for the contact information of veterans with diagnostic and procedural codes reflecting a history of TBI and motor impairment of one or both arms. A cover letter, brochure, card to indicate interest, and stamped, addressed return envelope were mailed in batches of 100 to 500 to veterans who fit these criteria. Since HRPO approval was received for partner site recruitment activity, the Birmingham VAMC site mailed materials to 554 veterans. The Richmond VAMC site database search yielded 9,695 records, out of which 284 were determined to be likely enough candidates to mail a letter after review. The Denver VAMC site mailed materials to 40,600 veterans, out of which 360 were determined to be likely enough candidates to refer to UAB. In addition, in Month 6, the Director of the TBI Model Systems Center at UAB, Thomas Novack, PhD, who is an investigator on this project, mailed materials to approximately 100 civilians with TBI. (Dr. Novack has also directed patients under his care who appeared to be likely candidates to the study.) In Year 2, the TBI Model Systems Centers at Moss Rehabilitation Center in Philadelphia and Craig Hospital in Denver mailed materials to approximately 100 civilians each. This recruitment strategy, targeted mailings, has proven to be most productive.

The recruitment efforts over the project period resulted in a total of 763 unique contacts of candidates with the project. Out of this number, telephone or videoconference screens were completed with at least 677. Out of this number, 464 did not pass the telephone or videoconference screen and 89 expressed lack of interest in taking part in the study. Out of the remaining 124 candidates, 57 have received comprehensive, on-site screening, met study criteria, and agreed to take part in the study. The breakdown of reasons candidates did not qualify for the study after screening was: arm function too high (60%), did not have a TBI (17%), arm function too low (12%), health issues that prevented the candidate from participating in the study (8%), and problems with cognition, memory, or behavior severe enough to prevent participation in the study (2%).

The reasons that enrollment fell short of the targets in the original statement of work are discussed in Section 5b. The reasons treatment and testing fell behind the targets for these activities is also discussed in this section.

Appendix A tables the work completed on data collection and entry. For the pre- and post-treatment testing occasions, 100% of the clinical outcome data from participants who have completed treatment has been collected and entered, except for two measures. General fitness data have been collected from 98% of participants. General fitness data was not collected from one participant because she could not tolerate additional testing; she completed the upper-extremity motor, cognitive, and quality of life testing before reaching her limit. As noted in our Year 3, Quarter 2 Progress Report, we discontinued administration of the Frontal Systems Behavioral Scale (FrSBe), which is a measure of a participant's executive function that is completed by a family caregiver, because of considerable difficulty with soliciting responses from family caregivers. The FrSBE is not one of the principal outcome measures for this project. Moreover, the Wisconsin Card Sorting Test, which is another test of executive function, has been completed with all of the participants to date. MRI scans have only been collected from 38% of participants. Reasons for and steps to remedy the shortfall in MRI data collection are discussed in Section 5b. One-year follow-up data for the primary outcome, i.e., the Motor Activity Log (MAL), have been collected for 80% of the participants who completed both pre- and post-treatment testing. A larger proportion of data are missing for the secondary outcome measures, since they require testing in person unlike the MAL. The MAL, which is a measure of quality and amount of use of the more-affected arm in the community, can be administered over the telephone permitting collection of data from participants who cannot return to the laboratory on their 1-year anniversary.

3c. What opportunities for training and professional development did the project provide?

This project does not have a formal training and professional development component. Training in the study procedures and in the conduct of research, however, has been provided to several staff members and students. Laura Reder, PTA, the blinded tester, has been trained to conduct the motor testing on a blinded basis. This training includes the Motor Activity Log and Wolf Motor Function Test, which are widely used in neurorehabilitation research, and the acquisition of data for kinematic studies of movement. Ms. Reder has also received training in the ethical conduct of research with humans. Brice Lambert, the data manager, has received training in processing the data from the movement monitors used to track changes in amount of movement of the more-affected arm in everyday life outside the laboratory and in searching the electronic medical records system in use at our University's health system and elsewhere. Michele

Haddad, one of the graduate students who works on the analysis of the neuroimaging data, has received further mentoring in voxel-based morphometry, a method for quantifying changes in grey matter. Brent Womble, the other graduate student who works on the analysis of the neuroimaging data, has received mentoring in tract-based spatial statistics and Freesurfer, which are methods for quantifying changes in white matter and grey matter, respectively. Ms. Haddad and Mr. Womble have also received mentoring in experimental strategy, study design, and interpretation and writing up of data. Eight undergraduates, four on a work study basis and four on a volunteer basis, have received training in the ethical conduct of research with humans, the data entry and processing procedures, and in selected components of the study testing and treatment procedures.

3d. How were the results disseminated to communities of interest?
In Year 4, the PI presented findings on the major outcomes at the: 4th Federal Interagency Conference on TBI in Washington, DC; American Congress of Rehabilitation Meeting 95th Annual Conference in Dallas, TX; and Military Health System Research Symposium in Kissimmee, FL. These three scientific conferences were attended by researchers, clinicians, and policymakers from the fields of neurorehabilitation, veteran healthcare, and military health care, permitting dissemination to these communities. In addition, a paper describing the study protocol was accepted for publication by the *Journal of Head Trauma Rehabilitation*, which is read widely by TBI researchers and clinicians and has a high impact factor (3.4). (See **6a** for reference list of the presentations and publications.) Please note that both the investigators and testing personnel on this project were blinded at the outset to exclude the possibility of experimenter bias from influencing the study results. Hence, analysis of the efficacy of the interventions tested and the write-up and dissemination of these results to the scientific, healthcare, and patient communities had to wait until Year 4, Quarter 2 when the study was unblinded.

Our recruitment efforts have increased awareness among veterans and the general public that impairment in the motor function of the arms after TBI may be amenable to treatment. Regrettably, little attention by healthcare professionals is paid to rehabilitation of motor function, particularly of the arms, after TBI because of the prominent nature of the cognitive impairments present after TBI. Hence, impairment of upper-extremity motor function often goes untreated and survivors live with persistent deficits. As noted, the project has been featured in several local television broadcasts, in a nationwide podcast, and in an article in the September, 2016 edition of the newsletter of the Brain Injury Association of America. In addition, letters and recruitment brochures have been mailed to approximately 40,000 veterans across the country and 5,000 brochures have distributed across the state of Alabama by AlaVetNet county

offices. We believe these efforts are starting to change the view of patients with TBI, at least in Alabama, from nothing can be done to something needs to and can be done about upper-extremity motor impairment after TBI.

3e. What do you plan to do during the next reporting period to accomplish the goals?

We will continue our efforts to disseminate the study results beyond the end of the project period. Over the next year, we plan to submit a manuscript to a major neurorehabilitation journal, such as *Neurorehabilitation and Neural Repair*, reporting the findings on the primary outcome, the MAL (see **4a**), and other motor rehabilitation outcomes. In addition, we plan to submit a manuscript reporting findings on the measures of psychiatric symptoms and another on findings on the measures of physical fitness. These manuscripts will be submitted to the *Journal of Head Trauma Rehabilitation*. The editor has invited multiple submissions from this project in recognition of the importance of the study findings to the field of TBI rehabilitation. In addition, we plan to submit one or more manuscripts reporting findings on the measures of brain structure and function and on the new method described in **6c.2** for generating synthetic brain images for the purpose of evaluating the validity of different neuroimaging techniques.

4. IMPACT

4a. What was the impact on the development of the principal discipline of the project?

We first present noteworthy findings on the motor rehabilitation outcomes, and then discuss their importance for neurorehabilitation and TBI care.

The primary outcome was the Motor Activity Log (MAL). The MAL Arm Use scale is a widely used, validated structured interview that assesses how much and how well a patient with upper-extremity paresis uses their more-affected arm in daily life. Scale values range from 0 to 5 points (0 = no use of the more-affected arm, 5 = normal use). , An important secondary outcome was the Wolf Motor Function Test (WMFT). The WMFT is a widely used, validated motor performance test that assesses the motor capacity of that arm in the laboratory setting. The WMFT Performance Rate score is the average number of repetitions of each task that a patient can perform in a minute.

To review, the study effectively had a 2 x 2 factorial design. The first factor was type of treatment: Constraint-Induced Movement therapy (CIMT) vs. Lakeshore Enriched Fitness Training (LEFT; LEFT is holistic fitness training program). The second factor was type of transfer package: standard vs. enhanced. The transfer package (TP) was the component of the interventions that was designed to promote transfer of gains from

the treatment setting to everyday life. The enhanced TP differed from the standard TP mainly in that enhanced TP participants were asked to place physical cues in their homes to prompt activities aligned with their treatment plan, keep the diary of daily activity in an online format that permits rapid feedback from the treatment team, and engage in additional interaction with the treatment team during the follow-up period. The two factors defined four groups: CIMT with the standard TP, CIMT with the enhanced TP, LEFT with the standard TP, and LEFT with the enhanced TP.

The pre-, post- and pre- to post-treatment change scores on the MAL Arm Use scale and WMFT Performance Time are tabled and graphed in Appendix B. On the MAL, CIMT resulted in a significantly larger improvement from pre- to post-treatment than LEFT ($p = .001$), independently of the type of TP used. CIMT participants, on average, showed an improvement of 166% in use of the more-affected arm in daily life; LEFT participants, on average showed an improvement of 42%. The type of TP did not have an independent effect on MAL gains ($p = .924$); nor did the effect of TP type vary with treatment type ($p = .21$). On the WMFT, none of the between-group differences in pre- to post-treatment gains were significant. All four of the groups showed an improvement in Performance Rate of about 25% ($p < .001$). The divergence in results between the MAL and WMFT is consistent with previous CIMT studies from our laboratory. As noted, the MAL assesses actual use of the more-affected arm in daily life, while the WMFT assesses how rapidly tasks are completed with that arm in the laboratory when the participant is asked to complete the tasks with that arm as rapidly as possible. In other words, the WMFT assesses maximum motor capacity. The learned nonuse formulation, on which CIMT is based, predicts a divergence between motor capacity and use of that capacity. This divergence has been observed in previous studies from this laboratory.

These findings represent the first evidence of efficacy from a rigorously designed study, i.e., a single-blinded, randomized controlled trial, for an upper-extremity physical rehabilitation intervention for adults with TBI. Regrettably, motor deficit after TBI has received little attention because cognitive impairments typically dominate the attention paid to symptoms exhibited by TBI patients. We expect that the availability of an efficacious intervention for upper extremity paresis after TBI, i.e., CI therapy, will prompt researchers to pay more attention to this aspect of impairment after TBI and prompt clinicians to offer CI therapy to adults with TBI who can benefit. The Department of Veterans Affairs has already designated CI therapy as an efficacious therapy for adults with upper extremity hemiparesis after stroke. We hope that the VA will make a similar recommendation with respect to TBI after the publication of the primary outcome paper from this project.

In addition to their implications for TBI care, the findings on the MAL and WMFT are of basic interest to the field of neurorehabilitation. The findings from this RCT add to the body of evidence showing that CI therapy is efficacious for upper extremity hemiparesis regardless of type of injury to the brain responsible for the motor impairment. Previous studies from our laboratory and elsewhere show that CI therapy is efficacious for upper extremity hemiparesis in adults after stroke (focal injury), adults with multiple sclerosis (diffuse, progressive injuries), and children with cerebral palsy (focal injury and/or inappropriate development of the brain). Together with the data from this study, the entire body of evidence is consistent with the formulation that CI therapy has two separate but related mechanisms of action. The two are: (a) counterconditioning a learned nonuse of the more affected arm and (b) stimulating neuroplastic changes in the brain that support increased use of that arm. The first mechanism is behavioral; the second mechanism is physiological. Both are general in the sense that these mechanisms are amenable to manipulation regardless of the type and location of brain injury. We hope that this now considerable body of evidence stimulates researchers to consider how they can take advantage of these general mechanisms to rehabilitate function across a variety of brain disorders.

4b. What was the impact on other disciplines?

First, we present noteworthy findings on the measures of psychiatric symptoms, and discuss their importance for clinical psychology, psychiatry, and TBI care. Second, we present noteworthy findings on the measures of brain structure and function, and discuss their importance for neurorehabilitation and behavioral neuroscience.

We found that the Lakeshore Enriched Fitness Training (LEFT) intervention produced marked improvement in post-traumatic stress disorder (PTSD) symptoms. PTSD symptoms were assessed using the PTSD Checklist-5 (PCL-5), which is a questionnaire that assesses the number and severity of post-traumatic stress disorder (PTSD) symptoms present. The score ranges from 0-80, with a 0 representing the absence of any PTSD symptoms and 80 representing the presence of all the symptoms with maximum severity. Scores equal to or greater than 33 are thought to reflect the presence of PTSD. Changes of 10 points or greater are considered to be clinically meaningful, while changes of 5 points or greater are considered to be reliable.

The LEFT intervention produced a marked reduction on the PCL-5 total score among those with a score consistent with the presence of PTSD before treatment. Five of the 21 participants in the LEFT group scored above the PTSD cut-off before treatment. The five (4 veterans) showed a mean reduction of 17.8 points ($SD = 5.6$; $p < .01$) after treatment. For all 5, the reductions were larger than the standard for a clinically meaningful change (i.e. more than 10 points). Moreover, 3 fell below the PTSD cut-off

after treatment. The main changes were in clusters D and E which relate to major depression and anxiety, respectively. Six of the 19 participants in the Constraint-Induced Movement therapy (CIMT) group scored above the PTSD cut-off before treatment. The six (4 veterans) had a mean increase of 0.7 points (SD = 8.2; n.s.) after treatment. None had a clinically meaningful reduction in symptoms. One participant who scored just above the PTSD cutoff before treatment fell below it after treatment. Pre- and post-treatment scores on the PCL-5 are graphed in Appendix B.

There are several mechanisms by which the LEFT intervention, a holistic fitness training program, might have produced a reduction in PTSD symptoms. LEFT included not only physical exercises such as aerobic exercise, gentle Hatha Yoga, and strengthening, flexibility and tone management exercises, but also meditation based on breathing (Pranayama), Tai Chi, and massage. Meditation and regulation of breathing, in particular, as well as Tai Chi and massage, have been shown to help adults manage stress and manage symptoms of anxiety and depressive disorders. Physical exercise has also been shown to have similar beneficial effects. Interestingly, selected forms of meditation and physical exercise have also been shown to stimulate neurogenesis, which has been shown to be important for relieving depressive symptoms in animal models.

We recognize that the number of observations that support the above result is small. However, the magnitude and consistency of the changes in the LEFT group are particularly noteworthy given the intractability of PTSD. Moreover, this study is one of less than a handful to attempt to combine physical activity with meditation for the treatment of PTSD or PTSD co-morbid with TBI, which is common in the veteran and military populations. Given that substantial numbers of civilians and veterans with PTSD do not tolerate the standard therapies, i.e., cognitive processing therapy (CPT), prolonged exposure therapy (PET), and pharmacotherapy, it is important to develop alternate forms of therapy that patients who dropped out of the standard therapies would accept. We plan to apply to the Department of Defense for funding to conduct a prospective, randomized controlled trial of the LEFT intervention.

Changes in neural activity, gray matter structures, and white matter tracts were measured using functional magnetic resonance imaging (fMRI), structural MRI, and diffusion weighted imaging (DWI), respectively. During collection of fMRI, participants were asked to alternate between extending their more-affected hand and resting their hand. During collection of structural MRI and DWI, participants were simply asked to rest. Increases in neural activity were observed in sensorimotor areas after CI therapy using multi-level modeling of the fMRI data, which were collected using a blood oxygen level dependent (BOLD) paradigm. These analyses revealed upregulation of brain

activities in brain regions that are responsible for visuomotor processing (i.e., precuneus), attention allocation, and decision-making (e.g., the anterior cingulate cortex). These are all functions that are engaged by CI therapy. Changes in grey matter structures, which were examined by applying longitudinal voxel-based morphometry (VBM) to the structural MRI scans, were not detected due to the small sample size (*n* = 6) in the CI therapy group. Interestingly, symmetric improvements in white matter (WM) integrity, assessed by tract-based spatial statistics (TBSS), were found in the LEFT group. The significant tracts spanned the whole brain (e.g., anterior thalamic radiation/ATR, forceps minor/FMI, etc), and were responsible for emotional processing (e.g., uncinated fasciculus/UF, cingulum cingulate/CC). These changes were thought to be related to the changes in PTSD symptoms observed in the LEFT group. Although these findings are preliminary, to the best of our knowledge, the white matter results represent the first report of such changes after a PTSD intervention. If we can confirm our preliminary findings in the prospective study that we plan to propose, the knowledge gained will advance understanding of the neurophysiological substrate of PTSD and its treatment.

4c. What was the impact on technology transfer?

We expect that the imminent publication of the study protocol, along with the anticipated publication of the primary outcome paper and accompanying manual of procedures, will support introduction of CI therapy as a treatment for upper extremity motor impairment after TBI into the VA and military and other healthcare systems. Our laboratory has conducted semiannual training programs at UAB for over a decade to rigorously train physical and occupational therapists to perform CI therapy. We have developed plans to create an online version of this training program, and can easily scale up our training activities to support widespread dissemination of CI therapy.

We expect that publication of a paper, which we plan to submit later this year, presenting the new method for generating synthetic data described in **6c.2**, will support adoption of this method by other research groups that employ structural MRI. This is an important development because the methods used by different research groups very widely, and there is not yet consensus about what is the best application of which methods. Nor is there a standard approach for evaluating this question.

4d. What was the impact on society beyond science and technology?

Please see the second paragraph of Section 3d**.**

5. CHANGES

5a. Changes in approach and reasons for change

There have been no other changes to our approach since our last annual report.

5b. Actual or anticipated problems or delays and actions or plans to resolve them
We fell short of our Year 1 target for enrollment in our original statement of work because of a long delay in gaining approval to recruit through our 3 partner VA recruitment sites. The measures we undertook to address this shortfall in Year 2 were successful. We met our Year 2 target for enrollment, i.e., 33 individuals, in our revised statement of work dated October 26, 2015. However, we did not meet our Year 3 target for enrollment, i.e., 32 individuals; we recruited only 12. A larger proportion of referrals to the study in Year 3 than in Year 2 did not meet the criteria for participation in the study. The funds available in the no-cost extension year, i.e., Year 4, did not permit enrollment, treatment, and testing of additional participants beyond the one participant treated and tested in Year 4, Quarter 1.

There was a long delay in gaining approval to recruit through our three VA recruitment sites in Year 1 because of multiple and lengthy administrative and regulatory hurdles to clear. Recruitment at the last VA site in Denver did not begin until May 18, 2015. These delays resulted despite our submitting the initial application for approval of this project to the IRB at UAB in January 2014, nine months before the start date of the award, and submitting initial versions of the applications for approval of recruitment activity at our three VA sites in June-July 2014, two-three months before the award start date. As reported previously, we initiated recruitment independently of our VA sites through the Department of Veterans Affairs in Alabama in October 2014 but that large effort, which involved distribution of recruitment brochures to all 67 AlaVetNeT county offices, among other measures, did not yield any candidates.

To address the shortfall in recruitment in Year 1, we expanded the recruitment activity that was originally planned for Year 2. At the Denver VAMC, the catchment area for candidates was expanded from the Denver VAMC to the entire VISN. At the Richmond VAMC, the original search of their electronic medical records limited the period to examined to 2005-2015; the search was expanded to 2001-2005. We sought the help of the TBI Model Systems Centers at Moss Rehabilitation Center in Philadelphia and Craig Hospital in Denver. Each center mailed materials to approximately 100 civilians each. We spoke about the project with Susan Conner, President of the Brain Injury Association of American. The Association published a full page article in its Fall newsletter about the project. As noted, the most successful form of outreach has been mailing a cover letter and brochure, along with a stamped, addressed return envelope, to likely candidates. To meet our target for enrollment in Year 3, which was 32 additional participants, we doubled the number of recruitment packets that are mailed out by the Denver VAMC to 600 per week.

Although we made substantial progress on treating and testing participants in Year 3, we fell short of the target. We completed treatment and testing with 17, which is 53% of the target of 32. The number we were able to treat and test was limited by the number we were able to recruit and the number of withdrawals from the study. As noted, we were only able to recruit 12 participants in Year 3. A similar number of candidates were referred to the study in Year 3 (n = 314), as in Year 2 (n = 297). However, the proportion eligible to take part in the study was substantially smaller in Year 3 (4%) than Year 2 (11%). The reason for this disparity is not clear since our recruitment methods did not change. In Year 3, five candidates who qualified for the study and agreed to participate withdrew or were withdrawn by study personnel before pre-treatment testing could take place. This number was the same as in Year 2. Two of the drop-outs in Year 3 did not identify a time to schedule treatment and testing after multiple attempts to do so. The other three developed health concerns that precluded taking part in the study.

As result of these challenges, the project will not reach the enrollment target in the revised statement of work for the entire project period, i.e., 77. We will also complete treatment and pre- and post-treatment testing with a smaller number of participants than planned, 40 vs. 62, because the withdrawal rate has been higher than anticipated, 30% vs. 20%. Nevertheless, the sample size present permits more than adequate power (> .99) to evaluate the first and most important specific aim of the study, which is to test whether CI therapy is an efficacious method for improving use in daily life of the more-affected of arm of adults with TBI. There is also adequate power to evaluate the second specific aim, which is whether any gains observed at post-treatment persist. Although we have collected 1-year follow-up data on the entire battery of study measures from a smaller number of participants than planned (see Section 3b), we have collected long-term follow-up data on the MAL, the primary outcome from 80% of the participants. We have been able to achieve this long-term follow-up collection rate because the MAL can be administered over the telephone, permitting collection of this key outcome even if a participant cannot return to the laboratory for collection of the other measures. The third aim was to determine whether any neuroplastic changes occur after the study interventions and whether any changes are related to the motor and other outcomes. As noted, we have collected MRI scans from only 38% of the participants who have completed treatment). The reason that scans were collected from only approximately a third of the participants is that many more participants than anticipated had shrapnel embedded in their bodies or medical implants, making it risky to a conduct a MRI scan. As a result, inadequate power is available to evaluate this aim in a comprehensive way. We were able to detect changes in neural activity and white matter structures in several regions of interest. The fourth aim of the study was to evaluate the effect of CI therapy on return to work and quality of life on a preliminary basis. We did not project adequate power to detect statistically significant differences between the study groups in the grant

application because measures of economic productivity and quality of life are typically highly variable. Any trends observed will help to decide whether it would be worthwhile for future studies with larger sample sizes to examine the effects of CI therapy on these outcomes.

5c. Changes that had a significant impact on expenditures

We noted in our previous reports that funds were being expended at a slower rate than planned because of the delays that resulted in enrollment at a lower rate in Year 1 than projected. As of end-Year 3, expenditures registered for total costs were $2,447,853. The amount budgeted was $2,664,760. The unexpended funds were carried into a no-cost extension year, i.e., Year 4. These funds were used to support recruitment, treatment, and testing of an additional participant, collection of one-year follow-up testing, and processing, analysis, and presentation of the study data. Expenditures for Year 4, including indirect costs, amounted to $224,091; expenditures for the entire project period totaled $2,671,944. Expenditures in excess of the amount awarded were absorbed by the Department of Psychology, the academic home of the PI.

5d. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report since the last annual report.

6. PRODUCTS

6a. Publications, conference papers, and presentations

Publications

Morris, D. M., Taub, E., Mark, V. W., Liu, W., Brenner, L., Pickett, T., Stearns-Yoder, K., Bishop-McKay, S., Taylor, A., Reder, L., Adams, T., Rimmer, J., Dew, D., Szaflarski, J., Womble, B., Stevens, L., Rothman, D., & Uswatte, G. (In press). Protocol for a randomized controlled trial of CI therapy for rehabilitation of upper extremity motor deficit: the Bringing Rehabilitation to American Veterans Everywhere (BRAVE) project. *The Journal of Head Trauma Rehabilitation*.

Conference Presentations

Taub, E., Morris, D., Corrigan, J., & Brenner, L. (2018, July). RCT of CI Therapy for Rehabilitating Upper Extremity Motor Function After TBI: The BRAVE Project. Paper presented at 4th Federal Interagency Conference on Traumatic Brain Injury, Washington D.C.

Taub, E., Uswatte, G., Morris, D., Brenner, L., Mark, V., Bishop-McKay, S., Adams, T., Liu, W., Pickett, T., Stearns-Yoder, K., Taylor, A., Reder, L., Rimmer, J., Dew, D., Szaflarski, J., Womble, B., Stevens, L., Rothman, D., & Allendorfer, J. (2018, August).

RCT of CI therapy vs. a meditation/exercise intervention (LEFT) for improving arm function and PTSD after TBI: The BRAVE Project. Poster presented at Military Health System Research Symposium, Kissimmee, FL.

Taub, E., Morris, D., Dos Anjos, S., Corrigan, J., & Brenner, L. (2018, October). RCT of CI vs. LEFT Therapy for Improving Arm Function and PTSD: The BRAVE Project. Paper presented at American Conference of Rehabilitation Medicine Annual Conference in TX, Dallas.

6b. Website or other Internet Site

We have developed a website for the purpose of recruiting participants. As noted, our recruitment activities had the benefit of increasing public awareness about the effects of TBI on motor function of the upper-extremities and the possibility of remedying those impairments. The website address is: **www.tbirehabtherapy.net.**

6c. Technology or techniques

1. *A manual of procedures that describes the treatment and testing procedures in detail has been completed.* It was submitted along with our Year 2, Quarter 2 Progress Report. When the study results are published, we will make the manual of procedures available as an electronic supplement or, if the journal that publishes the study results does not find that acceptable, via our laboratory website. Dissemination of the manual of procedures will permit researchers to replicate our study and clinicians to implement the interventions tested, if found to be efficacious, in their practices.

2. *A method was developed for generating synthetic data to permit evaluation of the sensitivity of the different types of structural MRI analyses proposed on the study.* Longitudinal structural analyses attempt to detect use-dependent structural neuroplasticity at a gross anatomical level. Longitudinal voxel-based morphometry (VBM) is traditionally used to detect changes in volume or density of grey matter relative to other tissue. Surface-based morphometry (e.g. Freesurfer) reconstructs the edge of the grey matter and white matter into 3-dimensional surfaces, then measures geometric values, e.g. distance (thickness), surface area, volume, and curvature (gyrification). These two methods were considered on this project to study if and what types of neuroplastic change CI therapy and LEFT induced in veterans and civilians with TBI.

   Longitudinal VBM and surface-based morphometry may be differentially sensitive to different types of cellular and gross anatomical changes taking place in use-dependent structural reorganization of the brain. Hence, a method was developed by our laboratory for generating synthetic data to permit evaluation of the sensitivity of these two structural MRI analysis methods to the different types of structural changes that we anticipated in the brain as a result of the study interventions.

We synthetically generated 3 longitudinal datasets with changes in each dataset isolated to a single gross anatomical (expansion or increased gyrification) or cellular (increased density) feature. All changes were made in the right superior frontal gyrus, using the anterior tip of the corpus callosum as a landmark. We used a point-based deformation technique to manually alter the shape of a gyrus. For cortical expansion, we pushed multiple points along the selected gyrus outward (**Fig. 1a**). For increased gyrification, we pushed two points along the selected gyrus inward, while keeping the overall shape of the gyrus intact (**Fig. 1b**). For increased density, we made a spherical region of the gyrus darker, with the change restricted to the grey matter (**Fig. 1c**). Finally, we processed these synthetic datasets using surface-based morphometry (Freesurfer 5.3), and we processed these datasets using VBM (SPM). Freesurfer accurately reconstructed the edge of the grey and white matter as the gyrus expanded and folded (**Fig. 1a-b**). Freesurfer did not detect the change in density (**Fig. 1c**). The VBM results suggested that SPM is more sensitive to changes in density than Freesurfer.

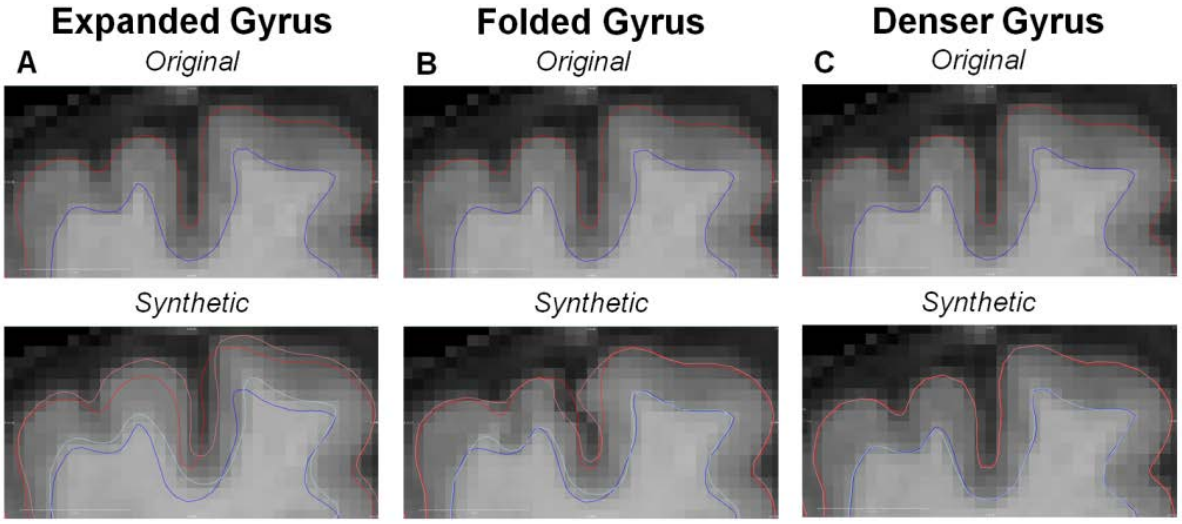


Figure 1. Freesurfer reconstruction of grey and white matter edges. The edges in the original brain are traced in red and blue. In the synthetic brains, the grey and white matter edges are traced in pink and light blue and are shown alongside the original traces.

This type of evaluation of imaging analysis methods has not been done to date. As noted, we plan to submit a manuscript later this year to a high impact neuroimaging journal describing the method for generating synthetic data and its application to evaluating the sensitivity of voxel-based morphometry and measurement of cortical thickness using Freesurfer.

6d. Inventions, patent applications, and/or licenses

Nothing to report.

6e. Other products

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

7a. What individuals have worked on the project?

Name: Edward Taub, PhD
Project Role: Principal Investigator, UAB
Researcher Identifier: n/a
Nearest person months worked: 2
Contribution to project: He supervised the design, implementation, and conduct of all aspects of the project. He wrote-up the study findings and presented them at several scientific conferences.
Alternate Funding Source: Department of Psychology, UAB

Name: David Morris, PhD
Project Role: Investigator, CIMT Training & Scoring Supervisor, UAB
Researcher Identifier: n/a
Nearest person months worked: 1
Contribution to project: Dr. Morris trained the Tester and ensured that she and others were able to perform the study procedures with adequate fidelity. He played in a major role in the design, implementation, and supervision of the LEFT intervention protocol. In addition, he wrote the manual of procedures and study protocol paper in conjunction with the PI.
Alternate Funding Source: Department of Physical Therapy, UAB

Name: Gitendra Uswatte, PhD
Project Role: Investigator, Accelerometry & Data Analysis Supervisor, UAB
Researcher Identifier: ORCID ID 0000-0003-4507-7098
Nearest person months worked: 3
Contribution to project: He trained the Data Manager to collect and process the data from the movement monitors worn by participants and supervised the construction of the database for the study as well as the analysis of the data. He also took part in the design of the testing and treatment procedures, design and implementation of the recruitment procedures, and in the preparation of the regulatory documents for the study.
Alternate Funding Source: Department of Psychology, UAB

Name: Staci McKay
Project Role: Trainer, UAB
Researcher Identifier: n/a
Nearest person months worked: 6

Contribution to project: She helped to design the enhanced Transfer Package procedures and has conducted recruitment and provided CI therapy in addition to coordinating work on the project on a day-to-day basis.
Alternate Funding Source: Department of Psychology, UAB

Name: Andrea Taylor
Project Role: Research Assistant, UAB
Researcher Identifier: n/a
Nearest person months worked: 1
Contribution to project: She helped to design the enhanced Transfer Package procedures and has conducted recruitment and provided CI therapy.
Alternate Funding Source: Department of Psychology, UAB

Name: Laura Reder
Project Role: Research Assistant, UAB
Researcher Identifier: n/a
Nearest person month worked: 2
Contribution to project: She conducted the blinded motor and other clinical testing of the participants and conducted on-site screening of participants.

Name: Brent Womble
Project Role: Graduate Student, UAB
Researcher Identifier: n/a
Nearest person months worked: 3
Contribution to project: He assisted with collection and processing of the neuroimaging data and developed a method for evaluating the sensitivity of the neuroimaging methods proposed for assessing changes in grey matter.
Alternate Funding Source: Department of Psychology, UAB

Name: Jeremiah A. Idigo
Project Role: Data Manager, UAB
Researcher Identifier: ORCID ID 0000-0003-1947-1569
Nearest person months worked: 3
Contribution to project: He managed and analyzed the study data under the supervision of Investigator Uswatte.
Alternate Funding Source: Department of Psychology, UAB

7b. Has there been a change in the active other support of the PI or senior/key personnel since the last report period?
Edward Taub, Principal Investigator

Compative Effectiveness of a Low-cost Virtual Reality Gaming Platform for Neurorehabilitation of Hemiparesis (Uswatte, PI, UAB clinical site, subcontract from The Ohio State University lead site)
0.18 academic months, 0 summer months
Patient-Centered Outcomes Research Institute
Geri Gunman, MBA
1828 L Street, NW, 9th Fl
Washington, DC 20006
Performance Period: 11/01/15 – 10/30/18
Annual Direct Costs:
The general objective of this project is to refine and test a video game delivery model of CI therapy against standard delivery of CI therapy and typical neurorehabilitation for rehabilitating use of the more-affected arm after stroke.
Aim 1. To compare the effectiveness of video game delivery CI therapy in the home to that of one-on-one, face-to-face delivery of CI therapy in the clinic and of one-on-one, face-to-face delivery of conventional neurorehabilitation.
Aim 2. To determine the patient characteristics that differentially influence response to the three interventions.
Dr. Taub committed 0.6 calendar months to this project until end-October, 2017. Since that date he has reduced his commitment to 0.18 months.

Gitendra Uswatte, Investigator
Compative Effectiveness of a Low-cost Virtual Reality Gaming Platform for Neurorehabilitation of Hemiparesis (Uswatte, PI, UAB clinical site, subcontract from The Ohio State University lead site)
0.9 academic months, 0 summer months
Patient-Centered Outcomes Research Institute
Geri Gunman, MBA
1828 L Street, NW, 9th Fl
Washington, DC 20006
Performance Period: 11/01/15 – 10/30/18
Annual Direct Costs:
The general objective of this project is to refine and test a video game delivery model of CI therapy against standard delivery of CI therapy and typical neurorehabilitation for rehabilitating use of the more-affected arm after stroke.
Aim 1. To compare the effectiveness of video game delivery CI therapy in the home to that of one-on-one, face-to-face delivery of CI therapy in the clinic and of one-on-one, face-to-face delivery of conventional neurorehabilitation.
Aim 2. To determine the patient characteristics that differentially influence response to the three interventions.

Dr. Uswatte committed 1.8 calendar months to this project until end-October, 2017. Since that date he has reduced his commitment to 0.9 months.

7c. What other organizations were involved as partners?

Organization Name: Alabama Department of Veterans Affairs
Location of Organization: 1815 Cogswell Ave #132, Pell City, AL 35125
Partner's contribution to the project: Collaboration. This partner posted recruitment materials in all of their county offices.

Organization Name: UAB TBI Model Systems
Location of Organization: 529 Spain Rehabilitation Center,1717 6th Avenue South Birmingham, AL 35249-7330
Partner's contribution to the project: Collaboration. This partner mailed recruitment materials to candidates for this study to adults with TBI in their patient registry.

Organization Name: The Moss Traumatic Brain Injury Model System
Location of Organization: 5o Township Line Rd, Elkins Park, PA 19027
Partner's contribution to the project: Collaboration. This partner mailed recruitment materials to candidates for this study to adults with TBI in their patient registry.

Organization Name: The Rocky Mountain Regional Brain Injury System
Location of Organization: 3425 S Clarkson St, Englewood, CO 80113
Partner's contribution to the project: Collaboration. This partner mailed recruitment materials to candidates for this study to adults with TBI in their patient registry.

Organization Name: Brain Injury Association of America
Location of Organization: 1608 Springhill Rd, Ste 110, Vienna, VA 22182
Partner's contribution to the project: Other. This BIAA featured an article about the project in its Fall 2016 newsletter.

Organization Name: Alabama AHEC
Location of Organization: 930 20th Street South, Room 307, Birmingham, AL 35205
Partner's contribution to the project: Facilities. This partner permitted project staff to host a booth promoting our study at a community fair for veterans and the organizations that provide services to veterans in Birmingham, AL.

Organization Name: Greater Birmingham Republican Women
Location of Organization: P.O. Box 43922, Birmingham, AL 35243

Partner's contribution to the project: Other. This partner hosted a presentation about the project by the PI and Co-investigator Uswatte at their monthly meeting with the aim of galvanizing community resources to support the project.

8. SPECIAL REPORTING REQUIREMENTS

None.

9. APPENDICES

Appendix A. Tables on Progress of Data Collection

Appendix B. Tables and Graphs Presenting Selected Study Results

Appendix C. Paper on Study Protocol In Press at *The Journal of Head Trauma Rehabilitation*

Appendix A

Tables on Progress of Data Collection

Table 1. Key to Data Collection Tables

Table 2. Clinical Data Collection

Table 3. Brain Scan Collection

Abbreviation in Table	Full Name	Parameter Assessed
MAL	Motor Activity Log	real world more-affectedarm use
WMFT	Wolf Motor Function Test	more-affected upper extremity motor ability
accel	accelerometer	real world more-affected arm movement
ashworth	Modified ashworth scale	more-affected arm spatisticity
FrSBe	Frontal Systems Behavior Scale	family member/caregiver rates behavior of patient to assess quality and quantity of problems caused by frontal lobe damage
HUI-3	Multi-Attribute Health Status Classification System: Health Utilities Index Mark 3	quality of life
MMSE	mini mental state exam	cognitive impairment
PCL-5	PTSD Checklist for DSM-5	PTSD
ROM	Range of Motion	active range of motion of more-affected arm
SWLS	Satisfaction with life scale	assessment of life satisfaction
TBI model systems	TBI model systems	quality of life
WCST	Wisconsin Card Sorting Task	executive function
WMS digit span	Wechsler memory scale	working memory
WMS logical memory	Wechsler memory scale - recall of details of a short narrative	narrative memory
WMS visual reproduction	Wechsler memory scale	visual memory
Fitness assessment	Fitness assessment	full body fitness assessment
pre	Pre-treatment	
post	Post-treatment	
f/u 1 yr	1-year follow-up	
Code in Table	**Explanation**	
.	Data missing	
YY	Data collected and entered	
Y	Data collected but not entered	
n/a	Test date has not yet occurred	
Note. Our data quality assurance protocol dictates that the person who filled out the physical form should		
be the one to enter the data. Data in database is compared it to physical form by personnel from study		
other than the person who entered it.		

Participant	status	MAL pre	MAL post	MAL f/u 1 yr	WMFT pre	WMFT post	WMFT f/u 1 yr	accel pre	accel post	accel f/u 1 yr	Ashworth pre	Ashworth post	Ashworth f/u 1 yr	FrSBe Pre	FrSBe Post	HUI - 3 pre
5201	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	.	YY	YY	YY	.	.	YY
5202	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	.	.	YY
5203	treatment complete	YY	YY	.	YY	YY	.	YY	YY	.	YY	YY	.	YY	YY	YY
5204	follow up complete	YY	YY	YY	YY	YY	.	YY	YY	.	YY	YY	.	.	.	YY
5205	follow up complete	YY	YY	YY	YY	YY	.	YY	YY	.	YY	YY	.	.	.	YY
5206	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5207	treatment complete	YY	YY	.	YY	YY	.	YY	YY	.	YY	YY	.	YY	.	YY
5208	follow up complete	YY	YY	YY	YY	YY	.	YY	YY	.	YY	YY	.	.	.	YY
5211	follow up complete	YY	YY	YY	YY	YY	.	YY	YY	.	YY	YY	.	YY	YY	YY
5212	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	.	.	YY
5213	follow up complete	YY	YY	YY	YY	YY	.	YY	YY	.	YY	YY	.	.	.	YY
5214	treatment complete	YY	YY	.	YY	YY	.	YY	YY	.	YY	YY	.	.	.	YY
5215	follow up complete	YY	YY	YY	YY	YY	.	YY	YY	.	YY	YY	.	.	.	YY
5217	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	.	.	YY
5218	treatment complete	YY	YY	.	YY	YY	.	YY	YY	.	YY	YY	.	.	.	YY
5219	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	.	YY
5222	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	.	.	YY
5227	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	.	.	YY
5228	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	.	.	YY
5232	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	.	.	YY
5233	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5234	follow up complete	YY	YY	YY	YY	YY	.	YY	YY	.	YY	YY	.		.	YY
5235	follow up complete	YY	YY	YY	YY	YY	.	YY	YY	.	YY	YY	.	YY	YY	YY
5237	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	.	.	YY
5238	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	.	.	YY
5239	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	.	.	YY
5240	follow up complete	YY	YY	YY	YY	YY	.	YY	YY	.	YY	YY	.	YY	.	YY
5241	follow up complete	YY	YY	YY	YY	YY	.	YY	YY	.	YY	YY	.	.	.	YY
5242	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5243	follow up complete	YY	YY	.	YY	YY	.	YY	YY	.	YY	YY	.	YY	.	YY
5245	follow up complete	YY	YY	YY	YY	YY	.	YY	YY	.	YY	YY	.	.	.	YY
5246	follow up complete	YY	YY	.	YY	YY	.	YY	YY	.	YY	YY	.	.	.	YY
5247	follow up complete	YY	YY	YY	YY	YY	.	YY	YY	.	YY	YY	.	.	.	YY
5248	follow up complete	YY	YY	YY	YY	YY	.	YY	YY	.	YY	YY	.	.	.	YY
5249	follow up complete	YY	YY	YY	YY	YY	.	YY	YY	.	YY	YY	.	.	.	YY
5250	follow up complete	YY	YY	YY	YY	YY	.	YY	YY	.	YY	YY	.	.	.	YY
5252	follow up complete	YY	YY	YY	YY	YY	.	YY	YY	.	YY	YY	.	.	.	YY
5253	treatment complete	YY	YY	.	YY	YY	.	YY	YY	.	YY	YY	.	.	.	YY
5255	follow up complete	YY	YY	YY	YY	YY	.	YY	YY	.	YY	YY	.	.	.	YY
5256	treatment complete	YY	YY	.	YY	YY	.	YY	YY	.	YY	YY	.	.	.	YY
% Completed		**100**	**100**	**80**	**100**	**100**	**38**	**100**	**100**	**35**	**100**	**100**	**44**	**26**	**15**	**100**

Participant	status	HUI_3 Post	HUI-3 F/u 1 ur	MMSE pre	PCL-5 pre	PCL-5 Post	PCL-5 f/u 1 yr	ROM pre	ROM Post	ROM f/u 1 yr	SWSL pre	SWLS Post	SWLS f/u 1yr	TBI model systems pre	TBI model systems f/u 1 yr
5201	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5202	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5203	treatment complete	YY	.	YY	YY	YY	.	YY	YY	.	YY	YY	.	YY	.
5204	follow up complete	YY	.	YY	YY	YY	YY	YY	YY	.	YY	YY	.	YY	.
5205	follow up complete	YY	.	YY	YY	YY	YY	YY	YY	.	YY	YY	.	YY	.
5206	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5207	treatment complete	YY	.	.	YY	YY	.	YY	YY	.	YY	YY	.	YY	.
5208	follow up complete	YY	.	.	YY	YY	.	YY	YY	.	YY	YY	.	YY	.
5211	follow up complete	YY	.	.	YY	YY	YY	YY	YY	.	YY	YY	.	YY	.
5212	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5213	follow up complete	YY	.	YY	YY	YY	.	YY	YY	.	YY	YY	.	YY	.
5214	treatment complete	YY	.	.	YY	YY	.	YY	YY	.	YY	YY	.	YY	.
5215	follow up complete	YY	.	.	YY	YY	YY	YY	YY	.	YY	YY	.	YY	.
5217	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5218	treatment complete	YY	.	YY	YY	YY	.	YY	YY	.	YY	YY	.	YY	.
5219	follow up complete	YY	YY	.	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5222	follow up complete	YY	YY	.	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5227	follow up complete	YY	YY	.	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5228	follow up complete	YY	YY	.	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5232	follow up complete	YY	YY	.	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5233	follow up complete	YY	YY	.	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5234	follow up complete	YY	.		YY	YY	YY	YY	YY	.	YY	YY	.	YY	.
5235	follow up complete	YY	.	YY	YY	YY	.	YY	YY	.	YY	YY	.	YY	.
5237	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5238	follow up complete	YY	YY	.	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5239	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5240	follow up complete	YY	.	.	YY	YY	.	YY	YY	.	YY	YY	.	YY	.
5241	follow up complete	YY	.	.	YY	YY	.	YY	YY	.	YY	YY	.	YY	.
5242	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5243	follow up complete	YY	.	YY	YY	YY	YY	YY	YY	.	YY	YY	.	YY	.
5245	follow up complete	YY	.	.	YY	YY	YY	YY	YY	.	YY	YY	.	YY	.
5246	follow up complete	YY	.	YY	YY	YY	.	YY	YY	.	YY	YY	.	YY	.
5247	follow up complete	YY	.	.	YY	YY	YY	YY	YY	.	YY	YY	.	YY	.
5248	follow up complete	YY	.	.	YY	YY	YY	YY	YY	.	YY	YY	.	YY	.
5249	follow up complete	YY	.	.	YY	YY	.	YY	YY	.	YY	YY	.	YY	.
5250	follow up complete	YY	.	.	YY	YY	YY	YY	YY	.	YY	YY	.	YY	.
5252	follow up complete	YY	.	.	YY	YY	YY	YY	YY	.	YY	YY	.	YY	.
5253	treatment complete	YY	.	.	YY	YY	YY	YY	YY	.	YY	YY	.	YY	.
5255	follow up complete	YY	.	.	YY	YY	YY	YY	YY	.	YY	YY	.	YY	.
5256	treatment complete	YY	.	.	YY	YY	.	YY	YY	.	YY	YY	.	YY	.
% Completed		**100**	**38**	**41**	**100**	**100**	**70**	**100**	**100**	**38**	**100**	**100**	**38**	**100**	**38**

Participant	status	WCST pre	WCST f/u 1 yr	WMS digit span pre	WMS digit span fu 1 yr	WMS log memory 1 pre	WMS log memory 1 f/u 1 yr	WMS log memory 2 pre	WMS log memory 2 f/u 1 yr	WMS log memory recogniti on pre	WMS log memory recognition f/u 1 yr	WMS visual reproduct ion pre	WMS visual reproduci ton f/u 1
5201	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5202	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5203	treatment complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5204	follow up complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5205	follow up complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5206	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5207	treatment complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5208	follow up complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5211	follow up complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5212	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5213	follow up complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5214	treatment complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5215	follow up complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5217	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5218	treatment complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5219	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5222	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5227	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5228	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5232	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5233	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5234	follow up complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5235	follow up complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5237	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5238	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5239	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5240	follow up complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5241	follow up complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5242	follow up complete	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY	YY
5243	follow up complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5245	follow up complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5246	follow up complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5247	follow up complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5248	follow up complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5249	follow up complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5250	follow up complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5252	follow up complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5253	treatment complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5255	follow up complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
5256	treatment complete	YY	.	YY	.	YY	.	YY	.	YY	.	YY	.
% Completed		**100**	**38**	**100**	**38**	**100**	**38**	**100**	**38**	**100**	**38**	**100**	**38**

Participant	status	fitness assesment pre	fitness assesment post	fitness assesment f/up 1 yr
5201	follow up complete	YY	YY	YY
5202	follow up complete	YY	YY	YY
5203	treatment complete	YY	YY	.
5204	follow up complete	YY	YY	.
5205	follow up complete	YY	YY	.
5206	follow up complete	YY	YY	YY
5207	treatment complete	YY	YY	.
5208	follow up complete	YY	YY	.
5211	follow up complete	YY	YY	.
5212	follow up complete	YY	YY	YY
5213	follow up complete	YY	YY	.
5214	treatment complete	YY	YY	.
5215	follow up complete	YY	YY	.
5217	follow up complete	YY	YY	YY
5218	treatment complete	YY	YY	.
5219	follow up complete	YY	YY	YY
5222	follow up complete	YY	YY	YY
5227	follow up complete	YY	YY	YY
5228	follow up complete	YY	YY	YY
5232	follow up complete	YY	YY	YY
5233	follow up complete	YY	YY	YY
5234	follow up complete	YY	YY	.
5235	follow up complete	YY	YY	.
5237	follow up complete	YY	YY	YY
5238	follow up complete	YY	YY	YY
5239	follow up complete	YY	YY	YY
5240	follow up complete	YY	YY	.
5241	follow up complete	YY	YY	.
5242	follow up complete	YY	YY	YY
5243	follow up complete	YY	YY	.
5245	follow up complete	YY	YY	.
5246	follow up complete	YY	YY	.
5247	follow up complete	.	.	.
5248	follow up complete	YY	YY	.
5249	follow up complete	YY	YY	.
5250	follow up complete	YY	YY	.
5252	follow up complete	YY	YY	.
5253	treatment complete	YY	YY	.
5255	follow up complete	YY	YY	.
5256	treatment complete	YY	YY	.
% Completed		**98**	**98**	**38**

Participant	status	Pre scan Status	Post Scan Status	1 yr f/up scan status
5201	follow up complete	YY	YY	YY
5202	follow up complete	YY	YY	YY
5203	treatment complete	.	.	.
5204	follow up complete	.	.	.
5205	follow up complete	.	.	.
5206	follow up complete	.	.	.
5207	treatment complete	.	.	.
5208	follow up complete	YY	YY	.
5211	follow up complete	.	.	.
5212	follow up complete	.	.	.
5213	follow up complete	.	.	.
5214	treatment complete	YY	YY	.
5215	follow up complete	.	.	.
5217	follow up complete	.	.	.
5218	treatment complete	YY	YY	.
5219	follow up complete	.	.	.
5222	follow up complete	.	.	.
5227	follow up complete	YY	YY	.
5228	follow up complete	.	.	.
5232	follow up complete	.	.	.
5233	follow up complete	.	.	.
5234	follow up complete	YY	YY	.
5235	follow up complete	.	.	.
5237	follow up complete	.	.	.
5238	follow up complete	YY	YY	YY
5239	follow up complete	YY	YY	YY
5240	follow up complete	.	.	.
5241	follow up complete	YY	YY	.
5242	follow up complete	.	.	.
5243	treatment complete	.	.	.
5245	follow up complete	.	.	.
5246	follow up complete	YY	YY	.
5247	follow up complete	.	.	.
5248	follow up complete	.	.	.
5249	follow up complete	YY	YY	.
5250	follow up complete	YY	YY	.
5252	follow up complete	.	.	.
5253	treatment complete	YY	YY	.
5255	follow up complete	.	.	.
5256	treatment complete	YY	YY	.
% Completed		**38**	**38**	**10**

Appendix B

Tables and Graphs Presenting Selected Study Results

Table 1. MAL Arm Use Scale: Mean Pre- and Post-treatment Values

Figure 1. MAL Arm Use Scale: Mean Change from Pre- to Post-treatment by Study Group

Table 2. WMFT Performance Rate Score: Mean Pre- and Post-treatment Values

Figure 2: WMFT Performance Rate Score: Mean Change from Pre- to Post-treatment by Study Group

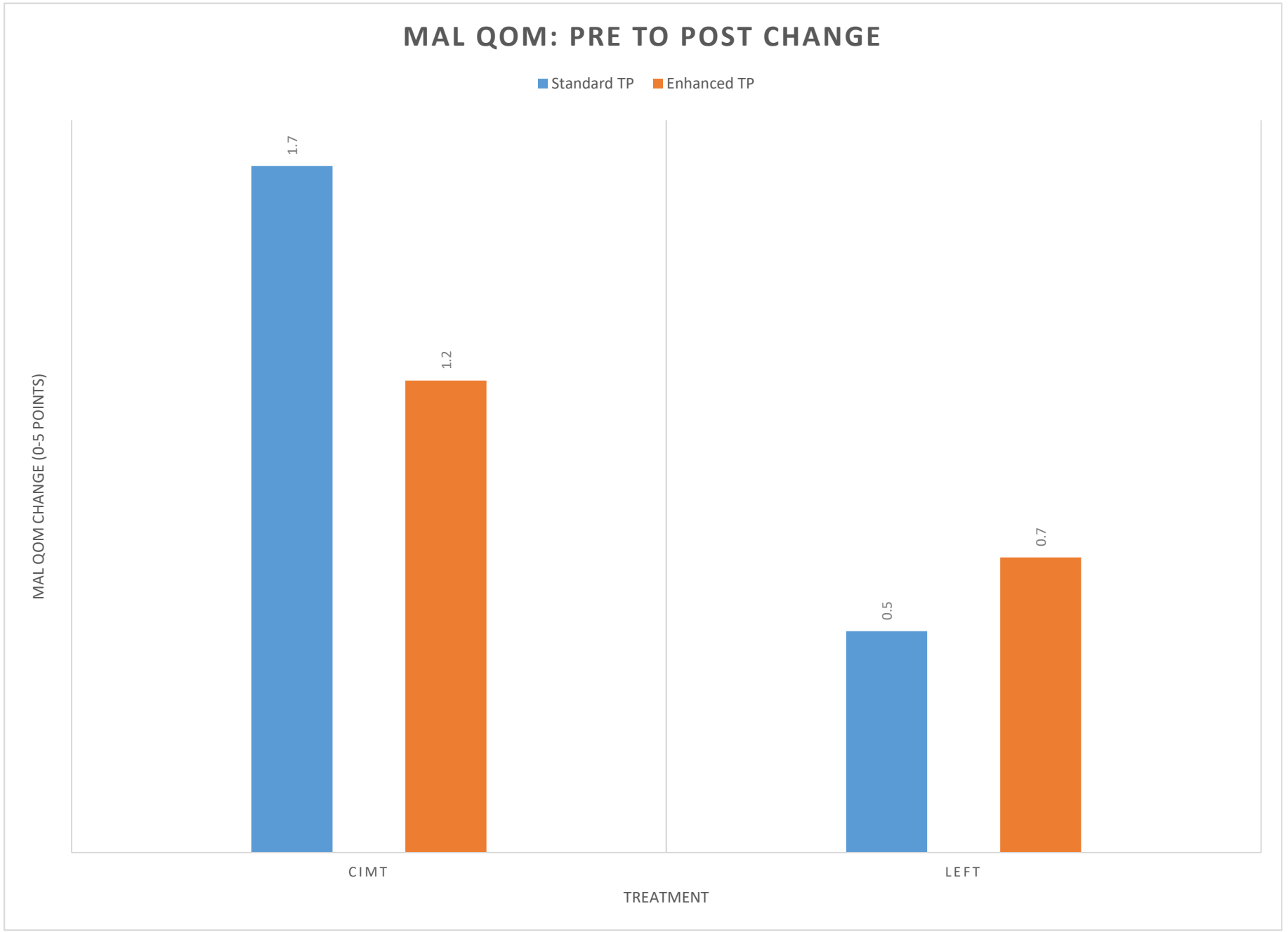
Figure 3. PCL-5 Mean Scores at Pre- and Post-treatment by Study Group

Figure 4. PCL-5 Mean Scores at Pre- and Post-treatment by Study Group Only for Participants with Initial PCL-5 Scores above the cutoff for PTSD

Table 3. Clinically Meaningful Changes in PTSD Symptoms by Study Group Only for Participants with Initial PCL-5 Scores above the cutoff for PTSD

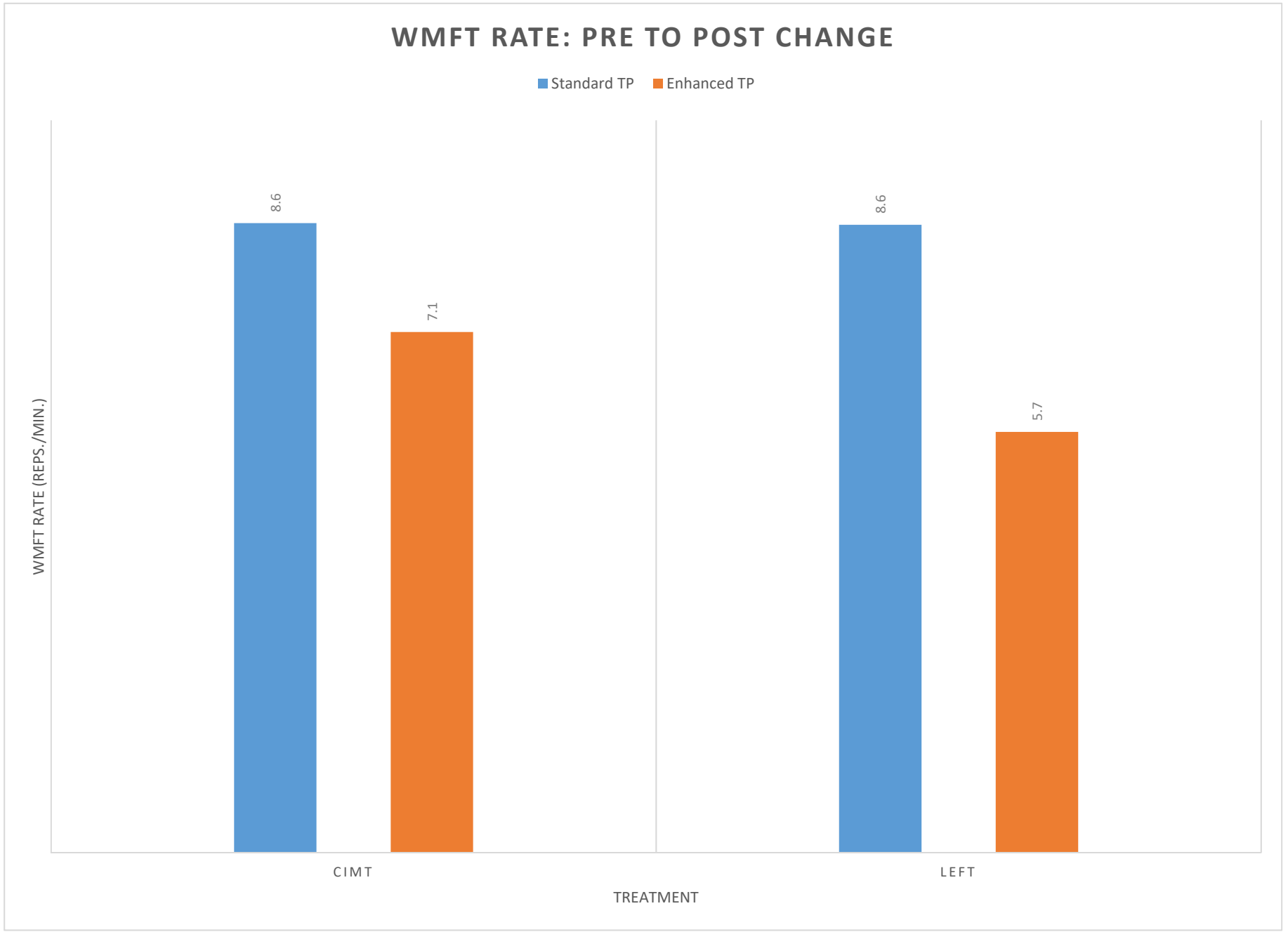
					PRE	POST	Change	% Change
ALL								
Mean					1.3	2.4	1.0	102%
SD					0.7	1.2	0.8	113%
d'							1.3	
N							40	
CIMT, Standard TP								
Mean					1.5	3.2	1.7	164%
SD					0.8	1.1	0.7	119%
CI Upper Bound								
CI Lower Bound								
d'							2.3	
n							11	
CIMT, Enhanced TP								
Mean					1.2	2.4	1.2	157%
SD					0.8	1.0	0.7	149%
d'							1.8	
n							9	
LEFT, Standard TP								
Mean					1.2	1.7	0.5	45%
SD					0.6	0.9	0.7	55%
d'							0.8	
n							11	
LEFT, Enhanced TP								
Mean					1.6	2.3	0.7	41%
SD					0.6	1.3	0.8	36%
d'							0.9	
n							9	
CIMT, All								
Mean					1.4	2.8	1.5	161%
SD					0.8	1.1	0.7	130%
d'							2.0	
n							20	
LEFT, ALL								
Mean					1.3	2.0	0.6	43%
SD					0.6	1.1	0.7	46%
d'							0.9	
n							20	

DOD Study, MAL Change Graph

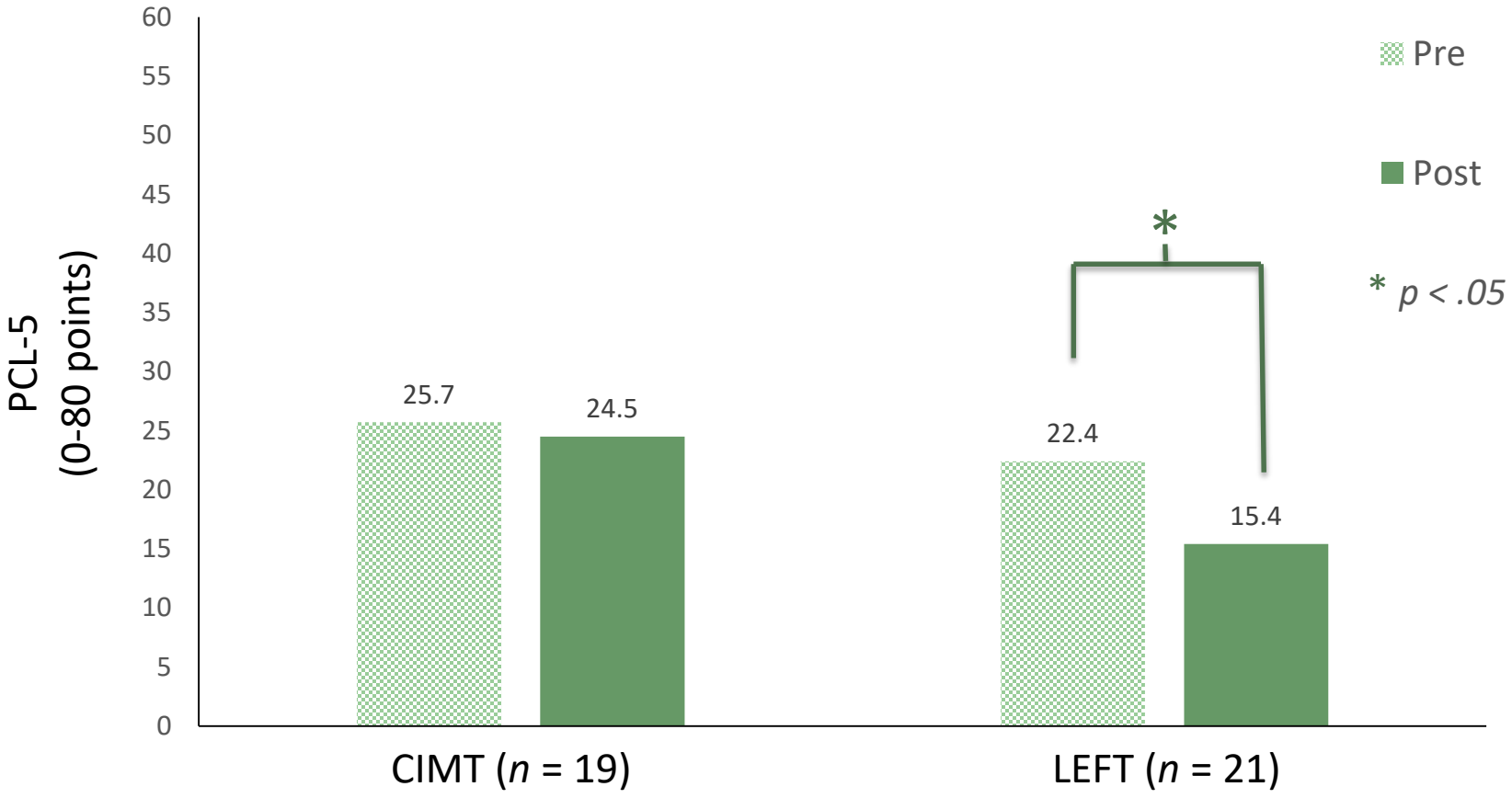


DOD_MALqom_Unblinded021918v3

	PRE	POST	Change	% Change
ALL				
Mean	33.7	41.3	7.6	25%
SD	16.0	20.4	7.7	22%
d'			1.0	
P value			0.000	
N			39	
CIMT, Standard TP				
Mean	38.0	46.6	8.6	22%
SD	13.0	19.0	7.6	16%
d'			1.1	
n			11	
CIMT, Enhanced TP				
Mean	26.8	33.9	7.1	30%
SD	16.0	21.2	7.5	29%
d'			0.9	
n			8	
LEFT, Standard TP				
Mean	37.5	46.0	8.6	29%
SD	18.9	22.7	9.6	25%
d'			0.9	
n			11	
LEFT, Enhanced TP				
Mean	30.1	35.8	5.7	20%
SD	15.2	18.0	6.4	17%
d'			0.9	
n			9	
CIMT, All				
Mean	33.3	41.3	8.0	25%
SD	15.0	20.4	7.4	22%
d'			1.1	
n			19	
LEFT, All				
Mean	34.1	41.4	7.3	25%
SD	17.3	20.9	8.2	22%
d'			0.9	
n			20	

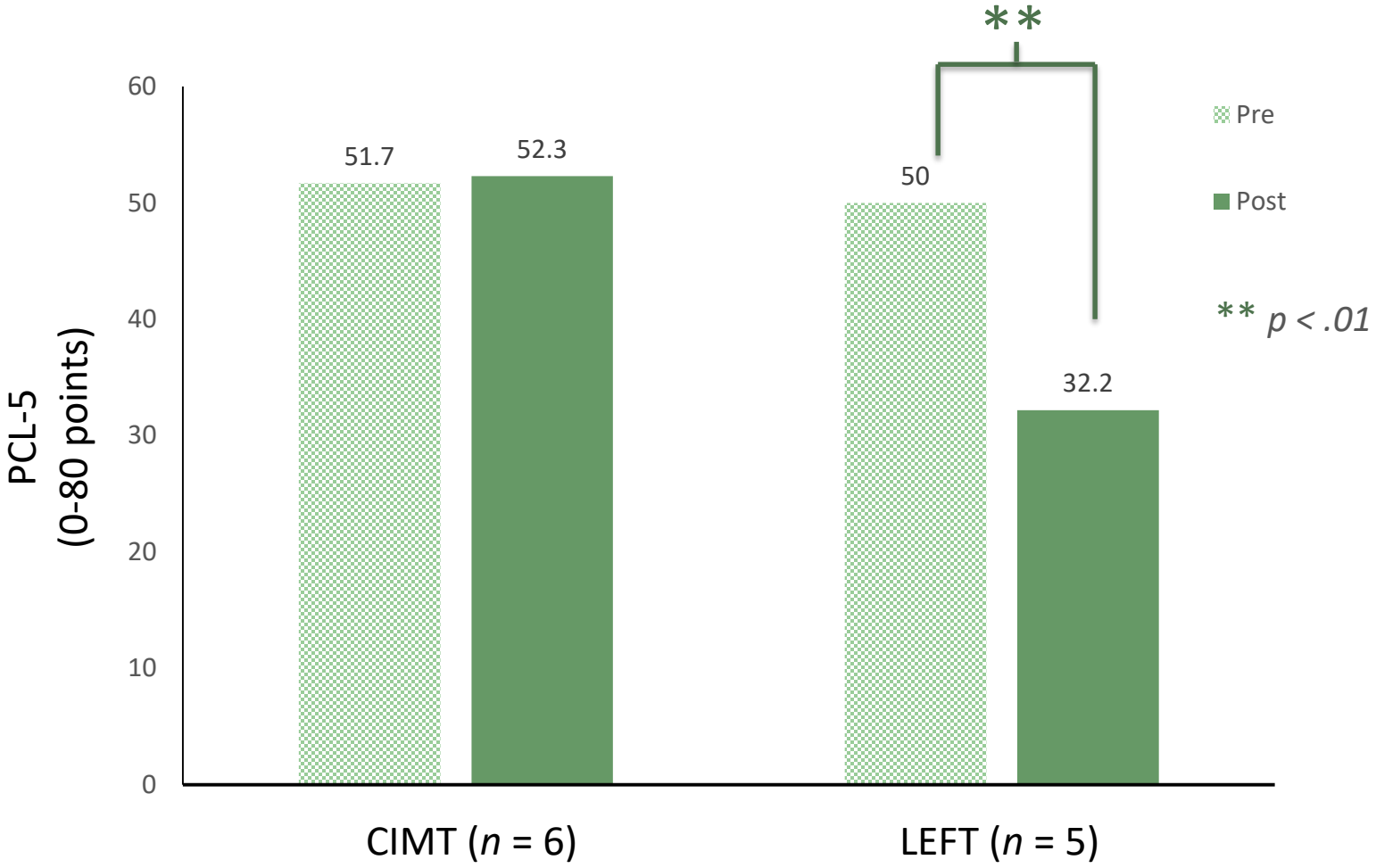

WMFT RATE: PRE TO POST CHANGE
Standard TP
Enhanced TP
WMFT RATE (REPS./MIN.)
8.6
7.1
8.6
5.7
CIMT
LEFT
TREATMENT

PCL-5
PTSD Symptom Severity



PCL-5
PTSD Symptom Severity

Only for participants with scores above the cut-off for PTSD*



*Note: Scores above 33 on the PCL-5 are thought to reflect PTSD.

Changes in PTSD Symptoms For Participants with PCL-5 Scores Above the cut-off For PTSD

	All Participants		Veterans	
	CIMT (n=19)	LEFT (n=21)	CIMT (n=9)	LEFT (n=11)
Number scoring above PTSD cut-off	6	5	4	4
Number with clinically meaningful improvement	0	5	0	4
Number of falling below cut-off after treatment	1	3	1	2
Mean change (SD)	0.7 (8.2)	-17.8(5.6)	1.3 (10.1)	-18.8 (6.0)
Within-group ES (d′)	0.1	-3.2	0.1	-3.1

Note: PCL-5 scores range from 0-80. Scores > 33 are thought to reflect PTSD. A change > 10 points in considered clinically meaningful.

Appendix C

Paper on Study Protocol
In Press at
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Protocol for a Randomized Controlled Trial of CI Therapy for Rehabilitation of Upper Extremity Motor Deficit: The *B*ringing *R*ehabilitation to *A*merican *V*eterans *E*verywhere Project

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Constraint-induced movement therapy (CI therapy) has been shown to reduce disability for individuals with upper extremity (UE) hemiparesis following different neurologic injuries. This article describes the study design and methodological considerations of the Bringing Rehabilitation to American Veterans Everywhere (BRAVE) Project, a randomized controlled trial of CI therapy to improve the motor deficit of participants with chronic and subacute traumatic brain injury. Our CI therapy protocol comprises 4 major components: (1) intensive training of the more-affected UE for target of 3 hour/day for 10 consecutive weekdays, (2) a behavioral technique termed shaping during training, (3) a "transfer package," 0.5 hour/day, of behavioral techniques to transfer therapeutic gains from the treatment setting to the life situation, and (4) prolonged restraint of use of the UE not being trained. The primary endpoint is posttreatment change on the Motor Activity Log, which assesses the use of the more-affected arm outside the laboratory in everyday life situations. Data from a number of secondary outcome measures are also being collected and can be categorized as physical, genomic, biologic, fitness, cognitive/behavioral, quality of life, and neuroimaging measures. **Key words:** *carryover effects*, *CI therapy*, *motor deficit*, *transfer package*, *traumatic brain injury*, *upper extremity*

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Concept/idea/project design provided by all the authors; participant recruitment by Uswatte, Taub, Mark, Bishop-McKay, Taylor, Brenner, Pickett, Stevens, Rothman, Stearns-Yoder, and Adams; data collection by Reder, Adams, Bishop-McKay, Taylor, Dew, Liu, Womble, and Szaflarski; intervention delivery by Bishop-McKay, Taylor, Adams, and Taub; data analysis by Uswatte and Taub; writing by Morris, Taub, and Uswatte; and project management by Uswatte, Taub, Bishop-McKay, Taylor, and Dew.

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The authors declare no conflicts of interest.

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TRAUMATIC BRAIN INJURY (TBI) is a leading cause of lifelong disability among young adults and children in the United States.[1] Its prevalence has significantly increased in recent years as a result of the Iraq/Afghanistan conflicts.[2] Spontaneous recovery of the motor deficit resulting from TBI can be complete. However, when it is partial, recovery is primarily in the first 6 months after injury and usually completes 1 year. TBI resulting from blast in a military environment appears to differ mechanistically from civilian TBI resulting from collision.[3,4] For example, the differentiating occurrence of subarachnoid hemorrhage and cerebral vasospasm in blast TBI does not appear to be different from the consequences of rupture of aneurysms in the many cases of this type that do not involve blast. Clinical opinion repeatedly indicates the need to improve controlled research on the efficacy of physical rehabilitation for functional recovery after TBI.[5–9] Estimates of the cost of caring for and maintaining veterans/war fighters with brain injury run into billions of dollars. Therapeutic interventions designed to enhance motor function and promote independent use of impaired upper extremity (UE) after TBI are quite limited.

Constraint-induced movement therapy (CI therapy) was derived from basic research with monkeys[10] and clinical research with humans.[11–14] When applied to UE function, intensive use of the more-impaired UE, regardless of premorbid hand dominance, is emphasized during most waking hours of the intervention period. The 4 main components of the signature protocol are intensive training, use of the behavioral training technique of shaping, the transfer package [TP], and prolonged restraint of the less-affected UE. Among these, research suggests that the TP is particularly important for therapeutic efficacy.[15,16] CI therapy was the subject of a successful multisite randomized controlled trial (RCT) involving UE function after stroke (EXCITE).[14] Our results have been confirmed in many studies and the therapy is in use in many countries.[17] There are at present more than 500 published studies on the use of CI therapy after stroke with positive results.

While most of the evidence concerning the efficacy of CI therapy was for stroke, we have obtained equivalent results with patients after TBI.[18,19] The Bringing Rehabilitation to American Veterans Everywhere (BRAVE) Project is a 3-year RCT designed to examine use of CI therapy as a treatment for impaired UE function following TBI. The project design compares CI therapy with a "fitness intervention" control group referred here to as the Lakeshore Enhanced Fitness Training (LEFT) Program. Both have standard TP components (described later) incorporated in their procedure. Two additional intervention protocols, the CI therapy and LEFT intervention plus *enhanced* TP elements, are being used to further explore the efficacy of an enhanced variant of the standard TP.[16] The purpose of this article is to describe the design and methods of the BRAVE Project. In addition, the potentially unique contribution of this study and lessons learned from previous research will be reviewed.

TRIAL DESIGN AND METHODS

Participants

Eighty participants are being recruited from among veterans with brain injury when possible. A consortium of VA medical centers, including those in Denver, Richmond, and Birmingham, have been established for this purpose. Civilian sources such as from the UAB TBI Model System Program will be included if necessary to meet trial quotas. It is recognized that military veterans of blast injury may have central nervous system damage that differs in many characteristics from civilians with TBI,[3] but the motor deficits are similar.

Movement and range of motion inclusion criteria are listed in Table 1. In addition, participants must score 4 or less on the modified Ashworth Scale.[20] Participants must also demonstrate limited use of the more-affected UE as is determined by a mean score of 2.5 or less on the 5-point Motor Activity Log (MAL). The MAL assesses the amount and quality of UE arm use for 30 activities of daily living.[21–23]

Exclusion criteria include (1) less than 3 months post-TBI, (2) frailty or insufficient stamina to carry out the requirements of the therapy (based on clinical judgment), (3) other neurologic or musculoskeletal conditions affecting UE function, (4) concurrent participation in any formal physical rehabilitation program or clinical trial, (5) excessive pain in any joint of the more-affected arm that could limit ability to cooperate with the intervention (based on clinical judgment), (6) serious cognitive deficits indicated by a Folstein Mini-Mental State Examination score of 24 or less,[24] (7) inadequate ability to follow test instructions as indicated by a Token Test of the Multilingual Aphasia Examination score of 36 or less,[25] (8) serious, uncontrolled medical problems as judged by the medical director, (9) motor problems that are not primarily unilateral, (10) poor motivation to participate in the study, (11) younger than 19 years, and (12) previous CI therapy. Medication is not exclusionary except in the following cases: (*a*) participation in any experimental drug study, (*b*) botulinum toxin injections to the more-affected UE less than 3 months prior to enrollment, and (*c*) baclofen or dantrolene taken orally or by a pump at the time of study, to minimize antispasticity effects of medications. The presence of ferromagnetic metal in the body, medical complications, or psychological problems that would prohibit undergoing MRI would preclude neuroimaging, but such persons could still be enrolled in the study and receive investigational therapy.

TABLE 1 *Minimum active and passive range of motion required for participation*[a]

	Shoulder	Elbow	Wrist	Fingers	Thumb
Minimum passive ROM	Flexion ≥90° Abduction ≥90° External rotation ≥45°	Extension to ≥150°	Extension ≥0° Forearm supination/pronation ≥45°	MCP extension to ≥145°	Extension or abduction ≥10°
Minimum active ROM	Flexion ≥45° Abduction ≥45°	Extension ≥20° from a 90° flexed starting position	Extension ≥10° from fully flexed starting position	Extension MCP and (PIP or DIP) joints of at least 2 fingers ≥10°	Extension or abduction ≥10°

Abbreviations: DIP, distal interphalangeal; MCP, metacarpophalangeal; PIP, proximal interphalangeal; ROM, range of motion.
[a]These criteria are for the grade 3 level of deficit.

Interventions

To achieve the aims of the BRAVE Study, participants are randomized to receive treatment procedures from 1 of 4 separate intervention protocols, delivered as an outpatient treatment program (ie, participants are not institutionalized during the intervention). Two intervention protocols will utilize variants of the CI therapy protocol to address UE function. One variant receives a standard TP,[16] which is designed to facilitate transfer of motor improvement to the everyday life situation; the other variant receives an enhanced TP, as described later. Two other intervention protocols will serve as control procedures for the CI therapy protocol. They both involve a physical fitness regimen; one group has a standard TP and the other receives an enhanced TP, parallel to the CI therapy groups. Table 2 summarizes components of the protocols used with each of the 4 participant groups.

CI therapy with standard transfer package

This group follows the standard method of delivering CI therapy, as documented by Taub and colleagues.[11,15] It includes the 4 major components previously described, as follows.

Massed motor practice and shaping (components 1 and 2)

On each weekday of the intervention period, participants engage in supervised motor training conducted over a 3-hour period in the research laboratory. The approach used, shaping, is a training method in which 2 related procedures are used: (1) within-task shaping—a participant is encouraged to keep improving progressively on their previous best task performance in small increments, and (2) between-task or task-change shaping—a task is gradually made more difficult or changed in difficulty in accordance with improvements in a subject's (motor) capabilities. Shaping has been a prominent aspect of much of past work,[11–14,26] and was employed extensively in the EXCITE multisite RCT.[14] Ten to 15 shaping tasks from a bank of 120 are selected for use with individual participants based on the nature of the presenting motor deficit and what the therapist feels would benefit the patient most. Coaching on improving the quality, skill, and range of movement is given at frequent intervals (ie, on at least 80% of attempts). The time in which each set of 10 trials is initiated and completed is recorded as well as the performance of all other activities (eg, rest and bathroom breaks).

Transfer package techniques (component 3)

During a recent study, our laboratory has found that the TP made a very important contribution to CI therapy treatment outcome, resulting in an increase by a factor of 2.4 in the amount of spontaneous use of the more-affected UE in everyday life situations compared with an intervention that was the same in the treatment setting but lacked the TP.[16] The standard TP consists of a number of components that include (1) separate behavioral contracts for participants and caregivers specifying agreed-upon real-world activities for which the more-affected arm would be used exclusively; it is signed by the participant or caregiver, a therapist, and a witness; (2) daily administration of the MAL, which collects information about use of the more-affected arm in 30 important activities of daily living; (3) a participant-kept daily diary, which details what a participant did when out of the laboratory overnight and the extent to which there was compliance with an agreed-upon amount of use of the more-affected arm (1, 2, and 3 are monitoring and accountability components); (4) problem-solving to help the participants overcome perceived barriers to real-world use of the more-affected arm identified during monitoring; (5) Home Skill Assignments-functional activities to complete with the more-affected UE assigned on a check-off list (eg, checked "yes" if completed and "no" if not done or done incompletely) taken home

TABLE 2 *Comparison of protocol elements in all intervention groups*

Four main components of CI therapy	CI therapy with standard TP	CI therapy with enhanced TP	Fitness training (LEFT) with standard TP	Fitness training (LEFT) with enhanced TP
Intensive training for 10 consecutive days	3-h supervised UE training for 10 consecutive days	3-h supervised UE training for 10 consecutive days	3-h supervised fitness training 10 consecutive days	3-h supervised fitness training 10 consecutive days
Behavioral technique termed "shaping"	Shaping done in traditional format	Shaping done in traditional format	No formal shaping, but supervised activities progressed systematically	No formal shaping, but supervised activities progressed systematically
Transfer package	Behavioral contract • Participant • Caregiver • Daily MAL • Daily BC adherence diary • Problem-solving • Home skill Assignment • Home task practice • Weekly phone calls first mo. F/U	All elements of CI therapy with standard TP protocol plus • BRAVE wristband-arm use reminder • Visual cues/reminders in living spaces • Motivational text messages • Adherence diary database • Token economy • Additional contacts in F/U	LEFT BC • Participant • Caregiver • Daily PSDQ-S • Daily fitness adherence diary • Problem-solving • Home fitness assignment • Home task practice • Weekly phone contacts first mo. F/U	All elements of LEFT with standard TP protocol plus • BRAVE wristband-exercise reminder • Visual cues/reminders in living spaces • Motivational text messages • Fitness adherence diary database • Token economy • Additional contacts in F/U
Prolonged restraint of the UE not being trained	Restraint mitt on less-affected UE for goal of 90% of waking hours	Restraint mitt on less-affected UE for goal of 90% of waking hours	No restraint used	No restraint used

Abbreviations: BRAVE, Bringing Rehabilitation to American Veterans Everywhere; BC, behavioral contract; CI, constraint-induced; F/U, follow-up period; LEFT, Lakeshore Enhanced Fitness Training; MAL, Motor Activity Log; PSDQ-S, Physical Self-Description Questionnaire-Short Form; TP, transfer package; UE, upper extremity.

by participants, filled in overnight, and monitored daily; (6) home practice of specified functional tasks and exercises similar to the formal tasks carried out in the treatment setting; and (7) weekly telephone contacts with patients for the first month after the end of treatment in which the MAL is administered and problem-solving is carried out. In most physical rehabilitation regimens, there is a passive element; the participant is responsible primarily for carrying out the therapist's instructions during treatment sessions. A major difference in CI therapy is the involvement of the individual as an active participant in all requirements of the therapy not only during the treatment sessions but also at home during the treatment period and after in-laboratory treatment has been completed (as monitored by the weekly phone calls during the first month after treatment). The TP makes the participant responsible for complying with the requirements of the therapy and therefore, in effect, they become responsible for their own improvement. Moreover, it has been recognized by many therapists from the beginning of rehabilitation as a separate field of practice that optimal therapy would be carried out during all waking hours every day, 7 days per week. Application of the TP may represent an initial step in this direction.

Restraint of the less-affected UE (component 4)

In addition to the massed-practice training by shaping of the more-affected UE for 10 consecutive weekdays, the less-affected UE is placed in a heavily padded protective safety mitt for all CI therapy participants. The mitt is a device that effectively prevents finger and thumb use. The less-affected limb is free to maintain balance through being swung during ambulation, and it can be used for protective responses in the event of losspc of balance. A protective safety mitt can therefore be used for restricting less-affected limb use with subjects who have balance problems. The mitt is used for a target

of 90% of waking hours except when certain agreed-upon activities are being carried out (eg, excretory functions, naps, and situations where safety might be compromised). As part of the formulation of the behavioral contract, the purposes for which the participant agrees to wear the mitt are specified with the agreement of the participant as well as the tasks for which the mitt can be removed. A compliance device, consisting of a capacitance circuit inserted inside the mitt, is used to objectively determine the amount of time the mitt is worn. This measure is also used as a proxy for estimating the amount of adherence to the specified requirements of the therapy to use the more-affected UE outside the laboratory. It appeared to work well for this purpose in the past with participants with TBI.[18]

The current approach, used in the BRAVE Study, is different from the previous study (ie, the 2005 CI therapy protocol) in several respects.[18,19] In the previous study, the supervised training (using shaping) was conducted for 6 hours each day as opposed to 3 hours each day in the current CI therapy protocols. Studies with individuals with stroke suggest that 3 hours of shaping daily is equally effective as 6 hours each day (note the similarity of results between Taub et al[11,13] and Taub et al[16]). The BRAVE Study is also different in that it includes a CI therapy arm with an enhanced TP that comprises additional behavior management strategies. Finally, the 2005 study used the participants as their own control and did not have a true control group.

CI therapy with enhanced transfer package

In addition to receiving the standard CI therapy intervention procedures, participants in this group receive additional TP strategies. These strategies are listed in Table 3 and described in more detail in Appendix A.

Fitness training with standard transfer package

Participants assigned to this group participate in a physical and mental fitness program that includes aerobic conditioning, strengthening exercises, land- and water-based sports and recreation, adapted yoga, breathing exercises, postural control, movement-to-music, massage therapy, and meditation or other relaxation exercises. The program, called the Lakeshore Enriched Fitness Training or LEFT, is carried out at Birmingham's Lakeshore Foundation. The protocol includes 3 major components: (1) supervised fitness training for 3 hours a day for 10 consecutive weekdays, (2) systematic progression of the fitness training activities to increase in complexity, intensity, duration, and independence as ability increases, and (3) a "transfer package" of behavioral techniques to promote adherence to the trainer's recommendations outside the treatment setting, requiring an additional 0.5 hour per day. The LEFT program was designed to mirror the CI therapy program with regard to schedule, interventionist supervision and inclusion of a TP. The LEFT protocol does not include any component equivalent to the restraint component of the CI therapy protocol.

These strategies are listed in Table 2 and described in more detail in Appendix A.

Fitness training with enhanced transfer package

In addition to receiving the LEFT protocol, participants in this group receive an enhanced TP that is similar in design to the one used with group 2 (the CI therapy with the enhanced TP group). These strategies are listed

TABLE 3 *Description of the token economy system used in the enhanced transfer package intervention groups*[a]

The token economy is a framework set up to enhance patient participation and ultimately therapy outcome by rewarding patients' hard work and progress. The token economy is used during therapy and throughout follow-up. The "rewards" of the token economy are a graded set of certificates of achievement given at the end of therapy and 1-y follow-up and also donated food vouchers for local and national food chains. The certificates of achievement and the food vouchers are awarded based on the patient's compliance with therapy components, as follows:

Certificates

- 90%-100% compliance: Awarded a gold certificate.
- 80%-90% compliance: Awarded a silver certificate.
- 70%-80% compliance: Awarded a bronze certificate.

Food vouchers

- During treatment: Awarded every third therapy day when compliance with home practice is over 70% and with mitt wearing as deemed appropriate for safety.
- Follow-up: Awarded once a month when compliance with home practice and mitt use is over 70%.

[a]If the patient does not meet the 70% compliance, the therapist discusses with the patient what they can do to improve and what the barriers or issues to compliance may be.

in Table 2 and described in more detail in Appendix A and Table 3.

Outcomes

The MAL,[21–23] the primary outcome, is a structured, scripted interview during which respondents are asked to rate how much and how well they use their more-affected arm for 30 activities of daily living items in the home over a specified period. The MAL is administered independently to the patient and a caregiver. The tasks include common manual activities as brushing teeth, buttoning a shirt or blouse, and eating with a fork or spoon. For each item the participant must report how often and how well (on 6-point scales) each activity was performed during a specified period. Outcome data information is gathered about use of the more-affected UE within 2 days prior to intervention, immediately following the intervention, and at the 6-month follow-up time points. The mean change score of all 30 items from pre- to posttreatment, for each rating scale, is the primary outcome measure for this trial, although the change in score for the follow-up time point is also of critical importance. The MAL has strong psychometric properties and has been used extensively in this and other research laboratory.[21–23]

Data from several secondary outcome measures are being collected and can be categorized as physical, genomic, biologic, fitness, cognitive/behavioral, quality of life, and neuroimaging measures. Table 4 lists the secondary measures employed, briefly describes each, provides a reference, and indicates the frequency of administration.

Random assignment

Participants are randomly assigned to group, with stratification of the randomization scheme by veteran/military versus civilian status and initial level of UE motor deficit (ie, mild/moderate deficit [grade 2] or moderate deficit [grade 3], Table 1). Random assignment is done by the Data Manager prior to enrollment of participants so that the process is independent of project members who have contact with participants and is independent of any knowledge about the participants. The Data Manager uses 2, independent random number generators to issue a pair of numbers that determine assignment to 1 of the 4 study groups, places the assignment in a numbered envelope, and then seals it. The Data Manager generates separate sequences of envelopes for each of the 4 study strata. When a new participant is scheduled for treatment, the Project Coordinator opens the next envelope in the sequence assembled for participants of that particular stratum. If a participant assigned to a group with an enhanced TP does not have Internet access at home, that individual receives the standard TP and the next participant in the same stratum receives the enhanced TP.

Sample size determination

There will be more than adequate power ($\geq$0.99) to test whether participants assigned to CI therapy obtain larger gains at posttreatment on the MAL (ie, the primary outcome) than participants assigned to LEFT. The sample size of 80 is selected to provide adequate power to detect large differences after treatment between the study groups in functional anisotropy values, which index white matter integrity. Even after permitting for a missing data rate of up to 20% due to invalid scans or participant dropout, power will be good ($\geq$0.88) to detect a large difference ($d = 0.8$), which is expected based on our gray matter findings in adults with stroke[27] and white matter findings in adults with multiple sclerosis.[28] For examining associations between baseline characteristics and outcomes within a group to answer important secondary questions such as the relationship between chronicity of motor impairment and MAL gains, adequate power ($\geq$0.87) will be available to detect correlations 0.5 or more.[29]

Data management and analysis

Data are entered into a Microsoft Access database[30] and ported into SAS[31] (SAS Institute Inc, Cary, North Carolina) for analysis. To reduce the likelihood of errors in data entry, all entries are checked against the hard copies of the data collection sheet by a different member of the research team than the individual who entered the data. Checklists are used to ensure that the tester records all the data that are collected at each testing occasion. To minimize the attrition rate, study personnel maintain telephone contact with the participants after they complete posttreatment testing. To reduce the amount of missing data on the primary outcome at 1-year follow-up, MAL data are collected by telephone from participants who cannot return to the laboratory for follow-up testing.

As noted, the primary aim of this study is to test whether CI therapy is an efficacious method for rehabilitating use of an impaired upper extremity in adults more than 3 months after TBI. Analysis of covariance will be used for this purpose. Type of intervention (CI therapy, LEFT), type of transfer package (standard, enhanced), severity of arm impairment (grade 2, grade 3), and veteran status (veteran, civilian) are entered as fixed, independent factors; the posttreatment MAL score is entered as the dependent variable. The pretreatment MAL score is entered as the covariate. The analysis will be conducted on an intention-to-treat basis.[32] To permit evaluation of the sensitivity of the statistical model to different methods of imputing missing data, a variety

TABLE 4 *List of additional outcome measures*[a]

Name of measure	Category	Description	Administration frequency code
Active range of motion	Physical	Determined with a goniometer at each joint of the affected arm and for the MP joints of both hands.	Pre, post, 1-y F/U
Modified Ashworth Scale[20]	Physical	Measures degree of spasticity in participants with lesions of the CNS. For this study—elbow flexors and extensors, forearm pronators and supinators, wrist flexors and extensor, individual MP, PIP, DIP flexors and extensors of digits 1, 2, and 5, and the MP, PIP, DIP flexors, and extensors of digits 2-5 collectively.	Pre, post, 1-y F/U
Anthropometric measures	Physical	Circumference measures taken: midpoint of the neck, the umbilicus, the top of the iliac spine of the pelvis, at the widest point of the hips	Pre
Blood draw	Physical	Measures fasting glucose and lipid profiles	Pre
Accelerometry[40,41]	Physical	The accelerometers are plastic units about the size and weight of a large wristwatch that are worn proximal to the wrist on modified wristbands. The accelerometer signal is digitized at a 10-Hz sampling rate, summed over a user-specific time epoch, and reported as an activity count for each epoch.[20] Approximately 20 activity counts, for example, are recorded in response to a human arm movement such as lifting a book from a stool 78 cm off the floor to a shelf 80 cm away in 1 s. The acceleration recordings are stored in the unit's RAM and can be downloaded to a PC using a computer interface reader unit. A 2-s recording epoch is used, and the units can record continuously for approximately 72 h.	Pre, post, 1-y F/U
Wolf Motor Function Test[42–44]	Physical	This impairment/disability-based test is used to quantify motor function in persons with CNS damage. Performance time (up to 120 s), strength (for lifting and handgrip), and quality of motor function (6-point scale of functional ability) are assessed.	Pre, post, 1-y F/U
Kinematic motion analysis	Physical	See Appendix B	Pre, post, 1-y F/U
DEXA scan	Biologic	Dual-energy x-ray absorptiometry; measures body fat, lean tissue mass, and bone density	Pre, 1-y F/U
PSDQ-S[29]	Fitness	PSDQ-S; multidimensional and hierarchical self-concept model in the physical self-concept area	Pre, post, during, 1-y F/U
Timed Up and Go[45]	Fitness	Tests physical mobility with standing up, walking 3 m, turning, and returning to a seated position.	Pre, post
Biodex—limits of stability[46]	Fitness	Measures dynamic limits of postural stability using the Biodex balance system.	Pre, post
Strength measures	Fitness	Biodex system 3; used to measure strength of combined motions using chest, upper back, shoulder, and arm muscles (ie, pushing and pulling motion). Also measure strength of knee flexors and extensors.	Pre, post
5-time sit-to-stand[47]	Fitness	Assesses time required to stand and sit 5 times in a row as a test of functional lower limb muscle strength.	Pre, post

(*continues*)

TABLE 4 *List of additional outcome measures*[a] (Continued)

Name of measure	Category	Description	Administration frequency code
6-min walk test[48]	Fitness	Assesses distance walked over 6 min as a submaximal test of aerobic capacity.	Pre, post
Wisconsin Card Sorting[49]	Cognitive/ behavioral	A measure of executive function that assesses perseveration and abstract thinking.	Pre, post, 1-y F/U
PCL-PTSD[50]	Cognitive/ behavioral	A 20-item self-report, structured interview to assess the 20 DSM-5 symptoms of PTSD.	Pre, post, 1-y F/U
WMS-IV logical memory[51]	Cognitive/ behavioral	Neuropsychological test designed to measure different memory functions. For this study, the Logical memory (I and II) are being used to examine immediate and delayed recall of story passages; provides a measure of declarative verbal memory.	Pre, post, 1-y F/U
Participant opinion survey	Cognitive/ behavioral	A self-administered survey, using Likert scales, that examines a participant's perceptions about different elements of the intervention protocol. At pretreatment, it examines anticipated benefit from the overall program confidence in being able to fully engage in each individual intervention activity and anticipated difficulty that will be encountered. When administered during and posttreatment, it examines perceived benefit, difficulty, frustration, and satisfaction overall and with each individual intervention activity.	Pre, post, during, 1-y F/U
Satisfaction with Life Scale[52]	Quality of life	Short 5-item assessment designed to measure global cognitive judgments of satisfaction with one's life. Participants indicate how much they agree or disagree with each of the 5 items using a 7-point scale.	Pre, post, 1-y F/U
TBI Model Systems Demographic Survey[53]	Quality of life	Structured questionnaire exploring a variety of demographic characteristics included in TBI Model Systems studies.	Pre, 1-y F/U
HUI3[54]	Quality of life	A series of health profiles and preference-based assessments measuring health status, reporting health-related quality of life, and producing utility scores. The HUI3 examines 8 attributes including vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain.	Pre, post, 1-y F/U
MRI	Neuroimaging	Gray matter-density/volume-VBM White matter tract Integrity-TBSS fMRI-resting state; Motor task-based	Pre, post, 1-y F/U

[a]Frequency of administration.

Abbreviations: DIP, distal interphalangeal; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition); CNS, central nervous system; during, during the intervention; HUI3, Multi-Attribute Health Status Classification System: Health Utilities Index Mark 3; MP, metacarpophalangeal; 1-y FU, 1-year follow-up; PCL, PTSD checklist; PIP, proximal interphalangeal; pre, pretreatment; post, posttreatment; PSDQ-S, Physical Self-Description Questionnaire-Short Form; PTSD, posttraumatic stress disorder; TBSS, tract-based spatial statistics; WMS-IV, Wechsler Memory Scale-fourth edition.

of methods, including the last observation carried forward, will be used.[32] This approach will permit testing of whether type of intervention, type of transfer package, severity of arm impairment, and veteran status have independent effects on use of the more-affected arm and whether the effect of type of intervention depends on one or more of the other independent factors. Parallel statistical models will be used to evaluate the secondary clinical aims of the study. Regression models will be used to evaluate whether baseline characteristics, such as chronicity of injury and degree of cognitive impairment, moderate any gains observed.

A physiatrist who is experienced in the care of individuals with TBI has been enlisted to monitor the safety of the trial.

DISCUSSION

As stated previously, CI therapy has been shown to reduce disability, increase use of the more-affected arm/hand, and promote brain plasticity for individuals with UE hemiparesis following neurologic injuries. The signature intervention protocol consists of the 4 main components described in the background section of this publication. The BRAVE Study was designed to explore the effectiveness of using 1 of 2 CI therapy protocols to improve UE function following TBI compared with physical fitness control groups given equivalent, dose-matched procedures. This study is particularly important because of the increased prevalence of TBI as a result of the Iraq and Afghanistan conflicts. At least 3 factors support a rationale for the conduct of the BRAVE RCT.

First, notwithstanding the extensive research and clinical work involving CI therapy after stroke, there has been only one preliminary case series[17,18,33–38] in which CI therapy has been applied to participants with TBI. Several factors related to TBI could influence the effect of CI therapy, including the diffuse brain damage involved in most TBIs as compared with that resulting from the typical stroke, the more extensive cognitive and behavior problems that tend to accompany TBI, and the difference in demographic profiles of individuals with TBI compared with those with stroke. Individuals with TBI tend to be younger, of a lower socioeconomic status, and more likely to lack caregiver support.[1] The BRAVE Study will provide valuable insight into the influence of these factors on the treatment effect produced by CI therapy.

Second, evidence suggests that the TP element of the CI therapy protocol appears to be the most influential when compared with the other protocol elements. The TP employs a number of behavior management techniques. The BRAVE Study design will examine use of an enhanced TP, for both the experimental and control interventions, to determine whether outcomes could be improved even more by using additional behavior management strategies.

Finally, the control intervention will explore use of 2 CI therapy training elements (intensive supervised training over 10 consecutive days and a TP to promote adherence outside of supervised training) applied to improving physical fitness. In addition to serving as a control for an intervention using CI therapy to improve real-world UE use following TBI, findings from this arm of the study could be useful for understanding the influence of behavior management and intensive training principles for influencing another important therapeutic outcome, improving physical fitness following TBI.

Several limitations exist for the BRAVE Project. First, the intensity of the therapy and amount of time required from interventionists exceeds that which is typical of standard therapy in the United States and many other countries. Also, the protocol differs from those that are currently reimbursable by most medical insurance companies in the United States. However, if shown to be effective, payment policy could change and/or the current protocol could be modified further to be more similar in intensity and supervision to interventions that are typical in standard care and reimbursable by major medical insurance companies. The effectiveness of the modified protocol would then need to be examined. Also, automated training approaches have been developed and show promise for reducing the amount of therapists' time and supervision that is needed.[39] Another limitation is that the LEFT fitness control intervention used in this study does not reflect usual and customary care for UE movement deficits associated with TBI. Standard care for UE movement dysfunction is relatively limited for individuals with TBI in the subacute and chronic phases of recovery. The LEFT fitness control was designed to mirror CI therapy with regard to schedule, interventionist supervision, and inclusion of a TP. As a result, we believe that these characteristics make it an appropriate control intervention for the BRAVE Study. Finally, the inclusion criterion for this study limits the study population to individuals with mild to moderate movement impairment and is not necessarily generalizable to more severely impaired populations.

Alternatives to the approaches used in this study include other rehabilitation approaches used in UE rehabilitation research and clinical practice including neurotherapeutic facilitation techniques, robotics, neurostimulation, and functional neuromuscular electrical stimulation.

Execution of the procedures of the BRAVE Study, as outlined in this article, is expected to provide valuable insight into the management of devastating body structure dysfunction and activity limitations following TBI.

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APPENDIX A

Description of enhanced transfer package components

BRAVE wristband on more-affected UE

At the beginning of the intervention period, participants are given a plastic wristband to be worn on the more-affected wrist to serve as a constant reminder to use that extremity as much as possible. The wristband is water-resistant and can be worn 24 hours/day.

Visual cues/reminders in living spaces

During the intervention period, participants are asked to place in their home environment 2 types of visual reminders to use the more-affected UE during functional tasks.[1] Adhesive letters ("L" for left or "R" for right) are placed on common household items or locations (eg, kitchen and bathroom sinks, light switches, and refrigerator door handle) to remind the participant to use the more-affected UE for the indicated purpose. For smaller items (eg, cellphone, toothbrush, and eating utensils), an adhesive dot is used for that purpose.

Motivational text messages

During the intervention period, participants receive motivational text messages via their cellphones and/or electronic tablets. These messages are preset and sent 2 times each day (early morning and late afternoon). The contents of the messages remind participants to use the more-affected extremity and/or are inspirational. Examples of such messages are "Believe in yourself … all things are possible" and "Don't give up!" If participants do not own a cellphone or electronic tablet, the project provides an electronic tablet to be used during the intervention period.

Adherence diary database

A Qualtrics database system has been created for use on an electronic tablet or computer for participants in the enhanced TP group to report adherence to mitt use and execution of the daily Home Skill Assignment (HSA) activities. During treatment, participants are asked to indicate the amount of time they used the mitt and the HSA activities they completed for the treatment day in question. Use of the Qualtrics database system continues into the follow-up period on a less frequent basis (ie, a weekly report, summarizing performance throughout the week, for the first year after the end of treatment).

Token economy system

During the intervention period, project staff monitor adherence rates of mitt use and follow-through with Home Skill Assignment Activities, as reported in the adherence diary database. Three graduated reward certificates are provided for adherence rates above 70%. The graduated rewards are described in Table 3.

Additional contacts during the follow-up period

In addition to the same weekly telephone contacts with participants in the standard TP group for the first month after the end of treatment in which the MAL is administered and problem-solving carried out, participants in the enhanced TP group receive monthly telephone calls of this type for posttreatment months 2 through 6. In addition, these telephone contacts make use of the information provided by the Qualtrics database reports that participants are asked to submit on a weekly basis. Substantial compliance declines are discussed and problem-solving to aid in improving compliance is carried out.

APPENDIX B

Kinematic motion analysis procedures

A 10-camera motion capture system (NaturalPoint, Inc, Corvallis, Oregon) was used to record the 3-dimensional (3D) positions of retroreflective markers at a frequency of 120 Hz and filtered with a Butterworth low-pass filter (6-Hz cutoff). A total of 27 markers, 5 mm in diameter, were placed on the participant's body using double-sided tape. The markers were attached to the hand, forearm, and upper arm of both upper extremities and to the torso, hips, and head. (See accompanying Figure 1 for location of markers.) Local segmental and laboratory coordinate systems were constructed so that

the *x*-axis is directed laterally to the right, the *y*-axis is directed anteriorly, and the *z*-axis is directed superiorly. Marker position data were collected first during a static calibration trial with the participant standing in the center of the testing area with shoulders slightly abducted and palm facing forward to keep the cameras' view from being obstructed. Participants were instructed to perform the Wolf Motor Function Test, and 3D kinematic data for each task were collected. 3D segmental Euler kinematics (*x-y-z* sequence) angles were computed based on the rotation matrix between the global and local coordinate systems of each segment. Consequently, joint angular displacement, velocity, and segmental angular velocity are derived from 3D Euler angles.

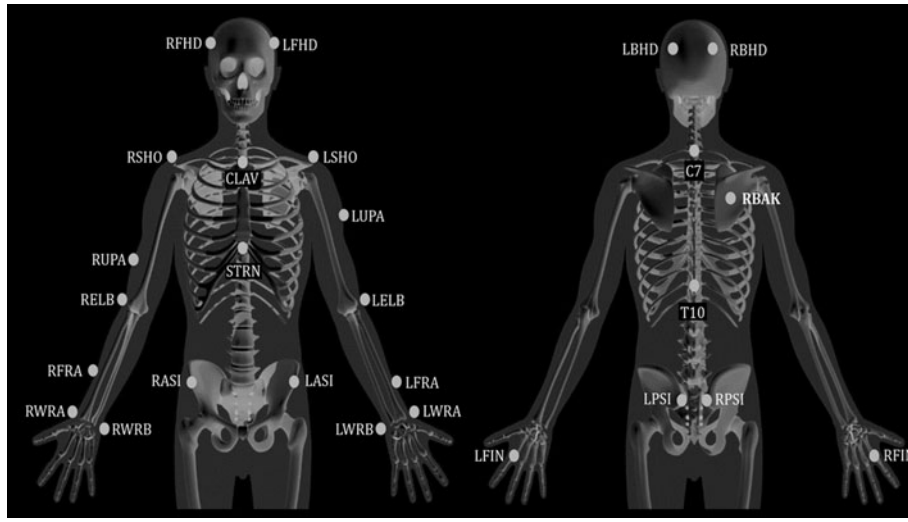

Figure 1. Location of markers for the motion capture system. CLAV indicates clavicle; C7, 7th cervical vertebra; LASI, left anterior superior iliac spine; LBHD, left back head; LELB, left elbow; LFHD, Left front head; LFIN, left finger; LFRA, left forearm marker; LPSI, left posterior superior iliac spine; LSHO, left shoulder marker; LUPA, left upper arm marker; LWRA, left wrist marker A; LWRB, left wrist marker B; RASI, right anterior superior iliac spine; RBAK, right back; RBHD, right back head; RELB, right elbow; RFHD, right front head; RFIN, right finger; RFRA, right forearm marker; RPSI, right posterior superior iliac spine; RSHO, left shoulder marker; RUPA, left upper arm marker; RWRA, right wrist marker A; RWRB, right wrist marker B; STRN, sternum; T10, 10th thoracic vertebra.