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TITLE: Advancing Clinical Outcomes, Biomarkers, and Treatments for Severe TBI

PRINCIPAL INVESTIGATOR: Theresa Pape, DrPH

CONTRACTING ORGANIZATION:
Chicago Association for Research and Education in Science
Hines, IL

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6. AUTHOR(S)

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

This study is a ***double blind randomized placebo-controlled clinical trial using repeated measures***. The ***objective*** is to improve recovery of functional skills for persons living in states of seriously impaired consciousness 3 to 12 months after severe TBI. This will be achieved by determining the neurobehavioral and neural effects of repetitive transcranial magnetic stimulation (rTMS), which is a non-invasive technique to stimulate the brain. The evidence of therapeutic efficacy from the literature in non-TBI related neurologic populations combined with our preliminary findings with severe TBI, indicate that rTMS merits investigation as a neurotherapeutic for severe TBI and that the proposed repetitive TMS protocol should be examined to determine effectiveness in inducing structural and functional neural plasticity and improving neurobehavioral recovery after severe TBI. ***Specific Aims***: Aim I will determine presence, direction and sustainability of rTMS-induced neurobehavioral effects measured with the Disability Rating Scale. Aim II will determine the presence, direction and sustainability of rTMS-induced changes in functional neural activation and whether or not these changes correlate with improving neurobehavioral function. Aim III will examine the effect of rTMS on white fiber tracts and whether or not the rTMS-related effects correlate with improving neurobehavioral function. Aim IV addresses the need to confirm rTMS safety for severe TBI.

15. SUBJECT TERMS

Disability Rating Scale (DRS), Neurobehavioral, Repetitive Transcranial Magnetic Stimulation (rTMS), Traumatic Brain Injury (TBI), Vegetative (VS), Minimally Conscious (MCS)

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Table of Contents

1. **INTRODUCTION:** Based on published evidence and pilot data from three subjects, repetitive Transcranial Magnetic Stimulation (rTMS) holds promise as a treatment for severe Traumatic Brain Injury (TBI). TBI alters the lives of the patient, their family, and society. Severe TBI is particularly devastating with some survivors recovering full consciousness swiftly while others remain in states of seriously impaired consciousness (SIC). Both recovery trajectories involve complex and potentially chronic cognitive and physical impairments. Evidence that cortical processing can occur even while unconscious and evidence of late recoveries continues to accumulate suggesting that SIC is a modifiable condition. Advanced medical care saves and sustains the lives of persons incurring severe TBI and there is a growing body of evidence indicating that this devastating injury is modifiable but there are few to no treatments that induce or accelerate functional and adaptive recovery for survivors of severe TBI. Optimal functional recovery after severe TBI, without targeted treatments, is unlikely. To address the need for targeted treatments that induce functional and structural changes in the brain, ultimately improving neurobehavioral functioning, we propose examining the therapeutic effectiveness of rTMS. The objective is to improve functional recovery for persons remaining in vegetative (VS) and minimally conscious (MCS) states 3 to 12 months after severe TBI. The approach is to determine the neurobehavioral effect of rTMS, the relationship between neurobehavioral changes and net neural effects, and to identify and define the neural mechanisms related to neurobehavioral improvements by providing 30 active or placebo rTMS sessions. The Disability Rating Scale (DRS), Coma Recovery Scale-Revised (CRSR), Disorders of Consciousness Scale-25 (DOCS-25), and Coma/Near Coma Scale (CNC) will be used at four time points to measure neurobehavioral recovery slopes. Net neural effects will be measured at three time points using fcMRI, resting state EEG (EEG-Rest), a language fMRI task and changes in EEG power spectrum when listening to a semantic processing task (EEG-Task). We will examine changes in structural integrity of fiber tracts using DTI. Measures are collected prior to, during, after and at follow up from active and placebo rTMS treatments.
   Subsequently, the JWMRP allows the study design to collect the Glasgow Outcomes Scale-Extended (GOS-E) at all four time-points. Further, the addition of paired ratings for all five neurobehavioral function measures creates an opportunity to examine these widely used assessments and establish key indices of change. This pivotal information will enable us to generate effect sizes and meaningful measures of change from which researchers can power clinical trials and better quantify the patient's improvement. Additionally, we will identify the micro-Ribonucleic acids (miRNA) within whole blood and microparticles that are altered by the rTMS intervention and correlated with the neurobehavioral and neurophysiological outcomes. We think that we can identify specific miRNA because evidence shows that severe TBI results in cellular damage and dysregulation of signaling pathways and structural proteins and also that miRNA play a critical role in translational regulation of cellular pathways in the recovery of TBI.. Furthermore, evidence from animal models demonstrate that rTMS promotes miRNA regulation involved with neural repair. Collectively, the evidence suggests that specific miRNA represent potentially useful biomarkers for therapeutic responsiveness to rTMS.

2. **KEYWORDS:**

   Disability Rating Scale (DRS)
   Coma Recovery Scale-Revised (CRSR)
   Disorders of Consciousness Scale-25 (DOCS-25)
   Coma/Near Coma Scale (CNC)
   Glasgow Outcomes Scale-Extended (GOS-E)

MicroRNA (miRNA)
Neurobehavioral
Repetitive Transcranial Magnetic Stimulation (rTMS)
Traumatic Brain Injury (TBI)
Vegetative State (VS)
Minimally Conscious State (MCS)

3. ACCOMPLISHMENTS:

Supplemental Project #2 Advancing Clinically Reported TBI Outcomes using Modern Psychometrics

Major Goal 1: Development and testing of meaningful change anchors (Months 1-6)
Milestones: Valid hierarchy of anchor descriptors

Accomplishments: We have created the four paired-comparison clinician surveys in RedCap. Our IRB under review at GWU was approved this quarter. Our next step is to publish the surveys in RedCap, obtain HRPO approval, and then create a website to host the surveys during recruitment. To describe the process of creating the vignettes, Ms. Weaver has started a manuscript to describe the process of creating the vignettes to evaluating them using Labov's checklist and cognitive testing with clinicians.

Major Goal 2: Create patient video cases and collection of linking data (Months 6-12)
Milestones: Complete standardize case videos;
Collect data on these videos;

Accomplishments: We have collected and reviewed the videos. The original purpose of the videos was to link raters for the Many Facet Rasch Analysis because we would have raters at multiple sites. Due to changes in the study sites, we have been able to pair all raters and plan to move forward with an item linking process if needed for our future analyses. Therefore, we will not be creating patient video cases.

Major Goal 3: Examine basic psychometrics for each assessment (Months 13-18)
Milestones: Complete rating scale, item, and person analyses;

Accomplishments:

Systematic Review on Outcomes Mapping: We conducted a thirty year search strategy to understand how outcome measures have been used for severe TBI (sTBI) intervention studies. The purpose of this is to ultimately describe the concepts of interest that are important for sTBI. We have completed the full-text review process for 400 studies. Our study team is of 30 persons and we recently collated all of the individual excel sheets utilized for data extraction. Additionally, we have started the analyses and have mapped all primary and secondary outcomes to the WHO ICF. We are also working on a protocol publication and it is 50% complete.

Systematic Review on Delineating Concepts of Interest for Neurobehavioral Function: The purpose of this systematic review is to understand the concepts of interest for outcome measures related to neurobehavioral function in patients with severe TBI in disordered states of consciousness. The outcome measures that evaluate NBF will stem from the parent study on outcomes mapping. This study will move forward once the measures have been categorized in the parent study.

Disorders of Consciousness Scale (DOCS-25): Basic psychometrics were completed prior to the award.

Coma Near Coma Scale (CNC): We have completed the primary analyses of the psychometric properties for the CNC scale. When we first submitted the paper for review, we received substantial requests for revisions. We made these revisions and submitted the revised CNC manuscript to Brain Injury in June of 2019. The journal responded with minimal revisions requested in January of 2020. We completed the requested revisions and resubmitted the manuscript at the end of January. Revisions came back requesting a different approach. We have received notification from Archives of Physical Medicine and Rehabilitation that they will accept the manuscript. A key output of this work was the development of a nomogram for use by clinicians to rapidly score and interpret the clinical meaningfulness of results. Data from the clinical trial will be validated against these initial calibrations. Because of the wide range of inconsistencies in how Rasch Measurement is reviewed and reported we initiated a collaborative effort with the ACRM Measurement Networking Group task force to develop a reporting guideline for Rasch Measurement theory. This guideline has been submitted for registration with the EQUATOR network. Tthe draft guideline and checklist was published to the ACRM website on August 1st and we plan to have the two elaboration manuscripts submitted for publication in Archives of PM&R by the end of the year.

Coma Recovery Scale-Revised (CRS-R): The psychometrics of the CRS-R have proved more challenging than initially anticipated. Work on the CNC and DOCS-25 demonstrated to us that stimulus-level data rather than item level data would be needed to evaluate the CRS-R because the ordering of the stimuli within CRS-R items (from least to most challenging) does not comport with what we have learned from our earlier studies of the CNC and DOCS. In addition, the hierarchical ordering of the CRS-R stimuli has never been empirically validated. If we were to only analyze of item level stimuli and find that rating scale steps or items were disordered, we would not know how to proceed to rectify the problem. To ensure we have sufficiently precise and robust findings from this clinical trial, we have developed and pilot tested a stimulus-level data collection form for the CRS-R, which we have implemented in the clinical trial and at TIRR Memorial Hermann Hospital in Houston Texas. We have an Institutional Authorization Agreement with TIRR and have received an initial dataset. We are in the process of converting the data to a format for analysis.

Recognizing that work on the stimulus level data while take time, we have moved forward with conducting analyses at the item-level. We located, requested, and have received data from three additional sources to supplement the clinical trial data for more robust analytic decisions. These additional data sources are the Shirley Ryan Ability lab (n=50); TIRR (n=19); Amantadine trial (Whyte & Giacino) (n=184). We have conducted preliminary Rasch Analyses and we are now in the process of writing up the results of the item-level Rasch Analysis and plan to submit the manuscript to Archives of Physical Medicine & Rehabilitation by November 2020. A poster was accepted and will be presented at the ACRM Annual Conference in October.

Disability Rating Scale (DRS): Data we received from the Amantadine trial and most recently from the NIDRR TBI Model systems (TBIMS) data set also included DRS item-level data enabling us to begin these psychometric analyses. We initially started the Rasch analysis with the Amantadine trial data and found the DRS to have significant Guttman-like responses; that is, once a patient has been scored on one or two items, their scores on the remaining items can be predicted with 100% accuracy, that is, the items don't capture any new information about person function. In addition, the items are "clumped" at the very low end of the scale and at the high end of the scale meaning there are few items to detect ability in the middle where most patient ability

actually is. This limits the ability of the tool to detect change in function over time and makes the items very challenging to calibrate with other tools. Analyses to resolve this problem are in progress. We plan to merge the TBIMS dataset in the next reporting period. During this reporting period, we transferred the data from SPSS to STATA.

Major Goal 4: Conduct the Rater Severity/Leniency analyses (Months 19-25)
Milestones: Item and rating scale anchors with effect of Rater Severity/Leniency removed;
Accomplishments: We have defined the methodology to conduct the rater severity/leniency analyses and have completed these analyses for the DOCS scale on a pre-existing data set. We will implement these analyses when more trial data are available and after all co-calibration has been completed.

Major Goal 5: Conduct Minimally Detectable Change, Minimally Clinically Important Difference, & Effect Size analyses

Milestones: Indices of change for each neurobehavioral functional assessment

Accomplishments:

Disorders of Consciousness Scale: The MDC, MCID, and effect size was already been published prior to this award however we recently recognized that the incorrect equation was used to calculate the MDC. We submitted a Letter to the Editor in the Journal of Head Trauma and Rehabilitation describing the revised results. This manuscript has been accepted for publication (see products). In the process, we found that new literature was recently published describing analyses for a conditional MDC (cMDC) which is more appropriate for Rasch-based measures. We have conducted these analyses in consultation with Dr. Kozlowski who developed the new approach. We are preparing these results for publication.

Coma Near Coma Scale: We have completed the analyses for the cMDC, MDC, and MCID for the CNC. We are in the process of preparing these results for publication.

Major Goal 6: Complete deliverables including conversion tables, crosswalks, and change indices tables (Months 33-36)

Milestones: Co-calibration tables/crosswalks;

Milestones: Tables of change indices for each of the assessments

Accomplishments: We have completed the primary analyses of the psychometric properties for the CNC scale and established preliminary alignment between the CNC and DOCS-25. A control file has been created to run these analyses in Facets to account for Rater severity and leniency.

Major Goal 7: Dissemination activities (Months 33-36)
Accomplishments: Finally, we have significantly improved our methodology for examining assessment psychometrics based on the Rasch Model and have used our experience as a springboard to initiate a separate but related effort by establishing and leading an ACRM Measurement Task Force focused on Rasch Analysis. This task force is a collaborative effort of 9 researchers from 8 institutions nationally. The results of this task force were presented at the ACRM Annual conference in 2019 and IOMC 2019 (a pre-conference to ACRM). The feedback received from the presentation are being integrated into a manuscript that will provide the most rigorous guidance to date for authors publishing articles using Rasch Analysis.

What opportunities for training and professional development has the project provided? Nothing new to report.

How were the results disseminated to communities of interest? Nothing to report.

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

Because we have acquired additional data sets, we will complete the co-calibration of the CNC, DOCS, and CRS-R simultaneously. We do not expect it will be possible to co-calibrate the DRS with these other assessments. We now have CRS-R analyses complete at the item level. However, prior to moving forward with the co-calibration, we plan to describe the novel approach for calculating indices of responsiveness (cMDC) in this next reporting period. We also plan to further the work on the paired comparison survey by submitting the modifications to HRPO, and publishing the RedCap surveys in preparation for recruitment activities. We will use existing data to advance techniques for examining rater severity/leniency to improve the precision of NBF measurement for patients in DoC.

4. **IMPACT:** Nothing to report.

5. **CHANGES/PROBLEMS:**

   We are proposing to not move forward with Major Goal 2 and have described our rationale up above.

6. **PRODUCTS:** Mallinson, Trudy PhD, OTR/L; Weaver, Jennifer Ann MA, OTR/L; Guernon, Ann MS, CCC-SLP/L; Bender Pape, Theresa DrPH, MA, CCC-SLP/L Letter to the Editor, Journal of Head Trauma Rehabilitation: May 27, 2020 - Volume Publish Ahead of Print - Issue - doi: 10.1097/HTR.0000000000000577

7. **PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS:**

   What individuals have worked on the project?

   Name: Theresa Pape. Dr. PH
   Project Role: Principal Investigator
   Nearest person months worked: 3
   Contribution to project: Dr. Pape has overseen protocol development, staffing at each site, and overall project flow.

   Name: Lisel Kwartnik
   Project Role: Project Manager
   Nearest person months worked: 3
   Contribution to project: Ms. Kwartnik is responsible for the development and monitoring of study budgets and ensuring all financial allocations and expenditures are in accordance with the grant and VA requirements for the currently funded research clinical trial and the three supplemental projects. She provides daily operational assistance to project staff. No Change.

Name: Ann Guernon, MS
Project Role: Clinical Research Manager
Nearest person months worked: 3
Contributions to project: Ms. Guernon is responsible for the oversight of regulatory submissions and clinical data collection. She works closely with Dr. Walsh, Mallinson and Pape to insure the quality of the data collected in these projects. No change.

Name: Elyse Walsh, DPT
Project Role: Research Therapist
Nearest person months worked: 3
Contributions to project: Dr. Walsh managed the specific IRB submission for the Clinician Language Protocol at all three submission sites. She also manages screening of potential participants for both protocols and schedule of research procedures. No change.

Name: Jen Weaver, OTR/L
Project Role: Research Associate:
Nearest person months worked: 5
Contributions to project: Ms. Weaver has led a team of thirty reviewers to complete the full-text review process on 400 intervention studies. She also led a team of 5 individuals to take each individual data extraction form and integrate the data into one file to enable the analytic process. We are in the final stages of cleaning this merged data set. She is also leading the development of the protocol paper that we plan to submit to JBI for peer review.
She is also actively engaged in the paired comparison survey process to evaluate meaningful change. She has overseen the process of creating four surveys that follow a particular protocol developed by Dr. Mallinson. She ensured the testing of each survey and created the IRB packet for submission. To describe the process of how the team created the short stories, Ms. Weaver is leading the writing of a manuscript with oversight from Dr. Papadimitriou. During this quarter, she successfully received GWU IRB approval.
She is also leading the CRS-R analyses and has a draft of the methods and results sections of a manuscript that will be submitted for the peer review process.Furthermore, Ms. Weaver led the re-submission of the CNC analyses to Archives of Physical Medicine & Rehabilitation.

Name: Trudy Mallinson, PhD
Project Role: PI of Supplemental Project # 2
Nearest person months worked: 2
Contributions to project: Trudy Mallinson directly oversees Jen Weaver, building capacity for the team to examine the psychometric properties of each outcome measure. She is working on the rater severity/leniency analyses plan and overseeing the CNC, DRS, and CRS-R analyses. She is leading the analyses of the primary outcome for the systematic review on outcome mapping to strengthen the content validity of the measures for neurobehavioral function. She discussed the video edits that are needed with Dr. Pape and concluded that the videos are no longer needed for their original purpose. The videos will be useful to create trainings, which are necessary and needed in this practice area; but it does not align with the purpose of this study.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report.

What other organizations were involved as partners?

Organization Name: George Washington University
Location of Organization: Washington, DC, USA
Partner's Contribution to the Project: Collaboration

8. **SPECIAL REPORTING REQUIREMENTS:** None.

9. **APPENDICES:** None

QUAD CHART: See attached Quad Chart.

AWARD NUMBER: W81XWH-16-2-0023

TITLE: rTMS: “Advancing Clinical Outcomes, Biomarkers and Treatments for Severe TBI”
Subproject: “miRNA as Biomarkers for Severe TBI and rTMS Mediated Gains in Neurobehavioral Activity”

PRINCIPAL INVESTIGATOR: Theresa Pape, DrPH

CONTRACTING ORGANIZATION:
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Glasgow Outcomes Scale-Extended (GOS-E)
MicroRNA (miRNA)
Neurobehavioral
Repetitive Transcranial Magnetic Stimulation (rTMS)
Traumatic Brain Injury (TBI)
Vegetative State (VS)
Minimally Conscious State (MCS)

3. ACCOMPLISHMENTS:

Supplemental Project #3 rTMS: miRNA as biomarkers for severe TBI and rTMS mediated gains in neurobehavioral activity

Major Goal 1: Regulatory Requirements (Months 1-6)
Milestones: Local IRB and safety approved

Accomplishments: 100% completed.

Major Goal 2: Coordinate Study Staff and Logistics for Study (Months 1-36)
Milestones: Milestone Achieved: Study staff hired and trained
Accomplishments: 100% completed.

Major Goal 3: Validation of sample collection, shipment, processing and storage
Milestones: Validation and standardization of sample collection, shipping, processing and storage;
Accomplishments: 100% completed.

Major Goal 4: Validation of miRNA in severe TBI patients
Milestones: Validation of target miRNA to follow in TBI patients;

Accomplishments: 18.8% completed- We have 9 out of the 48 patients complete.

Major Goal 5: Assessment of miRNA in entire study population
Milestones: All study participants recruited and completion of research participation;

Accomplishments: 44.1% completed- We have obtained samples for 10 TBI patients and have the miRNA isolated and sequenced for 7 of the patients. We have all healthy control samples collected, miRNA isolated and sequenced. The blood samples from the 8th patient is in the queue to be isolated and sequenced and we should have the data soon. Blood from the 9th patient has been drawn and blood from the 10th patient is currently being drawn. The RNA from both of these patients will be isolated within the next month and the process for miRNA sequencing following the RNA isolation.

Major Goal 6: Data Analysis (Months 37-48)

Accomplishments: **13.8% completed** - MicroRNAs (miRNAs) are small regulatory RNAs that post-transcriptionally regulate the expression of thousands of genes and play key roles in a number of essential cellular and developmental processes, in both normal physiologic and disease contexts. The miRNA expression profile can provide insights about up and down regulated genes and pathways, that when combined with clinical data, can help to explain the efficacy of treatments and further inform targeting of therapeutics. The miRNA from **8 TBI patients** have been completely isolated, sequenced and analyzed.

Methods: Blood samples of the severe TBI patients enrolled in the ongoing clinical trial examining efficacy and safety of transcranial magnetic stimulation (TMS) were collected. Samples were collected at different time points during active/sham TMS treatment and after stopping active/sham TMS treatment. Each sample was surveyed through miRNA sequencing on the Illumina MiSeq bench-top sequencer. Bioinformatic analysis was conducted using CutAdapt v2.3 tool to remove adapter sequences and Bowtie2 v2.3.5 to align the sequences to the Genome Reference Consortium Human Build 38 (GRCH38). The miRNAs that aligned to the reference genome were counted with HTSeq v0.3.7 tool. The count files were then used to analyze the miRNA expression with the tool DESeq2 v3.9 in R v3.5.1 software, using a fold-change of 2.0 and p-value <0.05 as cutoffs.

Analyses: To date, we have conducted three analyses. First, all 7 patients were examined as one group as this allows us to maintain blinding. We first compared the patients to their age and gender matched healthy controls. We conducted a second analysis by examining the changes in miRNA during active/sham TMS treatment provision for this group. To provide additional insights on TMS treatment responsiveness, we conducted a third analyses where we compared clinical gains for a patient optimally responding to TMS versus a sub-optimal clinical responder (both of whom were in active group).

Results: For the first group analysis (n=7, baseline timepoint), we found 30 up-regulated and 18 down-regulated miRNAs in patients vs. age and gender matched healthy controls. Our study has shown overlapping miRNA changes at baseline with other studies exploring miRNA changes in severe TBI patients within acute and subacute time points. These miRNAs include miRNA-335, miRNA-144, miRNA-9-3p, miRNA-618, miR142-3p, miR769-5p, miRNA 151a and miRNA-10b-5p. These miRNA are associated with regulation of cell cycle, proliferation, migration, and differentiation of cells, neuroplasticity, and inflammation. These miRNAs may be excellent candidates to consider as biomarkers for the diagnosis a severe TBI and to use as therapeutic targets to enhance behavioral function in these patients who are in a state of DoC.
Our study also correlated changes in serum and cellular miRNAs in severe TBI patients with a comprehensive set of neurobehavioral assessments. The patient's behavioral status was not limited to the observed GCS scale but also included the DOCS, CNC, CRS-R, and Spaulding behavioral tests. Findings identified 11 upregulated miRNA that were highly correlated with multiple behavioral assessments including miRNA-218-5p, miRNA-4482-3p, miRNA-145-3p, miRNA-145-5p, miRNA-149-5p, miRNA-335-5p, miRNA-618, miRNA-338-5p, miRNA-28-5p, miRNA-2115-5p, and miRNA-151a-3p. Six downregulated miRNAs were also found that were highly correlated with multiple assessments of these behavioral tests including miRNA-144-3p, miRNA-144-5p, miRNA-6815-5p, miRNA-6087, miRNA-7641 and miRNA-126-3p.
For our second group analysis (n=8), we will be looking analyzing the effect of treatment over the total time course. We will not only analyze the treatment arm in comparison to the healthy controls, but we will also be able to look at the severe TBI patients that were initially in the placebo compared to the timepoints when they were administered the treatment. This will be a more complete analysis and the results will be written up into a second manuscript.

Conclusions: Overall, findings indicate that miRNA expression is likely useful as a biomarker of TBI severity. For a population with many challenges for demonstrating treatment efficacy, findings also indicate that changes in miRNA expression advance understanding of TMS treatment efficacy. Our findings also indicate that miRNA expression will likely be helpful in understanding differences in treatment responsiveness and identifying potential therapeutic targets (e.g. let-7i). We found several regulated miRNAs of interest and particularly the miR-9 family, which is associated with neuron differentiation and brain development. The let-7 family

been reported to be related to cortical plasticity. miR-9-3p, miR20a, and miR151 have all been previously reported to correlate with severity of injury after mild and severe TBI. Increased circulating serum levels of these miRNAs have also been shown to correlate with more neurocognitive impairment, and two of them are significantly downregulated in our study. These miRNAs may lead to novel biomarkers for response to treatment and efficacy.

What opportunities for training and professional development has the project provided? Nothing new to report.

How were the results disseminated to communities of interest? Although no dissemination has occurred thus far, we are revising the first manuscript for publication. A second manuscript is also in preparation describing the changes in miRNA induced by TMS in severe TBI patients over time.

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

For the next reporting period, the goals are to continue subject recruitment at all sites for microRNA.
We are revising the first manuscript for publication. This manuscript details the miRNA that are significantly altered at baseline in the severe TBI patients as compared to age and sex matched healthy controls. It also describes the correlation between behavioral assessments and miRNA changes. Our will continue the analysis for the treatment responsiveness and begin the writing process for the second manuscript that will explore miRNA changes following TMS to determine a panel of miRNA as biomarkers for patients who will have enhanced treatment responsiveness.

4. **IMPACT:** Nothing to report.

5. **CHANGES/PROBLEMS:**

Recruitment for the parent grant (no. W81XWH-14-1-0568) has a direct impact on progress for this study as the subjects recruited to the parent study are also recruited to this study. Recruitment delays have been addressed in the progress report for the parent grant.

6. **PRODUCTS:** Nothing to Report

7. **PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS:**

What individuals have worked on the project?

Name: Theresa Pape. Dr. PH
Project Role: Principal Investigator
Nearest person months worked: 3
Contribution to project: Dr. Pape has overseen protocol development, staffing at each site, and overall project flow.

Name: Lisel Kwartnik
Project Role: Project Manager

Nearest person months worked: 3
Contribution to project: Ms. Kwartnik is responsible for the development and monitoring of study budgets and ensuring all financial allocations and expenditures are in accordance with the grant and VA requirements for the currently funded research clinical trial and the three supplemental projects. She provides daily operational assistance to project staff. No Change.

Name: Ann Guernon, MS
Project Role: Clinical Research Manager
Nearest person months worked: 3
Contributions to project: Ms. Guernon is responsible for the oversight of regulatory submissions and clinical data collection. She works closely with Dr. Walsh, Mallinson and Pape to insure the quality of the data collected in these projects. No change.

Name: Elyse Walsh, DPT
Project Role: Research Therapist
Nearest person months worked: 3
Contributions to project: Dr. Walsh managed the specific IRB submission for the Clinician Language Protocol at all three submission sites. She also manages screening of potential participants for both protocols and schedule of research procedures. No change.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

There have been no changes since the last reporting period.

What other organizations were involved as partners?

Organization Name: Northwestern University
Location of Organization: Chicago, IL, USA
Partner's Contribution to the Project: Collaboration

Organization Name: Santa Clara Valley Medical Center **(STUDY SITE CLOSED)**
Location of Organization: San Jose, CA, USA
Partner's Contribution to the Project: Collaboration

Organization Name: Loyola Genomics Facility
Location of Organization: Maywood, IL, USA
Partner's Contribution to the Project: Quality control testing of blood cell RNA

8. SPECIAL REPORTING REQUIREMENTS: None.

9. APPENDICES: Quad Chart.