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TITLE: Assessment and Rehabilitation of Central Sensory Impairments for Balance in mTBI

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14. ABSTRACT

Objectives: Control of balance requires complex integration of sensory and motor systems. Balance measurement is often over-simplified, preventing balance deficits from being identified and treated after mTBI. Our central hypothesis is that chronic balance deficits after mTBI result from impairments in central sensorimotor integration that may be helped by rehabilitation. This research has two objectives; 1) to characterize balance deficits in people with mTBI, and 2) to use a novel auditory biofeedback device to improve measures central sensorimotor integration and balance control.

Methods: Aim I) Balance Assessment: mTBI patients with non-resolving balance deficits following injury and healthy control participants with no history of mTBI are currently being recruited and tested on a battery of vestibular, neurocognitive, and balance-related tests. Aim II) Balance Rehabilitation: mTBI patients (a subgroup from Aim 1) are randomly allocated into a standard of care balance rehabilitation program either with, or without auditory biofeedback. Both groups receive rehabilitation two times per week for six weeks. All participants are tested at baseline during Aim I testing, and are tested again following the intervention period, and again 6 weeks later to determine retention of changes.

Status: Number of subjects enrolled / original planned target: 132 subjects have been enrolled out of 130 planned total (67 out of 65 mTBI, 65 out of 65 controls. Number of subjects screened/ original planned target: 192 subjects have been screened out of 170 planned total. Number of patients completed/ original planned target: 123 subjects have completed Aim 1 testing out of 130 planned total, 10 control subjects have returned for the 6-week follow up testing out of 10 planned total, 32 mTBI subjects have returned for the 6- and 26 for the 12-week follow up testing out of 40 planned total. We are no longer enrolling subjects.

Findings to date: People with chronic mTBI reported worse symptoms relating to balance and vestibular dysfunction than the healthy controls. People with chronic mTBI performed worse on the ANAM neurocognitive testing battery, and were slower to respond to stimuli during the dual-task. Turning speed was slower in people with chronic mTBI, and coordination and walking rhythm appear to be effected. People with chronic mTBI weighted sensory information differently during the test of central sensorimotor integration. During quiet standing chronic mTBI exhibit more sway at the head compared with healthy controls.

15. SUBJECT TERMS
Balance, mTBI, Rehabilitation, Brain Injury, BESS, Dynamic Posturography, SOT, Inertial Sensors, Auditory Biofeedback, Central Sensory Integration, Concussion

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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Table of contents

1. INTRODUCTION:

Control of balance requires complex integration of sensory and motor systems. In the clinic or in the field, balance measurement is often over-simplified, preventing balance deficits from being identified and treated after mTBI. Our central hypothesis is that chronic balance deficits after mTBI result from impairments in central sensorimotor integration that may be helped by rehabilitation. There are two objectives of this proposal; the first objective is to characterize balance deficits in people with mTBI. The second objective is to use a novel auditory biofeedback (ABF) device to improve measures of central sensorimotor integration and balance control.

2. KEYWORDS:

mTBI, Rehabilitation, Brain Injury, BESS, Inertial Sensors, Balance, Auditory Biofeedback, Central Sensory Integration, Concussion

3. ACCOMPLISHMENTS:

What were the major goals and objectives of the project?

Goal	Target Completion Date	Percentage of Completion/ Date of Completion
Specific Aim 1 (Study 1: Assessment n=130 mTBI)		
Major Task 1: Launch Study Activities	30-Feb-2016	100%
Major Task 2: Recruitment and Testing (n=130)	30-Feb-2019	100%
Major Task 3: Data Analysis and Publications	30-Sep-2019	80%
Specific Aim 2 (Study 2: Rehabilitation n=40 mTBI)		
Major Task 1: Launch Study Activities	30-Feb-2016	100%
Major Task 2: Prepare Technology and Protocol for Intervention	30-Sep-2016	100%
Major Task 3: Randomized Interventions (n=40 mTBI)	30-Feb-2019	100%

Major Task 4: Assess Efficacy of Interventions (n=40)	30-Feb-2019	100%
Major Task 5: Data Analysis and Publications	30-Sep-2019	60%

What was accomplished under these goals?

Status of major activities and specific objectives:
Specific Aim 1 (Study 1: Assessment n=130)

Major task 1: Launch study activities

Subtask 1: Prepare regulatory documents and research protocol; 100% complete.

Major Task 2: Recruitment and testing (n=130)

Subtask 1: Recruitment (n=130)

- Recruitment, screening, and scheduling of participants was finalized during the last quarter. 132 subjects were tested. All testing has concluded; 100% complete.

Subtask 2: Data collection/management (n=130)

- Schedule testing sites for data collection; Testing sessions were completed at both OHSU and the VA; 100% complete.
- Data collection for Aim 1; Testing sessions were completed at both OHSU and the VA; 100% complete.
- Data back-up onto server including manual data entry; All raw data has been entered into REDCap and stored on the secure server; 100% complete.
- Screen and verify data on server; The study team performed the last data check September 2019; 100% complete.
- Upload data to FITBIR; Completed September 2019; 100% complete.

Major Task 3: Data analysis and publications

Subtask 1: Data analysis

- Perform all analysis-according proposal and share all findings with investigators; we have continued analysis of data collected to date. We are currently analyzing data to address Aim 1.a and Aim 1.b. All data have been processed for use and we are working with our team statistician to ensure our analyses are robust. We hope to finalize analysis for these aims within the next quarter. For Aim 1.c, we are in the early stages of mediation analysis preparing all of our relational data; 80% complete.

Subtask 2: Manuscripts and presentations

- Disseminate findings (abstracts, presentations, papers, DoD); During this reporting period we have focused on generating a number of manuscripts that form the foundation for the remaining analyses. A number of presentations have additionally been given throughout the year. Details are provided in the Products sections below; 80% complete.

Specific Aim 2 (Study 2: Rehabilitation n=40 mTBI)

Major Task 3: Randomized interventions (n=40 mTBI patients)
Subtask 1:

- All interventions have concluded; 100% complete.
- PTs document compliance, adverse events and progression of exercise for each subject; all documentation has been entered and securely stored by PTs; 100% complete.

Major Task 4: Assess efficacy of interventions (n=40)

Subtask 1:

- Immediate post-test after intervention and long-term assessment (6 weeks later) have been completed; 100% complete.

Subtask 2:

- A subset of controls was tested at a 6 week follow up in order to determine any natural changes in the CSMI test over 6 weeks; 100% complete.

Major Task 5: Data analysis and publications
Subtask 1: Data Analysis

- Perform all analysis-according proposal and share all findings with investigators; we have processed all CSMI data for pre, post and retention sessions and will begin running statistical evaluation on these data in the next quarter. All home monitoring data have been processed and we have been running preliminary linear models on these data to evaluate changes with rehabilitation; 60% complete

Subtask 2: Manuscripts and presentations

- Disseminate findings (abstracts, presentations, papers, DoD), including American Physical Therapy Association and American Congress of Rehabilitative Medicine and rehabilitation journals to share with clinicians; Details are provided in the Products sections below; 40% complete.

Significant Results/ Key Outcomes:

Summary of screening, enrolment and completion:

At the conclusion of the study 123 participants (60 chronic mTBI and 63 controls) completed both Day 1 and Day 2 testing for Aim 1. Demographic information for these participants is provided in Table 1. Thirty-two chronic mTBI participants completed post-rehabilitation follow-up testing. Six chronic mTBI patients were lost to follow up. Twenty-six mTBI completed retention.

Table 1. Demographics for chronic mTBI and control groups, provided as mean (standard deviation).

	mTBI (n=60)	**Control (n=63)**	**P-Value**
Gender (n)	18m, 42f	26m, 37f	-
Age (years)	39(11)	38(13)	0.44
Height (m)	1.7(0.1)	1.7(0.1)	0.82
Mass (kg)	80.4(20.1)	75.2(19.0)	0.14
Time since injury (years)	2(3)	-	

The following summaries may not reflect the complete sample of participants, and are therefore subject to change on reanalysis with a complete dataset:

We calculated Minimal Detectable Change to aid clinical interpretation of differences in Sensory Weight, estimated through the CSMI test. We conducted the CSMI test on a sample of 26 healthy young adults aged 18-35. The CSMI test was completed two times, 6 weeks apart, in order to assess test-retest reliability of the CSMI Sensory Weight score, and calculate minimal detectable change (MDC). For the 8 conditions of the CSMI, the retest-reliability ranged from poor to fair (ICC = 0.31-0.71), and minimal detectable change as a percentage of the measurement mean ranged between 20-40%, suggesting that large changes in Sensory Weight would be required to reflect a clinically meaningful difference.

Persons with chronic mTBI show more sway at the head than healthy controls. We tested postural sway in chronic mTBI (n=59) and healthy controls (n=63) using inertial sensors worn on the head, sternum and lumbar region. Four different standing conditions were evaluated: 1) eyes open on a firm surface (EO-firm), 2) eyes closed on a firm surface (EC-firm), 3) eyes open on an unstable foam pad (EO-foam), and 4) eyes closed on foam (EC-foam). Postural sway was quantified using the root-mean-square (RMS) of the acceleration in anteroposterior (AP) and mediolateral (ML) directions. The chronic mTBI group showed greater sway than controls in the ML direction at each the head, sternum and lumbar region. Interestingly, healthy controls reduced the ML sway at their head relative to their lumbar during foam-surface conditions, while chronic mTBI did not change their sway at the head relative to sway at the lumbar across conditions.

Gait in mTBI and healthy controls can be characterized by four domains: Variability, Rhythm, Pace, and Turning. We performed a Principal Component Analysis (PCA) to help identify key domains of gait, and form a framework to guide further evaluation of gait measures in mTBI cohorts. Four gait domains were derived (variability, rhythm, pace and turning), accounting for 80.8% of variance in gait in chronic mTBI. Findings were replicated in a separate control cohort, with the same gait domains derived, accounting for 77.4% of variance in gait. Domains, the percentage of variance each domain accounts for, and the individual variables that compose the domains are provided in Figure 1.

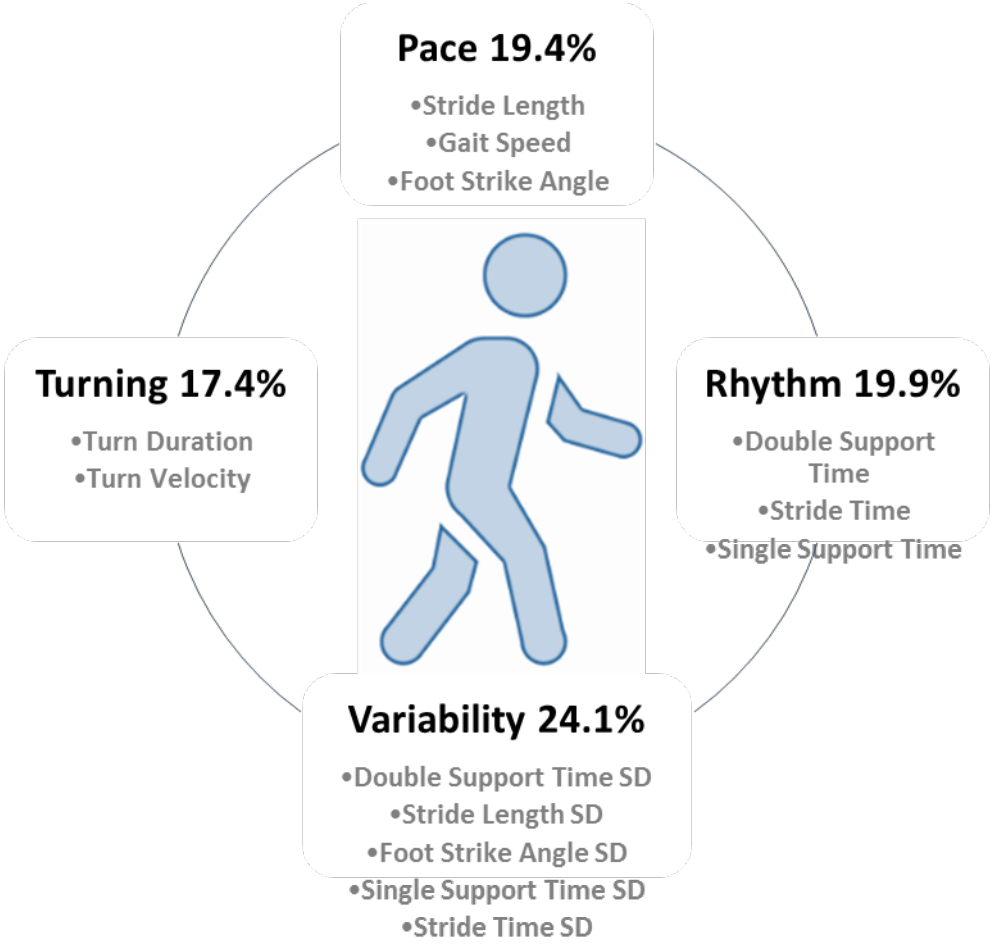

Figure 1. Gait model for chronic mTBI

People with symptomatic, chronic mTBI have altered gait compared to healthy controls. We evaluated whether gait was affected in our symptomatic chronic mTBI group (*n*=67, 3.3 years from since injury) in comparison with healthy controls (*n*=58). Gait was assessed under single- (ST) and dual-task (DT) conditions using gait domains (pace, rhythm, variability, and turning) calculated from instrumented gait variables measured using inertial sensors. The DT condition involved walking while responding to an auditory Stroop task. Results indicated that the chronic mTBI group turned slower in both walking conditions, and walked and slower and with less

rhythm during the DT condition (all $p<0.003$). Cohen's d, representing the effect size of the difference between the chronic mTBI and the healthy control are presented for each gait domain in Figure 1.

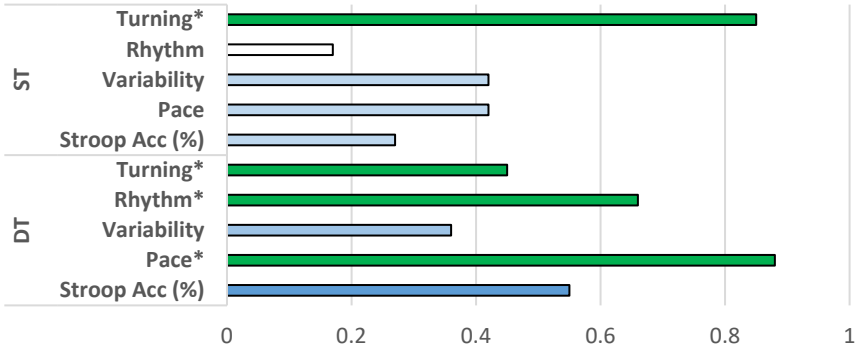

Figure 1. Effect size of the between-group difference (Cohen's d) presented for each of the gait domains (Turning, Rhythm, Variability, and Pace), as well as response accuracy for the auditory Stroop task. Green bars reflect significant differences, blue bars indicate large effect sizes (blight blue) and medium effect sizes (light blue).

We have begun evaluating the sensitivity and specificity of our objective measures in comparison with clinical subjective measures. We have initiated investigation into whether objective balance and gait assessments are better than the current clinical/subjective assessments at separating individuals with chronic mTBI from healthy controls. Receiver operator curves were used to determine the sensitivity and specificity of the objective versus subjective outcomes in distinguishing chronic mTBI from controls. Thus far, these analyses revealed that using inertial sensors (objective) to characterize postural sway during balance were significantly better than the Clinical Test of Sensory Interaction on Balance (CTSIB, subjective) characterization of balance. We are continuing to evaluate this across each of our objective gait and balance measures and a manuscript is in preparation to report these findings.

What opportunities for training and professional development has the project provided?

Our research team have had multiple opportunities throughout the reporting period to attend national (i.e. MHSRS) and international conferences (i.e. International Society of Posture and Gait Research, ISPGR). These conferences have provided the opportunity for our research team to discuss current and future work, and domestic and international collaborations. Additionally, our student intern was given the opportunity to present our research at OHSU Research Week (May, 2019), which was a fantastic opportunity for his development.

How were the results disseminated to communities of interest?

The results have been disseminated to broad communities of interest, such as:

- Other scientists (MHSRS, APTA CSM Meeting, Society for Neuroscience Annual Meeting; ISPGR; OHSU Research Week)
- Clinician audience (Columbia Memorial Hospital; Keizer Oregon; Reed College; Oregon Physical Therapy Association PT Education; Oregon Athletic Training Symposium)

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

We were approved for a no-cost extension that will allow us time to focus on data analysis and the dissemination of research findings through reports, conference presentations and manuscripts. Analyses of data thus far has primarily focused on cross-sectional data (Aim 1), however, we have now begun analyzing longitudinal data also (Aim 2). In the next reporting period, we hope to have the main findings of Aim 1 reported.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

This project is allowing researchers in the area of mTBI to understand more about the role that sensory integration plays in chronic balance deficits. Furthermore, it is creating awareness in clinicians of the need to use more objective measurements of balance deficit. We hope that this project will give insight into how audio biofeedback can be used to help the rehabilitation process, by helping to guide and recalibrate the way people use (i.e. integrate) their sensory information to balance and perform day to day tasks. We believe this research will impact clinical practice, by first, providing information on how to more objectively quantify chronic balance problems related to mTBI, and second, in guiding the standard of care to use audio biofeedback technology.

What was the impact on other disciplines?

Our research team has continued to meet once per month with mTBI treating OHSU doctors, physical therapists and athletic trainers, and affiliated clinicians from other clinics. We have found that these meetings allow an open discussion between researchers and clinicians, to discuss research findings, and work towards translating research knowledge into clinical practice.

What was the impact on technology transfer?

During the last annual report we identified two primary impacts of our work – 1) a manuscript identifying how to run the CSMI protocol, and 2) development of information on home monitoring in patients after mTBI. We have continued work on these impact areas, and during this reporting period, have been successful in publishing manuscripts for both of these.

What was the impact on society beyond science and technology?

In March 2019 members of our team attended the OHSU Brain Fair, an annual event held at the Oregon Museum of Science and Industry (OMSI). The fair is open to the public and people of all ages were present. Members of our research team discussed issues around balance and gait, and reaction time in chronic mTBI, performed demonstrations and invited fair attendees to test their reaction time using our clinical reaction time test.

Our research team has continued to help mentor the development of young researchers completing undergraduate and high-school programs of education. Over the summer months we had several student volunteers working on study activities. One student received an award from NIH Build Exito to join our lab for two years to help with this project.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them

In Year 4, Quarter 1: Problems taken from the quarterly report) /Resolution

1) N/A

In Year 4, Quarter 2: Problems taken from the quarterly report /Resolution

1) N/A

In Year 4, Quarter 3: Problems taken from the quarterly report /Resolution

1) We found some erroneous data present in the CSMI output from a system at the VA testing site.
   Resolution: We generated a new analysis program for the output of data from this system and are in the stage of reprocessing and finalizing.
2) Some vestibular data (approximately 10 subjects) that was backed-up and stored on our server has been found to be corrupt and unusable. Unfortunately, the computer that was used to collect data malfunctioned and as a result is no longer able to be used.
   Resolution: IT has not yet been successful in extracting the data from the drive. We are continually in contact with our audiology team from OHSU and IT in attempt to resolve this issue. We have also spoken to a statistician recently to see what methods can be used to impute these data in a meaningful and statistically robust way.

In Year 4, Quarter 4: Problems taken from the quarterly report /Resolution

1) We have not had the opportunity to finalize all data analysis.
   Resolution: We have requested a no-cost extension so we can finalize study reporting and disseminate findings.

Changes that had a significant impact on expenditures

Nothing to report

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

Nothing to report

6. PRODUCTS:

Publications, conference papers, and presentations

Publications, conference papers, and presentations submitted, accepted, and presented during the reporting period October 2018 through September 2019:

Published manuscripts:

- Peterka, RJ, Murchison, CF, Parrington, L, Fino, PC, & King, LA. (2018). Implementation of a Central Sensorimotor Integration Test for characterization of human balance control during stance. Frontiers in Neurology, 9, 1045.
- Stuart, S, Parrington, L, Martini, DN, Kreter, N, Chesnutt, J, Fino, PC, & King, LA. (2019). Analysis of free-living mobility in people with mild traumatic brain injury and healthy controls: Quality over quantity. Submitted to the Journal of Neurotrauma. Advance Online Publication.

Submitted manuscripts under peer review:

- Parrington, L, King, LA, Kreter, N, & Peterka, RJ. Retest reliability of a test of Central Sensory Motor Integration (CSMI) in healthy young adults. Submitted to Gait & Posture.
- Stuart, S, Parrington, L, Morris, R, Martini, DN, Fino PC, King LA. Gait measurement in chronic mild traumatic brain injury: A model approach. Submitted to Human Movement Science.

Manuscripts in preparation:

- Martini, DN, Parrington, L, Stuart, S, Fino PC, & King LA. Gait Performance in Symptomatic, Chronic Mild Traumatic Brain Injury.
- Fino, PC, Raffegeau, TE, Parrington, L, Peterka, R, & King LA. Abnormal Head Stabilization During Quiet Standing in People with Chronic Mild Traumatic Brain Injury

Accepted conference educational session:

- Scherer, M, King, LA, Lester, M, McCulloch, K, & Weightman, M. Functional return-to-duty decision making post mTBI and musculoskeletal injury. Combined Sections Meeting, APTA, Jan 23-26, 2019. Washington, DC.

Platform presentation:

- Motowar B, Wilhelm J, Martini D, Kampel, S, & King LA. Relationship between dizziness and oculomotor function in chronic mTBI. Combined Sections Meeting, American Physical Therapy Association, Washington DC.
- Martini, D, Parrington, L, Kreter, N, Chesnutt, J, & King, L. Assessing the relationship between symptom severity and gait performance in a symptomatic, chronic mTBI population before and after vestibular rehabilitation. Military Health System Research Symposium (MHSRS), August 2019.

Conference poster:

- King LA, Parrington, L, Jehu DA, Hullar T, Kampel S, Stuart S, & Peterka R. Sensory weighting in chronic mTBI with vestibular and oculomotor dysfunction. Poster presented at the Society for Neuroscience Annual Meeting, San Diego, CA, November 3-7 2018.
- Koch, J, Parrington, L, & King, L. Gait velocity variances in chronic mild Traumatic Brain Injury (mTBI) subjects through single and dual-task activity. OHSU Research Week, May 2019.
- Martini D, Parrington L, Fino, PC, Peterka R, & King LA. Central sensorimotor integration delays: does response latency to pseudorandom balance perturbations relate to reaction time? Presented at the International Society of Posture and Gait Research, Edinburgh Scotland, June 30 – July 4.
- Raffegeau T, Clark M, Parrington L, Peterka R, Chesnutt J, King LA, & Fino PC. Sensory contributions to head and lumbar sway in healthy individuals and those with mild traumatic brain injury. Presented at the International Society of Posture and Gait Research, Edinburgh Scotland, June 30 – July 4.

Community presentations:

- Chesnutt, JC, “The Medical Perspective of TBI. Brain Injury: Clinical Implications Across the Spectrum of Care”, October 30 2018, Keizer Oregon.
- Wilhelm JL, Chesnutt JC: “Updates on Concussion Rehabilitation”, March 15 2019, Reed College.
- Wilhelm JC, Chesnutt JC: “Active Concussion Rehabilitation”, April 12 2019, Columbia Memorial Hospital.
- Wilhelm JC, Pettigrew N, Stuart S: “Updates on Concussion Rehabilitation”, April 25 2019, Oregon Physical Therapy Association PT Education.
- Wilhelm JL, Rockwood R: “Updates in Concussion Assessment and Rehabilitation”, June 8 2019, Oregon Athletic Training Symposium.

Community outreach event (1000 attendees):

- OMSI Brain Fair, March 16th 2019, Portland Oregon.

Website(s) or other Internet site(s)

Nothing to report

Technologies or techniques

Nothing to report

Inventions, patent applications, and/or licenses

Nothing to report

Other products

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

What individuals have worked on the project?

Name:	Daniel Putterman- No Change
Name:	Laurie King - No Change
Name:	Lucy Parrington - No Change
Name:	Shelby Martin- No Change
Name:	Robert Peterka - No Change
Name:	Jennifer Wilhelm- No Change
Name:	Sean Kampel - No Change
Name:	Samuel Stuart- No Change
Name:	Natalie Pettigrew- 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?

Nothing to report

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

9. APPENDICES