Award Number: W81XWH-11-2-0198

TITLE: Advanced Pediatric Brain Imaging Research and Training Program

PRINCIPAL INVESTIGATOR: Catherine Limperopoulos, PhD

CONTRACTING ORGANIZATION: Children’s National Medical Center Washington, DC 20010

REPORT DATE: October 2016

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland  21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release; Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.
Brain injury is a leading cause of death and disability in children. Recent advances in pediatric magnetic resonance imaging (MRI) techniques are revolutionizing our understanding of brain injury, its potential for recovery, and demonstrating enormous potential for advancing the field of neuroprotection. We have created a highly structured, collaborative, and multidisciplinary training program in BRAIN (Brain Research Advanced Imaging with NMR) to advance research skills of investigators from all branches of the US military focusing on pediatric brain injury. Our goal is to train, with the highest rigor, military trainees in conducting clinical research using advanced brain imaging technologies to study the causes and consequences of pediatric brain injury. Over the past year, we successfully our online learning management system, by creating and implementing methods for converting the existing in-classroom educational BRAIN seminars into self-directed online learning modules and courseware. Specifically, we developed a web-based portal site located at www.MilitaryMedED.com and completed 14 e-learning BRAIN modules and conducted internal field testing of our BRAIN courseware for learning effectiveness among military and civilian trainees.
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>Body</td>
<td>2</td>
</tr>
<tr>
<td>Key Research Accomplishments</td>
<td>13</td>
</tr>
<tr>
<td>Reportable Outcomes</td>
<td>14</td>
</tr>
<tr>
<td>Conclusion</td>
<td>15</td>
</tr>
<tr>
<td>Appendices</td>
<td>16</td>
</tr>
</tbody>
</table>
INTRODUCTION

This report documents the activities conducted between September 2015 – September 2016 for the Brain Research Advanced Imaging with Nuclear Magnetic Resonance” (BRAIN) training program. The overarching goal of this grant is to advance the training of military clinician scientists in the field of investigative brain imaging technologies to understand the causes of brain injury and the mechanisms underlying brain plasticity following injury. In this annual report, we provide an update on our web-based BRAIN training courseware. Specifically, we summarize our online e-learning BRAIN module accomplishments, and the updated results of the internally field testing performed on both military and civilian trainees. To date, our online assessment scores continue to demonstrate that web-based approaches to teaching topics within the BRAIN program has significant training benefits for healthcare providers across multiple specialties and subspecialties.
Over the past 12 months, we continued converting our clinical teaching seminars into a web-based format, and developed six new BRAIN e-modules for which we also performed internal field testing. To date, the survey data from the in-person lectures and online assessment scores demonstrate that both in-classroom and web-based approaches to teaching topics within the BRAIN program has significant training benefits for healthcare providers across multiple specialties and subspecialties.

During this phase (year 5) of the project, we achieved the following milestones:

- Continual enhancements of the web-based learning management system that houses the BRAIN online courseware:
  - **Maintained**: Updated the graphical user interface and mobile client for the web-based learning management portal system. The site is located at www.MilitaryMedED.com. The site can be accessed from any device web browser (personal computer, tablet or phone) and operating system (e.g. Windows, OS X, Linux, etc.) (Appendix A).
  - **Enhanced**: Developed 6 new (20 total) SCORM-compliant online training modules on the fundamentals of MRI and fetal development. SMEs converted their PowerPoint presentations by storyboarding their content for instructional technologists and multimedia developers to begin producing interactive learning objects and assessments.

- Held ongoing internal workshops to teach SMEs and Co-PIs how to design, develop, and implement online BRAIN courseware training modules #15-20 (see Table 1).

- Performed field testing of the learning management system and the additional six online BRAIN seminar courses. Conducted field tests at Children’s National Medical Center main campus. There were 100 total field testers (45 trainees in last 12 months; 25 of which were residents/fellows from the National Capital Consortium rotating through our Radiology program) across all evaluated courses with an average of 4.2 years of experience in neurology, and radiology. The average rating for how beneficial the web-based instructional content was to their learning showed a combined average of 3.8 on a scale of 5 (1=No improvement to 5=Exceptional improvement). Trainees' scores improved 54.6% from their pre to post assessment scores (combined pretest AVG =63.9% to combined post-test AVG=98.8%). The scores confirm that online multimedia learning provides a highly engaging educational method to teaching complex subject matter on brain development, brain injury, recovery, and application of advanced multimodal MRI techniques.
Statement of work-progress to date:

Specific Aim 1: To advance the understanding of the fundamental principles and clinical application of sophisticated MRI techniques that is revolutionizing clinical research into the causes, consequences and care of pediatric brain injury.

Over the past year, we continued working closely with our subject matter experts (SME) to develop and refine e-learning courseware on the fundamental principles and applications of advanced MRI techniques. We developed three additional modules to address specific aim 1 and included introduction to MNR spectroscopy (level II); the role of rest-state functional MRI for the developing brain, and digital imagine theory and clinical applications (Table 1). We have also introduced our e-learning seminars to Walter Reed Military Medical Center.

Specific Aim 2: To enhance through didactic and clinical teaching the basic science and clinical understanding of the causes, mechanisms, and consequences of pediatric brain injury.

We have developed three new comprehensive e-learning modules on pediatric brain injury that capture a wide scope of themes in pediatric brain injury including understanding for fetal cerebral development and the role of MRI (level 1 and level 2), and a third module that focuses on assessing neuropsychological outcomes following traumatic brain injury (Table 1). We have also introduced our seminars to Walter Reed Military Medical Center.

Specific Aim 3: To provide training in clinical research methodology through courses and seminars in biostatistics and research design, and responsible conduct of clinical investigation.

Our Good Clinical Practice (GCP) training program was further refined, and now provides a scalable capability to deliver GCP content in a dynamic and interactive fashion to the clinical and translational research (CTR) workforce using an immersive learning simulation technique. For our e-learning BRAIN modules we have updated our on-line FACTS (Focus on Clinical and Translational Science) curriculum with additional resources that cover study design, developing goals and objectives, research implementation, statistical analyses, sources of error, etc. (Appendix B).

a. Updates on our e-Module Training Design/Development

During this year’s design phase, we:

- Developed six new (20 total) SCORM-compliant online training modules. SMEs converted their Power Point presentations by storyboarding their content for instructional
technologists and multimedia developers to begin producing interactive learning objects and assessments.

- Held internal workshops to teach SMEs and Co-PIs how to design, develop, and implement online BRAIN courseware training modules #15-20 (see Table 1).
- Performed field testing of the learning management system and six online BRAIN seminar courses. Conducted field tests at Children’s National Medical Center main campus. There were 100 total field testers (45 trainees in the last 12 months; 25 of which came from the National Capital Consortium) across all evaluated courses with an average of 4.7 years of experience in neurology, radiology, computer science and neuroimaging. The average rating for how beneficial the web-based instructional content was to their learning showed a combined average of 3.8 on a scale of 5 (1=No improvement to 5=Exceptional improvement). Trainees’ scores improved 54.6% from their pre to post assessment scores (combined pretest AVG =63.9% to combined post-test AVG=98.8%).

**New Training Module Overview**

**Module 15** provides an overview of Neuropsychological Outcomes in traumatic brain injury and summarizes tools to assist evaluation & management and how to begin evaluating and managing concussion. **Module 16** presents the application of resting State fMRI to the developing brain, where the learner becomes familiar with the properties of resting state networks, learns ways to analyze the data, and how it is applied to the developing brain. **Module 17 & 18** review the role of MRI in understanding fetal supratentorial brain development, the appearance of normal development, the germinal matrix and myelination, neuronal migration and gyrification, as well as structural and metabolic maturation. **Module 19** elaborates on NMR Spectroscopy with understanding ex-vivo spectroscopy using high res R spectra, learning metabolic identification and neurochemicals as well as metabolic pathways and single model spectral peaks. Finally, **module 20** demonstrates the broad principles of image acquisition, understanding & defining numerical images, learning the basics of image quality assessment and understanding the applications of image processing for medical image analysis.
<table>
<thead>
<tr>
<th>Module Title</th>
<th>Learning Objectives</th>
</tr>
</thead>
</table>
| **Module #16: Assessing Neuropsychological Outcomes in TBI (Dr. Gerry Gioia)** | • Articulate knowledge of evaluation & management of concussion  
• Describe tools to assist concussion evaluation & Management  
• How to begin evaluating & managing concussion in your practice                                                                                     |
| **Module #17: Resting State fMRI and the developing brain (Dr. Josepheen Cruz)** | • Understand what resting state functional MRI is  
• Know the properties of resting state networks  
• Learn ways to analyze resting state data  
• Learn how resting state functional connectivity-MRI (rs-fcMRI) is applied in fetal & neonatal imaging                                                                 |
| **Module #18: Understanding Fetal Supratentorial Brain Development: Role of MRI I (Dr. Gilbert Vezina)** | • Understand what fetal MRI can reveal about cerebral development  
• Become familiar with the appearance of the normally developing cerebrum                                                                                           |
| **Module #19: Understanding Fetal Supratentorial Brain Development: Role of MRI II (Dr. Gilbert Vezina)** | • Understand Neuronal migration and Gyrification  
• Understand the Involution of the Germinal matrix and early Myelination  
• Learn about Structural (DTI) and Metabolic maturation (MRS)                                                                                          |
| **Module #20: Intro to NMR Spectroscopy II Ex-Vivo (Dr. Stanley Fricke)**    | • Understanding Ex-Vivo Spectroscopy  
• Understand High Res R Spectra & High/Low Frequency  
• Know the Metabolic Identification and Neurochemicals in 1H and 31P NMR  
• Understanding of Metabolic Pathways and Single Model Spectral Peaks                                                                                     |
| **Module #21: Digital Imaging Theory & Application (Dr. Sonia Dahdouh)**     | • Learn Broad Principles of image acquisition  
• Understand & Define Numerical Image  
• Know the Basics of Image Quality Assessment  
• Understanding Applications of Image Processing for Medical Image Analysis                                                                                 |
**Ongoing Visual Enhancements to BRAIN**

We continue to create, improve upon and implement multimedia objects (e.g. graphics, audio, animations) throughout application scenes to assist learners in the visualization of new knowledge and concepts. The animations are created not only to convey instructional points, but also to promote active engagement and immerse learners by conveying a realistic medical situation series of events. The text elements, interactive and composite still graphics support the visual learner while the audio narration supports the auditory learner.

![Figure 1. Novel Animation Example](image-url)
In addition to the visual enhancements of MilitaryMedED.com, we have implemented a vast range of new UI/UX improvements (frontend and backend). **Main Highlights:**

- Competencies support in MilitaryMedED.com
- Improvements to the Assignment grading user interface
- Global Search API allows users to search forums, wikis, and other content throughout the entire site.
- Significant performance improvements in gradebook calculations
- Significant performance improvements in user interface and responsive screens - now using Bootstrap 4

**Forum**

- Allow users to “pin” discussions thus keeping them on the top of the list
- Allow forum email subject to be customized
- Added permalink option to forum posts
- Forum does not observe message notification settings for digest emails

Figure 2. Novel Animation Example
**Assignment**

- Feedback for Assignments is not sent if the assignment grade time modified setting was set to two days ago
- Added a ‘maxperpage’ site wide setting for grading table size (to mitigate broken grading pages in large courses)
- Improved cross referencing users with their blind identities
- Allows downloads of selected assign submissions as a zip file
- "Download all submissions as a zip" should maintain the folder structure in students submissions

**Feedback**

- Various improvements to UI and bug fixes, including:
  - Performance improvement to download responses as raw data in multiple formats (CSV, Excel, etc.) - now available on "Show responses" page instead of "Analysis"
- Allow any characters in labels, do not display empty labels
- Do not display empty pages
- Map front page feedback to multiple courses without leaving the form
- Improved display of automatic question numbers
- Disable "Response time" for anonymous feedbacks
- Use MilitaryMedED.com forms to display feedback

**SCORM**

- Added result field to the SCORM Interactions Report
- Added score and status submission events to SCORM activity
- Added group support to SCORM activity
Quiz

- Quiz attempt/review page should have a previous button to match next
- Rationalize confirmations when you start a quiz
- Show right answers when manually grading automatically marked questions
- Immediate feedback behaviors should not show a disabled check button when you can’t use it

Workshop

- Option to delete a workshop submission
- Restricting file types as attachments to a workshop

Other activity modules

- Folder: Bulk download all files within a folder activity as ZIP file
- Lesson: Allow Default Settings for Lesson Module Settings
- URL/File: Make setting up a URL/File resource more obvious

Gradebook

- Option to rescale existing grades when changing max points
- Tab Down Grade Column in Single View of Gradebook

B. Knowledge Assessments

Pre and post assessment were developed and implemented for the training modules. In addition to the pre and post assessment data, we gathered participant feedback using a post-run module questionnaire accessible from inside the training portal. The post-run module questionnaire depicts information pertaining to perceived improvement of the module learning objectives, usability, organization and challenging/engaging nature of the instructional content as well as open-ended responses on what they liked and didn’t like about the module, and recommendations for future module development.
Internal Field Testing: Test Pre and Post Assessment Summary

Since September 2015, we have carried out several field tests with our online BRAIN training modules. The field tests were facilitated by Ben Scalise. There were 100 total field testers (45 trainees in last 12 months) across all evaluated courses with an average of 4.7 years of experience in neurology and radiology. The average rating for how beneficial the web-based instructional content was to their learning showed a combined average of 3.6 on a scale of 5 (1=No improvement to 5=Exceptional improvement). Trainees’ scores improved 54.6% from their pre to post assessment scores (combined pretest AVG =63.9% to combined post test AVG=98.8%). The prior year, 2015, the Pretest Mean result was 6.45 and Posttest mean result was 9.4 (64% and 94% respectively). This represents a 19.3% increase in evaluation improvement from year 2015 to 2016. These data demonstrate that online multimedia learning provides a highly engaging and effective educational method for complicated topics about the developing pediatric brain and MRI techniques (Table 2).

This field test(s) included a (pre/post: pre-test vs. post-test) mixed design, with training being a between-subjects factor. We randomly assigned participants to the training condition of different brain seminar topics:

Table 2: Internal Field Testing: Test Pre and Post Assessment Summary

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Investigating Brain Plasticity and Connectivity with Structural MRI Techniques Overall Average</td>
<td>Fundamentals of Digital Imaging Overall Average</td>
</tr>
<tr>
<td>Post Test 60.0 Post Test 96.3</td>
<td>Pre-Test 72.4 Post Test 95.9</td>
</tr>
<tr>
<td>• Intro to MRI Overall Average Pre-Test 83.9 Post Test 95.8</td>
<td>Pediatric MRI Without Sedation Overall Average Pre-Test 61.8 Post Test 85.3</td>
</tr>
<tr>
<td>• Normal/Abnormal Development of the Cerebellum Overall Average Pre-Test 41.7 Post Test 89.1</td>
<td>Corpus Callosum and other Major Commissures Overall Average Pre-Test 54.0 Post Test 98.1%</td>
</tr>
</tbody>
</table>

Field Test Post-Run Questionnaire Summary:

The primary questions considered in the evaluation were comparable to the ones used in our previous report (annual report 2015) and included the following:
What are the participant’s feelings and attitudes towards achievement of critical learning objectives during the training module?

Did the training module present relevant content that could be applied in real-world medical situations?

Did the training module content teach participants about the pediatric brain or MRI that they previously didn’t know?

Will the participant apply the knowledge learning in the training module while practicing at their institution and use other resources and activities housed in the MilitaryMedED.com platform in the future?

As previously described, the first set of questions measured participants’ responses to our intended learning objectives for the training module. The second set of questions measured the relevancy of the training content, their user experience, and recommendations for improving content. The third set of questions measured responses to general expectations for the interactive training, importance of incorporating content for use in clinician professional development, and areas users like best / least about the activities/resources.

**Questionnaire Results**

At the conclusion of the first field test, participants were asked to rate their progress on three to five tailored learning objectives intended for the training module content using a one-to-five Likert scale to measure their improvement on BRAIN seminar topics (1 = no improvement, 5 = exceptional improvement). Learning objectives included the ability of participants to understand key concepts of the brain and MRI, define function and terminology, reflect and discuss critical ideas presented throughout the module.

Overall, participants made above average progress in understanding the intended learning objectives (combined mean = 3.98, SD = 0.25). Participants also evaluated intended learning objectives for the training modules, and provided both written and numeric feedback rating. Participants indicated they felt strongly that the training modules presented relevant content that could be applied to real-world medical situations (combined mean=3.86, SD = 0.32), learned new information about the pediatric brain and MRI that they previously didn’t know (combined mean=4.46, SD=0.54), improved their understanding about the topics in the module (combined mean=3.7, SD=0.3), felt that they will apply the learned techniques at their institution (combined mean= 3.9, SD=0.23), and finally will participate in BRAIN training modules (combined mean=4.23, SD=0.19).
C. BRAIN e-module Military Implementation Plan-Next Steps

We plan to disseminate the BRAIN courseware to additional military bases to be used as a tool for providing distance learning and training on advanced neuroimaging technologies to study and understanding pediatric brain injury and recovery following injury. We will also refine and optimize the existing 20 BRAIN modules based on the user feedback we have obtained to date.

We plan to work with the Uniformed Services University and the U.S. Army Medical Research and Materiel Command in order to provide credibility and acceptance to the site, and help accomplish the project’s objectives for creating innovative medical education on emerging medical areas such as pediatric brain development.

We plan to pursue organizational buy-in and implement the training portal as follows. In order to familiarize the target audiences at the military bases with the tool’s capacities, we will continue to set-up meetings to demonstrate MilitaryMedED.com’s training tool at military medical bases and provide ongoing technical and training support to assist military users in problems or challenges that may arise.

D. Future Activities

- In the next year, we will document and write-up the learning effectiveness experiments results and begin enhancing the existing training content and developing additional training modules based on data results.
- We will document the work and conclusions in the annual report which will include an analysis of the field test events and training effectiveness evaluations, as well as a report on the current status of any issues and suggestions arising from the field test events. The report will also summarize our data including research methods, results, interpretation of results and benefits.

For the next 12 months, we plan to complete the following:

- Complete remaining storyboards that need to be converted from in-classroom lectures to e-learning modules
- Perform ongoing field tests at Children’s National Medical Center and targeted military medical facilities.
- Systematically document, analyze and summarize our initial military field test results.
KEY RESEARCH ACCOMPLISHMENTS

1. Ongoing quality improvements of the web-based BRAIN curriculum

- Enhanced and maintained the web-based learning management system that houses the BRAIN online courseware at www.MilitaryMedEd.com

- The site can now be accessed from any device, web browser and operating system

- Developed, optimized and uploaded 20 SCORM-compliant online training modules

- Refined our online FACTS (Focus on Clinical and Translational Science) curriculum onto our portal site

- Held ongoing internal workshops to teach co-investigators and SMEs how to design, develop, and implement online BRAIN courseware training modules

- Performed field testing of the learning management system and six online seminar courses which lead to further improvements on the BRAIN courseware modules.

2. Introduced our e-BRAIN courseware to Walter Reed Military Medical Center (Neonatal Seminars) and have started implementing the training curriculum on site.
REPORTABLE OUTCOMES

- We trained 45 residents/fellows, of which over 50% came from the National Capital Consortium.

- We introduced our BRAIN e-courseware locally (Walter Reed) and at nationally scientific conferences:


Manuscripts in preparation:
CONCLUSION

We developed and enhanced 20 BRAIN e-learning modules and refined our online learning management system. Our initial internal field-testing results on over 100 military and civilian trainees demonstrated the effectiveness and responsiveness of our novel eLearning Instructional BRAIN courses. The success of this online training is further illustrated with a 19.3% increase in evaluation improvement from year 2015 to 2016. More recently, we successfully introduced our e-BRAIN courseware to Walter Reed National Military Medical center and will continue to make known the BRAIN curriculum within the pediatric military milieu. Our goal in the coming year will be to implement and conduct learning effectiveness experiments and training within military medical residency programs. This is currently underway.
APPENDICES

Appendix A

Appendix B
TBI Mechanisms & Neuropsychological Effects

- PreTest - TBI Mechanisms & Neuropsychological Effects
- TBI Mechanisms & Neuropsychological Effects

Define Traumatic Brain Injury and its Mechanisms
Identify Factors Involved in Brain Development
Describe Neuropsychological Outcomes Following Brain Injury

Intro to Perfusion Imaging

- PreTest - Intro to Perfusion Imaging
- Intro to Perfusion Imaging

Not available unless: The activity PreTest - Intro to Perfusion Imaging is marked complete
1. Users can select the **GCP vignette player** from a variety of courses available on the CTSI-CN portal, FACTS (http://www.childrensmedicaleducation.org/research/).

2. Once a user has selected the GCP course, they are directed to the course homepage where they will begin their GCP experience completing the **pretest**.
3. There are over 100 external plugins are integrated into the FACTS portal including virtual conferencing, game and quiz makers, and more.

4. Within the pretest, existing knowledge of International Conference on Harmonization (ICH) GCP training including: GCP Overview, the Principles of ICH GCP and Investigator responsibilities, as they pertain to informed consent/assent, are assessed. Immediate feedback is given upon completion.
5. Once users launch the GCP vignette, they are taken to the **home page** of the player where they will initiate the course.

6. **Knowledge checks** are performed throughout the various scenes of the vignette player.
7. Immediate **feedback** is given based on the selected response.

8. Finally, a **post assessment** is given at the completion of the vignette player. The user is given further information about where in the ICH document the concept is further explained.