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TITLE: Evaluating impact of cerebral contusions on brain network dysfunction and epileptogenesis among patients with traumatic brain injuries

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**13. SUPPLEMENTARY NOTES**

**14. ABSTRACT** – The funding for study EP170034 was granted to LSU Health Sciences Center (LSUHSC) Shreveport on September 15th, 2018. In the past 12 months, we worked with the U.S. Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) to obtain the approval of our research protocol. These agencies guided us in the revision of the study protocol, which gained its final approval on June 7th, 2019. In March of 2019, the PI, Dr. Hai Sun was recruited by Rutgers University to join the Department of Neurosurgery at Robert Wood Johnson Medical School (RWJMS) in New Brunswick, NJ. This possible career change was brought up to the grant officers: Mr. Robert Doan, Drs. Grate and Pacifico. Dr. Hai Sun sought the guidance from the officers on transferring the grant from LSUHSC to Rutgers University. Dr. Hai Sun began serving as an associate professor in the Department of Neurosurgery at RWJMS on September 9th, 2019. LSUHSC submitted the letter to relinquish the award, while Rutgers University submitted the letter to express willingness to accept the award to Department of Defense. Both institutions are currently working diligently to transfer the grant.

**15. SUBJECT TERMS**
Post-traumatic epilepsy (PTE), cerebral contusion, brain connectivity, epileptogenesis, traumatic brain injury (TBI), magnetic resonance imaging (MRI)

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1. **INTRODUCTION:**

Traumatic brain injury (TBI) is a leading cause of acquired epilepsy. In veterans, 57% of seizures can be linked to TBI. Seizures not only account for heightened morbidity and mortality following TBI, but also remain the leading cause of death several years after TBI. The underlying mechanisms that may contribute to Post-traumatic Epilepsy (PTE) are poorly understood, making PTE more likely to be refractory to both medical and surgical treatments. In addition, PTE is heterogeneous. The injury mechanism and severity can vary a great deal and the seizure onset zone may be multifocal and differ among patients. These characteristics of PTE make the investigation of its pathophysiology challenging. Here we propose to study the epileptogenesis of PTE among patients with cerebral contusions from close head injuries by quantitatively measuring both regional and global changes in brain networks. Our underlying hypothesis is that cerebral contusions result in regional atrophic changes in brain parenchyma and global increase in network connectivity, which may in turn lead to seizures. In order to quantitatively measure these changes, we construct structural and functional connectomes from diffusion tensor images and resting state functional magnetic resonance images, respectively. Advanced mathematical tools such as graph theory will be used to generate metrics to capture the pathological changes in connectomics related to PTE. We plan to compare these changes among patients with PTE, and patients with a history of TBI who experience no seizures and normal controls. These changes in connectomics may serve as biomarkers for predicting the development of PTE.

2. **KEYWORDS:**

Post-traumatic Epilepsy (PTE), epileptogeneisis, cerebral contusion, brain networks, brain connectomics, magnetic resonance imagining (MRI), electroencephalogram (EEG), neuropsychological testing.

3. **ACCOMPLISHMENTS:**

- **What were the major goals of the project?**

Our primary objective is to identify local and global changes related to PTE development in the setting of cerebral contusion resulting from traumatic brain injury. Our underlying hypothesis states that PTE is a result of decreased structural connectivity, disruption of known functional networks, and abnormal increases in spurious functional connectivity. These changes are proportional to the severity of TBI measured by morphometric parameters of the cerebral contusion. Abnormal changes are perhaps an over-exaggerated recovery response to trauma. Development of PTE is directly related to the development of this response over time among individuals affected by seizures.

In order to combat challenges facing the study of PTE, we plan to only include participants with moderate to severe TBI that result in brain contusions. In addition, we divide the study into retrospective and prospective arms. In the retrospective arm, we recruit two groups of participants: those diagnosed with PTE and a group of healthy controls. For the prospective study, we begin with the recruitment of participants with traumatic cerebral contusions at the time of TBI. All participants will be followed for up to 18 months with repeated data

collections. The final comparison will be conducted among the participants who develop PTE, those who do not, and matched healthy controls. The following specific aims are proposed.

**Aim 1.** Perform participant-tailored and contusion-centric analyses to compare changes related to areas of encephalomalasia (from previous cerebral contusion) among participants with PTE relative to controls. Identify statistically significant differences in morphometric parameters and network characteristics associated with areas of encephalomalasia relative to the homologous regions in controls. Our hypothesis states, cerebral contusion related morphometric and connectivity changes promote loss of brain volume, white matter fiber density, loss of functional connectivity symmetry and global increase in spurious functional connectivity among participants with PTE relative to healthy controls.

**Aim 2.** Evaluate structural and functional connectomes with shared nodes for a retrospectively identified PTE and control group, and perform statistical comparison of node associated characteristics and network metrics between PTE and control. Investigate the correlation between the changes in PTE connectomics and cognitive performance. Our hypothesis is that morphometric changes taking place distant from the brain injury site, such as the reduction of hippocampal volume, are also responsible for the development of PTE. In addition, the abnormal decrease in structural connectivity and increase in functional connectivity involve regions of the brain beyond the site of injury.

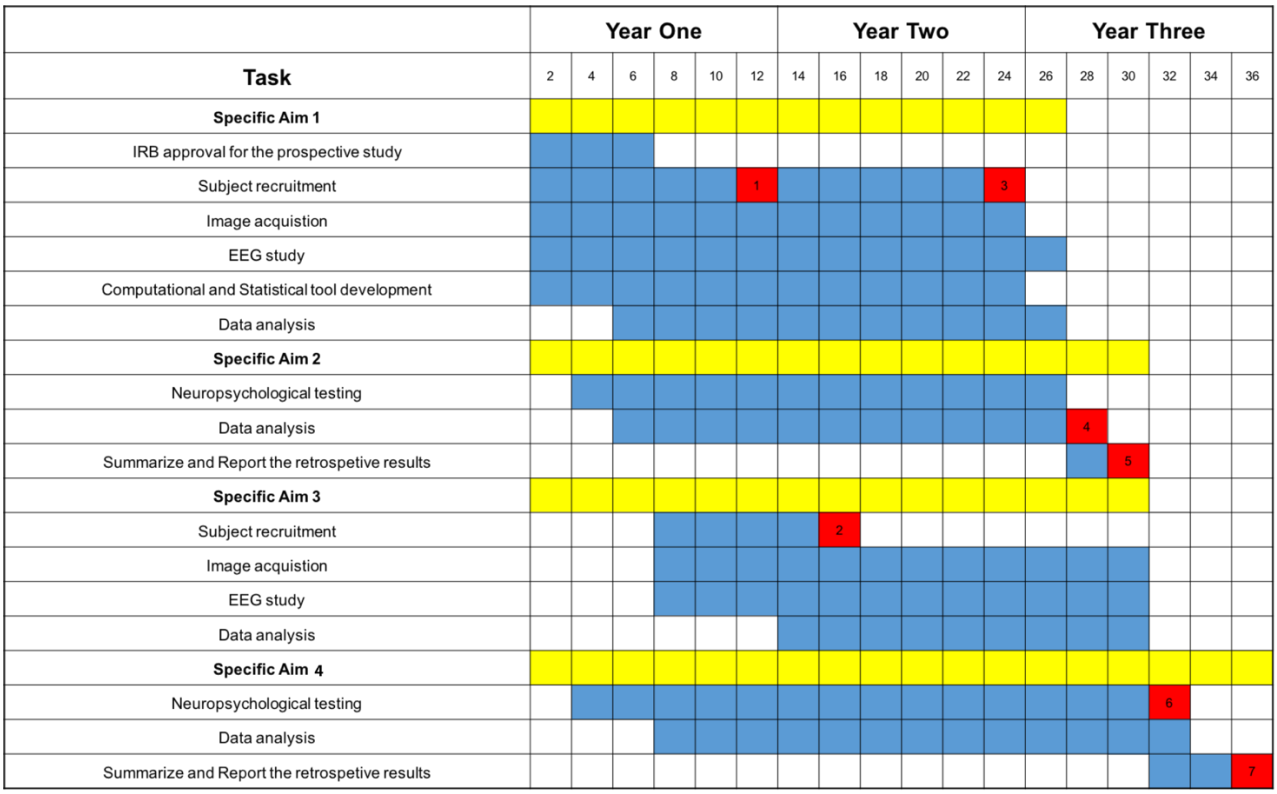
**Aim 3.** Perform longitudinal and prospective study on the cohort of patients with moderate to severe TBI and cerebral contusions with MRI, EEG and neuropsychological testing at acute (within three months), subacute (between 5 to 8 months) and chronic phase (> 10 months). Divide the cohort into a PTE group and a TBI (without seizures) group based on EEG findings conducted at the chronic phase. Perform a participant-specific and time dependent analyses on the longitudinal changes in connectomics among PTE group and TBI group. Identify possible correlation between network connectivy changes and change in cognitive performance over time. Our hypothesis is that PTE is the result of maladaptive injury recovery that manifests as structural hypoconnectivity and functional hyperconnectivity over time. In addition, cognitive performance is negatively affected with the development of PTE.

**Aim 4.** Apply machine learning algorithms to build linear classifiers to identify potential image and network biomarkers for the development of PTE. Apply the techniques to both the retrospective dataset and the prospective dataset and test the ability of the algorithm to predict the onset of PTE and neuropsychological impairment using a subset of statistically significant morphometric and network metrics. Our hypothesis is that, despite large volume of data generated from our connectomics, these are a small subset of changes reliably associated with the development of PTE.

**Project Milestones**

We plan to begin patient enrollment immediately after the funding for the study becomes available. A Gantt chart is created to show some anticipated project milestones. There are eight milestones for this proposed study, that are listed in chronological order and marked in red below:

***Table 1*** *The Gantt chart of the proposed study*




**Milestone 1:** At the end of 12th month, we plan to enroll at least half of the anticipated participants of the retrospective study (10 participants with PTE, and 20 healthy controls).
**Milestone 2:** At the end of 16th month, we plan to enroll 80 TBI participants for the prospective study in anticipation of attrition. The eventual target is 60 TBI participants in the prospective study. Please see section 6.1 for the details. We plan to reach the enrollment of 70 for the control cohort at this point. Both retrospective and prospective studies will use the same group of healthy controls. We will also increase the target of the enrollment for controls due to the need to create demographics matching between PTE, TBI and control groups.
**Milestone 3:** At the end of the second funding year, we plan to complete the enrollment of the retrospective study, which includes a total of 20 participants with PTE.
**Milestone 4:** At the end of 28th month, we plan to complete all data acquisition for the retrospective study including all MRI scans, EEG recordings and neuropsychological tests.
**Milestone 5:** At the end of the 30th month, we plan to report the study results of the retrospective study at a national meeting such as SFN.
**Milestone 6:** At the end of August of the third funding year, we plan to complete all data acquisition for the prospective study including all MRI scans, EEG recordings and neuropsychological tests for at least 60 TBI participants. We also anticipate that approximately 10 participants would develop PTE among 60 participants.
**Milestone 7:** At the end of the third funding year, we plan to report the study results of the prospective study.

- **What was accomplished under these goals?**

  Our funding was granted to LSU Health Sciences Center (LSUHSC) Shreveport on September 15th, 2018. We immediately began working with the U.S. Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) to obtain the approval of our research protocol involving human subjects.

The subject protocol (version 1, April 19th, 2018) was initially approved by the LSUHSC Institutional Review Board (IRB) on June 18th, 2018. Revisions to the protocol and continuing review were approved on June 7th, 2019 by the USAMRMC, ORP, and HRPO. These organizations found that the protocol complies with applicable DOD, U.S. Army, and USAMRMC human subjects protection requirements.

In March of 2019, the PI, Dr. Hai Sun was recruited by Rutgers University to join the Department of Neurosurgery at Robert Wood Johnson Medical School (RWJMS) in New Brunswick, NJ. Dr. Hai Sun brought up this possible career change and the need for transfer of the study EP170034 from LSUHSC to Rutgers University to the grant officers: Mr. Robert Doan, Drs. Grate and Pacifico and sought their advice on the possible change.

In May of 2019, Dr. Hai Sun accepted the job offer from Rutgers University. He resigned from LSUHSC effectively on August 31st, 2019 and began serving as an associate professor in the Department of Neurosurgery at RWJMS at Rutgers University on September 9th, 2019. LSUHSC submitted the letter to relinquish the award, while Rutgers University submitted the letter to express willingness to accept the award to the DOD. Both institutions are currently working diligently to facilitate the transfer of the grant.

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

  **None so far**

- **How were the results disseminated to communities of interest?**

  **None so far**

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

  Dr. Sun is working with Rutgers University to submit necessary documents for the grant transfer. He is also working on the approval of the study protocol by the institutional review board (IRB) by the University and Medical Center. The protocol will be resubmitted to the USAMRMC, ORP, and HRPO for their approval. As soon as the study receives approval from the university and all the oversight organizations, we will adhere to the proposed SOW for the funding duration (3 years). We anticipate being able to enroll study subjects between 6 to 12 months from the time this report has been submitted.

4. **IMPACT:** *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

   **None to report.**

5. **CHANGES/PROBLEMS:** *The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

   **Nothing to report.**

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

   **Nothing to report**

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

   - **What individuals have worked on the project?**

| | |
|---|---|
| Name | Hai Sun, MD, PhD |
| Project Role | Principal Investigator |
| Researcher Identifier | ORCID ID: 0000-0001-8878-8776 |
| Nearest person month worked | 0.25 |
| Contribution to the project | Revised the research project and gained the approval from the USAMRMC, ORP, and HRPO. |
| Funding | DOD Epilepsy Idea Development Award EP 170034, Louisiana State University Health Science Center (LSUHSC) Intramural Grant and LSUHSC M. Feist Seed Grant for young investigators |

   - **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. **APPENDICES:** *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc. Reminder: Pages shall be consecutively numbered throughout the report.* ***DO NOT RENUMBER PAGES IN THE APPENDICES.***