

AWARD NUMBER: W81XWH-17-1-0049

TITLE: Reduced GABAergic Tonic Inhibition as a Shared Mechanism of Post-Traumatic Sleep Disorders and Epilepsy

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14. ABSTRACT

Traumatic brain injury (TBI) can lead to a wide range of sequelae including posttraumatic epilepsy (PTE). Epidemiological data suggest that as many as 20% of patients with TBI in the general population and up to 50% of patients injured in military service will develop epilepsy. There is evidence linking the severity of a TBI to the probability of developing PTE, however there still remains a large amount of uncertainty surrounding which patients will ultimately develop PTE. Thus, identifying early markers that are predictive of PTE development is imperative. Here, we performed TBI (controlled cortical impact, CCI) on 8 CD-1 mice with electroencephalogram (EEG) recordings obtained 1 week, 2 months and 3 months following surgery. Visual inspection of EEG revealed that ~30% of TBI animals displayed seizures, often only at later time points, whereas almost all TBI animals had interictal spikes (IISs), spike clusters or trains at each time point. Therefore, nonconvulsive spikes may be a valuable predictor of later seizures but their quantitative scoring and characterization remains a major bottleneck to diagnosis. We applied a novel, probability-based algorithm (see Pfammatter et al. elsewhere at this meeting) to identify, categorize, and longitudinally track interictal activity from EEG. The algorithm first identifies events that 'stand out' of the background signal using a two-threshold method (events start if they cross 5 std above the signal mean and end when they cross 1 std below the mean). Then, identified events (across multiple animals and recording days) are concatenated, normalized, and projected into Principle Components (PC) space. The first three PCs are used to cluster events and calculate a probability of risk for epilepsy, based on the ratio of events within each cluster belonging to TBI versus sham-treated animals. We then correlated the events in each cluster with the incidence of electrographic seizures to establish which clusters hold events that are predictive of the development of PTE. Initial application of the algorithm in kainate-treated (KA) mice reveals successful prediction of risk for epilepsy. We find over 6x as many events above a threshold of 5 std in TBI animals as compared to KA animals. Three of the TBI animals developed convulsive seizures, one of which died as a result, and all three showed elevated predictive scores. We also note sleep disturbances following TBI that are different acutely compared to later time points. Treatment with dual Orexin receptor antagonist (DORA-22) resulted in no further seizures at week 1 or month 1 and in addition sleep improvements were noted. Future studies will aim to determine which clusters (i.e., spike waveforms) and sleep disturbances are most predictive and whether this method can predict outcomes in response to early diagnosis and treatment during epileptogenesis.

15. SUBJECT TERMS

NONE PROVIDED

16. SECURITY CLASSIFICATION OF:**a. REPORT**

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b. ABSTRACT

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c. THIS PAGE

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1. INTRODUCTION: *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

Traumatic brain injury (TBI) is a common problem in civilians and military personnel alike. According to CDC, there are over 5 million survivors with TBI related disability in the United States. It is also the signature injury in Veterans from OEF/OIF/OND. TBI can lead to several sequelae that include sleep disorders, post-traumatic epilepsy (PTE), cognitive and motor deficits and even post-traumatic stress disorder¹. Of these sequelae, epidemiological data shows that PTE can develop immediately or years after the injury, in up to 20% of patients and may be even higher in military injuries. Many of these patients remain intractable to conventional anti-epileptic drugs as well. Similar to PTE, post-traumatic sleep disruptions can be a chronic sequela of TBI and persist long after sustaining the injury in humans and animal models. In humans 20-50% of patients report post-traumatic sleep disruptions that range from insomnia to hypersomnia.

Gaps in TBI research: While TBI and its sequelae remain a huge problem, currently there is no way to predict who gets these complications, why they get it and how to prevent them. Studies that translate from the bench to the bedside or the clinic are lacking. If sequelae of TBI have a common or shared mechanism, perhaps similar treatments may work for both.

Focus of our research: We proposed to focus on GABAA receptor mediated functions which are known to be affected in the lesion core, thalamus, amygdala and hippocampus following TBI. Reductions in GABAergic tonic inhibition (GTI) and changes in GABA receptor subunits that favor phasic inhibition had been shown in models of TBI. Moreover, reduced GTI is known to occur in hippocampus in models of epilepsy and reduced GTI, especially in thalamus had been shown to be associated with sleep disruptions. Taken together, we hypothesized that *persistently reduced GTI in the hippocampus and thalamus contributes to persistent sleep disruptions, network hyper excitability and pathogenesis of PTE*

Experimental Aims:

Aim 1: To measure sleep disruptions and seizures followed by electrophysiological measures of GTI, at 1 week, 1 month and 3 months following a temporal-parietal CCI or sham control.

Aim 2: To measure if a) GTI can be rescued; b) sleep disruptions and network excitability restored and c) seizures prevented, with a selective agonist of δ subunit-containing GABAA receptors gaboxadol OR a dual orexin antagonist.

2. KEYWORDS: *Provide a brief list of keywords (limit to 20 words).*

TBI; Post-traumatic epilepsy; sleep disturbances, tonic inhibition
--

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Study Endpoints:

1. Following CCI, compared to sham injury, what percentage of animals develop seizures (PTE) and sleep disturbances? Do we see one or both and in what percentage of animals?
2. How are electrophysiological measures such as GTI, mIPSCs and EPSCs altered in hippocampus and thalamus after TBI and what is the association or correlation of these changes to PTE or post-traumatic sleep disruptions (PSD)
3. Do drugs that alter GTI (Gaboxadol) or drugs that are Orexin antagonists (eg: almorexant) restore PSD; restore electrophysiological changes and prevent development of PTE?

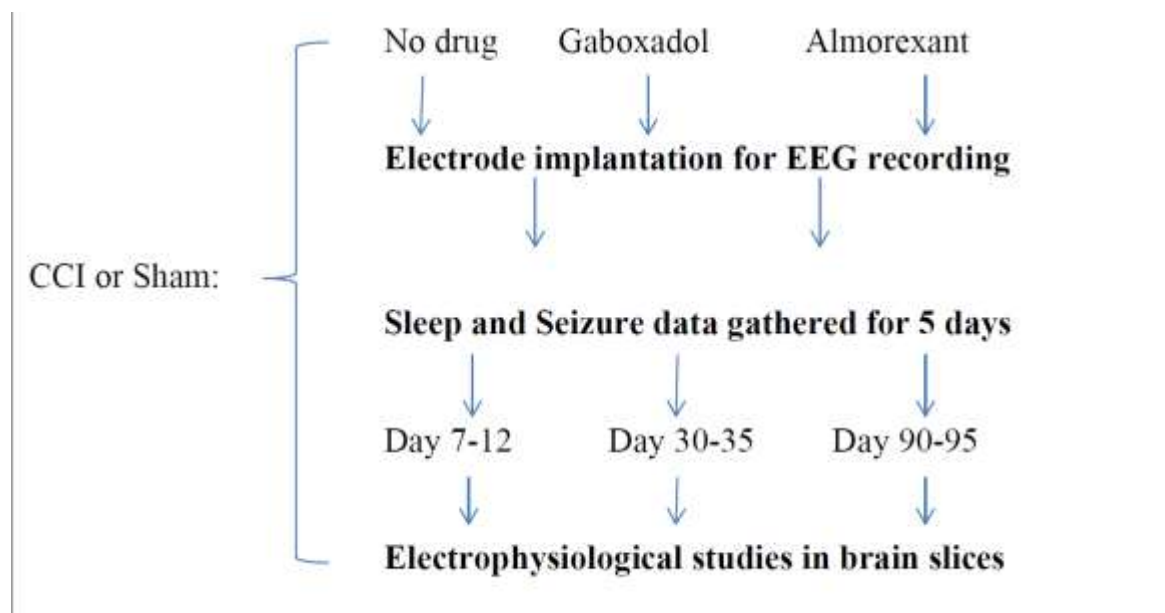
The Unique nature of our hypothesis:

In other words, does “normalizing sleep and its homeostasis” following TBI prevent development of PTE??? If our hypothesis is proven to be true, administration of one the above or related drugs may potentially prevent some of the sequelae of TBI.

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Experimental Schematic proposed originally:



Please see statement of work format for experiments completed:

SOW:

ACUC and ACURO approvals	June to September 2017	
Hiring of Post Doc (Paulo Rodrigues, PhD) and training set up	Sept to Nov 2017	
Obtaining equipment for CCI and training/trouble shooting	Oct to Dec 2017	
Research Aim: Specific Aim 1: Sleep, EEG recording and slice electrophysiology following TBI and no drugs	Dates	Number of animals
TBI Cohort 1 first recordings in CD-1 mice (for 25 days)	Dec 2018	4
TBI Cohort 2-Week 1 recording	Jan 2018	6
TBI Cohort 3-Week 1 Recording	Jan 2018	8
TBI Cohort 4- Week 1 Recording	Feb 2018	8
TBI Cohort 1 Month 1 recording	Jan 2018	4
TBI Cohort 2- Month 1 recording	Feb-March 2018	6
TBI Cohort 3-Month 1 recording	March 2018	8

TBI Cohort 4- Month 1 recording	March-April 2018	8
TBI Cohort 1 Month 2 and 3 recording	Feb and March 2018	4
TBI Cohort 2 Month 2 and 3 recording	March-April 2018	6
TBI Cohort 3- Month 2 and 3 recording	April and May 2018	8
TBI Cohort 4- Month 2 recording (did not do month 3 because some head caps fell off and other used for Electrophysiology)	May 2018	8
Sham injury Cohort 1- week 1 EEG recording	April 2018	6
Sham injury Cohort 2- week 1 EEG recording	May 2018	8
Sham injury Cohort 3 week 1 EEG recording	April 2018	6
Sham injury Cohort 1- Month 1 EEG recording	May 2018	6
Sham injury Cohort 2- Month 1 EEG recording	June 2018	8
Sham injury Cohort 2- Month 1 EEG recording	May 2018	6
In each of the above some animals died or some head caps fell off and data is not available. They were not counted here.		
Specific Aim 2: Sleep/EEG recording and Slice Electrophysiology with drugs- Completed EEG recordings with Dual Orexin Antagonist- DORA 22 (Obtained from Merck Pharmaceutical)		
We have 4 groups- TBI treated with DORA-22; TBI treated with vehicle; Sham injury treated with DORA-22 and Sham injury treated with vehicle	May-June 2018	8 animals in each cohort
Cohort 1 with DORA-22 or Vehicle- trouble shooting oral gavage	May	8 animals but all died
Cohort 2 with DORA-22 or Vehicle Week 1 recording	May	8
Cohort 3 with DORA-22 or Vehicle Week 1 recording	May	8
Cohort 4 with DORA-22 or Vehicle Week 1 recording	May	7
Cohort 2 with DORA-22 or Vehicle Month 1 recording	June	8

Cohort 3 with DORA-22 or Vehicle Month 1 recording	June	8
Cohort 4 with Dora-22 or Vehicle Month 1 recording	June-July	8
Electrophysiology Recordings so far		
TBI with no drugs		4 recordings
Sham with no drugs		3 recordings
TBI and Sham with drug (DORA-22 or Vehicle)		Recordings form 1 animal each
Future studies planned		
1. EEG Recordings at 6 months from TBI/Sham Injury groups	July/Aug 2018	From 2 cohorts at least
2. EEG recordings at week 1 and month 1 at least with Drug-2 namely Gaboxadol	July/Aug 2018	3 cohorts
3. Electrophysiology recordings in different groups	July-Sept 2018	2 slices from each group at least
4. Data Analysis	Oct-Nov 2018	

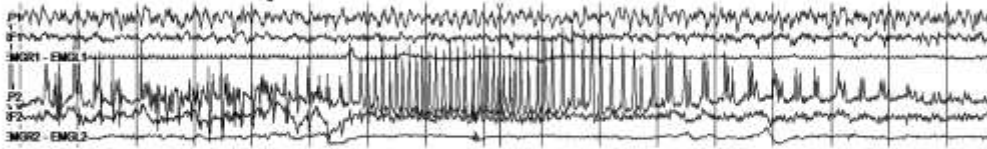
Results:

1. Seizures and Interictal Phenomena after TBI:

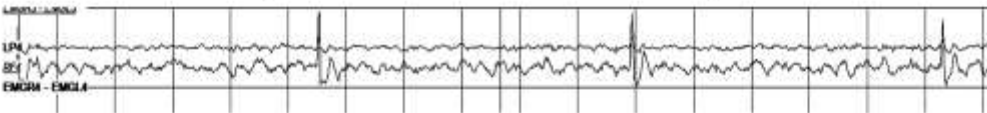
Seizures or Ictal events: About 30% of TBI animals developed Convulsive seizures anywhere from week 1 of recording to Month 2 of recording. None of the sham injury animals had seizures thus far (week 1 and month 2).

Interictal phenomena: Several different types of interictal phenomena were observed including: isolated spikes; spike clusters and brief rhythmic ictal discharges. These were seen in about 70% of the TBI animals and NONE in sham injury group

Example of convulsive seizure



Examples of interictal spikes



Example of interictal spike clusters

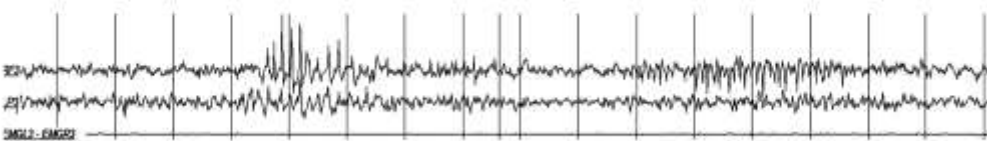


Figure 1: Examples of a Convulsive Seizure (Racine Class V) and Interictal spikes or spike cluster recordings from TBI animals

Using a Matlab algorithm, we are scoring interictal spike burden in animals of different groups and different treatments to understand: a) how many or what percentage of animals develop interictal phenomena after TBI or sham; b) how does the burden of spikes change with different treatments; c) how to interictal spike burden change from week 1 to month 1, 2 or 3; d) what is the relationship between spike burden and sleep disturbances or vice versa. An example of such analysis is shown below.

The algorithm first identifies events that ‘stand out’ of the background signal using a two-threshold method (events start if they cross 5 std above the signal mean and end when they cross 1 std below the mean). Then, identified events (across multiple animals and recording days) are concatenated, normalized, and projected into Principle Components (PC) space. The first three PCs are used to cluster events and calculate a probability of risk for epilepsy, based on the ratio of events within each cluster belonging to TBI versus sham-treated animals. We then correlated the events in each cluster with the incidence of electrographic seizures to establish which clusters hold events that are predictive of the development of PTE. Initial application of the algorithm in kainate-treated (KA) mice reveals successful prediction of risk for epilepsy. We find over 6x as many events above a threshold of 5 std in TBI animals as compared to KA animals. Three of the TBI animals developed convulsive seizures, one of which died as a result, and all three showed elevated predictive scores.

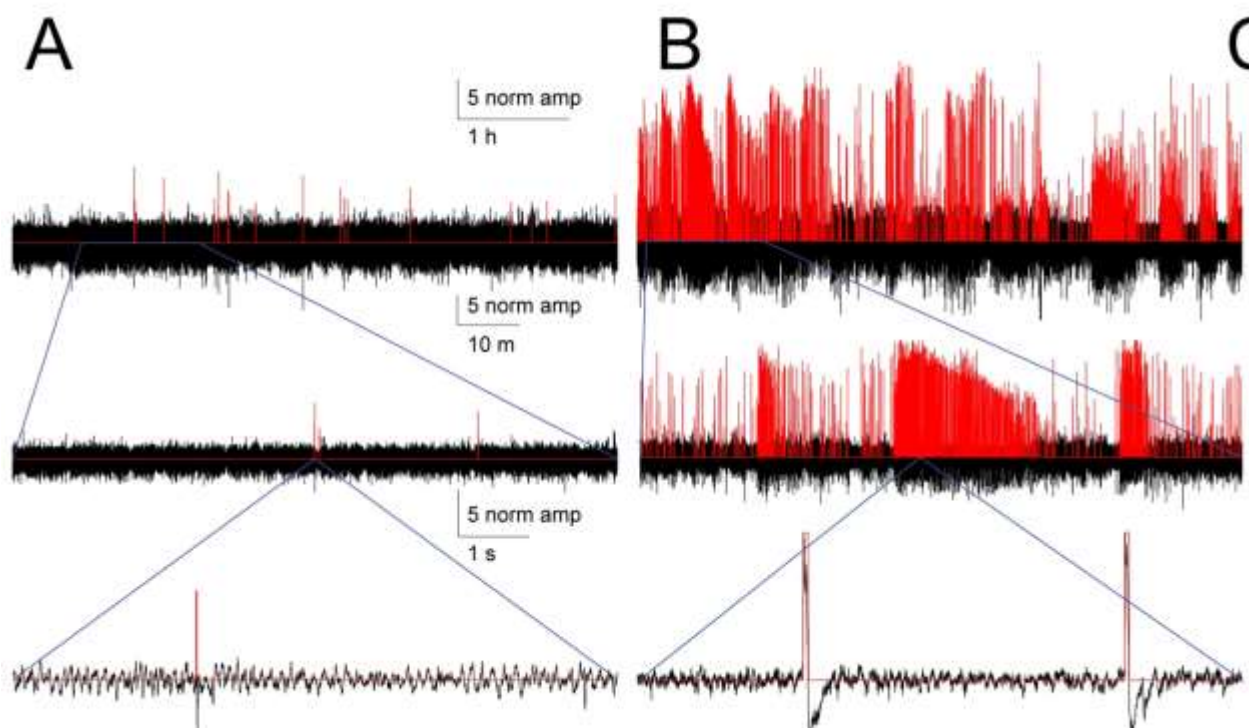


Figure 2: On the left panel is a sham injury animal with a EEG recording which shows very few to no “spike like” events (high amplitude discharges). On the right is a TBI animal which has classic interictal spikes that are seen for a large part of the recording. Top is a 1 hr compressed recording; middle is a 10 min recording compressed and lower is a few seconds of EEG. All “high amplitude events” which are presumed spikes were identified by the designed algorithm.

2. Sleep disturbances following TBI:

Along with seizures we recorded sleep-wake patterns in TBI and sham injury animals. Following TBI or sham injury with no drugs, we have recorded sleep-wake patterns at first week and month 2 so far where data had been analyzed. We found that while there were no big differences in overall time spent in awake or sleep (Non-REM vs REM) patterns, closer examination showed that the ratio of time spent in sleep to time spent in awake was different in TBI animals compared to sham injury groups.

At week 1 TBI animals spent lot more time in sleep compared to wake (ratio of sleep:wake being higher) at week 1 and the same ratio being much smaller in TBI animals compared to a sham injury animals. This is similar to “hypersomnia” reported acutely and “insomnia” reported chronically after TBI in humans. In addition, we also found that following TBI sleep bouts are longer at week compared to sham and much shorter at month 2 compared to sham. This suggests that sleep quality following TBI possibly dwindles over time.

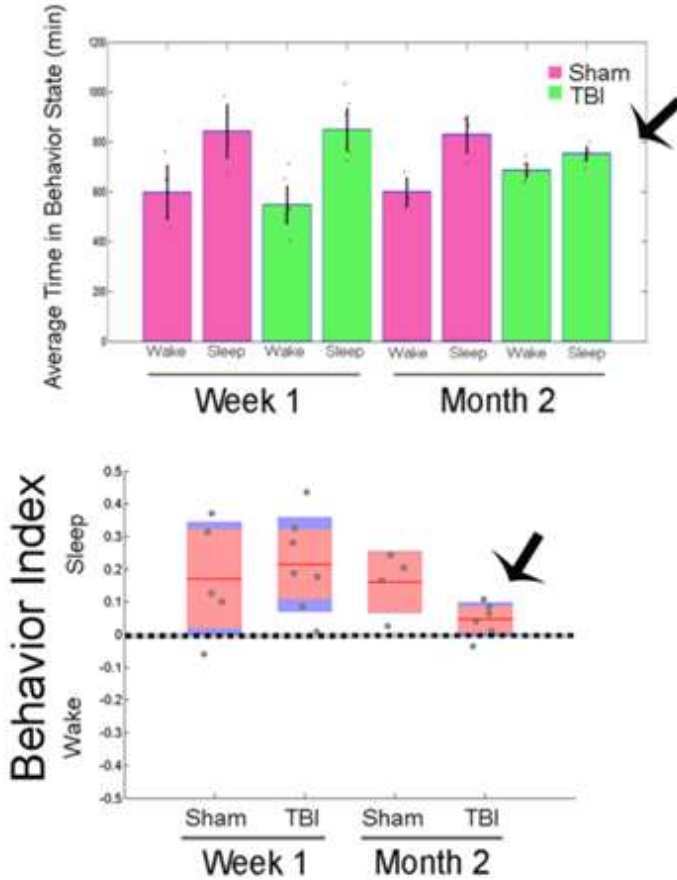


Figure 3: Sleep wake pattern analysis in TBI and Sham injury groups at week 1 and Month 2 (n=6 each). Top Panel shows the relative time spent in each behavioral state at week 1 and month 2. Bottom Panel shows relative ratio of time spent in sleep to wake at week 1 and Month 2. Note that TBI animals spend relatively more time sleeping at week 1 and relatively less time sleeping (or more awake) at month 1.

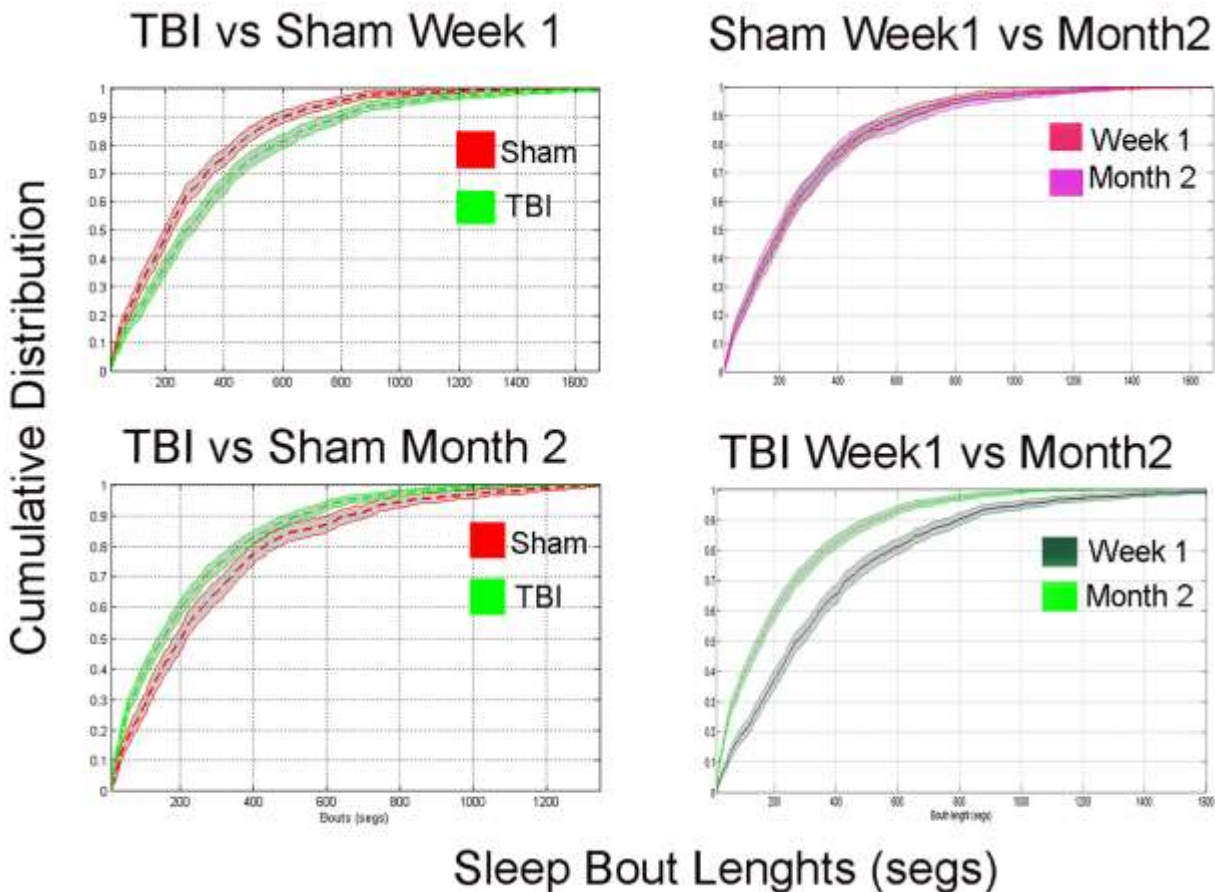


Figure 4: Cumulative distribution analysis of sleep bouts showing TBI or sham injury (n=6 each). Left top: showed that TBI group had longer sleep bouts at week 1 compared to sham. Left bottom: TBI animals shorter sleep bouts compared to sham at month 2. Right top: Sham group of animals have same length of sleep bouts at week 1 or month 2; Right bottom: TBI group at week 1 have longer sleep bouts compared to month 2.

3. Seizures and interictal spikes following treatment with DORA-22:

Following treatment with DORA-22 or Vehicle in TBI and Sham injury groups at week 1 and Month 1 so far with the drug treatments given daily for 37 days by oral gavage (with 10%DMSO as a vehicle). Upon visual inspection of none of the DORA-22 TBI cohort had seizures. Furthermore, interictal spike burden is dramatically decreased in DORA-22 treated TBI group compared to Vehicle treated TBI group. In addition 1 out of the 7 Vehicle treated TBI animals had convulsive seizures, and all vehicle treated TBI animals had lot more frequent interictal spikes or spike clusters. This analysis is still being done now. No figures attached.

4. Sleep changes following treatment with DORA-22:

We also examined sleep wake patterns in DORA-22 or Vehicle treated TBI and Sham injury animals. Analysis is only partly completed at this point, but it is noteworthy that the ratio of time spent in sleep vs awake is higher for all groups at week 1 and there was no difference. When sleep bouts were analyzed, TBI animals treated with DORA-22 had more long sleep bouts compared to TBI-vehicle treated animals suggesting that DORA-22 so far appears to increase time spent in sleep.

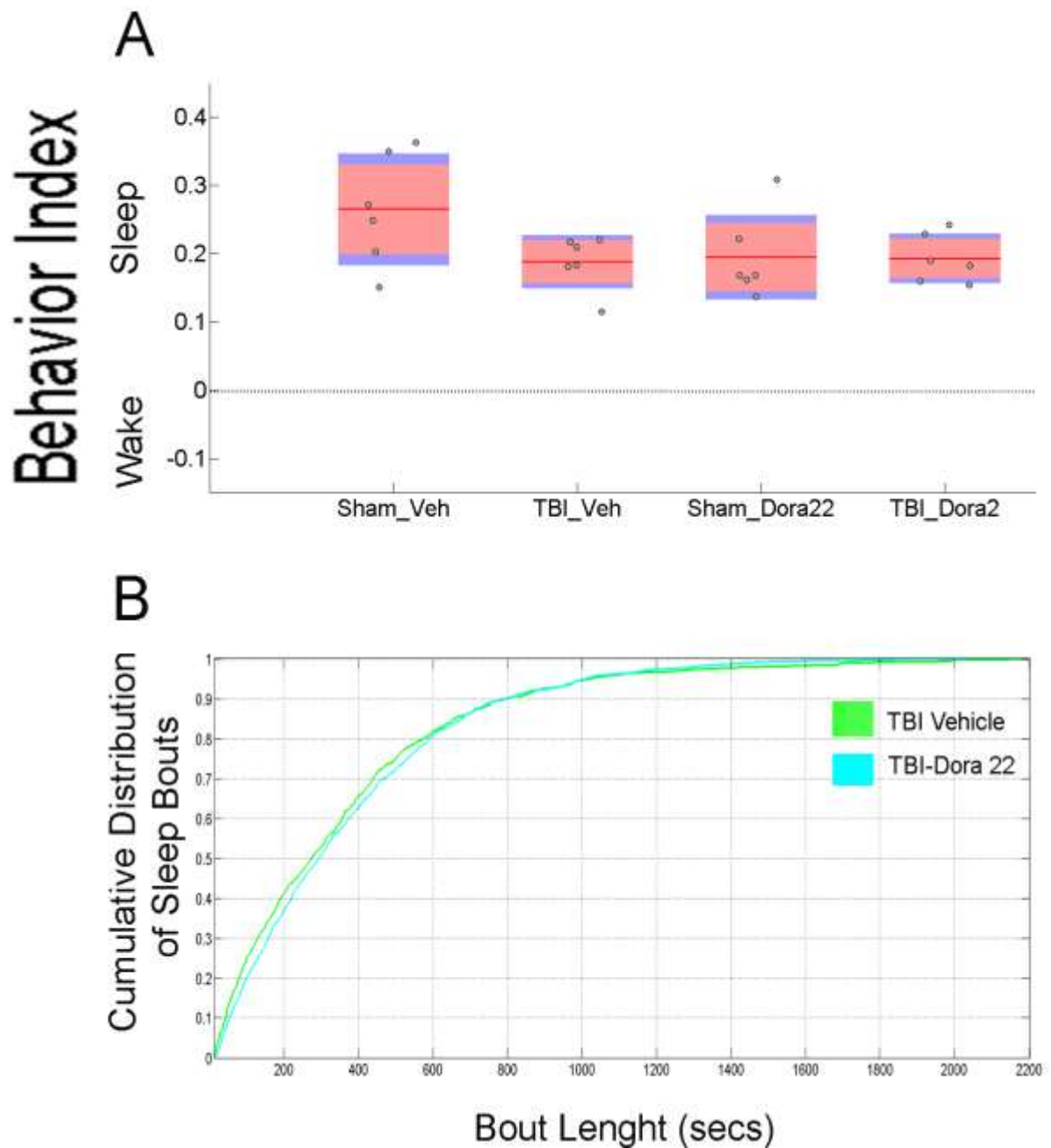


Figure 5: Showing sleep wake and sleep bout analysis between different treatment groups. On the top data for sleep wake patterns among the 4 treatment groups is shown and it can be noted that there is no overall difference in the ratio of sleep to wake. The bottom panel shows sleep bout analysis difference between vehicle and DORA-22 treated TBI animals and it can be seen that there is a “rightward shift” in DORA-22 treated animals suggesting that have longer sleep bouts with the drug.

We do not have an adequate sample size to do any analysis or come up with conclusions.

Next Experimental Steps:

1. Record sleep and seizures with DORA and Gaboxadol at week 1, month 1, 2 and 3 among TBI and sham injury groups- n=8 each
2. Perform patch clamp electrophysiology in TBI and sham injury with and without drugs. We have started this and performed on a small number of animals so far, but data is yet to be analyzed and therefore we do not report here.
3. Perform RT-PCR to look at GABAA receptor submits following TBI (1 week after TBI) in ipsilateral thalamus and cortex
4. Data Analysis

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

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. “Training” activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. “Professional development” activities result in increased knowledge or skill in one’s area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

There are 2 Post-Doctoral Fellows on the grant with both having learned new techniques and new methods of analysis. Our automated analysis of interictal spike scoring was developed by Jesse Pfammatter, PhD and will be publishing on this. Paulo Rodrigues, PhD who is another post-doctoral fellow had mastered the technique of EEG electrode implantation, performing the TBI (controlled cortical impactor) and in performing patch clamp electrophysiology. In addition two lab technologists were trained on TBI surgery, sleep analysis, oral gavaging of drugs etc. Lastly 2 under graduates initiated their own sleep analysis projects on the data collected thus far.

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of

these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to report.

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

If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Please see SOW above.

Next Experimental Steps:

1. Record sleep and seizures with DORA and Gaboxadol at week 1, month 1, 2 and 3 among TBI and sham injury groups- n=8 each
2. Perform patch clamp electrophysiology in TBI and sham injury with and without drugs. We have started this and performed on a small number of animals so far, but data is yet to be analyzed and therefore we do not report here.
3. Perform RT-PCR to look at GABAA receptor submits following TBI (1 week after TBI) in ipsilateral thalamus and cortex
4. Data Analysis

the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report. We cannot make any major conclusions until after the project is complete.

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official 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:*

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

The only change we made is that initially we planned to do the experiments in Sprague-Dawley rats that are fast kindlers. However, we switched to mice, specifically CD-1 mice based on other available Literature. However we submitted the change in this approach as well as reasons for it to ACURO as well as our ACUC and obtained permissions. Apart from this there were no other protocol changes.

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

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

No further problems are expected in the experimental plan.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

None

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

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Significant changes in use or care of vertebrate animals

None

Significant changes in use of biohazards and/or select agents

None

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.”*

- **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal;*

volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).

Nothing to report

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

None

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

None

- **Website(s) or other Internet site(s)**

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

None

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

None

- **Inventions, patent applications, and/or licenses**

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

None

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- data or databases;

- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

None

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate “no change”.

Paulo Rodrigues, PhD:

Project Role: Post-doctoral fellow

Contribution to the project: Paulo was the person performing many of the TBI surgeries, recording data for seizures and sleep (converting all acquired EEG data to sleep scoring formats); monitoring all animals as well as performing the patch clamp electrophysiology.

Jesse Pfammater, PhD:

Project role: Post-Doctoral fellow

Contribution: Jesse is responsible for analysis of data using automated soft wares or for statistical analysis. He was also responsible for fine tuning and preparing/running an old Electrophysiology rig to run patch clamp experiments. He also assisted Paulo in performing and designing the experiments.

Sruthi Reddy Konduru:

Project Role: Lab Tech

Contribution: Sruthi learned and performed some TBI and sham surgeries as EEG electrode implantation. In addition she assisted in scoring some of the sleep data

Funding source: None

Undergraduate students:

Project role: Students for data analysis and lab experience

Contribution: Students for primarily responsible for scoring all sleep files which is a very labor intensive process.

Funding source: UW Medical Foundation- in part.

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

If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Yes, the PI Rama Maganti, MD and Co-PI Mathew Jones PhD now have a NIH R21 grant awarded.

Grant Number: 1R21NS104612-01A1

FAIN: R21NS104612

Principal Investigator(s):

Rama k Maganti, MD

Project Title: Sleep deprivation-induced seizure exacerbation: Targeting tonic inhibition as a therapeutic strategy

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:

Organization Name:

Location of Organization: (if foreign location list country)

Partner’s contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner’s facilities for project activities);*
- *Collaboration (e.g., partner’s staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner’s staff use each other’s facilities, work at each other’s site); and*
- *Other.*

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ers.amedd.army.mil> for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments.*

- 9. 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.*