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TITLE: Persisting Resting State fMRI Hyperconnectivity as a Risk Factor for Alzheimer's Disease after TBI

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None

14. ABSTRACT
The overall hypothesis to be investigated is that Abeta associated paroxysmal hyperconnectivity episodes thought to represent the task free fMRI equivalent of paroxysmal network hypersynchrony play a decisive role in the progression from preclinical to clinical AD. A critical role for network hypersynchrony could also explain why TBI is a risk factor for the development of AD in later life since impaired Abeta clearance and permanently altered neuronal excitability favoring paroxysmal network hypersynchrony have shown to be features of the chronic stage of TBI. Patients with a history of TBI whose task-free fMRI shows paroxysmal hyperconnectivity episodes are therefore expected to have a higher risk to develop AD in later life, i.e., have higher Abeta plaque loads and worse cognitive abilities, than those who do not show this abnormality. The project will use completely de-identified longitudinal imaging and clinical data from the DoD ADNI data repository to address these questions. Year 2 was spent on processing the downloaded imaging data and preparing it for the statistical analysis.

15. SUBJECT TERMS
Alzheimer's Disease, TBI, hypersynchrony, risk factor, DoD ADNI

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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1. INTRODUCTION: **Background:** Amyloid (Abeta) plaques are one of the defining features of Alzheimer's disease (AD) but increased levels of soluble Abeta can already be observed several years before plaque build-up and the appearance of clinical symptoms. Recent findings indicate that increased levels of soluble Abeta cause paroxysmal abnormal neuronal firing or network hypersynchrony when plaques are still absent. Normal neuronal activity plays an important role in the control of Abeta production, degradation and transport between neurons. Therefore, Abeta induced abnormal neuronal firing could have a decisive role in facilitating Abeta build-up and deposition in the brain. Increased Abeta brain levels and hyperexcitability in form of network hypersynchrony with an increased risk for epileptic seizures are also well-known features of acute and chronic traumatic brain injury (TBI). **The overall hypothesis** to be investigated is that Abeta associated paroxysmal hyperconnectivity episodes thought to represent the task free fMRI equivalent of paroxysmal network hypersynchrony play a decisive role in the progression from preclinical to clinical AD. An impaired Abeta clearance and permanently altered neuronal excitability favoring paroxysmal network hypersynchrony have been shown to be features of the chronic stage of TBI and could therefore be a risk factor for developing AD in later life.. **The aim is to identify paroxysmal hyperconnectivity episodes in subjects with a history of TBI and to investigate their relationship with cognition, Abeta load and TBI severity**. Task-free fMRI data from subjects with and without a history of TBI from DoD-ADNI project will be analyzed to detect Abeta associated hyperconnectivity episodes. The characteristics of these connectivity states will be compared with those of the paroxysmal hyperconnectivity state observed in previous studies to identify the state most likely to represent its equivalent in the DoD-ADNI population. The association between duration of the paroxysmal hyperconnectivity state in each subject and cognition, global Abeta load and TBI severity will be investigated. It is expected that their duration is negatively associated with cognition and positively with Abeta load and TBI severity. A positive proof of the relationship between paroxysmal hyperconnectivity and AD risk in TBI could open a pathway to a preventive treatment of at risk patients.

2. KEYWORDS:

Amyloid, TBI, risk factor, hypersynchrony, hyperconnectivity, fMRI, DOD ADNI data repository

3. ACCOMPLISHMENTS:

What were the major goals of the project?

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Specific Aim 1: To identify paroxysmal hyperconnectivity episodes in subjects with a history of TBI and to investigate their relationship with cognition, Abeta load and TBI severity using data from the DoD-ADNI project.

Major Task 1: DoD-ADNI MR and PET Processing
Subtask 1. Setting up data processing structure, project database: Month 1:
Subtask 2. Identification & download of functional and structural MR imaging, amyloid and tau PET imaging and behavioral data of DoD-ADNI subjects with/ without TBI regardless of PTSD status: Month 2-6
Subtask 3. Data conversion and visual and numerical quality control of MR and PET imaging data: Months 6-12.
Subtask 3. Processing of MR (SPM, conn, cluster, graph analysis): Months 12 – 24

Major Task 2: DoD-ADNI Analysis
Subtask 1. Analysis of MR and PET data: Month 24-30
Subtask 2. Publication of results: Months 30 -36

What was accomplished under these goals?

.

Major Task 1: DoD-ADNI MR and PET Processing
Subtask 1. Setting up data processing structure, project database: Month 1: **Completed**
Subtask 2. Identification & download of functional and structural MR imaging, amyloid and tau PET imaging and behavioral data of DoD-ADNI subjects with/ without TBI regardless of PTSD status: Month 2-6: **Completed**
Subtask 3. Data conversion and visual and numerical quality control of MR and PET imaging data: Months 6-12. **Completed**
Subtask 3. Processing of MR (SPM, conn, cluster, graph analysis): Months 12 – 24: Pre-processing: **Completed.**

Major Task 2:
Subtask 1: Analysis of MR and PET data: Initiated

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

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Nothing to report.

How were the results disseminated to communities of interest?

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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.

Finishing Major Task 2/Subtask 1 Statistical analysis with biostatistician.
Initiate Major Task 2/Subtask 2: Publication of the results.

4. IMPACT:

Project still in the stage of data analysis. At the time of the writing of this report, the non-imaging data (demographics, disease groups etc) is being analyzed to better understand how the different disease states, ie., PTSD, TBI etc. relate to each other.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to Report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

1. Review of "exempt research" proposals by UCSF IRB were delayed by 6 months which introduced a delay. Confirmation of "exempt research" by HRPO was delayed by 3 months. Because of this the processing of the imaging data was delayed by about 6 months.

2. COVID 19 outbreak prevented use of CIND processing servers.

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

No problems anticipated.

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

Significant changes in use or care of human subjects

The project uses completely de-identified data from the DoD ADNI repository and was categorized as non-human subjects project by UCSF IRB and HRPO.

Significant changes in use or care of vertebrate animals

NA.

Significant changes in use of biohazards and/or select agents

NO.

6. PRODUCTS:

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

Journal publications.

Nothing to report.

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers and presentations.

Nothing to report.

- **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 : Susanne Mueller Dr. med.
Project Role: PI
Research Identifier: ORCID 0000-0002-5515-4432
Nearest person month worked: 1.44
Contribution to Project: PI, set-up of processing pipelines, processing of imaging data,

Name: Charles McCulloch PhD
Project Role: Co-investigator, Supervising Biostatistician
Research Identifier NA
Nearest person month worked: None in Year 2
Contribution to Project: Oversight of statistical analysis

Name: Efstathios Gennatas PhD
Project Role: Biostatistician
Research Identifier: ORCID 0000-0001-9280-3609
Nearest person month worked: 0.48 (starting June 21)
Contribution to Project: Statistical analysis

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

Dr. E. Gennatas was added as the lead statistician to the project. Dr. McCulloch will take on an advisory role.

What other organizations were involved as partners?

No

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

NOT REQUIRED FOR THIS PROJECT

QUAD CHARTS:

SEPARATELY SUBMITTED.

9APPENDICES:

NO APPENDICES