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TITLE: Persistent 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 1 was spent on obtaining the confirmation that this project falls under the category of non-human subjects research, identifying the relevant imaging data (490 data sets with structural MRI, 319 data sets with fMRI, 266 AV45 PET data sets, 120 AV1451 PET data sets)) in the repository, down-loading it and setting up the pre-processing pipelines, pre-processing the data and performing quality control/trouble shooting.

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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TABLE OF CONTENTS

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

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

3. ACCOMPLISHMENTS:

What were the major goals of the project?

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?

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.

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, final processing imitated.
The goals of year 1 have been met. The final processing will be initiated. There are currently no results to report.

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

Nothing to report.

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.

Finishing Task 1/Subtask 3 and prepare resulting data for statistical analysis with biostatistician.
Initiate Major Task 2.

4. **IMPACT:** D*escribe 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:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from 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).

Project still in the stage of data processing/analysis. No findings/results as of yet.

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.

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.

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

No problems anticipated.

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.

Nothing to report.

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

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: *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).*

Nothing to report.

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.*

Nothing to report.

- ## 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.

Nothing to report.

- ## Technologies or techniques

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

Nothing to report

- **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.

Nothing to report.

- **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.*

Nothing to report.

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".

Name : Susanne Mueller Dr. med.
Project Role: PI
Research Identifier: ORCID 0000-0002-5515-4432
Nearest person month worked: 1
Contribution to Project: PI, set-up of processing pipelines, processing of imaging data,

Name: Charles McCulloch PhD
Project Role: Co-investigator, Biostatistician
Research Identifier NA
Nearest person month worked: None in Year 1
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?
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.

None.

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.*

No

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.*

NOT REQUIRED FOR THIS PROJECT

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

SEPARATELY SUBMITTED.

9APPENDICES: *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.*

NO APPENDICES