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TITLE: Persistent Resting-State fMRI Hyperconnectivity as a Risk Factor for Alzheimer's Disease After TBI

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CONTRACTING ORGANIZATION: University of California, San Francisco, CA

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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 4 was spent 1. On investigating how the gray matter/tau load pattern identified in the previous reporting period influence gray matter loss over time. 2. Identification of the hypothesized hyperconnectivity state and its relationship to amyloid and tau load as well as disease state (TBI, PTSD) gray volume loss.

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: *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.* *Page | 4*

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 -3

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 in May 2020**
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 in July 2020**
Subtask 3. Data conversion and visual and numerical quality control of MR and PET imaging data: Months 6-12. **Completed in August 2020**

Subtask 3. Processing of MR (SPM, conn, cluster, graph analysis): Months 12 – 24: Pre-processing: **Completed in October 2021**

Major Task 2:
Subtask 1: Analysis of MR and PET data: **Initiated and ongoing**.
Subtask 2: Publication of results: Months 30 -3

Summary of major findings in report period

Part 1: Volumetry

Does the ageN-T mismatch score predict gray matter loss over time?

The Y3 report described the development of the ageN-T mismatch score that allowed to investigate how age corrected regional gray matter atrophy predicts regional tau load. Using this score it was shown that that only a subset of the patients with PTSD and/or remote TBI had evidence of various degrees of AD pathology (subgroups 1,2, and 3) and that neither TBI nor PTSD modify AD-associated tau binding patterns to create PTSD or post TBI specific patterns. This was interpreted as evidence that at least in the DoDADNI population TBI history represents just one of several factors that need to come together to increase the AD risk. The next step was to investigate if one or all three of the subgroups with AD pathology had greater gray matter volume loss compared to the two other subgroups over time. Only 61 subjects of the 89 with tau/amyloid data had also more than one structural MRI at different TP allowing to calculate the percentage of GM loss/year (%GMloss). %GM losses were not different between the five age-NT subgroups ($p = 0.81$). %GMloss in subgroup 3 (characterized by the highest tau/amyloid loads and age-NT) was -1.70, followed by subgroup 2 (2^{nd} highest age-NT) with -1.27 and subgroup 1 (3^{rd} highest age-NT) with -1.03. The two subgroups with negative age-NT values indicating that GM loss is not driven by tau had %GMloss of -1.14 (subgroup 4) and -1.81 (subgroup 5 characterized by high CAPS). **Although the five subgroups differed re %GM losses over time, the differences were not significantly different** (ANOVA $p = 0.81$). A possible explanation is that the analysis that was restricted to subjects with tau, amyloid PET and longitudinal MRI was underpowered. The next step was therefore to investigate longitudinal GM loss in the larger population.

Longitudinal gray matter loss

The objective of this analysis was to identify in each subject gray matter regions where the gray matter (gm) atrophy exceeded that expected by age. A modification of the approach used in the previous section was employed to accomplish this goal. 92 cortical and subcortical (hippocampus, amygdala) ROIs of the AAL atlas were used to extract gm volumes from the ICV corrected gm maps (n = 539) from all 272 DOD subjects with good quality imaging data (151 with multiple TP, interval approx. 1 year, 121 with single TP) and 30 amyloid negative age matched ADNI subjects (30 multiple TP). Robust regression analysis with gm volume in roi as dependent and age as independent variable was used to identify 60 rois with significant gm-age associations. Rois with residuals exceeding 2SD or -2SD were identified as rois with significantly more gm (resilient) or less gm (atrophic) gray matter than expected by age. 32 rois showed no significant sig gm-age associations. The gm volumes of these 32 rois were converted into z-scores. ROIs with z-scores equal or exceeding 2 were identified as resilient rois and those with -2 less were atrophic rois. A 539 x 92 matrix was generated by coding all atrophic rois with -1, all resilient rois with 1 and all other rois with 0. An atrophy index was calculated for each of the 539 entries by summing up all roi codes and total gm volume (TotalGM) was calculated by summing up all 92 gm roi volumes for each entry. The 539 x 92 matrix was used as input for a hierarchical cluster analysis and the critical clustering criterion used to identified 15 different clusters or gray matter patterns. Of these 15 clusters, cluster 1 had not only the highest frequency (251 instances, 141 individual subjects) but also with a mean atrophy index (AI) of 1.6. also the atrophy index closest to 0, indicating that it represents the normal gray matter aging pattern in this population. It is used as reference to distinguish atrophy patterns (clusters with negative atrophy indices and significantly lower TotalGM (ANOVA, Tukey Kramer post-hoc test) compared to cluster 1 and other clusters: 2,5,6,4,3) from resilience patterns (clusters with positive atrophy indices: 10,9,7,12,11,8,14,15,13). 83 subjects (4 ADNI, 79 DADNI had atrophy patterns and 79 subjects had resilience patterns at TP1. Of the 181 subjects with multiple TP only 11 (1 ADNI, 10 DoD) showed a progression, i.e., progressed from a normal or resilience pattern to an atrophy pattern or progressed from an atrophy pattern to a more severe atrophy pattern during the observation period. In sum**, about 30% of the DoD subjects showed various degrees of brain atrophy exceeding that normal for age and about 7% showed progressive gray matter loss during the observation period.**

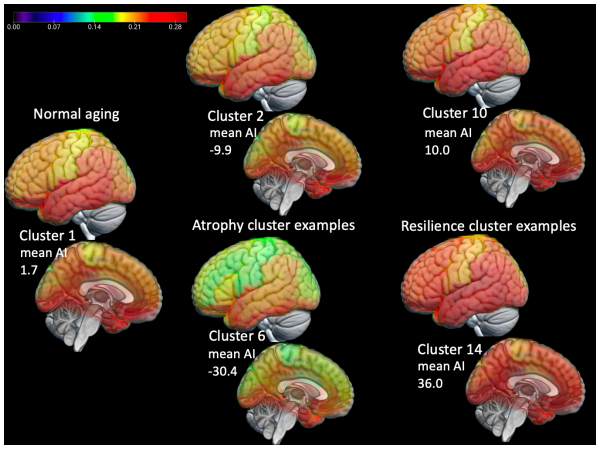

Figure 1. Examples of gm clusters

The 3 (normal aging, atrophy, resilience) cluster types (DoD only, 231 with aBeta, 96 with tau) did not differ re mean aBeta load or mean tau load. TotalGM loss between TP1 and TP2 was positively associated with aBeta load (147 DoD, beta = 0.014, p = 0.01) but unexpectedly not with tau load (72 DoD subjects, beta = 0.02, p = 0.13). A power analysis showed that the lack of a tau load GM loss association was most likely caused by the smaller sample size. The findings suggests that **AD pathology promotes the development of atrophy in this population.**

The next step was to investigate if diagnosis has an influence on gray matter pattern (cluster 1-15) or cluster type (atrophy, normal aging, resilient). It was hypothesized that PTSD that where specific gray matter atrophy pattern have been shown previously would be the most likely to be associated with a specific cluster. TBI though where the TBI type a patient experiences has likely a major influence on of gray matter atrophy pattern was not expected to be associated with a specific cluster. It was also assumed that PTSD, TBI and TBI&PTSD would be more likely to be assigned to an atrophy cluster and controls to the normal aging or resilient clusters. There were no significant associations between diagnosis and cluster (Pearson ChiSquare 53.2 p =0.11) but there was a significant association (Pearson ChiSquare 14.2, p=0.023) between diagnosis (control, PTSD, TBI, PTSD&TBI) and cluster type (atrophy, normal aging, resilience) at TP1. Follow-up analyses found that this was driven by the observation that a higher number of subjects with PTSD&TBI was assigned to either a resilience cluster or the normal aging cluster than would have been expected by chance. The diagnostic groups did not differ re chance of being assigned to an atrophy cluster or a specific cluster within the atrophy group (clusters 2-6). This confirms the observation made in the ageNT subsample that **a history of TBI or PTSD is only one of several factors driving brain atrophy of which AD pathology is one of the more important factors.**

Part 2. Hyperconnectivity state

The available resting state fMRI data (184 DoD ADNI subjects enriched by 39 cognitively intact aBeta negative ADNI3 subjects) underwent a dynamic analysis that identified 8 different states. State 7 had with 3.6 the highest positive strength z-score (state 1: -1.55, state 2: -2.68, state 3: -5.35, state 4: -1.96, state: 5, 1.4, state 6: -0.69 state 8: 1.64) and thus fulfilled the previously defined criteria of a hyperconnectivity state. It most commonly evolved/transitioned from the intermediate connectivity state 6 followed by the high connectivity state 8 (see Figure 2).

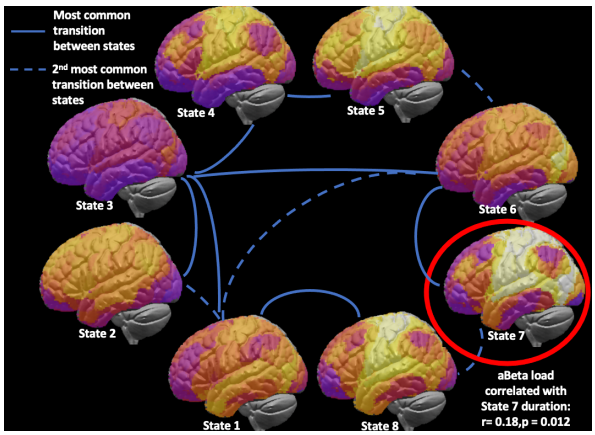

Figure 2

State 7 duration at TP1 was positively correlated with aBeta (n = 184, r = 0.166, p = 0.028) and with tau load (n = 80, r = 0.19, p = 0.046). ApoE4 carrier state had no effect on state 7 duration. Taken together, the findings suggest that **AD pathology facilitates the appearance of the hyperconnectivity state.**

The next step was to investigate how TBI and PTSD influence State 7 appearance in 131 DoD ADNI participants. State 7 duration (mean lnCluster7 count 1.6 vs 1.9, p = 0.02) was shorter in subjects with a history of PTSD (CAPS life and or CAPS current >30)

compared to subjects without PTSD history (mean lnCluster7 count 1.6 vs 1.9, p = 0.02) but was not correlated with PTSD severity. State 7 duration was not different in subjects with a history of TBI compared to those without TBI (mean lnCluster7 count 1.7 vs 1.7, p = 0.02) nor was its duration correlated with TBI severity. The duration of the other states was not influenced by PTSD or TBI history. **The findings suggest that either a history of PTSD protects against the occurrence of the hyperconnectivity state or that TBI in the absence of PTSD facilitates the appearance of hyperconnectivity states but that the number of subjects with TBI without PTSD is too small for reach significance.**

Although the differences did not reach statistical significance (131 DoD subjects with TP1 volumetric and resting state fMRI), subjects with atrophic gray matter patterns had longer state 7 episodes (%LNCluster 7 counts: 1.83) than subjects with normal aging patterns (%LNCluster 7 counts: 1.71) or subjects with resilient patters (%LNCluster 7 counts: 1.63). There were no significant associations between state 7 duration at TP1 with TotalGM at TP1 nor with loss of TotalGM between TP1 and TP2. Taken together these findings suggest that the **hyperconnectivity state has no direct effect on gray matter volume or gray matter volume loss over time.**

Preliminary Conclusions: The findings so far confirm the hypothesis that progressive AD pathology, evidenced by increasing aBeta and tau loads, is associated with a hyperconnectivity state. There is no evidence that these states are more severe in patients with a history of TBI but rather that they are less severe in patients with a history of PTSD. The DoDADNI with its focus on an over 60 years of age population does not allow to answer the probably most important question re hyperconnectivity state, i.e., is hyperconnectivity just a symptom of the AD pathology, i.e., occur simultaneously, or the cause of the AD pathology, i.e., precede it and if so, does previous TBI facilitate its occurrence. This would require a study in a younger population with more recent TBI. AD pathology is also one of the main factors driving progressive atrophy. TBI history and PTSD history play no or a smaller role in atrophy progression. The results reported here will be used to inform the final statistical analyses.

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

Nothing to report.

How were the results disseminated to communities of interest?

Manuscript describing different subgroups within the study populations based on different gray matter/tau load interaction patterns and will be submitted for publication.

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 Cross-sectional analysis of dynamic resting state analysis (identification of hypersynchrony episodes, characterization at TP 1 and TP2. Investigate how regional Abeta and tau load influence hyperconnectivity pattern in contrast to this reporting period that investigated global gray matter, tau etc.. Design longitudinal analyses of dynamic resting state analysis and its impact on longitudinal gray matter loss with biostatistician.
Initiate Major Task 2/Subtask 2: Publication of the results.

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).

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.

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.

No changes in approach

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.

Request for NCE in Year 5 submitted and approved in Sept 2023.

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
Non applicable

Significant changes in use of biohazards and/or select agents

Non applicable.

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).*

  Manuscript "Are Traumatic Brain Injury and Post-traumatic Stress Disorder Risk Factors for Alzheimer's Disease in later life?" submitted for publication in Brain Communications but has been rejected after being under review for 7 months. It will be slightly modified and re-submitted to a different Journal

  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: 1.44
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 3
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
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.*

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.*

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