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14. ABSTRACT
The purpose of this grant is to understand how the circuitry associated with the central lateral thalamic nucleus (CL) plays a role in enhancing the risk for Alzheimer's disease (AD) following a traumatic brain injury (TBI). Animal connectivity work shows that CL has strong connections with the dorsal anterior cingulate cortex (dACC), which is heavily involved in both attention and memory. We hypothesize that the downregulation of CL in TBI leads to decreased activity in the dACC, which in turn downregulates the memory system and enhances the risk for AD. This will be tested by quantifying the connectivity strength between CL and dACC in resting-state fMRI and DTI neuroimaging data from healthy versus TBI versus AD subjects from the ADNI and DoD-ADNI databases. We will then examine whether the CL-dACC connectivity strength inversely correlates with markers of AD (performance on the Logical Memory II test, global PET-amyloid burden, and amyloid and tau levels in the cerebrospinal fluid). Thus far, per the Statement of Work for Year 1, Major Task 1 Subtask 1 has been completed: data have been downloaded from the ADNI and DoD-ADNI databases. Major Task 1 Subtask 2 is partially complete. Subject-specific PHC and dACC ROIs have been defined for all subjects. Work is in progress for defining subject-specific CL ROIs. Progress has been slowed because of a delay in hiring a Data Analyst to assist with tasks. We expect that the remainder of Year 1 tasks will be accomplished within three months in Year 2.

15. SUBJECT TERMS
Amyloid beta, Alzheimer's disease, central lateral thalamic nucleus, dorsal anterior cingulate cortex, diffusion tensor imaging, positron emission tomography, parahippocampal cortex, phosphorylated tau, resting-state functional connectivity MRI, traumatic brain injury

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1. Introduction

The purpose of this grant is to understand the circuitry underlying how sustaining a traumatic brain injury (TBI) leads to enhanced risk for Alzheimer's disease (AD). The central lateral thalamic nucleus (CL) is a key region in the arousal system of the brain that has broad connections throughout the brain. The mesocircuit hypothesis posits that it is through these broad connections that TBIs lead to the common downregulation of CL and subsequent downregulation of connected brain regions. One of CL's strongly connected brain regions is the dorsal anterior cingulate cortex (dACC), which is heavily involved in both attention and memory. Animal connectivity work shows that both CL and the parahippocampal cortex (PHC) of the memory system have strong connections with the dACC. Supporting this connectivity, CL stimulation in rodents and a patient showed memory effects: behavioral improvements in memory and increased gene and protein expression changes in the hippocampus. Using our recently developed technology that accurately identifies CL in human anatomical MRI scans, we will map CL's connections to the dACC in TBI subjects, measure its connectivity strengths, and measure its correlation with markers of AD (performance on the Logical Memory II test, global amyloid burden as measured by position emission tomography (PET), and levels of amyloid and tau protein in the cerebrospinal fluid). We hypothesize that the downregulation of CL in TBI leads to decreased connectivity with the dACC, and the enhanced risk of developing AD as assessed by increased levels of AD markers. Results will be compared with those from healthy and AD cohorts, and compared with PHC's connectivity with the dACC.

2. Keywords

Abeta—amyloid beta
AD—Alzheimer's disease
CL—central lateral thalamic nucleus
dACC—dorsal anterior cingulate cortex
DTI—diffusion tensor imaging
PET—positron emission tomography
PHC—parahippocampal cortex
p-Tau—phosphorylated tau
rsfMRI—resting-state functional connectivity MRI
TBI—traumatic brain injury

3. Accomplishments

What were the major goals of the project?

Year	Specific Aim	Major Task	Subtask	Months (per SOW)	% Completed
1	Specific Aim 1: Map the connectivity of CL and PHC in TBI, AD, and healthy control groups.	Major Task 1: Obtain all relevant data from databases and define ROIs in structural MRIs in preparation for analyses.	Subtask 1. Goal: Identify TBI and healthy controls from the DoD-ADNI database. Identify matched AD patients from the ADNI database. Obtain all the relevant data needed for this grant: structural MRI, rsfMRI, DTI, PET-amyloid imaging, cognitive measures, and CSF biomarker levels. The DoD-ADNI and ADNI databases are publicly available and deidentified of direct identifiers, but retain some indirect identifiers (e.g., birth date, gender, race, ethnicity) that are needed for analysis.	1-8	100
1			Subtask 2. Goal: Define all ROIs for all subjects. All ROIs except	9-10	50

			CL will be defined by passing the T1 structural images through FreeSurfer. CL will be defined using a modified thalamic segmentation method appropriate for the T1 structural image.		
1	PI's Maternity Leave			11-13	100
2		Major Task 2: Map the connections of CL and PHC to the cortex using rsfMRI. Quantify connectivity strength between CL and PHC to dACC.	Subtask 1. Goal: Preprocess all subject rsfMRI data using the CONN toolbox.	14-15	0
2			Subtask 2. Goal: Run rsfMRI analyses using the CL or PHC ROIs and the cerebral cortex for each subject using the CONN toolbox. Create group correlation maps for each of the TBI, AD, and healthy groups. Quantify the correlation strength between CL or PHC and the dACC for individual subjects and the groups.	16-17	0
2			Subtask 3. Goal: Conduct a comparative spatial analysis of the maps across TBI, AD, and healthy groups using Matlab. Compare correlation strength between CL or PHC and dACC across groups.	18	0
2		Major Task 3 Map the connections of CL and PHC to the cortex using DTI. Quantify connectivity strength between CL and PHC to dACC.	Subtask 1. Goal: Preprocess all subjects' DTI data using FSL and NiftyReg.	19-20	0
2			Subtask 2. Goal: Run DTI analyses using the CL or PHC ROIs with the cerebral cortex for each subject using FSL. Create group connectivity maps for each of the TBI, AD, and healthy groups. Quantify the connectivity strength between CL or PHC and the dACC for individual subjects and the groups.	21-22	0
2			Subtask 3. Goal: Conduct a comparative spatial analysis of the maps across TBI, AD, and healthy groups using Matlab. Compare connectivity strength between CL or PHC and dACC across groups.	23-24	0
3			Subtask 4. Goal: Write and submit publication #1 on Specific Aim 1 work.	25-26	0
3	Specific Aim	Major Task 4 Obtain global	Subtask 1. Goal: Preprocess all	27-28	0

	2: Correlate the connectivity strength between CL or PHC and dACC with AD markers.	PET-amyloid burden measures from all subjects.	subject PET-amyloid data using SPM12.		
3			Subtask 2. Goal: Obtain global amyloid burden for all subjects using Matlab.	29	0
3		Major Task 5 Test the hypothesis that CL's connections to the dACC are correlated with an increase in markers of AD in TBI.			0
3			Subtask 1. Goal: Examine association of connectivity strength metrics with markers of AD obtained from Major Tasks 1 and 4 (global amyloid burden, memory performance on the Logical Memory II, CSF Abeta42/Abeta40, and CSF p-Tau levels) with a simple linear correlation analysis using SPSS.	30-31	0
3			Subtask 2. Examine association of connectivity strength metrics with markers of AD with multiple linear regression using SPSS.	31-32	0
3			Subtask 3. Goal: Write and submit publication #2 on Specific Aim 2 work.	33-34	0
3			Subtask 4. Goal: Write and submit publication #3 on Specific Aim 2 work.	35-36	0

What was accomplished under these goals?

Per the Statement of Work (revised 10/18/2021), Year 1's tasks are (Major Task 1, Subtask 1) to download all relevant data from the ADNI and DoD-ADNI databases, and (Major Task 1, Subtask 2) to define all regions of interest (ROIs) in all subjects.

Major Task 1, Subtask 1 has been completed: data have been identified and downloaded from the ADNI and DoD-ADNI databases onto a workstation for processing and analysis.

Major Task 1, Subtask 2 is partially complete. Subject-specific PHC and dACC ROIs have been defined from the structural MRI scans for all healthy, TBI, and AD subjects using FreeSurfer software. Work is in progress for defining subject-specific CL ROIs using a modified thalamic segmentation method that allows for the thalamus to be segmented using structural MRI scans available from the ADNI and DoD-ADNI databases. Currently, one healthy subject's data are being used to set up this method. Once the pipeline is established, all subjects' data will be processed to obtain subject-specific CL ROIs.

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

Training: During Year 1, Dr. Choi has received one-on-one training with Dr. Brian Rutt (Collaborator) to enhance Dr. Choi's knowledge and skill in the modified thalamic segmentation method needed for this project.

Professional development: Dr. Choi has participated in the Research Career Accelerator Program at Stanford for individuals in the medical school who have obtained career development awards, including the present DoD award. This program fosters the development of professional skills needed to achieve research independence through monthly seminars and moderated small group discussion. Topics include how to give a job talk, setting up and managing a lab, promotion process, mentoring, K-to-R transition, and therapeutic development in academia.

How were the results disseminated to communities of interest?
Nothing to Report.

What do you plan to do during the next reporting period to accomplish the goals?
Dr. Choi plans to complete the remainder of the tasks from Year 1 (Major Task 1, Subtask 2) and complete the Year 2 tasks. Dr. Choi will continue to search for a qualified Data Analyst to assist with task completion. Dr. Choi will continue to receive scientific and professional training from Dr. Brian Rutt and her mentoring team and participate in the Research Career Accelerator Program, as well as other training and professional development opportunities as they arise.

4. Impact

What was the impact on the development of the principal discipline(s) of the project?
Nothing to Report.

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
There have not been any changes in approach.

Actual or anticipated problems or delays and actions or plans to resolve them
The major problem has been that we have not been able to hire a Data Analyst yet due to not finding anyone of sufficient qualifications for the role. In general, we have observed fewer qualified candidates than in previous years. This has lead to a delay in finishing all of Year 1's tasks. However, we expect that the remainder of these Year 1 tasks will be accomplished by available personnel (the PI) within three months in Year 2. We will continue to search for a qualified Data Analyst to assist with Year 2 and Year 3 tasks.

Changes that had a significant impact on expenditures
The budget included funds for the salary of a Data Analyst during Year 1. Since a Data Analyst has not been hired yet, those funds have not yet been used.

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

Significant changes in use or care of human subjects

N/A.

Significant changes in use or care of vertebrate animals.

N/A.

Significant changes in use of biohazards and/or select agents
N/A.

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:	Eun Young Choi
Project Role:	PI
Research Identifier (e.g. ORCID ID):	0000-0003-3226-1486
Nearest person month worked:	3
Contribution to Project:	Dr. Choi has performed all work thus far.
Funding Support:	NIH BRAIN

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to Report.

What other organizations were involved as partners?
Nothing to Report.

8. Special Reporting Requirements

N/A.

9. Appendices

None.