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TITLE: Novel Neuroimaging Assessments of Glymphatic Disruption in Humans, a Plausible Key Pathophysiological Mechanism for CNS Lupus

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14. ABSTRACT
This project develops and applies novel brain imaging to probe a new route by which SLE can lead to neuronal degradation. It adds the glymphatic system to the array of neurovascular components that plausibly underlie the pathobiology of lupus, even before overt neuro-psychiatric syndromes. We have generated a combination of neuroimaging protocols allowing regional characterization of glymphatic structural and functional integrity. A vascular space occupancy (VASO) imaging sequence is being used to measure amplitude of fluctuations in vascular volume driven by respiratory and cardiac cycles, a purported mechanism for glymphatic flow. Protocol development led to a focus on detecting the glymphatic-specific microenvironment by adopting "microdynamic" imaging methods based on relaxation-diffusion correlation spectroscopy. In this way, we aim to detect a restricted diffusion microenvironment of CSF-like fluid (e.g. glymphatics) by employing wide regimes of relaxation and diffusion. To date, we have successfully imaged 4 lupus subjects using this protocol. We are also establishing advanced analysis pipelines for these novel datasets.

15. SUBJECT TERMS
Lupus, glymphatics, vasculature, brain, relaxation-diffusion correlation, VASO, MRI, tissue microenvironment

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TABLE OF CONTENTS

	Page
1. Introduction	1
2. Keywords	1
3. Accomplishments	1-2
4. Impact	2-3
5. Changes/Problems	3-4
6. Products	4-5
7. Participants & Other Collaborating Organizations	6-8
8. Special Reporting Requirements	8
9. Appendices	8

1. INTRODUCTION:

This project applies novel brain imaging to detect and characterize the glymphatic system, a neurovascular component that may underlie mechanisms of pathology in neuropsychiatric lupus. Methods detect glymphatic flow-inducing vascular fluctuations due to respiration and cardiac cycles and the unique microenvironment of fluid-bearing glymphatic channels surrounding blood vessels. With these new measures, we are comparing lupus patients to matched healthy controls.

2. KEYWORDS:

Lupus, glymphatics, vasculature, brain, relaxation-diffusion correlation, VASO, MRI, tissue microenvironment

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Original goals for Aim 1: Develop and install three MRI approaches to characterize the glymphatic system: 1. CSF-spin labeling, 2. Ultra-high b-value DWI, 3. VASO correlated to respiration. Obtain local IRB and HRPO approval. (complete by end of November 2018)
Status of Aim 1: Development effort led to abandonment of CSF-spin labeling in favor of expanding the multiple b-value DWI approach to perform relaxation-diffusion correlation spectroscopy along dimensions of b-value, echo time (TE, for T2 relaxometry), and inversion time for T1 relaxometry. VASO was developed with respiration, cardiac, and CO2 monitoring. These are challenging approaches and they were developed and tested throughout the winter and installed in final form in May 2019. Local IRB approval was obtained in December 2018. HRPO approval was obtained mid-January 2019.
Original goals for Aim 2: Compare 16 lupus patients to 16 healthy controls using the new imaging protocol. Complete imaging acquisition by beginning of August 2019 and complete analysis by end of August 2019.
Status of Aim 2: 4 lupus patients successfully scanned. Recruitment of remaining lupus patients and matched controls ongoing. Streamlined analysis pipeline development underway.
No-Cost Extension requested May 2019 and granted June 2019 for one year.

What was accomplished under these goals?

1) major activities: development and installation of new imaging protocols for assessment of glymphatic structure and function. Compare these assessments between lupus and healthy controls.
2) objectives: Be the first to use MRI to characterize the glymphatic system in humans and to gather the first evidence that glymphatic disruption may contribute to the pathology of neuropsychiatric lupus.
3) outcomes to date: while the general imaging approach did not change, our development efforts resulted in a change in strategy to detect glymphatic-specific microstructure: relaxation-diffusion correlation spectroscopy along T1, T2, and diffusion dimensions. This approach has been described in animals, but we adopted it for humans with challenging extensions of relaxation/diffusion regimes to capture glymphatic properties. We also developed the VASO method using a short TR and with concurrent monitoring of respiratory, cardiac, and CO2 variations. Four lupus patients have been scanned to date and recruitment continues.

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

This project was not intended to provide training.
However, a University of Cincinnati medical physics graduate student, Steven Ewart, has taken an interest in the project and has been observing and participating in the development of the new imaging protocol. It is Steven's desire to take part in the analysis of the imaging data.
Several internal presentations have been given covering the objectives and strategy of the project. Most notably, these have been given to members of the Rheumatology and Radiology Departments at Cincinnati Children's Hospital.

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?

1) With the protocol installed, we are striving to maintain recruitment to achieve our goal of completing image acquisition for 16 lupus and 16 healthy control subjects. Target completion by August 2020.
2) We are working on finalizing the analysis pipeline within the next few months. (Target January 2020) This will include VASO analysis to extract both respiratory and cardiac contributions to blood vessel volume fluctuations. It will also include analysis to extract specific micro-environment properties adopted from the "MADCO" approach (e.g. Benjamini and Basser, Neuroimage (2017) 163: 183-196).

4. **IMPACT:**

What was the impact on the development of the principal discipline(s) of the project?

The imaging methods developed for this project may be the first to detect and to provide quantitative measures of a system (glymphatics) in the brain that is purported to have a role in clearing debris and maintaining immunological function. Lupus is known to degrade vasculature and may lead to neurodegeneration by disruption of the glymphatic system. Detection of this process would have a large impact on the study and treatment of lupus by providing a new route for early pathogenesis and a promising brain biomarker for early disease.

What was the impact on other disciplines?

Other neurodegenerative disorders may have a pathological pathway that includes degradation of vascular integrity and the associated glymphatic system. These include small vessel disease, Alzheimer's Disease, Parkinson's Disease, diabetes, chronic hypoxia (sleep apnea), and traumatic brain injury.

What was the impact on technology transfer?

If this pilot work leads to larger studies, the methodology could eventually enter clinical radiology practice for lupus and other neurovascular disorders.

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Though our imaging protocol development effort resulted in some changes in approach from our original proposal, these changes did not result in significant deviation from the scope or objectives of the study.

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

Inadequate recruitment rate is always a potential concern. We are engaged in weekly meetings to discuss recruitment strategy and status. If recruitment rate (particularly for the lupus group) should fall short, we have the option to consider modest adjustments to the inclusion/exclusion criteria, such as reducing the minimum SLEDAI scores required, or the age range of inclusion, for example. Our ambitious data collection and analysis plan may not produce the glymphatic-specific signature we seek. The data are nevertheless rich and offer the potential for a variety of analysis approaches.

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

Nothing to Report

Significant changes in use or care of vertebrate animals

Not Applicable

Significant changes in use of biohazards and/or select agents

Not Applicable

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. Only internal presentations.

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

Nothing to Report

- **Technologies or techniques**

Besides the new imaging protocol for MRI and potentially new analysis methods, nothing to report. Nothing shared.

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

Nothing to Report

- **Other Products**

Nothing to report yet that has been disseminated.
Potential for new imaging sequences and tissue microstructure models.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Mark DiFrancesco, PhD. PI 1.5 months
Experiment design, development of imaging protocol, image acquisition, analysis development.

Hermine Brunner, MD, 1 month
Subject recruitment, neuropsychological testing

Gregory Lee, PhD, 1 month
Development of imaging protocol

Arjun Mather, (coordinator) 2.5 months
Study coordination, IRB communications, data acquisition, ushering of subjects through neuropsychological testing and imaging.

Research Associate and Biostatistian Mekibib Altaye: < 1 month.

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

Mark DiFrancesco
New:
NIH/NIDCD R21_08012018 Vannest(PI) 9/2019 -8/2021
Multimodal Neuroimaging Distinguishes Developmental and Disordered Phenotypes in Speech Sound Disorders

Research Innovation/Pilot Funding Program, University of Cincinnati, DiFrancesco(PI) 6/1/19-5/31/20
Non-contrast Lung Perfusion Mapping Applied for New Insights in Cystic Fibrosis

Completed:
Research Innovation/Pilot Funding Program, University of Cincinnati, DiFrancesco(PI) 7/1/14 - 9/30/18, $70,000
Calibration of Resting-state fMRI to Predict Language Laterality in Children

NIH/NHLBI 1RO1HL120879-01A1 Beebe(PI) 09/01/14–06/30/18 $1,842,824
Sleep Restriction and the Adolescent Diet: Impact and Mechanisms

Neuroscience Institute Pilot Grant, University of Cincinnati, Coleman(PI) 1/2016 – 12/2018
Language Recovery in Aphasic Acute Stroke Patients
Pilot Study of Language Recovery in Acute Aphasic Stroke Patients

Change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period (Continued)

Hermine Brunner
New:
NIH/NIAMS R34 AR071651 06/01/2018-02/29/2020 1.8 calendar $300,000
Improving Pediatric Lupus Nephritis through Personalized Mycophenolate Mofetil Therapy

NIH/NIAMS R01AR073311 (Yu(Nationwide)) 04/01/2018 – 03/31/2023 0.12 months $308,162
Complement in Human Lupus: Deficiencies, Profiles and Complications

NIH/NIAMS P30 AR076316 (Brunner/Kashikar-Zuck) 09/16/19 -- 06/30/2 1.80 calendar $436,644
Pediatric musculOskeletal & RheumaTology Innovation COre center (PORTICO)

NIH/NIAMS P50 DK096418 - Pilot and Feasibility Project (Devarjan) 09/01/19-08/31/21 0.6 calendar $100,000
Lupus Nephritis Biomarkers for The Advancement of Therapies for Lupus

Completed:
NIH/NIAMS U01AR067166 (Brunner) 09/15/2014-08/31/2018 2.04 calendar $698,213
Optimization of Outcome Measures For Clinical Trials in Children with Lupus

ME-1408-19894 (Huang) 09/01/2015-08/31/2018 0.60 calendar
PCORI Patient-Center Outcomes Research Institute $999,998
"Patient Centered Adaptive Treatment Strategies (PCATS) using Bayesian Causal Inference"

Gregory Lee
New:
NIH/NCCIH R01AT009982-01 (Powers/Coghill)09/01/18 – 8/31/23 0.6 months $499,999: Dissecting Neural Mechanisms Supporting Mind and Body Approaches to Pain Reduction in Youth with Migraine

Mekibib Altaye
New:
NIH/NCATS 1UL1TR001425 Heubi (PI) 08/14/2015 – extended to 03/31/2020
Center for Clinical and Translational Science and Training

NIH R21 HD094085-01 He (PI) 08/01/2018 – 07/31/2020
Early Prediction of Cognitive Deficits in Very Preterm Infants using Machine Learning and Brain Connectome

NIH/NICHD R01 HD093754-01A1 Esbensen (PI) 07/01/2018 – 06/30/2023
Cognitive Outcome Measures in School Age Children with Down Syndrome

Completed:
NIH 90IF0122-01-00 Meinzen-Derr (PI) 09/30/2016 – 09/29/2019
Improving Outcomes Using Aided Augmentative and Alternative Communication for Children who are Deaf or Hard of Hearing

What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Not applicable

QUAD CHARTS: Not applicable

9. APPENDICES: none