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

PRINCIPAL INVESTIGATOR: Mark DiFrancesco, PhD

CONTRACTING ORGANIZATION: Children's Hospital Medical Center, Cincinnati, OH

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Mark DiFrancesco, PhD & Hermine Brunner, MD

E-Mail: mark.difrancesco@cchmc.org & Hermine.brunner@cchmc.org

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Children's Hospital Medical Center
3333 Burnet Ave
Cincinnati, OH 45229-3026

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12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

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. We have successfully imaged the target 16 lupus subjects and 16 controls using this protocol. We are undertaking 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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Unclassified	Unclassified	Unclassified	Unclassified	9	19b. TELEPHONE NUMBER *(include area code)*

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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 2018-2019 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: As of September 2019, 4 lupus patients successfully scanned. Streamlined analysis pipeline development underway.
No-Cost Extension requested May 2019 and granted June 2019 for one year: September 1, 2019 to August 31, 2020.
October 2019-January 2020: recruitment efforts continued, with modifications for PedANAM cognitive test requirements, and expanded advertisement materials.
January 2020-February 2020: 3 more lupus patients enrolled and imaged.
March 2020: COVID-19 shutdown of research MRI.
No-Cost Extension requested July 2020 and granted August 2020 for one year: September 1, 2020 to August 31, 2021.
September 2020: partial resumption of research MRI activities.
September 2020 – August 2021: total of 9 lupus and 9 controls scanned.
No-Cost Extension requested July 2021 and granted August 2021 for one year: September 1, 2021 to August 31, 2022.
Target enrollment was achieved (16 lupus, 16 controls)during the last reporting period. Analyses are ongoing as of the date of this report.

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.
The targeted 16 lupus patients and 16 healthy controls have been scanned. Data for diffusion-relaxation correlation, VASO, and multi-echo resting-state fMRI (secondary aim) are undergoing preprocessing and analysis. Preliminary results of VASO processing may be suitable for abstract submission in January 2023 to Organization for Human Brain Mapping or to the EULAR Conference. Otherwise, we will target abstract submissions for the ACR in June.

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

This project was not intended to provide training.
A University of Cincinnati medical physics graduate student, Steven Ewart, took an interest in the project during its early stages. COVID-19 interrupted Steven's participation and he has since not resumed contact with the research team.
Several internal presentations continue to be 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?

Nothing to report, as this is the final technical report. Analyses are ongoing. Manuscripts anticipated starting in March/April 2023.

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

Our ambitious data collection and analysis protocol may not produce the glymphatic-specific signature we seek. The limited analyses to date suggest we may be detecting a confined CSF-like component in the microstructure, but more complete analyses are still necessary. 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

Nothing to Report

Significant changes in use of biohazards and/or select agents

Nothing to Report

6. PRODUCTS:

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

Journal publications.

Nothing to Report for this period. Anticipated manuscript submissions by March/April 2023.

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

Nothing to Report

Other publications, conference papers and presentations.

Internal institutional presentations.
Preliminary results of VASO processing may be suitable for abstract submission in January 2023 to Organization for Human Brain Mapping or to the EULAR Conference. Otherwise, we will target abstract submissions for the ACR in June.

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

Nothing to Report

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- **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?

For the past year with more than 1 person month:

Name: Mark DiFrancesco, PhD.
Project Role: PI
Researcher ID (ORCID): 0000-0001-8002-0332
Person months: 1.5
Contribution: Experiment design, development of imaging protocol, image acquisition, analysis development and execution.

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

1R01NS125316-01 (Shah/DiFrancesco)	**02/01/2022 – 01/31/2027**	**2.4 calendar**
R01DC019337 (Washington)	**09/15/2021 - 07/01/2025**	**1.8 calendar**
DoD W81XWH2210633 (DiFrancesco)	**07/15/2022-07/14/2025**	**1.8 calendar**

Completed

Nothing to report

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