AWARD NUMBER: W81XWH-22-2-0038

TITLE: In Vivo Imaging of Glymphatic Circulation: Measurement of Brain Interstitial Fluid Flow During Wake and Sleep with Ultra-High Performance MRI

PRINCIPAL INVESTIGATOR: Dr. Luca Marinelli

CONTRACTING ORGANIZATION: General Electric Global Research

REPORT DATE: SEPTEMBER 2023

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
SEPTEMBER 2023	ANNUAL	15AUG2022 - 14AUG2023

4. TITLE AND SUBTITLE

In Vivo Imaging of Glymphatic Circulation: Measurement of Brain Interstitial Fluid Flow During Wake and Sleep with Ultra-High Performance MRI

5a. CONTRACT NUMBER
W81XWH- 22-2-0038

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Luca Marinelli, PhD; J. Kent Werner, Jr., MD, PhD

E-Mail:

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

General Electric Global Research

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT:

The demands of the military operational environment impose chronic insufficient or nonrestorative sleep for the warfighter, resulting in decreased vigilance and fatigue during daytime that can pose safety risks and threaten mission success. Studies estimate that, on average, over 70% of active-duty warfighters sleep less than six hours per night, and even fewer while deployed. Recent studies have shown the association between clearance of metabolic waste from the brain via the glymphatic system and sleep. While the underlying mechanisms are not yet fully understood, it is demonstrated that sleep deprivation impairs molecular clearance and that glymphatic exchange was specifically active during deep sleep. Currently, MRI is the most promising tool for imaging noninvasively and quantitatively glymphatic flow in vivo in humans. Previous mechanisms have been invasive, or unable to reach the velocity resolution to map slow-moving CSF-ISF glymphatic exchange (estimated at ~20 m/s). The Microstructure Anatomy Gradient for Neuroimaging with Ultrafast Scanning (MAGNUS) Magnetic resonance imaging (MRI) system addresses these limitations and is located at Walter Reed National Military Medical Center. This project aims to leverage this system to implement a MRI pulse sequence that detects glymphatic activity and measure this activity in warfighters and sleepy watch standers/shift workers.

15. SUBJECT TERMS

NONE LISTED

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRDC
U	U	U	UU	20	**19b. TELEPHONE NUMBER** *(include area code)*

TABLE OF CONTENTS

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

The demands of the military operational environment impose chronic insufficient or nonrestorative sleep for the warfighter, resulting in decreased vigilance and fatigue during daytime that can pose safety risks and threaten mission success. Studies estimate that, on average, over 70% of active-duty warfighters sleep less than six hours per night, and even fewer while deployed. Recent studies have shown the association between clearance of metabolic waste from the brain via the glymphatic system and sleep. While the underlying mechanisms are not yet fully understood, it is demonstrated that sleep deprivation impairs molecular clearance and that glymphatic exchange was specifically active during deep sleep. Currently, MRI is the most promising tool for imaging noninvasively and quantitatively glymphatic flow in vivo in humans. Previous mechanisms have been invasive, or unable to reach the velocity resolution to map slow-moving CSF-ISF glymphatic exchange (estimated at ~20 m/s). The Microstructure Anatomy Gradient for Neuroimaging with Ultrafast Scanning (MAGNUS) Magnetic resonance imaging (MRI) system addresses these limitations and is located at Walter Reed National Military Medical Center. This project aims to leverage this system to implement a MRI pulse sequence that detects glymphatic activity and measure this activity in warfighters and sleepy watch standers/shift workers.

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

Glymphatic activity; sleep; MRI; MAGNUS

3. **ACCOMPLISHMENTS:** *The 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.*

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Please see the attached timeline.

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.

The following activities have been completed by the GE team under Aim 1:

1. Sequence modifications were completed to allow separate optimization of b-value and VENC.
2. Phase-sensitive reconstruction improvements completed.
3. Protocol optimization with multishell diffusion sequence is in progress and will be tested on volunteers after human subject research approval.
4. Post-processing pipeline for MBME fMRI with multi-echo processing and physiological data regression was created.
5. Automated interleaved SCIMI and MBME fMRI sequence completed.
6. Prototype sequences tested on MAGNUS and modifications to run on latest version of system software (DV29) were made.
7. Tradeoff analysis between acoustic noise and imaging performance was completed.
8. Acoustic noise optimization of the pulse sequences is in progress. We have developed a new hardware solution with an acoustic dampening layer to reduce sound pressure levels of all sequences. We are evaluating imaging protocols based on a silent fMRI sequence (looping star fMRI), which would enable completely silent functional MRI during sleep.

Pipeline Updates & Improvements

Major additions to the Simultaneous Coherent/Incoherent Motion Imaging (SCIMI) pipeline are marked above with the green background. Beginning from the raw MR data, we have implemented complex scan archive reconstruction with Homodyne recon enabled. The addition of Homodyne recon allows the scan to be acquired in less time, reducing TE by around 30ms (FOV dependent), and boosting SNR across the board. The scan archive recon outputs real, imaginary, and magnitude images.

Magnitude:

An entire section of the pipeline (left) was added based on processing the magnitude data. First, each volume is registered to the first, to correct for potential patient motion. Similarly, each volume has the eddy current distortion correction calculated and applied. The transformations for each of these steps is combined to create a forward map for each volume, the use of which will be discussed below.

With each volume now in the same registered space, a mask is created via skull-stripping. This masking step replaces an algorithm in the previous pipeline, where magnitude data was used to create an approximate mask based on intensity. These masks are more accurate in removing the skull, csf, and ventricles from the processing.

Lastly, the magnitude data is passed through GNC (Gradient Nonlinearity Correction—specific to MAGNUS) to determine the spatially-dependent warping of q-vectors, generating maps for each voxel in every volume.

Complex Images:

The initial processing steps of the pipeline focus on "slice-wise" correction operations that must happen before volume registration. The forward maps are modified from an "ideal" registration process. Due to the differences in slice timing and the synchronization of the reconstruction with the cardiac cycle, there can be no inter-slice interpolation: each voxel must come from one and only one slice. With a forward map, this is achieved by rounding the z-axis of the map to the nearest integer.

The mask is then "deregistered" for each volume by using the forward map to reverse the interpolation. This allows for noisy voxels that disrupt the unwrapping and background phase correction algorithm to be removed, while preserving the ability to run those algorithms.

We used a phantom to study the effects of background phase correction, to verify the effect of different orders of fit. It was obvious that some amount of fit was required given the difference in results using a 0^{th}, 1^{st}, and 2^{nd} order correction, but the pipeline previously assumed the needed order. Using an agar phantom where no motion was expected, we found that a 3^{rd}-order fit yielded the best results.

Once the phase was unwrapped and the background phase removed, the volumes were each registered to the common space (first volume) using the forward map. The original slice of each voxel was tracked for timing and cardiac binning purposes.

Cardiac Gating:

A small change was made to the peak finding algorithm used ahead of CAPTOR that takes in an additional "trigger" file along with the cardiac trace. These triggers are generated by the scanner for use in prospective gating algorithms, and is a significantly more reliable method of determining the R-R intervals that CAPTOR takes as input.

Velocity Fit:

The final q-space linear fit is now done voxel-wise instead of slice-wise. This is to account for a.) each voxel having a unique set of q-space vectors according to the output of GNC and b.) each voxel having a unique set of cardiac bins determined by the original slice before registration. After looping through all voxels contained in the mask, the final velocities are saved as NIfTI files.

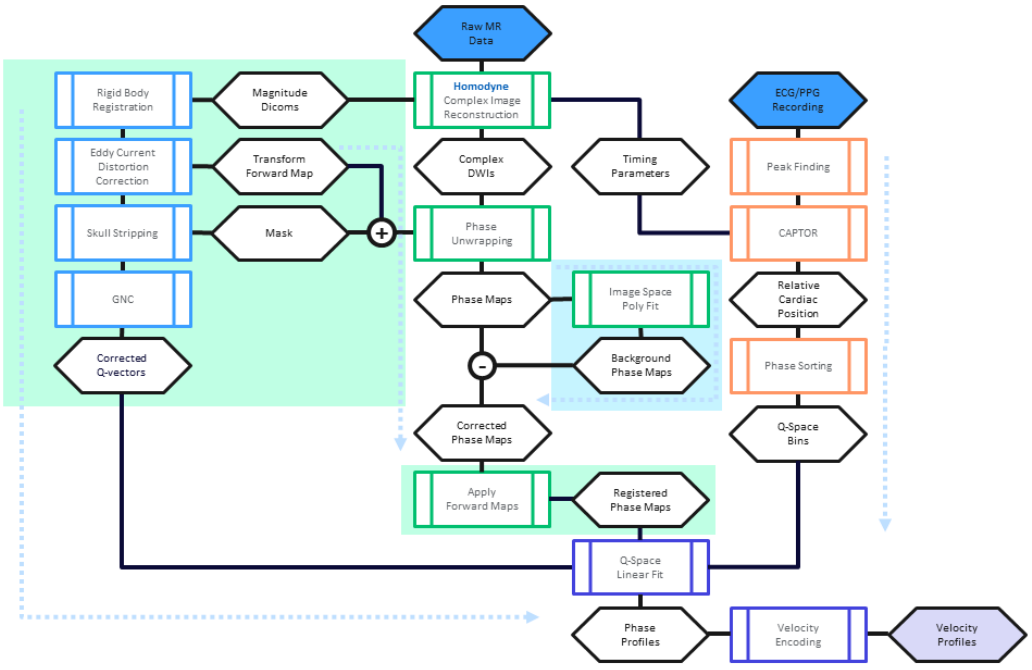


Figure 1 SCIMI image reconstruction pipeline. Green blocks represent significant improvements implemented over the past year.

Acoustic Noise Minimization for the Simultaneous Coherent and Incoherent Motion Imaging (SCIMI) Method

A common patient complaint of MR imaging is the acoustic discomfort during scanning. Acoustic noise is a result of intensive gradient switching and associated mechanical vibrations. The faster the imaging gradients and higher the field strength, the louder the acoustic noise. Noise intensity depends on many factors, including the gradient strength and slew rate, and easily exceeds 100 dB for a 3T scanners coming close to human auditory pain levels (120–130 dB).

Recent interest to simultaneously understand the waste removal processes and the microstructures of the gray/white matter has led to the customization of the well-known Stejskal-Tanner diffusion imaging method for incoherent and coherent flow measurements in the brain parenchyma using the magnitude and phase information respectively. To simultaneously maximize the signal to noise ratio of the measurements while minimizing the acoustic signatures of the scan requires a non-trivial optimization of the pulse sequence gradient timing and waveform parameters. A summary of the current state of the acoustic optimization work done so far is presented here for the MAGNUS-1 system that is equipped with a maximum gradient strength and slew rate of 200 mT/m and 500 T/m/s respectively. Methods explored for the acoustic noise minimization include passive acoustic treatment of the space between the gradient and RF body-coil former and readout waveform stretching. We developed and tested the effectiveness of a physical acoustic dampening layer between the MAGNUS gradient coil and the radiofrequency coil. We also optimized the pulse sequence timing to ensure major spectral peaks are removed from resonances of the mechanical structure. An acoustic noise simulator that utilizes the acoustic response function of the MAGNUS-1 gradient with and without the acoustic treatment was used to obtain the equivalent continuous sound pressure level (LAeq) for any given pulse sequence waveform.

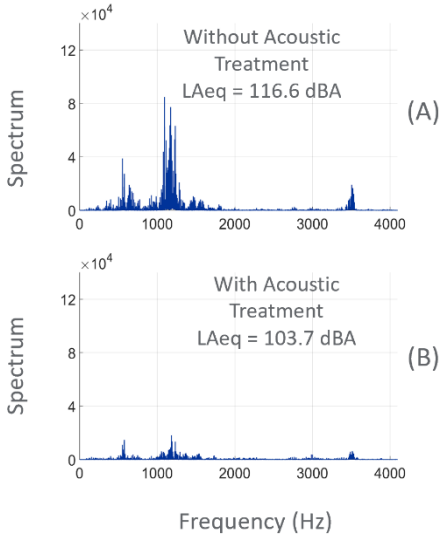
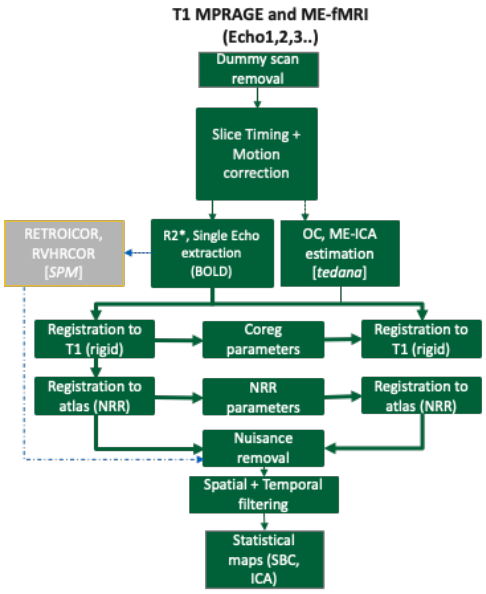


Figure 2 The insertion of an acoustic dampening material between the gradient and RF body coil yielded a significant reduction (~12%) in the acoustic signature of the SCIMI pulse sequence. The acoustic spectrum with (A) and without (B) the acoustic treatment shows the dampening of the high and low-frequency peaks due to the insertion of the acoustic material. The high frequency peaks are due to the readout gradients waveform in the SCIMI pulse sequence and the lower frequency peaks are because of the other gradients in the pulse sequence.

Multi-echo functional MRI image processing pipeline

To be meaningful at the individual level, functional connectivity measurements need to exhibit high repeatability. However reliable brain functional connectivity measurements require the collection of large amounts of data. Further, changes in physiology—modulated concomitantly in response to neuronal activity—elicit fluctuations in fMRI time series, and manifest as artifactual correlations between brain regions, obscuring detection of brain activation using BOLD fMRI. ME-fMRI reduces physiological noise and has been reported to enable rapid and reliable mapping of functional brain networks. Simply, ME-fMRI models multiple images over different echo-times (over the same scan time) to provide reduced sensitivity to blood inflow, resulting in better representation of functional or neuronal activation, in contrast to conventional single echo (SE)-fMRI techniques. Prior work demonstrates that ME- fMRI is up to three-fold more efficient than SE-fMRI in separating non-BOLD effects from the fMRI signal, resulting in increased brain-wide test-retest reliability.

We have completed implementation of an end-to-end multi-echo, multi-band fMRI pipeline in a self-contained, distributable package that includes integration with SPM-based physiological waveform regression (cardiac and respiratory). The output maps generated include single echo (from the second echo), R2*, optimal combination (weighted combination with peak on the second echo), and multi-echo independent component analysis (ME-ICA).



Outputs: R2, OC, ME-ICA, Single Echo (w. physiologic regression)*

R2* and M_0 Estimation:

Single-compartment mono-exponential MR signal model

$$s(TE_i) = s_i \approx S_0 \exp(-R_2^* \times TE_i)$$

TE_i = i^{th} echo-time
S_0 = initial magnetization
R_2^* = transverse relaxation rate

Least squares fit for R2* and S0

OC + ME-ICA denoised estimation:

Voxel-wise weights for the OC time series are given by

$$w_{i,v} = TE_i \cdot e^{-TE_i / \widehat{T_2^*}}$$

where i = 1..3 refers to echo, v refers to voxel and T2* corresponds to voxel-wise estimates of T2* obtained via a log-linear firs to the multi-echo dataset.
Run spatial ICA on OC image and identify non-BOLD and BOLD components by estimating their TE-dependence
Reconstruct image by removing the non-BOLD components

Compare single echo to R2*, OC, ME-ICA maps

Silent functional MRI: implementation of Looping Star pulse sequence on MAGNUS

Looping star is a novel acoustically silent, 3D radial, multi-gradient echo MR imaging pulse sequence. The method is based on 3D radial Rotating Ultra-Fast Imaging Sequence (RUFIS) extended by a time multiplexed gradient refocusing mechanism; providing an initial free-induction decay (FID) image followed by equidistant gradient echo (GRE) images. The time multiplexed scheme allows for additional T2* weighting and susceptibility to be captured.

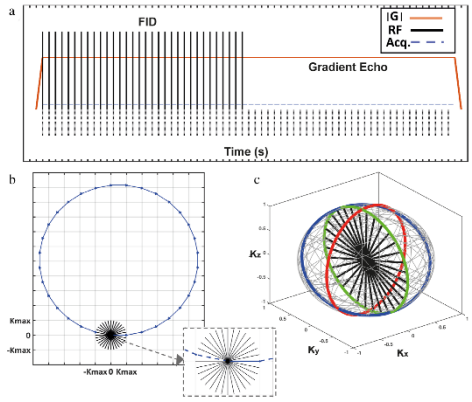


Figure 3 Pulse sequence diagram for looping star.

Figure 3 reflects the simplified pulse sequence for looping star and its circular k-space traversal for looping star and its radial encoding. (a) a constant readout gradient (solid red) is applied with minor directional gradient updates in between repetitions. Minimal gradient switching in the form of small directional readout updates is what results in the silent features of this imaging sequence. The directional updates are through ultra-short (8 us) RF pulse excitation (black) with low flip angles (typically < 5°) such that the excitation bandwidth encompasses the full imaging bandwidth. (b) Highlights the self-refocusing trajectory of the first excitation. Here a single segment of spokes (as in insert a) is arranged in a 2D circle with constant phase increments, where after X repetitions each spoke is refused to form a gradient echo. (c) Via rotation of 2D planes along Z-axis, full 3D k-space coverage can be obtained. Though the spokes are represented as straight in this image, in reality they are slightly smoothed to allow for additional acoustic comfort. Image encoding happens in a 3D radial manner and starts immediately after RF excitation (TE=0 ms).

Looping star allows for whole-brain coverage and BOLD sensitivity at just a few dB above ambient noise. The utility of the sequence was previously demonstrated in block design, event-related paradigms. Currently GEHC and GE-research are working on extending the implementation to a silent multi-echo resting state fMRI. Multi-echo fMRI allows for the increase in contrast-to-noise ratios, reduction in thermal noise and reduction in signal drop-out, demonstrating increased sensitivity and reliability of functional networks. Silent fMRI has a multitude of advantages, ranging from the ability to conduct sleep studies and evaluate the impact on neuro-correlates of sleep dysregulation, auditory-sensory studies, with neurological disorders such as schizophrenia and the ability to provide a more immersive experience by combining sound with visual stimuli in the MR environment.

We have implemented the looping star sequence on MAGNUS and demonstrated its silent imaging capability. Currently, we are comparing image quality with varying acceleration factors to understand the trade-off between repetition time and acceleration factor vs artifact power in images and spectral features. We expect to adopt looping star in the sleep study due to its extremely attractive acoustic performance compared to conventional EPI fMRI.

Hyperband Echo Planar Imaging image quality improvement

To enable hyperband (also known as multiband or simultaneous multislice excitation), acceleration of the EPI pulse sequences (both gradient echo (EPI) and spin echo (EPI2)) that will be used to acquire whole brain volumes with a repetition rate sufficient to extract BOLD spectral features characteristic of sleep stages, we determined that the current implementation of Multiband EPI suffered from artifacts that needed to be addressed.

EPI/EPI2 PSD enhancement

Inaccurate alignment of data acquisition window with the readout window of the pulse sequence, resulted in shifts in k-space data and inaccuracies in reconstruction. This was due to imperfect calculation of the CAIPI shifts needed for the aliased data and was subsequently fixes on the host computer. A new pulse sequence was compiled and tested on phantoms to confirm removal of aliasing artifact.

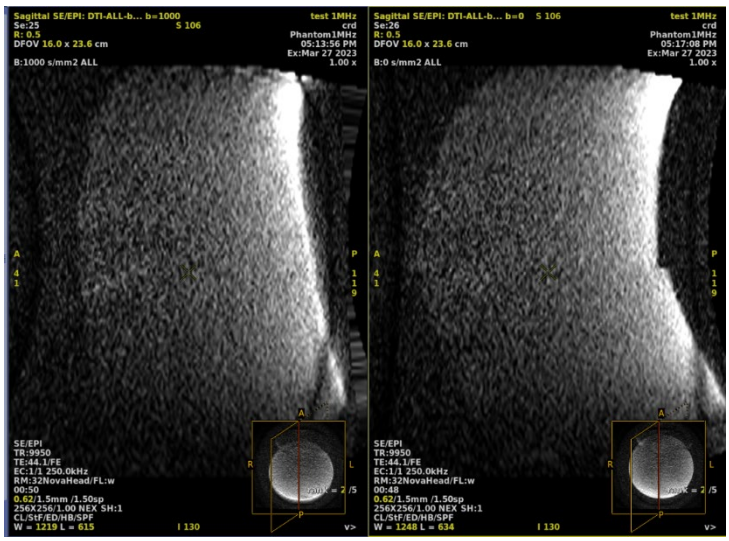


Figure 4 Left: Phantom image acquired with prototype Maxwell term correction Right: Image acquired without maxwell term correction. Notice the step artifact, which results in incorrectly unaliased images. R=2x1, 122 slices, FOV=16 cm, resolution=0.6x0.6x1.5 mm^3.

Maxwell correction

Maxwell correction is applied in the EPI / EPI2 pulse sequences by adding additional phase modulation during the receive portion of each echo. The Maxwell phase calculation routine is called in the base pulse sequence where the delta phase correction applied to each successive echo is equal to z^2 * ((gx^2 * pw_gx) + (gy*2 * pw_gy)) * (2 * pi * gamma) / (2 * B0_field). The calculation of the phase correction depends on the distance of the slice from gradient coil isocenter. For hyperband the pulse sequence only knows about the slice position for slices in the central slab. All other slices come from the RF modulation. Therefore, in this case for multiband acquisitions information from n-aliased slices was not accurately passed into the firmware packet, and only information from the central slice was used resulting in an inaccurate linear phase ramp or image shift in the phase encode direction. A mitigation approach was to turn off real time phase modulation and instead to pass the coefficients into the reconstruction engine.

The following activities have been completed under Aim 2:

7. The IRB protocol has been drafted.
8. The Geneva Foundation/USUHS personnel hired (Research Coordinator and Post-Doctoral Fellow).
9. Necessary supplies have been identified.
10. Recruiting systems have been established, including clinic and table recruiting pathways.
11. Weekly meetings for collaboration occurred.
12. Outreach to potential recruiting clinics and those needed for conducting the protocol was completed.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

July 11th, 2023: MRI Safety Training was conducted at USUHS/WRNMMC.

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.

Werner, J. K. Uniformed Services University Glymphatics Team. Oral presentation at the annual Military Health System Research Symposium MTEC Glymphatic Talk, Kissimmee, FL.

Werner, J. K., Metzger, E., Coon, W., Marinelli, L., Simons, S., Schelp, S., Amyot, F. (2023, August). Applying Non-Invasive Technology to Measure and Modulate Sleep Physiology in U.S. Warfighters. Poster presentation at the annual Military Health System Research Symposium MTEC Spotlight, Kissimmee, FL.

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.

1. Submit and receive IRB and HRPO approval.
2. Secure all identified supplies.
3. Deploy imaging sequences at USU/WRNMMC sites.
4. Optimize the acoustic noise in healthy controls and 3-hour sleep window achieved in 4 out of 5 volunteers.
5. Analyze the data from the 4-5 volunteers and perform slow-flow measurements using SCIMI during sleep characterized.
6. Make improvements to the system prior to conducting the sleep study in a population of healthy warfighters and sleepy watch standers/shift workers.
7. Recruit 35 participants and conduct scan sequence in the population.

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).

We have developed a protocol that will identify novel physiological signals associated with sleep, as well as validate the significance of previously reported signals.

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.

This approach will extend into every other neurological discipline, as these signatures may carry weight when examining neurological disorders, from brain trauma to dementia.

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.*

MAGNUS as an advanced brain imaging platform originally funded by CDMRP has been distributed to additional sites through NIH instrumentation grants (currently 4 installations with 2 more under development) and is rapidly becoming a powerful neuroimaging discovery and collaboration tool. The development of applications such as the sequences and image reconstruction techniques funded under this grant will greatly enhance the capabilities of academic teams and the pace of scientific discovery.

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.*

Impact of novel biomarkers related to sleep and its relationship to neurological disorders will alleviate suffering as they will facilitate mechanistic investigations and therapeutic development.

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.

Nothing to report.

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.

IRB processes at military sites can be a timely process, originating in completing a lengthy application and associated documents. It is also imperative that the experts in the respective fields agree to the details in approach. Taken together, the IRB draft has been delayed. It will be submitted in the next month to avoid any further delay.

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.

There was not any significant impact on expenditures.

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 IRB protocol is currently nearing submission at this time.

Significant changes in use or care of vertebrate animals

Not applicable to this project.

Significant changes in use of biohazards and/or select agents

Not applicable to this project.

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).*

  Not applicable at this time.

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).*

Not applicable at this time.

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.*

Werner, J. K. Uniformed Services University Glymphatics Team. Oral presentation at the annual Military Health System Research Symposium MTEC Glymphatic Talk, Kissimmee, FL.

Werner, J. K., Metzger, E., Coon, W., Marinelli, L., Simons, S., Schelp, S., Amyot, F. (2023, August). Applying Non-Invasive Technology to Measure and Modulate Sleep Physiology in U.S. Warfighters. Poster presentation at the annual Military Health System Research Symposium MTEC Spotlight, Kissimmee, FL.

- **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.

Not applicable at this time.

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

Not applicable at this time.

- **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.

N/A

- **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.*

N/A

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". 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.

Name:	*Dr. John Kent Werner*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	*0000-0001-9858-2931*
Nearest person month worked:	*.6*
Contribution to Project:	*Dr. Werner has attended project team meetings, advocated for study support at meetings w/ colleagues; wrote and edited study protocol; maintained communication with IRB.*
Funding Support:	*Federal Government*
Name:	*Sonja Skeete*
Project Role:	*Site Program Manager*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-5252-8419*
Nearest person month worked:	*3*
Contribution to Project:	*Ms. Skeete has provided continued program oversight, assisted with executing study start-up activities, attended team meetings, wrote/submitted required program reports, and served as a liaison with the USUHS/WRNMMC site, Geneva and Teledyne collaborators.*
Name:	*Samrawit Yalewayker*
Project Role:	*Study Coordinator*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*6*
Contribution to Project:	*Ms. Yalewayker drafted the study protocol and coordinated amongst the team members, focusing on tasks for successful study start-up.*
Name:	*Dr. James DeMarco*
Project Role:	*AI*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*.6*
Contribution to Project:	*Dr. DeMarco has attended project team meetings, advocated for study support at meetings w/ colleagues; wrote and edited study protocol; maintained communication with IRB.*
Funding Support:	*Federal Government*

Name:	*Dr. Luca Marinelli*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	*0000-0001-7775-5952*
Nearest person month worked:	*3.0*
Contribution to Project:	*Dr. Marinelli has led all technical activities for aim 1; provided scientific direction and guidance to the GE team; attended project team meetings; advocated for study support at meetings w/ colleagues; wrote and edited study protocol; maintained communication with IRB.*
Funding Support:	*General Electric*
Name:	*Dr. Nastaren Abad*
Project Role:	*AI*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-7020-0492*
Nearest person month worked:	*1.5*
Contribution to Project:	*Dr. Abad was responsible for development of functional MRI image processing pipelines; implementation and testing of looping star sequence on MAGNUS; multiband EPI enhancements; attended project team meetings.*
Funding Support:	*General Electric*
Name:	*Dr. Afis Ajala*
Project Role:	*AI*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-7020-0492*
Nearest person month worked:	*4.5*
Contribution to Project:	*Dr. Ajala was responsible for acoustic studies and mitigation strategies; optimization of SCIMI pulse sequence; implementation of independent b-value/VENC settings; attended project team meetings.*
Funding Support:	*General Electric*
Name:	*Isabelle Jansen*
Project Role:	*AI*
Researcher Identifier (e.g. ORCID ID):	*0000-0004-6490-4882*
Nearest person month worked:	*5.2*
Contribution to Project:	*Ms. Jansen was responsible for development of SCIMI image processing pipeline; optimization of SCIMI pulse sequence; attended project team meetings.*
Funding Support:	*General Electric*

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.*

N/A

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *N/A*

QUAD CHARTS: *N/A*

9. APPENDICES: *N/A*