Disruption Opportunity
DARPA-PA-23-03-02
Rapid Eye Movement Restoration and Enhancement for Sleep-deprived Trauma-adaptation (REM REST)

I. Opportunity Description

The Defense Advanced Research Projects Agency (DARPA) Defense Sciences Office (DSO) is issuing a Disruption Opportunity (DO), inviting submissions of innovative basic or applied research concepts in the technical domain of neuromodulation as a means of enhancing Rapid Eye Movement (REM) sleep mechanisms associated with stress adaption and traumatic memory consolidation. This DO is issued under the Program Announcement for Disruptioneering, DARPA-PA-23-03. All awards will be made in the form of an Other Transaction (OT) for prototype project. The total award value for the combined Phase 1 base (Feasibility Study) and Phase 2 option (Proof of Concept) is limited to $1,000,000. This total award value includes Government funding and performer cost share if required or proposed.

To view the original DARPA Program Announcement (PA) for Disruptioneering, visit SAM.gov under solicitation number DARPA-PA-23-03:
https://sam.gov/opp/7b5569bc369f408392e9c5306a928c28/view.

A. Introduction

Disrupted sleep is a major cause of poor physical, mental, and emotional health and performance. As such, good sleep is essential to military service members’ ability to perform optimally. Reduced sleep time by even 1 hour per night over three days results in impaired performance\(^1\) and over longer periods, leads to substantially poorer performance and multiple long-term negative health outcomes ranging from increased metabolic disease rates to behavioral health disorders.\(^2\) Healthy sleep has been identified as critical to emotional well-being and emotional recovery following stressful and traumatic experiences. Among military service members in particular, research indicates that disrupted sleep prior to deployment predicts a nearly 5-times increase in the likelihood of post-deployment PTSD or other behavioral health disorders.\(^3\)

Sleep restores physical, mental, and emotional health via multiple mechanisms occurring across the different stages of sleep. Sleep progresses through a series of stages, including non-rapid eye movement (NREM) and rapid eye movement (REM) sleep, each with associated neural mechanisms that support health. To improve overall sleep, solutions are needed to effectively enhance the restorative mechanisms associated with both NREM and REM stages. The emergence of automated sleep staging and non-invasive brain stimulation capable of reaching the deep brain structures associated with those stages now makes closed-loop neural stimulation based on sleep stage to target and enhance both NREM and REM mechanisms more feasible; however, approaches to enhancing REM sleep are lacking.


\(^3\) https://media.defense.gov/2023/Mar/20/2003182278/-1/-1/WRAIR%20SLEEP%20DISPATCH%202020.PDF
Non-invasive brain stimulation, such as electrical and auditory stimulation, have demonstrated effectiveness in improving the efficiency and power of NREM mechanisms.\textsuperscript{4} Improving NREM mechanisms has been shown to effectively enhance performance and health outcomes such as memory, immune system functioning, and subjective sleep quality.\textsuperscript{4,6,7} Current state-of-the-art neural stimulation devices and protocols enhance NREM. Examples include open and closed-loop Transcranial electrical stimulation (TES), transcranial magnetic stimulation (TMS), and acoustic stimulation, which have all proven capable of improving sleep outcomes.\textsuperscript{4,5,6,7}

Relatively fewer approaches have been developed to enhance REM sleep.\textsuperscript{4} REM sleep is now widely understood to play an essential role in emotional well-being and resilience, supporting healthy adaptation to stress and trauma. During REM sleep, brain regions strongly associated with emotion regulation and processing are active, including the anterior cingulate cortex (ACC), retrosplenial cortex (RSC), hippocampus, and amygdala. Theta activity during REM sleep is understood to support emotion processing, possibly through the integration and consolidation of emotion memories between limbic structures and the neocortex.\textsuperscript{8} Conversely, disrupted REM, possibly driven by locus coeruleus activity, is associated with post-traumatic stress disorder (PTSD) and impaired emotional memory consolidation.\textsuperscript{9,10} Therefore, novel solutions to restoring and enhancing the mechanisms by which REM sleep promotes stress and trauma adaptation could provide important breakthroughs for treating sleep disturbances, improving overall sleep quality, and preventing PTSD and other behavioral health outcomes, such as suicide, associated with disrupted REM sleep.

\textbf{B. Objective/Technical Scope}

REM REST aims to identify neural mechanisms and demonstrate the ability to modulate REM sleep that improves stress adaptation and traumatic memory consolidation. Although demonstrations will not be required to show clinical efficacy, performer objectives should demonstrate the ability to improve REM sleep metrics associated with improved health or performance outcomes. Target neural mechanisms by which REM sleep supports healthy outcomes must be described and justified in proposals. The proposed targeted mechanisms of REM sleep must be objectively measurable, and proposers should provide a plan to evaluate the mechanistic relationship with stress adaptation, traumatic memory consolidation, and/or other related emotional health and psychological resilience outcomes.

\textsuperscript{5} Fröhlich F, Lustenberger C. Neurmodulation of sleep rhythms in schizophrenia: Towards the rational design of non-invasive brain stimulation. Schizophrenia research. 2020 Jul 1;221:71-80.
\textsuperscript{7} Grimaldi D, Papalambros NA, Zee PC, Malkani RG. Neurostimulation techniques to enhance sleep and improve cognition in aging. Neurobiology of disease. 2020 Jul 1;141:104865.
\textsuperscript{8} Rho YA, Sherfey J, Vijayan S. Emotional Memory Processing during REM Sleep with Implications for Post-Traumatic Stress Disorder. Journal of Neuroscience. 2023 Jan 18;43(3):433-46.
Performers must use established neuromodulation technologies that do not require extensive safety testing prior to human studies. Although DARPA is seeking emerging technologies, performers must be able to conduct proof-of-concept human subject trials within the 21-month time frame of this Disruption Opportunity and will need to articulate a feasible research plan to accomplish the requisite human subjects testing. The novel applications of existing neuromodulation technologies to target REM sleep and demonstrate ability to measure and enhance neural mechanisms of stress and trauma adaption are of particular interest. Furthermore, although innovative open-loop approaches are within scope, performers are encouraged to develop closed-loop systems for personalized enhancement of REM while sleeping.

C. Structure

Phase 1 may include human subject demonstrations, but human subjects research is not required in Phase 1. Phase 1 includes specification of REM mechanisms as well as the development of neuromodulation technology and protocols to enhance the mechanism(s). Performer approaches will be evaluated on the ability to identify and measure (i.e., validate) REM sleep mechanisms and model the mechanistic relationship to improved health or performance outcomes, including modeling the effect of the proposed neuromodulation technique.

In Phase 2, selected performers will use the models and techniques developed in Phase 1 to conduct or continue proof-of-concept human studies to demonstrate the ability to improve health or performance outcomes by enhancing REM sleep. Proposals will be evaluated on the mechanistic specificity of the approach and the quantifiability of outcome measures to demonstrate the most significant enhancement of warfighter health or performance.

Proposals submitted to DARPA-PA-23-03-02 in response to the technical area of this DO must be UNCLASSIFIED and must address two independent and sequential project phases (a Phase 1 Feasibility Study (base) and a Phase 2 Proof of Concept (option)). The periods of performance for these phases are nine months for the Phase 1 base effort and 12 months for the Phase 2 option effort. Combined Phase 1 base and Phase 2 option efforts for this DO should not exceed 21 months. The total award value for the combined Phase 1 and Phase 2 is limited to $1,000,000. This total award value includes Government funding and performer cost share, if required or if proposed.

D. Schedule/Milestones

Proposers must address the following fixed payable milestones in their proposals. Proposers must complete the “Schedule of Milestones and Payments” Excel Attachment provided with this DO to submit a complete proposal and fulfill the requirements under Volume 2, Price Volume. If selected for award negotiation, the fixed payable milestones provided will be directly incorporated into Attachment 3 of the OT agreement (“Schedule of Milestones and Payments”). Proposers must use the Task Description Document template provided with the Program Announcement DARPA-PA-23-03, which will be Attachment 1 of the OT agreement.

Phase 1 fixed milestones for this program must include, at a minimum, the following:

- Month 1:
  - Phase 1 project kick-off meeting.
  - All supporting positions identified in the proposal are assigned to personnel, and names are provided to the Government.
  - All personnel working on the DO must be identified.
Month 3:
- Submission of Phase 1 (as necessary) Independent Review Board (IRB)-approved protocol(s) for Human Subjects Research for secondary Human Research Protection Office (HRPO) review.
- Report on proposed mechanisms, metrics, and relationship to emotional health outcomes.
- All proposed personnel must be working on the effort at the planned level of effort.

Month 6:
- Preliminary report on models of REM sleep mechanisms, neuromodulation system design, stimulation parameters, and stimulation effects on target mechanisms.

Month 9:
- Complete hardware development.
- Feasibility report on the ability to modulate the target mechanism(s), including the final model specifying the relationship between neural stimulation, REM sleep, target neural mechanism(s), and health outcomes.
- Submission of Phase 2 Independent Review Board (IRB)-approved protocol(s) for Human Subjects Research for secondary Human Research Protection Office (HRPO) review.

Phase 2 fixed milestones for this program must include, at a minimum, the following:

- Month 10:
  - Phase 2 Kick-Off Meeting.

- Month 12: Begin proof-of-concept human studies (i.e., pilot study of health-related effects). All proposed personnel must be working on the effort at the planned level of effort.

- Month 15: Interim report on user experience and system design (e.g., system comfort, acceptability, subjective impact on sleep, etc.).

- Month 18: Preliminary report on results (i.e., REM sleep outcomes, target mechanism enhancement) and mechanism validation (e.g., change in stress adaptation/traumatic memory consolidation, change in other associated emotional and behavioral outcomes, correlation between change in target mechanism and predicted outcomes).

- Month 21: Comprehensive final report.

For planning and budgetary purposes, proposers should assume a program start date of December 1, 2023. Schedules will be synchronized across performers, as required, and monitored/revised as necessary throughout the program’s period of performance.

All proposals must include the following meetings and travel in the proposed schedule and costs:

- To foster collaboration between teams and disseminate program developments, a two-day virtual Principal Investigator (PI) meeting will be held approximately every six months.

- Regular teleconference meetings will be scheduled with the Government team for progress reporting and problem identification and mitigation. Proposers should also anticipate at least one site visit per phase by the DARPA Program Manager, during which they will have the opportunity to demonstrate progress towards agreed-upon milestones.

**E. Deliverables**

Performers will be expected to provide, at a minimum, the following deliverables:
Negotiated deliverables specific to the objectives of the individual efforts. These may include registered reports, experimental protocols, publications, intermediate and final versions of software libraries, code, and APIs, including documentation and user manuals, and/or a comprehensive assemblage of design documents, models, modeling data and results, and model validation data.

II. Award Information

Selected proposals that are successfully negotiated will result in the award of an OT for prototype project. See Section 3 of DARPA-PA-23-03 for information on awards that may result from proposals submitted in response to this announcement.

Proposers must review the model OT for prototype agreement provided as an attachment to DARPA-PA-23-03 prior to submitting a proposal. DARPA has provided the model OT to expedite the negotiation and award process and ensure DARPA achieves the goal of Disruptioneering, which is to enable DARPA to initiate a new investment in less than 120 calendar days from idea inception. The model OT is representative of the terms and conditions that DARPA intends to include in all DO awards. The task description document, schedule of milestones and payments, and data rights assertions requested under Volumes 1, 2, and 3 will be included as attachments to the OT agreement upon negotiation and award.

Proposers may suggest edits to the model OT for consideration by DARPA and provide a copy of the model OT with track changes as part of their proposal package. DARPA may not accept suggested edits. The Government reserves the right to remove a proposal from award consideration should the parties fail to reach an agreement on OT award terms and conditions. If edits to the model OT are not provided as part of the proposal package, DARPA assumes that the proposer has reviewed and accepted the award terms and conditions to which they may have to adhere and the model OT agreement provided as an attachment, indicating agreement (in principle) with the listed terms and conditions applicable to the specific award instrument.

To ensure that DARPA achieves the Disruptioneering goal of an award within 120 calendar days from the posting date (August 1, 2023) of this announcement, DARPA reserves the right to cease negotiations when an award is not executed by both parties (DARPA and the selected organization) on or before December 1, 2023).

III. Eligibility

See Section 7 of DARPA-PA-23-03 for information on who may be eligible to respond to this announcement.

IV. Disruption Opportunity Responses

A. Proposal Content and Format

All proposals submitted in response to this announcement must comply with the content and format instructions in Section 5 of DARPA-PA-23-03. All proposals must use the templates provided as Attachments to the PA and the “Schedule of Milestones and Payments” Excel Attachment provided with this DO and follow the instructions therein.

Information not explicitly requested in DARPA-PA-23-03, its Attachments, or this announcement may not be evaluated.

B. Proposal Submission Instructions

DARPA will acknowledge receipt of complete submissions via email and assign identifying numbers that should be used in all further correspondence regarding those submissions. If no confirmation is received within two (2) business days, please contact REMREST@darpa.mil to verify receipt.

When planning a response to this DO, proposers should take into account the submission time zone and that some parts of the submission process may take from one business day to one month to complete (e.g., registering for a SAM Unique Entity ID (UEI) number or Tax Identification Number (TIN)).

Electronic Upload

First-time users of the DARPA BAA Portal must complete a two-step account creation process. The first step consists of registering for an extranet account by going to the URL above and selecting the “Account Request” link. Upon completion of the online form, proposers will receive two separate emails; one will contain a username, and the second will provide a temporary password. Once both emails have been received, the second step requires proposers to go back to the submission website and log in using that username and password. After accessing the extranet, proposers may then create a user account for the DARPA Submission website by selecting the “Register your Organization” link at the top of the page. Once the user account is created, proposers will be able to see a list of solicitations open for submissions, view submission instructions, and upload/finalize their proposal.

Proposers who already have an account on the DARPA BAA Portal may log in at https://baa.darpa.mil, select this solicitation from the list of open DARPA solicitations and proceed with their proposal submission. Note: proposers who have created a DARPA Submission website account to submit to another DARPA Technical Office’s solicitations do not need to create a new account to submit to this solicitation.

All full proposals submitted electronically through the DARPA Submission website must meet the following requirements: (1) uploaded as a zip file (.zip or .zipx extension); (2) only contain the document(s) requested herein; (3) only contain unclassified information; and (4) must not exceed 100 MB in size. Only one zip file will be accepted per full proposal. DARPA will reject full proposals not uploaded as zip files. Technical support for the DARPA Submission website is available during regular business hours, Monday – Friday, 9:00 a.m. – 5:00 p.m. Requests for technical support must be emailed to BAAT_Support@darpa.mil with a copy to REMREST@darpa.mil. Questions regarding submission contents, format, deadlines, etc., should be emailed to REMREST@darpa.mil. Questions/requests for support sent to any other email address may result in delayed/no response.

Since proposers may encounter heavy traffic on the web server, DARPA discourages waiting until the day proposals are due to request an account and/or upload the submission. Note: Proposers submitting a proposal via the DARPA Submission site MUST (1) click the “Finalize” button for the submission to upload AND (2) do so with sufficient time for the upload to complete prior to the deadline. Failure to do so will result in a late submission.

C. Proposal Due Date and Time

Proposals in response to this announcement are due no later than 4:00 p.m. on September 15,
2023. As described in Section 5 of DARPA-PA-23-03, full proposal packages must be submitted per the instructions outlined in this DO and received by DARPA no later than the above time and date. Proposals received after this time and date may not be reviewed.

Proposers are warned that the proposal deadline outlined herein is in Eastern Time and will be strictly enforced. When planning a response to this announcement, proposers should consider that some parts of the submission process may take from one (1) business day to one (1) month to complete.

V. Proposal Evaluation and Selection

Proposals will be evaluated and selected in accordance with Section 6 of DARPA-PA-23-03. Proposers will be notified of the results of this process as described in Section 8.1 of DARPA-PA-23-03.

VI. Administrative and National Policy Requirements

Section 8.2 of DARPA-PA-23-03 provides information on Administrative and National Policy Requirements that may be applicable for proposal submission and performance under an award.

VII. Point of Contact Information

Greg Witkop, Program Manager, DARPA/DSO, REMREST@darpa.mil

VIII. Frequently Asked Questions (FAQs)

All technical, contractual, and administrative questions regarding this announcement must be emailed to REMREST@darpa.mil. Emails sent directly to the Program Manager or any other address may result in delayed or no response.

All questions must be in English and must include the name, email address, and telephone number of a point of contact. DARPA will attempt to answer questions publicly in a timely manner; however, questions submitted within seven (7) calendar days of the proposal due date listed herein may not be answered.

DARPA will post an FAQ list under the DO on the DARPA/DSO Opportunities page at (http://www.darpa.mil/work-with-us/opportunities). The list will be updated on an ongoing basis until one (1) week before the proposal due date.