AWARD NUMBER: W81XWH-17-1-0320

TITLE: A Pilot Trial of Remotely Supervised Transcranial Direct Current Stimulation (RS-tDCS) to Enhance Motor Learning in Progressive Multiple Sclerosis (MS)

PRINCIPAL INVESTIGATOR: Leigh Charvet, PhD

CONTRACTING ORGANIZATION: New York University School of Medicine

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Fort Detrick, Maryland 21702-5012

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4.TITLE AND SUBTITLE

A Pilot Trial of Remotely Supervised Transcranial Direct Current Stimulation (RS-tDCS) to Enhance Motor Learning in Progressive Multiple Sclerosis (MS)

5a. CONTRACT NUMBER
W81XWH-17-1-0320

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
New York University School of Medicine, 240 East 38th Street, Floor 10, 10016

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U.S. Army Medical Research and Materiel Command
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12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The purpose of this randomized, double-blind pilot clinical trial is to test the novel treatment approach of anodal transcranial direct current stimulation (tDCS) to augment manual dexterity training targeted to rehabilitate fine motor functioning in individuals living with progressive multiple sclerosis (MS). Treatment will be delivered to individuals at home using a state-of-the-art remotely-supervised tele-medicine protocol, a major advantage for patients with respect to ease of access, feasibility, and minimal burden of in-clinic study visit participation. Specific Aim 1 is to determine the extent to which tDCS paired with manual dexterity training improves fine motor execution on a grasp and lift task. *We expect that the impairment in grasp execution will be significantly reduced with active tDCS versus sham tDCS from pre- to post-treatment.* Specific Aim 2 is to assess the adaptation or learning of fingertip forces to object weight when tDCS is paired with manual dexterity training. We predict that active vs. sham tDCS paired with training will optimize the difference in the peak load force rates between the light and heavy objects pre- to post-intervention. Training, material and database creation, and randomization/matching procedures complete. First participant enrolled and completed. Participant enrollment ongoing. Interim data analysis compiled for American Academy of Neurology 2020 abstract.

15. SUBJECT TERMS

tDCS, telemedicine, motor, MS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	14	19b. TELEPHONE NUMBER *(include area code)*

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1. **Accomplishments:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer 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.

Approved Statement of Work (SOW) 5.27.17

<u>Achieved</u> Major Task 1 (100% Completed): Prepare for Study Enrollment, Months 1 – 9

Subtask 1: Finalize Supporting Documents Months 1-3

- Finalize methods for administering eligibility criteria, exclusion criteria, screening protocol: Months 1-3
- Finalize consent form & human subjects protocol: Months 1-3
- Submit amendments, adverse events, and protocol deviations as needed

Milestone achieved: Local IRB approval at NYULMC Month 6
Milestone achieved: HRPO approval of all protocols and local IRB approval through NYULMC Month 9

Subtask 2: Measures, equipment purchasing, and staff training

- Finalize training of study staff: Months 6-9
- Acquire all necessary devices, equipment, and study computer setup: Months 6-9

Milestone Achieved: Study kits created and research staff trained Month 9

Subtask 3: Database creation, randomization, and matching procedures in place Months 6-9

Milestone Achieved: Database created, randomization and group matching procedure in place Month 9

Subtask 4: Initial advertising for recruitment: Month 8

Milestone Achieved: Initial screening waitlist finalized Month 9

<u>Achieved</u> Major task 2: Study Enrollment Months 9-30

Subtask 1: Screening and study entry Month 9-27

Milestone Achieved: 1st participant consented, screened, and enrolled Month 9

Subject task 2: Pilot study (20 sessions of 20 minutes each remotely supervised; 40 active vs 40 sham) Months 9 -31

Milestone Achieved: Study 1 begins Month 9

- Begin subject recruitment and extends over 18 months, average enrollment 15pts/quarter Months 9-27
- Last participant (n=80) complete 4 week randomly-assigned condition (active or sham) Month 28
- Follow-up assessment period Months 10-31

Milestone Achieved: Last participant to complete follow-up assessment Month 31

<u>In progress</u> Study End Data Analyses and Reporting

- Perform all analyzes according to specifications, share output, and finding with all investigators Months 31-36
- Work with data core and dissemination of findings (abstracts, presentation, publications, DoD) Months 33-36

Milestone to Achieve: Report results from data analyses Month 36

Major activities accomplished:
Annual Year 4

Achieved Major task 2: Study Enrollment Months 9-30

Subtask 1 (100% Completed): Screening and study entry Month 9-27

Subject task 2 (100% Completed): Pilot study (20 sessions of 20 minutes each remotely supervised; 40 active vs 40 sham) Months 9 -40: Ongoing

- Begin subject recruitment and extends over 18 months, average enrollment 15pts/month Months 9-38: Achieved
    - Participants enrolled during this period = 10
    - Participants completed during this period = 12
    - Participants enrolled since study initiation = 67/80, including 5 withdrawals and 2 screen fails.
- Last participant (n=80) complete 4 week randomly-assigned condition (active or sham) Month 40
- Follow-up assessment period Months 10 - 40

Achieved (100% Complete): Last participant to complete follow-up assessment Month 40

Study End Data Analyses and Reporting (Preliminary analysis ongoing)
- Perform all analyzes according to specifications, share output, and finding with all investigators Months 48 - 52
- Work with data core and dissemination of findings (abstracts, presentation, publications, DoD) Months 48 - 52

Milestone to Achieve: Report results from data analyses Month 52

Due to the continued effects of the global pandemic, data cleanup and analysis is ongoing. We will be able to disseminate results by Month 52 and will be requesting a NCE for this continued work.

What was accomplished under these goals?

For this annual reporting period only 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.

Annual Year 4

1) Major activities
    a. Completed enrollment reaching 67 out of 80 participants.
2) Specific objectives: Continued collecting data per protocol to address specific aim 1 "To determine the extent to which tDCS paired with manual dexterity training improves fine motor execution on a grasp and lift task" and specific aim 2 "To assess the adaptation or learning of fingertip forces to object weight when tDCS is paired with manual dexterity training."
3) Significant results/key outcomes: Ongoing preliminary analysis shows a program of daily manual dexterity training delivered at home via telerehabilitation is feasible for individuals with progressive MS despite advanced disability, cognitive impairment and older age. 98.1% participant adherence to the protocol. Dr. Raghavan is preprocessing grip device data in prep for analysis.
4) Other achievements:

Describe the Regulatory Protocol and Activity Status (if applicable).

Describe the Protocol and Activity Status for sections a-c, as applicable, using the format described for each section. If there is nothing significant to report during this reporting period, state "Nothing to Report."

(a) ***Human Use Regulatory Protocols***

TOTAL PROTOCOLS: *State the total number of human use protocols required to complete this project (e.g., 5 human subject research protocols will be required to complete the Statement of Work."). If not applicable, write "No human subjects research will be performed to complete the Statement of Work."*

PROTOCOL(S): *List the identifier and title for all human use protocols needed to complete the project. Include information about the approved target number for clinical significance, type of submission, type of approval with associated dates, and performance status.*

The following format shall be used:

Protocol (of total):

Protocol [HRPO Assigned Number]:

Title:

Target required for clinical significance:

Target approved for clinical significance:

Submitted to and Approved by:

Provide bullet point list of protocol development, submission, amendments, and approvals (include IRB in addition to HRPO).

Status:

Report (i) progress on subject recruitment, screening, enrollment, completion, and numbers of each compared to original planned target(s), e.g., number of subjects enrolled versus total number proposed; (ii) amendments submitted to the IRB and USAMRMC HRPO for review; and (iii) any adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation.

TOTAL PROTOCOLS: 1 human subjects protocol will be required to complete the Statement of Work.

PROTOCOL (1 of 1 total):

Protocol A-20444.1a:

Title: A Pilot Trial of Remotely Supervised Transcranial Direct Current Stimulation (RS-tDCS) to Enhance Motor Learning in Progressive Multiple Sclerosis (MS)

Target required for clinical significance: 60

Target approved for clinical significance: 80

SUBMITTED TO AND APPROVED BY:

- New York University School of Medicine IRB on 10/09/17:Approval on 11/27/17

STATUS:

(i) Number of subjects recruited during this annual report period: 14
Number of subjects screened during this annual report period: 14
Number of patients enrolled during this annual report period: 10
Number of patients completed during this annual report period: 12

(ii) Report amendments submitted to the IRB and USAMRMC HRPO for review:

Submitted continuing review to HRPO 6.2.21. In the correspondence we indicated that we inadvertently didn't send the HRPO information in October 2020.

MOD 32 (*IRB approved on 08/05/2020):* Personnel modification to add Valerie Saha to study team and to remove Chelsea Prudent.

Protocol Exception *(IRB approved on 08/18/2020).* A protocol exception was submitted to include a participant who was 2 years over the age inclusion criteria but who was otherwise eligible and could potentially benefit from participation.

MOD 33 *(IRB approved on 10/7/2020).* Personnel modification to remove Jon Links, Hannah Zimmermann, Amy Ro, and Kelly Lee from study team.

Continuing Review 3 *(IRB approved on 10/13/2020)* for renewal period 10/13/2020-10/12/2021.

MOD 34 *(IRB approved on 12/14/2020).* Personnel modification to add Hannah Zimmermann to study team.

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:

There were no adverse events/unanticipated problems that involved risk or harm to subjects or others.

(b) Use of Human Cadavers for Research Development Test & Evaluation (RDT&E), Education or Training

"Cadaver" is defined as a deceased person or portion thereof, and is synonymous with the terms "human cadaver" and "post-mortem human subject" or "PMHS." The term includes organs, tissues, eyes, bones, arteries or other specimens obtained from an individual upon or after death. The term "cadaver" does not include portions of an individual person, such as organs, tissue or blood, that were removed while the individual was alive (for example, if a living person donated tissue for use in future research protocols, that tissue is not considered a "cadaver" under this policy, regardless of whether the donor is living or deceased at the time of tissue use).

***TOTAL ACTIVITIES**: State the total number of RDT&E, education or training activities that will involve cadavers. If not applicable, write "No RDT&E, education or training activities involving human cadavers will be performed to complete the Statement of Work (SOW)."*

***ACTIVITIES:** Provide the following information in a bulleted list for all RDT&E, education or training activities involving human cadavers conducted or supported during the quarter:*

- *Title of the RDT&E, education or training activity*
- *SOW task/aim associated with the activity*
- *Date the activity was conducted*
- *Identification of the organization's responsible individual (e.g., PI or individual primarily responsible for the activity's conduct)*
- *Brief description of the use(s) of cadavers in the activity and the total number of cadavers used during the reporting period*
- *Brief description of the Department of Army organization's involvement in the activity*
- *Status of document submission and approvals*
- *Problems encountered in the procurement, inventory, use, storage, transfer, transportation and disposition of cadavers used for RDT&E, education or training. Examples of problems include but are not limited to: loss of confidentiality of cadaveric donors, breach of security, significant deviation from the approved protocol, failure to comply with state laws and/or institutional policies and public relations issues.*

***TOTAL ACTIVITIES:** No RDT&E, education or training activities involving human cadavers will be performed to complete the Statement of Work (SOW).*

ACTIVITES:

(c) Animal Use Regulatory Protocols

TOTAL PROTOCOL(S):

State the total number of animal use protocols required to complete this project (e.g., 2 animal use research protocols will be required to complete the Statement of Work.). If not applicable, write "No animal use research will be performed to complete the Statement of Work."

PROTOCOL(S):

List the identifier and title for all animal use protocols needed to complete the project. Include information about the approved target number for statistical significance, type of submission, type of approval with associated dates, and performance status.

The following format shall be used:

Protocol (_ of _ total):

Protocol [ACURO Assigned Number]:

Title:

Target required for statistical significance:

Target approved for statistical significance:

Submitted to and Approved by:

Provide bullet point list of protocol development, submission, amendments, and approvals (include IACUC in addition to ACURO).

Status:

Provide bullet point list of performance and/or progress status relating to the above protocol and discuss any administrative, technical, or logistical issues that may impact performance or progress of the study (e.g. animal use protocol needs revision to minimize animal suffering, animal protocol modification to include additional staff) for the above ACURO approved protocol.

TOTAL PROTOCOL(S): *No animal use research will be performed to complete the Statement of Work.*

PROTOCOL (_ of _ total):

Protocol [ACURO Assigned Number]:

Title:

Target required for statistical significance:

Target approved for statistical significance:

SUBMITTED TO AND APPROVED BY:

STATUS:

What do you plan to do during the next reporting period to accomplish the goals and objectives?

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

- Complete data analysis and disseminate results

2. Products: List any products resulting from the project during the reporting period. If there are no products to report for the current quarter, state "Nothing to report."

Examples of products include:

- *publications, conference papers, and presentations;*
- *website(s) or other Internet site(s);*
- *technologies or techniques;*

- *inventions, patent applications, and/or licenses; and*
- *other products, such as data or databases, biospecimen collections, germplasm, audio or video products, software, models, educational aids or curricula, instruments or equipment, data and research material, clinical or educational interventions, or new business creation.*

Nothing to report

3. Participants & Other Collaborating Organizations

What individuals have worked on the project?

Provide the following information for: (1) Project Directors (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).

Provide the name and identify the role the person played in the project. Indicate the nearest whole person month (Calendar, Academic, Summer) that the individual worked on the project. Show the most senior role in which the person worked on the project for any significant length of time. For example, if an undergraduate student graduated, entered graduate school, and continued to work on the project, show that person as a graduate student, preferably explaining the change in involvement.
Describe how this person contributed to the project. If information is unchanged from a previous submission, provide the name only and indicate "no change."

Example:
Name: *Mary Smith*
Project Role: *Graduate Student*
Researcher Identifier (e.g. ORCID ID): 1234567
Nearest person month worked: *5*
Contribution to Project: *Ms. Smith has performed work in the area of combined error-control and constrained coding.*

Name: Leigh Charvet
Project Role: PI
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1.2calendar months
Contribution to Project: Oversight of all aspects of the study. Oversees patient recruitment and enrollment. Confirm eligibility of potential participants. Attended biweekly study meetings to provide guidance for study improvements. Provided suggestions about additional study kit generation and fund allocation. Oversees patient recruitment and enrollment.

Name: Lauren Krupp
Project Role: Co-I
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 0.6 calendar months (no salary support on this award)
Contribution to Project: Dr. Krupp reviews and completes medical clearance for enrolled participants.

Name: Preeti Raghavan
Project Role:Co-I
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1.08 calendar months
Contribution to Project: Dr. Raghavan continues to receive updates from Dr. Charvet on the progress of the project. Fully executed subcontract effective 2.25.2020 and data analysis resumes on data to-date.

Name: Vikram Kapila
Project Role: Engineer
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 0.82 calendar month
Contribution to Project: No change

Name: Ying Lu
Project Role: Statistician
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 0.428 summer month
Contribution to Project: No change.

Name: Marom Bikson
Project Role: Co-I
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 0.3 summer months
Contribution to Project No change.

Name: Martin Malik
Project Role: MS Division Data Associate
Nearest person month worked: 8.40 calendar months.
Contribution to Project: Runs sessions for participants and assists with data entry. Recruits, screens and consents participants. Performs baseline and follow-up assessments. Completed his position on 5.7.2020.

Name: Matthew Lustberg
Project Role: MS Division Coordinator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 3.5 calendar months (no salary support on this award)
Contribution to Project: Coordinates study needs, runs sessions, and collects baseline and follow-up data for participants. Manages regulatory compliance and serves as primary regulatory contact with IRB. Prepares weekly meeting agenda and coordinates additional meetings as needed.

Name: Ashwin Raj Kumar
Role: Engineering post-doc
Nearest person month worked: 6.0 calendar months
Contribution to Project: Attended both biweekly meeting and additional meetings with Mr. Lustberg. Oversees effectiveness of the grip device program and compatibility of all software and hardware programming used in the study.

Name: Kathleen Sherman
Project Role: Program Manager
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 0.25 calendar months (no salary support from this award)
Contribution to Project: Assist with award management, progress reports, regulatory and IRB requirements.

Name: Giuseppina Pilloni
Project Role: MS Division Coordinator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 0.5 calendar months (no salary support from this award)
Contribution to Project: Helps in coordinating study needs and runs sessions with participants

Name: Tehila Eilam-Stock
Project Role: MS Division Post-doctoral fellow
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 0.1 calendar months (no salary support from this award)
Contribution to Project: Runs sessions for participants.

Name: Allan George
Project Role: MS Division Research Coordinator
Nearest person month worked: 0.2 calendar months (no salary support from this award).
Contribution to Project: Helps run sessions with participants

Name: Lillian Walton Masters
Project Role: MS Division Research Coordinator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 0.5 calendar months (no salary support on this award).
Contribution to Project: Runs sessions for participants and assists with data entry.

Name: Pamela Best
Project Role: MS Division Research Coordinator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 0.5 calendar months (no salary support on this award).
Contribution to Project: Runs sessions for participants and assists with data entry

Name: John Shymansky
Project Role: MS Division Student Research Intern
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 0.1 calendar months (no salary support from this award)
Contribution to Project: Runs sessions for participants and assists with data entry

Name: Ibraheem Mirza
Project Role: MS Division Student Research Intern
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 0.1 calendar months (no salary support from this award)
Contribution to Project: Runs sessions for participants and assists with data entry.

Name: Hannah Zimmermann
Project Role: MS Division Volunteer
Research Identifier (e.g. ORCID ID):
Nearest person month worked: 0.1
Contribution to Project: Runs sessions for participants and assists with data entry

4. Changes/Problems: The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer 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:

a. Actual Problems or delays and actions to resolve them

Provide a description of current problems or issues that may impede performance or progress of this project along with proposed corrective action. Also 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.

For an award that includes the recruitment of human subjects for clinical research or a clinical trial, discuss any problems or barriers encountered, if applicable, and what has been done to mitigate those issues. Discussion may highlight enrollment problems, retention problems, and actions taken to increase enrollment and/or improve retention.

The COVID-19 pandemic slowed down recruitment; however we were able to complete enrollment goal of 67 out of 80 participants. Timing was still delayed due to the pandemic – data were cleaned and is in the process of being analyzed and then compiled for manuscript.

b. Anticipated Problems/Issues

Provide a description of anticipated problems or issues that have a potential to impede performance or progress. Also provide course of actions planned to mitigate problems or to take should the problem materialize.

While we were able to resume research visits virtually, completing the enrollment of 80 participants took us into Quarter 4 of the NCE year. Data analysis has been delayed and is in progress.

5. Special Reporting Requirements:

Quad Charts: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.