Title: Using Combined EEG and Non-invasive Brain Stimulation to Examine and Improve Reward Functioning in Opioid Use Disorder

NCT number: NCT04432493

Date: 12/12/2022

Section 1 - Basic Information (Study 297707)

OMB Number: 0925-0001

Expiration Date: 02/28/2023

1.1. Study Title *

Using combined EEG and non-invasive brain stimulation to examine and improve cognitive control functioning in opioid use disorder

1.2. Is this study exempt from Federal Regulations * ○ Yes ● No

1.3. Exemption Number ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?	● Yes	○ No
1.4.b. Are the participants prospectively assigned to an intervention?	● Yes	○ No
1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?	● Yes	○ No
1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?	● Yes	○ No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics (Study 297707)

2.1. Conditions or Focus of Study

- Opioid use disorder

2.2. Eligibility Criteria

Inclusion criteria will be as follows: 1. Opioid dependent individuals according to the ASSIST opioid dependence score (OUD group, ASSIST opioid Score >12), or healthy controls with no significant history of opioid use (ASSIST opioid Score < 11), or other drug-types (ASSIST score < 11 for each drug category). 2. Native English speakers, 3. Males and Females aged 18-55 years old, 4. Ability to provide informed written or verbal consent, 5. Only participants who clearly understand the research and are able to indicate consent to participate can be enrolled in the study. Exclusion criteria will include uncorrectable visual impairment, uninterruptable central nervous system medication, severe brain injury (traumatic or acquired). Given the nature of the OUD group, opioid users will only be excluded for severe mental health issues (e.g. schizophrenia, bipolar) but not mood disorders such as depression or anxiety, nor will they be excluded for substance abuse. Additional exclusion criteria include any TMS contraindications (e.g., pregnancy, braces, history of seizures).

2.3. Age Limits	Min Age: 18 Years Max Age: 55 Years
2.3.a. Inclusion of Individuals Across the Lifespan	INCLUSION_LIFESPAN_Study1.pdf
2.4. Inclusion of Women and Minorities	Women_minorities_children_R21_opioid.pdf
2.5. Recruitment and Retention Plan	Recruitment_and_Retention_Plan_R21_opioid.pdf
2.6. Recruitment Status	Recruiting
2.7. Study Timeline	TIMELINE.pdf
2.8. Enrollment of First Participant (SEE SECTION 6.3)	

INCLUSION OF INDIVIDUALS ACROSS THE LIFESPAN

Inclusion of Children and Older Adults: We will be including 18-55 year-old individuals in our study. Thus, we will not be including children or older adults in this project. Note that the investigators have had ample previous experience working with participants in this age range, and all study procedures are appropriate for this age range. Children below age 18 and individuals above 55 years old will not be studied in this project because separate age-specific projects are warranted, and even preferred, given that 1) normal developmental changes in reward processes during childhood are prominent but not yet well understood and 2) normal decline in goal-directed processes in older age (above age 55) are known to be prominent but not well understood.

Inclusion of Women, Minorities, and Children

Inclusion of Women: No participant will be excluded on the basis of sex or gender. As described above, participants will be recruited from multiple sources, including student populations and the general community. We will strive for an approximately equal gender balance for the studies proposed here. Given our past inclusion experience, we do not anticipate needing specific outreach programs for recruiting women for this project.

Inclusion of Minorities: No participant will be excluded on the basis of race or ethnicity. As described above, participants will be recruited from multiple sources, including various student populations and the general community. We will make special outreach efforts in recruiting African-American participants for our study, since the College of Arts and Sciences at Rutgers-Newark University where we typically recruit, has an African-American population that under-represents the demographics of Newark, NJ. We have had success in recruiting African-American participants from the general community and from other nearby schools whose enrollment includes a greater number of minority students. Specifically, we will strive to match the demographics of Newark area, which at the time the 2010 census had the following breakdown:

Racial Categories

White 26.31%

Black (African American) 52.35%

Asian (including Pacific Islander / Hawaii Native) 1.62%

American Indian / Alaska Native 0.61%

Other / Unknown 15.22%

More than One Race 3.85%

Ethnic Categories

Hispanic / Latino 33.83%

Inclusion of Children: Previously, NIH considered individuals under 21 years of age to be children, but this has now changed (children are now defined as under 18; see NIH NOT-OD-16-010). We will be including 18- 55 year olds in our study. Thus, we will not be including children in this project. Note that the investigators have had ample previous experience working with participants in this age range (e.g., those 18-20 years old), and all study procedures are appropriate for this age range. Children below age 18 will not be studied in this project because a separate age-specific project is warranted, and even preferred, given that normal developmental changes in cognitive control processes during childhood are prominent, but not yet well understood.

Recruitment and Retention Plan

In total, we plan to collect 60 participants (30 opioid users, 30 controls) over 2 years for the proposed study. Participants will be randomized into TMS or sham groups (15 participants per group). Standard practice in electrophysiological studies commonly use a minimum of 15 participants per experimental group. Further, basing the analyses on our previous results, a priori power analysis indicated that a sample size of 15 would be sufficient to detect a significant effect with a power of .82 and an alpha of .05. Potential OUD participants will be recruited through the community using an `expression of interest' flyer. The flyer will be distributed throughout pharmacies, clinics, universities, community recreation venues, via email, social networking websites and possibly through media outlets such as through newspapers and radio. Control participants will be recruited using personal networks, advertisements on volunteer job sites and by placing flyers in local community settings.

TIMELINE

Months 1–18. Aim 1 and Aim 2 (initiation) Recruiting and testing control and OUD subjects with our virtual T-maze task with Ri-TMS capabilities, which is already developed.

Months 18–24. Completion of Aim 1 and Aim 2. Analyse data from Months 1–18 for publication. Prepare and submit manuscript for publication.

2.9. Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
IER 296360	Domestic	Newark

Inclusion Enrollment Report 296360

1. Inclusion Enrollment Report Title* : Using combined EEG and non-invasive brain stimulation to examine and improve cognitive control functioning in opioid use disorder

2. Using an Existing Dataset or Resource* : ❍ Yes ● No

3. Enrollment Location Type* : ● Domestic ❍ Foreign

4. Enrollment Country(ies): USA: UNITED STATES

5. Enrollment Location(s): Newark

6. Comments:

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	1	1	0	0	2
Asian	1	1	0	0	2
Native Hawaiian or Other Pacific Islander	1	1	0	0	2
Black or African American	7	8	2	2	19
White	7	8	5	5	25
More than One Race	3	3	2	2	10
Total	20	22	9	9	60

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	1	0	0	0	0	0	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	3	0	0	0	0	0	0	0	3
White	1	4	0	1	1	0	0	0	0	7
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	11	1	0	12
Total	1	8	0	1	1	0	11	1	0	23

Section 3 - Protection and Monitoring Plans (Study 297707)

3.1. Protection of Human Subjects	Protection_of_human_subjects_R21_final.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	❍ Yes ● No ❍ N/A
If yes, describe the single IRB plan	
3.3. Data and Safety Monitoring Plan	Data_Monitoring_Plan_R21_opioid.pdf
3.4. Will a Data and Safety Monitoring Board be appointed for this study?	❍ Yes ● No
3.5. Overall structure of the study team	

PROTECTION OF HUMAN SUBJECTS

1. Risks to the Subjects:

1.a. Human Subjects Involvement and Characteristics: The subjects participating in this study will be healthy adults and individuals with opioid use disorder (ages 18 to 55). Participants will be recruited from the Rutgers University-Newark campus and nearby community. Recruitment will be through advertisements posted around the Rutgers University campus, advertising in local media, community forums, clinics and from maintained lists of volunteers interested in repeated participation behavioral studies. We will be seeking a broad sample of adults, such that exclusion criteria will be minimized when possible. Nonetheless, participants will be excluded for the following reasons: 1) taking any medication with potential cognitive effects (e.g., sleeping pills); 2) taking any psychotropic medications (e.g., antidepressants, anti-anxiety agents, anti-psychotics); 3) the presence of any clinically unstable medical disorder, or a medical disorder that affects cognitive or motor function (e.g., epilepsy, Parkinson's Disease); 4) present or past head injury with documented neurological sequelae, and/or causing loss of consciousness, 5) pregnancy; and 6) history of seizures. Note that the Rutgers University- Newark campus and surrounding community have an especially diverse population. Thus, the included participants may involve more diversity than most psychological and neuroscientific studies, possibly allowing for scientific findings that are more representative of the overall population of the nation and the world (see Inclusion of Women, Minorities and Children).

1.b Sources of Materials: All materials for this project will be collected specifically for research purposes. We will collect data regarding brain function using electroencephalography. We will collect behavioral data (reaction times and error rates) based on performance of computer-administered cognitive tasks. Additionally, we may collect self-report information based on personality questionnaires.

1.c. Potential Risks: The potential risks of this project include those associated with routine cognitive testing. The testing instruments to be used for the project are not invasive and pose minimal risk. The testing procedures could induce boredom and fatigue.

There are no known risks associated with TMS when all technical parameters remain within FDA guidelines and the International Federation of Clinical Neurophysiology and the International Society for Transcranial Stimulation, and participants with medical contraindications to TMS are excluded. These guidelines will not be exceeded in the work proposed. The application of TMS may cause the subject some temporary discomfort, such as a mild tingling or minor headache, where the coil is placed on the scalp. An addition risk of TMS is seizures, which has occurred following parameters that exceeded clinical safety guidelines. The current study is accordance with these guidelines. Robotic neuronavigation for TMS poses minimum risk to the subject. The robotic arm does not touch the patient's head. However, there is a theoretical risk of failure of the computer due to a program "bug". In the unlikely event of a failure, security mechanisms are in place.

There are no known risks associated with EEG. EEGs are safe and painless. The greatest inconvenience is the electrode gel left in subject’s hair after the cap is removed, but it can easily be rinsed out at the end of the experiment in the lab, with no damage to the scalp.

2. Adequacy of Protection against Risk:

2.a. Recruitment and Informed Consent: Subjects will be recruited from advertisements and existing subject pools, at Rutgers University and in the surrounding community, to ensure a diverse sample. Consent will be obtained and documented with an institution approved consent form for all subjects. Informed Consent will always be obtained before a subject participates in any component of the current protocol. For all participants, the consent form will be explained to participants as well as having them read the consent themselves. This consent will contain a detailed description of all study procedures, as well as any possible risks and/or benefits. The consent will also indicate (and this will be verbally reinforced by the experimenter) that the participant is free to withdraw from the experiment at any time without penalty or repercussion. Consent will be documented by having the participant and the individuals obtaining consent both sign and date the consent form.

2.b. Protection Against Risk: The routine testing instruments to be used for the project could induce boredom and fatigue. Breaks in experimental sessions will be given whenever the subject requests or obvious fatigue is observed. The motivational incentives and self-disclosing questionnaires could cause anxiety or other negative reactions. Participants will be fully informed of the nature of these experimental components before beginning the session, and explicitly be given the option to decline to participate. Moreover, participants will be assured that their data is being obtained only for research purposes, will only be evaluated in the aggregate, and that all identifying information will be removed (see below).

All of the data collected for these studies will be kept strictly confidential. The person's name and identifying information will be associated with their study ID in a master file that contains no diagnostic information. This

master file will be stored on a computer without Internet access. All other research materials will contain only the participant's study number, and not any identifying information. Only research personnel listed on this application will have access to files containing participant identities. Under no circumstances will individually identifiable data be released to anyone without the expressed written consent of the participant. In the past we have found that all of these procedures are effective at reducing risk for study participants.
To ensure safe practices in the event of any side effects of TMS exhibited by the subjects, Dr. Huey-Jen Lee, MD (a neuroradiologist and Director of Radiology at New Jersey Medical School, Rutgers Newark), will work on this project as the contact physician. In the event of a seizure, there is no need to go more than just stay with the participant and monitor them for up to an hour for signs of post-seizure confusion. Seizures are thought to be caused by group of neurons that become hyper-synchronized and are categorized as "absent-type", which cause lapses in awareness, sometime with staring, and last less than a few seconds. In some cases, confusion post-seizures to be expected up to 30 minutes, max. No one has ever developed a recurring seizure disorder (epilepsy) after a TMS-induced seizure. Any side effects exhibited by subjects will be reported to Dr. Lee before they leave the lab. If post-seizure confusion exceeds 30 minutes, and after consulting with Dr. Lee, we will advise and accompany the participant to the University Hospital Emergency Room for safety. We will have subjects fill out a short questionnaire at the end of sessions to formally track and document any adverse side effects which may occur.
In the unlikely event of a computer failure during robot-guided TMS, security mechanisms are in place: There is an immediate shut off button held by the subject, the experimenter, and one on the robotic arm itself. Once the button is pressed, the arm will stop immediately without movement and will remain in the position where it stood at the time.

3. Potential Benefits of the Proposed Research to the Subject and Others: There will be no direct benefits to individuals for participating in this proposed project, other than the knowledge that they are contributing to our understanding of human cognitive and motivational processes and their biological underpinnings. However, the risks of this project are relatively small. If successful, substantial knowledge will be gained about cognitive control deficits associated with OUD. Furthermore, a closer examination of the role of TMS in modulating ACC activity may advance clinical research and treatment development of OUD. In consideration of the small risks and substantial scientific benefit of this work, we consider the risk/benefit ratio to be favorable.

4. Importance of Knowledge to be Gained: Cognitive control is critical component of human behavior, and the breakdown of this process in OUD may contribute to relapse and treatment failure in this group. A better understanding impaired reward processing via electrophysiological methods may highlight a highly sensitive biomarker of addiction severity and treatment efficacy. Further, stimulation of a dysfunctional ACC network may help to restore cognitive control functioning in opioid users, and may therefore have promising future applicability for addiction research. As noted above, the risks of this project are relatively small, and not appreciably greater than the risks of ordinary computerized testing and imaging procedures. Thus, given that the risks to participants in this study are small, we believe such risks are reasonable in relation to the importance of the knowledge that we will gain about the psychological and neural mechanisms of cognitive control in OUD.

Human Subjects Education: In accordance with the NIH policy effective October 1, 2000, this is to certify that all key personnel involved in the design and conduct of the human subjects research aspect of the above referenced grant have been educated on the protection of human research participants.

Data safety and monitoring plan

Participant confidentiality. Participants' records will be kept strictly confidential. Confidentiality will be ensured by assigning a random ID number to each participant. Identifying information will be maintained only in a password-protected database. All other data and records will contain only the ID number. Electronic data will be accessed via password-protected computers that are available only to the PI and co-PIs for this study. Long-term storage will be necessary to provide sufficient time for follow-up analysis and publication of deidentified data. The link between identifiable information and test data, as described in part "2b" above, will be stored exclusively in a password-protected database accessible only by the PI and co-investigators for this study.

Participants will also be protected by a Certificate of Confidentiality, which will be obtained from the NIH. This Certificate can be used by the researchers to legally refuse to disclose information that may identify participants in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify participants, except in cases where information is requested by personnel of the United States federal or state government agency sponsoring the project and that will be used for auditing or program evaluation of agency funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). The Certificate of Confidentiality will not be used to prevent disclosure to state or local authorities of child abuse and neglect, or harm to self or others.

Section 4 - Protocol Synopsis (Study 297707)

4.1. Study Design

4.1.a. Detailed Description

Thirty opioid dependent and 30 healthy control participants will be recruited for the purposes of this study. Participants in each group will be randomized into either TMS or sham conditions (15 participants per group). Standard practice in electrophysiological studies commonly use a minimum of 15 participants per experimental group. All participants will complete consent protocols, and questionnaires regarding demographic and drug use history, and will be fitted with an EEG cap for ERP recording while they engage in a virtual T-maze choice
task. A neuronavigation robot will position the TMS coil over a predetermined area of the brain, and TMS pulses will be delivered at 110% of the participants resting motor threshold at 10 Hz continuously over the predefined DLFPC target immediately before each of the 20 blocks of 10 trials, for a total of 1000 pulses and 200 trials (fixed at 100 reward and 100 no-reward). Identical parameters will be applied to the SHAM group with the exception that the TMS coil will be flipped 180º to mimic auditory stimulation.

4.1.b. Primary Purpose: Basic Science

4.1.c. Interventions

Type	Name	Description
Device (including sham)	TMS	Participants will be randomized into either the TMS (active) or SHAM group (coil flipped 180º to mimic auditory stimulation) during task performance. The TMS stimulator device used on our laboratory is a MagPro X100 with the Cool-B70 figure-of-eight coil (MagVenture, Falun, Denmark). The selection of stimulation intensity will be based on Resting Motor Threshold (rMT). In keeping within the safety guidelines, stimulation intensity will be set as 110% of rMT for the repetitive TMS. 50 rTMS pulses will be delivered at 110% of participants' resting motor threshold at 10 Hz continuously over the predefined DLFPC target immediately before each of the 20 blocks of 10 trials, for a total of 1000 pulses and 200 trials (fixed at 100 reward and 100 no-reward). Identical parameters will be applied to the SHAM group with the exception that the TMS coil will be flipped 180º to mimic auditory stimulation.

4.1.d. Study Phase: Early Phase 1 (or Phase 0)

Is this an NIH-defined Phase III Clinical Trial? ❍ Yes ● No

4.1.e. Intervention Model: Parallel

4.1.f. Masking ● Yes ❍ No

☑ Participant ❑ Care Provider ❑ Investigator ❑ Outcomes Assessor

4.1.g. Allocation: Randomized

4.2. Outcome Measures

Type	Name	Time Frame	Brief Description

Primary	Reward positivity amplitude	During intervention	Our project will utilize a highly sensitive biomarker of anterior cingulate cortex (ACC) control and reward function –the reward positivity– to image ACC function and monitor ACC modulation following TMS. Reward positivity amplitude will be determined by identifying the maximum absolute amplitude of the difference wave within a 200- to 400-ms window following feedback onset. The difference wave method, which was recommended in a recent metaanalysis of reward positivity studies [49], isolates the reward positivity from other ERP components. The reward positivity will be evaluated along front-central electrodes (Fz, FCz, Cz).

4.3. Statistical Design and Power — Statistical_design_and_power_R21_opioid.pdf

4.4. Subject Participation Duration — Subjects will participate in one session lasting up to 2 hours.

4.5. Will the study use an FDA-regulated intervention? — ❍ Yes ● No

4.5.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.6. Is this an applicable clinical trial under FDAAA? (SEE SECTION 6.6)

4.7. Dissemination Plan — Dissemination_R21_opioid.pdf

Statistical design and power

This study will adopt a randomized sham-controlled design. Participants will be randomized into either the TMS (active) or SHAM group (coil flipped 180º to mimic auditory stimulation) during task performance. Thirty dependent opioid users (OUD group) and 30 controls with no history of alcohol or drug dependence will be recruited for this study (15 participants per TMS/sham group). Standard practice in electrophysiological studies commonly use a minimum of 15 participants per experimental group. Further, based on previous work [27-29] an estimated 60 subjects in total will be required to identify a moderate to large main effect on the reward positivity, critical $F(4, 55) = 4.01$, $p = 0.05$, 85% power.