

AWARD NUMBER: W81XWH-19-C-0093

TITLE: Optimizing Attention Bias Modification for Posttraumatic Stress Disorder: An Entirely Remote Study

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CONTRACTING ORGANIZATION: Northern California Institute for Research & Education (NCIRE); San Francisco, CA

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14. ABSTRACT Our overall goal is to develop an app that allows us to test various options for mobile app-based threat-related attentional training for posttraumatic stress symptoms (PTSS), and to ultimately optimize the training based on our findings. This report summarizes work completed on the project during the third year of the award (09/01/2021-08/31/2022). In summary, we had to transfer the app development task to a new app development company in order to overcome major delays and personnel changes that occurred at our first company, which involved transfer of the design and code to the new company, redesign of some features that weren't functional, and relaunch our bug testing protocols for both the app itself and the backend. Although this was a lot of work, it led us to a much better and more reliable product, which is now fully functional. We also improved all systems and protocols to maximize efficiency and automate key tasks to ensure that we can run large numbers of participants at once. We also had the UCSF Institutional Review Board and Information Technology (IT) team review the final app and backend. After originally approving us to collect our deidentified app data outside of the UCSF Secure Enterprise Cloud, UCSF IT Security have now determined that we need to be within the SEC and we have worked with our developers to make this happen. Our UCSF IT Security liaison estimates 2-3 weeks to move the app and deploy. Ultimately, this will benefit the project in terms of providing greater security for our data, but unfortunately caused another delay. Estimated completion date for migration to the UCSF SEC is 10/21/22, and our estimated roll out of recruitment is one week later on 10/31/22.		

15. SUBJECT TERMS Posttraumatic stress disorder (PTSD), attention bias modification (ABM), attention control training (ACT), cognitive training, mobile application			
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1. INTRODUCTION:

New treatments for posttraumatic stress symptoms (PTSS) are desperately needed because existing treatments are limited by high costs, low uptake, poor adherence and retention, negative side effects, and ineffectiveness for a large proportion of patients. Moreover, among active component service members and military veterans, stigma remains a significant barrier to traditional mental health care. Computerized cognitive training programs such as attention bias modification (ABM) target the threat-related attention biases underlying PTSS and have potential to overcome many of these issues. If effective, such applications may be particularly desirable for contexts where access to traditional mental health care is difficult or impossible (e.g., during deployment). However, there are two critical knowledge gaps that limit progress. First, emerging data indicate that PTSS may be characterized by increased attention bias variability (i.e. rapid fluctuations in attention towards and away from threat), not mere individual differences in aggregate bias towards threat. A variant of ABM called attention control training (ACT) targets such attention bias variability and may be more effective than ABM in reducing PTSS. However, only a few small studies and no remote studies have examined the effectiveness of ACT. Second, ABM and ACT either use threatening words or threatening faces as stimuli. Although some evidence indicates that words may be the optimal stimuli for ABM, few studies have actually compared ABM with words and faces and thus, critical decisions about stimuli are not evidence based. We propose to recruit individuals with clinically significant PTSS who are demographically matched to the post-9/11 military population (N = 1,056 completers; 85% male; ages 18-55) in order to test two active interventions (ABM and ACT) *and* optimize mobile threat-related attentional training for PTSS. People interested in taking part in the study will complete the PTSD Checklist-5 (PCL-5) and report age and gender online. We will randomize eligible participants to one of four active conditions to include ABM with words or images and ACT with words or images, to one of two control conditions to include matched attentional training with only neutral words or images (176 participants per group), or . Participants will complete 14 days of training during a 4-week period. PTSS severity and threat-related attention biases (aggregate bias and variability) will be assessed at baseline, after 1 week and 2 weeks of training, and at 8 weeks. Our aims are to determine the effects of both ABM and ACT on threat-related attentional biases and PTSS severity, to determine if any positive effects are durable at eight weeks, and to compare words and faces as stimuli.

2. KEYWORDS:

Posttraumatic stress symptoms (PTSS), mobile application, remote study, attention bias modification (ABM), attention control training (ACT)

3. ACCOMPLISHMENTS:

a. What were the major goals of the project?

Major Task 1: Study Preparation and Regulatory Approval

Subtasks include: hire and train study coordinator (Completed 9/01/19); buy relevant study supplies (Completed 10/01/19); receive UCSF Institutional Review Board approval of study protocol (Completed 6/7/20); receive HRPO approval of study protocol (Completed 9/20/20); UCSF IT Risk Assessment of finalized mobile app (Completed 9/25/21); receive updated UCSF Institutional Review Board approval of finalized mobile app (Completed 9/22/22) and of *new* Department of Defense supplements (Completed 9/8/22); discuss mobile app deployment process to ensure adherence to *new* UCSF Data Security Policies with Central IT Secure Enterprise Solution Architects (Completed 9/13/22); deploy developed mobile app to UCSF Central IT Secure Enterprise Cloud Amazon Web Services Account (Predicted 10/25/22).

Timeline: Months 1-4; Actual Completion: 99%

SITE: SFVAMC, PI's: Woolley, O'Donovan

Major Task 2: Complete development of study software

Subtasks include: begin upgrade of mobile application (Completed 3/17/20); provide detailed analysis of app functioning and data requirements to developers (Completed 10/31/2020); test successful functioning of study protocol in app across full two-month cycles (Completed 6/1/2021 and 8/1/2021); crash test the app across

different devices (Completed 8/20/21); bug testing and sign off on app screens for FAQ section, daily reminders, login help, display of images for attention bias training completed troubleshoot and debugging of the mobile application (Completed 9/1/2021); contract and construct clinical trial management system, Ripple Science (Completed 5/13/21); troubleshoot potential study issues in new version of Ripple Science (Completed 2/28/22); Create code to automatically determine inclusion/exclusion and randomize participants to allow for faster participant enrollment (Completed 7/30/21); Create iOS and Android developer accounts to upload mobile app (Completed 9/15/21); Discovered critical problems with our app and CodeBrew Inc who were our original app developers and decided to move to new development company (Fall 2021); Found a new app development company Alternova Inc., transferred all knowledge about design and code of the app, worked with Alternova to develop a modified app with new architecture, bug tested iterations of the app, finalized the app (Completed 6/2/22); Pilot testing and identification of minor bugs and opportunities for enhancing the app (8/18/22); Transfer the app to UCSF SEC (Estimated 10/25/22); deploy app in Apple and Android app store (Estimated 10/26/22); Final bug testing of the app in the UCSF SEC (Estimated 10/30/22); Finalize app based on study data and make available for future researchers (End of Study)

Timeline: Months 1-7; Actual Completion: 99%

SITE: SFVAMC+UCSF, Collaboration of all PI's: Woolley, O'Donovan, Anguera

Major Task 3: Recruit and enroll participants

Subtasks include: develop study-specific website for recruitment (Completed 08/31/21); creation of advertisements for online platforms (Completed 3/30/20); contact local organizations that can post advertisements in newsletters and develop plan for circulating flyers (Completed 6/30/21); finalize study website (Completed 8/30/21); created social media accounts for recruitment (Completed 10/25/20); compile list of subreddits and craigslist locations for study ad placement (Completed 9/13/22); optimized study operation and recruitment protocols given evolving landscape (Completed 9/29/22); place ads on social media and begin recruitment and enrollment (Predicted 10/30/22); enroll participants (Predicted 10/31/22).

Timeline: Months 7-30; Actual Completion: 50%

SITE: UCSF, Site-PI: Anguera (Collaboration with PIs Woolley and O'Donovan)

Major Task 4: De-identify and transfer data

Timeline: Month 30

SITE: UCSF, Site-PI: Anguera (Collaboration with PIs Woolley and O'Donovan)

Major Task 5: Analyze data, present poster, begin manuscript preparation

Timeline: Months 31-33

SITE: SFVAMC, PI's: Woolley, O'Donovan

b. What was accomplished under these goals?

During the past year, our attention was focused on Major Task 2 and specifically, on overcoming issues that we discovered related to our original app development company CodeBrew Inc. During 2021 and early 2021, the company experienced major disruption due to COVID-19. Further, during early-mid 2021, we observed major personnel changes at CodeBrew Inc, with high levels of instability in the team working on our app. As a result of these personnel changes, we had to engage in large amounts of knowledge transfer multiple times, repeatedly explaining our app and its functionality to new managers. Despite the advanced stage of development of the app, we lost complete faith in the development team when they were unable to deliver the final functions of our app and we were discovering new bugs as

they attempted to resolve issues. Thus, during the Fall of 2021, we left CodeBrew Inc and moved the task of finalizing our app and backend to a new development company, Alternova Inc. Thankfully, our new app developer Alternova are outstanding, completing app development, fixing bugs left by CodeBrew, and deploying the app on their own servers. We have done extensive testing on the new app and it is functioning reliably in all conditions. Moreover, Alternova were highly responsive when we experienced any cosmetic or functional issues with the app, resolving them quickly and at a high level of quality. Due to relatively limited budgets and cultural differences, developing an app is highly challenging within an academic setting and we are relieved to have found an outstanding partner for this effort in Alternova Inc.

For Majors Task 1 and 2, the final task is to move the app from the Alternova servers to our own servers with the approval of UCSF IT. Both the PIs (O'Donovan/Woolley) and Site PI (Anguera) have extensive experience conducting digital health projects with apps at UCSF. On all previous occasions, apps collected only deidentified data and were launched outside of the UCSF Secure Enterprise Cloud (SEC), which is a cloud service at UCSF designed to provide a secure computing environment, but previously used only for apps collecting protected health information and personal identifiable information. To our knowledge, we are the first app with deidentified data that is required to launch within the SEC, which is why we did not foresee this delay. In the past few weeks, we have developed expertise on this SEC, worked with UCSF Central IT Secure Enterprise Solution Architects, and have navigated moving our app to this SEC with Alternova. Our UCSF contact estimates 2-3 weeks to move the app and deploy with all of the benefits provided by the UCSF SEC. Ultimately, this will benefit the project in terms of providing greater security for all data that we collect, but unfortunately has caused another delay. As stated, we have been given an estimate of 2-3 weeks to complete this approval process (Estimated completion date: 10/21/22)

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

Nothing to report.

• How were the results disseminated to communities of interest?

Nothing to report.

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

App Deployment: As mentioned above, we have had to move our fully functioning app to the UCSF SEC, which involves extra review by UCSF IT. UCSF IT have given us an estimate of 2-3 weeks from 9/27/22 to complete this process.

Recruitment: We greatly look forward to launching our recruitment efforts for this project. We have prepared all protocols, materials, and standard operating procedures for this project and will be ready to launch as soon as the app is finalized and approved by the CHR and HRPO. We also have a fully functioning website that is already receiving attention.

We plan to accomplish the following goals in our next reporting period: Begin recruitment and data collection on 10/30/22, aiming to recruit approximately 150 participants per month. Based on previous experience as well as the extensive research we have conducted regarding recruitment techniques, this is a realistic goal.

4. IMPACT:

a. What was the impact on the development of the principal discipline(s) of the project?

Nothing to report.

b. What was the impact on other disciplines?

Nothing to report.

c. What was the impact on technology transfer?

The final mobile application and online backend will be delivered to the Department of Defense to allow for use by other investigators that may be able to deploy the app for future studies.

d. What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS:

a. Changes in approach and reasons for change

Nothing to report.

b. Actual or anticipated problems or delays and actions or plans to resolve them

This project has had multiple delays, many of them due to COVID-19 issues within our original app development company Code Brew, and new delays due to **new** UCSF requirements that our app be deployed within the UCSF SEC. To deal with these delays, we have found a new app development company with whom we have created a fully functioning app, worked with UCSF IT Security team to understand security requirements for the app, developed a plan to launch the app using the UCSF SEC, and coordinated between Alternova and UCSF IT to launch within UCSF SEC.

As a result of pandemic-related losses in administrative staff, we have experienced exceptional delays within UCSF during the past year because everyone's workload is higher. One potential issue is that it will take longer than UCSF IT have promised (2-3 weeks) for them to deploy our app within the SEC. In

order to move things along, we are staying in constant contact with UCSF IT and Alternova to ensure the smooth transfer of the app to the UCSF SEC.

We now expect to begin enrollment of participants one week after migrating to the app to the UCSF SEC, after completing some final checks to ensure that the app is working as intended in the SEC (Estimated enrollment date: 10/31/22). Our plan to ensure the overall success of the project is to request a one-year no cost extension and dedicate resources to recruitment and to the development of systems that will allow us to automate as much of the study as possible when recruitment takes off. For example, much of our clinical trials management will be automated using the software Ripple, which will allow us to run many more participants at once than would otherwise be possible.

c. Changes that had a significant impact on expenditures

Our expenditure is less than expected as no participant costs have incurred and we have conserved funds by removing our Study Coordinator during these delays. We expect to use these funds in the next year of the award as we will enroll all participants in the upcoming year.

d. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

e. Significant changes in use or care of human subjects

Nothing to report.

f. Significant changes in use or care of vertebrate animals

g. Significant changes in use of biohazards and/or select agents

6. PRODUCTS:

a. Publications, conference papers, and presentations

i. Journal publications.

1. Nothing to report

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

1. Nothing to report

iii. Other publications, conference papers, and presentations.

1. Nothing to report

b. Website(s) or other Internet site(s)

1. We have developed a study website to facilitate recruitment and screening as well as appropriate dissemination of study information and data.

c. Technologies or techniques

- i. Both the mobile application as well as the online backend will be given to the DoD upon the completion of this project. The backend allows researchers to customize questions, duration of cognitive training, and the specific protocol for cognitive training. The mobile app collects all pertinent data. All code that is necessary to run either the application or the backend will be sent to the proper administrator as requested. Further, we will provide a written description of all functionalities of the app and backend.

d. Inventions, patent applications, and/or licenses

- 1. Nothing to report

e. Other Products

- 1. Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

a. What individuals have worked on the project?

Name: Paige Tripp
Project Role: Study Coordinator
Nearest person month worked: 22
Contribution to Project: No change

Name: Aoife O'Donovan
Project Role: Co-PI
Nearest person month worked: 19
Contribution to Project: No change

Name: Joshua Woolley
Project Role: Co-PI
Nearest person month worked: 10
Contribution to Project: No change

Name: Jennifer Mitchell
Project Role: UCSF Site PI
Nearest person month worked: 2
Contribution to Project: Dr. Mitchell has recently taken on a new role at the SFVAMC and is no longer available to work on the project. Her role as site-PI has been reassigned to Dr. Joaquin Anguera (approval received 5/14/2020).

Name: Joaquin Anguera
Project Role: UCSF Site PI
Nearest person month worked: 7
Contribution to Project: Dr. Anguera has taken over all roles and responsibilities previously held by Dr. Jennifer Mitchell

Name: Thomas Neylan
Project Role: Co-I
Nearest person month worked: 8
Contribution to Project: No change

Name: Phillip Quartana

Project Role: Co-I
Nearest person month worked: 4
Contribution to Project: No change

- b. **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Nothing to report.

- c. **What other organizations were involved as partners?**

1. **Organization Name:** University of California, San Francisco
2. **Location of Organization:** San Francisco, CA
3. **Partner's contribution to the project**
 - a. **Financial support;**
 - b. **In-kind support**
 - c. **Facilities:** All study procedures and activities involving identifiable participant data will be collected and accessed at the UCSF site. Only de-identified data will be transferred back to the SFVAMC for final data analysis.
 - d. **Collaboration:** Dr. Joaquin Anguera (UCSF site-PI) has provided his expertise in mobile application development and studies to ensure optimal results of the technology and protocols. All study PI's (Woolley, O'Donovan, Anguera) collaborate to ensure the progression of preparation and oversight.
 - e. **Personnel exchanges:** The study team will have access to Dr. Anguera's UCSF facilities while running participants through the study protocols.
 - f. **Other**

8. **SPECIAL REPORTING REQUIREMENTS**

- a. **COLLABORATIVE AWARDS:**

- b. **QUAD CHARTS:**

9. **APPENDICES:** *None.*