APPLICATION FOR FEDERAL ASSISTANCE

SF 424 R&R

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION

❍Pre-application ●Application ❍Changed/Corrected Application

2. DATE SUBMITTED

Applicant Identifier

4. a. Federal Identifier

b. Agency Routing Identifier

c. Previous Grants.gov Tracking ID

5. APPLICANT INFORMATION **Organizational DUNS:** 092530369

Legal Name: The Regents of the University of California, Los Angeles

Department: Division:

Street1: Office of Contract and Grant Administration Street2: 10889 Wilshire Boulevard, Suite 700

City: Los Angeles County/Parish: Los Angeles County State: CA: California

Province: Country: USA: UNITED STATES ZIP / Postal Code: 90095-1406

Person to be contacted on matters involving this application

Prefix:	First Name:	Middle Name:	Last Name:	Suffix:
Mr.	Evan		Garcia	

Position/Title: Grant Officer

Street1: 10889 Wilshire Boulevard, Suite 700 Street2:

City: Los Angeles County/Parish: Los Angeles County State: CA: California

Province: Country: USA: UNITED STATES ZIP / Postal Code: 90095-1406

Phone Number: 310-794-0171 Fax Number: 310-943-1658 Email: ocga3@research.ucla.edu

6. EMPLOYER IDENTIFICATION NUMBER*(EIN) or (TIN)*: 1-956006143-A1

7. TYPE OF APPLICANT: H: Public/State Controlled Institution of Higher Education

Other (Specify):

Small Business Organization Type ❍Women Owned ❍Socially and Economically Disadvantaged

8. TYPE OF APPLICATION:

●New ❍Resubmission

❍Renewal ❍Continuation ❍Revision

If Revision, mark appropriate box(es).

❍A. Increase Award ❍B. Decrease Award ❍C. Increase Duration

❍D. Decrease Duration ❍E. Other*(specify)*:

Is this application being submitted to other agencies? ❍ Yes ● No What other Agencies?

9. NAME OF FEDERAL AGENCY:

National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER:

TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:

Probing Inflammation and Reward Sensitivity in Alcohol Use Disorder

12. PROPOSED PROJECT:

Start Date	Ending Date
09/01/2020	08/31/2023

13. CONGRESSIONAL DISTRICT OF THE APPLICANT:

CA-033

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix:	First Name:	Middle Name:	Last Name:	Suffix:
	Elizabeth		Burnette	

Position/Title: Graduate Student Researcher
Organization Name: The Regents of the University of California, Los Angeles
Department: Psychology
Division: College of Letters and Science
Street1: UCLA Department of Psychology
Street2: Psychology Building, Box 156304
City: Los Angeles
County/Parish: Los Angeles County
State: CA: California
Province:
Country: USA: UNITED STATES
ZIP / Postal Code: 90095-1406
Phone Number: 310-206-6756
Fax Number:
Email: eburnette@g.ucla.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested	$129,798.00
b. Total Non-Federal Funds	$0.00
c. Total Federal & Non-Federal Funds	$129,798.00
d. Estimated Program Income	$0.00

16. IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?

a. YES ❍ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR

❍ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree

The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.

18. SFLLL or other Explanatory Documentation. File Name: Mime Type:

19. Authorized Representative

Prefix:	First Name:	Middle Name:	Last Name:	Suffix:
Mr.	Evan		Garcia	

Position/Title: Grant Officer
Organization Name: The Regents of the University of California, Los Angeles
Department: Office of Contract & Grant Adm
Division:
Street1: 10889 Wilshire Boulevard, Suite 700
Street2:
City: Los Angeles
County/Parish: Los Angeles County
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Province:
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Signature of Authorized Representative **Date Signed**

20. Pre-application File Name: Mime Type:

21. Cover Letter Attachment File Name: Burnette_NRSA_FINAL_CoverLetter1059942805.pdf Mime Type: application/pdf

UNIVERSITY OF CALIFORNIA, LOS ANGELES **UCLA**

BERKELEY • DAVIS • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO SANTA BARBARA • SANTA CRUZ

ELIZABETH MAR BURNETTE
NEUROSCIENCE INTERDEPARTMENTAL PHD PROGRAM
DEPARTMENT OF PSYCHOLOGY
1285 FRANZ HALL
LOS ANGELES, CALIFORNIA 90095-1563

April 8, 2020

Division of Receipt and Referral
Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Rockledge II, MSC – 7768

RE: PA-19-195 – Ruth L. Kirschstein National Research Service Award Individual Predoctoral Fellowship (F31) Application

Dear Division of Receipt and Referral,

It is with great enthusiasm that I submit this F31 Ruth L. Kirschstein National Research Service Award Individual Predoctoral Fellowship (F31) application, entitled Probing Inflammation and Reward Sensitivity in Alcohol Use Disorder. The objective of this NRSA application is to foster my development in the fields of clinical addictions neuroscience, reward learning, and psychoneuroimmunology. To do this, the proposed study includes an endotoxin-induced inflammatory challenge in a sample of non-treatment-seeking participants with Alcohol Use Disorders and healthy controls, while measuring their mood, reward sensitivity, and inflammatory cytokine levels throughout the challenge.

The Sponsor of this application is Dr. Lara Ray at the University of California, Los Angeles. In addition, I will be collaborating with two other faculty members in UCLA's Department of Psychology, Dr. Naomi Eisenberger and Dr. Kate Wassum.

I respectfully request that this application be routed to the following area:
Institute/Center: National Institute on Alcohol Abuse and Alcoholism – NIAAA
The reason for this request is that the conclusions and expected results of the proposed study will directly contribute to our understanding of mechanisms underpinning Alcohol Use Disorder.

The following is a list of application referees:
Jamie D. Feusner, M.D. – Professor, Psychiatry and Biobehavioral Sciences, University of California, Los Angeles
Andrew F. Leuchter, M.D. – Director, Transcranial Magnetic Stimulation Clinical and Research Program, University of California, Los Angeles
Erin G. Piker, Ph.D. – Director, Vestibular Sciences Laboratory, James Madison University

Thank you for your consideration, and I look forward to receiving feedback on this proposal.

Sincerely,

Elizabeth Mar Burnette
Neuroscience Interdepartmental Ph.D. Program
Department of Psychology
University of California, Los Angeles

Project/Performance Site Location(s)

Project/Performance Site Primary Location

Organization Name: The Regents of the University of California, Los Angeles

* Street1: 502 Portola Plaza		Street2: Psychology Building, Room A349
* City: Los Angeles	County: Los Angeles County	* State: CA: California
Province:	* Country: USA: UNITED STATES	* Zip / Postal Code: 90095-1563
DUNS Number: 092530369	* Project/Performance Site Congressional District: CA-033	

File Name	Mime Type

Additional Location(s)

RESEARCH & RELATED Other Project Information

1. * Are Human Subjects Involved? ● Yes ❍ No

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ❍ Yes ● No

If yes, check appropriate exemption number

Exemption Number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6 _ 7 _ 8

If no, is the IRB review Pending? ● Yes ❍ No

IRB Approval Date:

Human Subject Assurance Number 00004642

2. * Are Vertebrate Animals Used? ❍ Yes ● No

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ❍ Yes ❍ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. * Is proprietary/privileged information included in the application? ❍ Yes ● No

4.a. * Does the Project have an Actual or Perceived Impact – positive or negative – on the environment? ❍ Yes ● No

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ❍ Yes ❍ No

4.d. If yes, please explain:

5.a. * Is the research performance site designated, or eligible to be designated, as a historic place? ❍ Yes ● No

5.b. If yes, please explain:

6.a. * Does this project involve activities outside the U.S. or partnership with International Collaborators? ❍ Yes ● No

6.b. If yes, identify countries:

6.c. Optional Explanation:

7. Project Summary/Abstract	Burnette_NRSA_FINAL_Abstract1060019827.pdf	Mime Type: application/pdf
8. Project Narrative	Burnette_NRSA_FINAL_ProjectNarrative1059942802.pdf	Mime Type: application/pdf
9. Bibliography & References Cited	Burnette_NRSA_FINAL_References1059942806.pdf	Mime Type: application/pdf
10. Facilities & Other Resources	Burnette_NRSA_FINAL_FacilitiesResour1059942803.pdf	Mime Type: application/pdf
11. Equipment	Burnette_NRSA_FINAL_Equipment1059942804.pdf	Mime Type: application/pdf

Project Summary / Abstract

The proposed predoctoral NRSA aims to examine the role of neuroinflammation in modulating reward response and negative mood in Alcohol Use Disorder (AUD). Chronic alcohol exposure has been shown in animal models to increase both neural and systemic markers of inflammation. Alcohol-induced inflammation has been linked to both chronic alcohol seeking and the behavioral and neurotoxic effects of alcohol. However, the literature on inflammatory signaling and AUD is overwhelmingly preclinical and it is unknown if this relationship can be extrapolated to humans. Therefore, translation to clinical samples is necessary. In humans, addiction is often conceptualized as a reward deficit disorder. Negative emotionality is also implicated in AUD, such that individuals with AUD demonstrate higher levels of negative mood, with a high comorbidity between mood disorders and AUD. Neuroinflammation is associated with negative emotionality, such that cytokines have been shown to play a causal role in the onset of negative mood. Further, brain activation in response to reward stimuli is decreased after inflammation-provoking endotoxin infusion. However, associations between AUD, inflammation, and behavioral outcomes have not yet been established.

The proposed study aims to fill this gap in the literature by examining the role of inflammation in negative mood and reward response in a clinical sample of individuals with AUD and light-drinking healthy controls. We will experimentally provoke a systemic inflammatory response, measurable by plasma levels of proinflammatory cytokines. Participants will receive a low dose of endotoxin that has been shown to increase cytokine levels without significant changes in vital signs, therefore safely and acutely mimicking a low-grade inflammatory response. Over the course of 4 hours post-infusion of endotoxin (or placebo) – during which cytokine levels peak at 2 hours and return to near-baseline by hour 4 – participants will be assessed for negative mood at hourly intervals and reward response at peak (hour 2). The first aim of the project is to examine the effects of neuroinflammation on negative mood in AUD versus controls. The second aim is to examine the effects of acute inflammation on reward response in AUD and controls. This proposal's findings will help to elucidate the role that inflammation plays in modulating mood and reward response in AUD.

In addition to these study aims, the proposed F31 will provide me with a breadth of training in psychoneuroimmunology and clinical addictions neuroscience with a focus on the psychobiology of reward, through coursework, collaboration with experts in these fields, and career development including presentations at journal clubs and conferences. This training will take place in Dr. Lara Ray's Addictions Lab, which utilizes a broad range of laboratory techniques to understand the causes and correlates of substance use disorders. This lab is located at UCLA, a world-class research and training environment.

Project Narrative

Reward sensitivity and negative emotionality have been separately associated with both neuroinflammation and Alcohol Use Disorder (AUD), but the associations between inflammation, AUD, and behavioral outcomes have not been established in humans. The proposed study will provoke inflammation while assessing negative mood, reward response, and inflammatory markers in individuals with AUD and healthy controls. Probing the role of neuroinflammation in modulating negative mood and reward response in AUD will help elucidate novel underpinnings of AUD pathophysiology.

References

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4. Cui, C., L. Grandison, and A. Noronha, *Neuroimmune mechanisms of brain function and alcohol related disorders.* Brain Behav Immun, 2011. **25 Suppl 1**: p. S1-3.
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Facilities and Resources

Ray Laboratory: The proposed project will be conducted in the Sponsor's (Dr. Lara Ray) Addictions Research Laboratory in the Psychology Department at the University of California, Los Angeles (UCLA). Dr. Ray's lab has been newly renovated and includes a large main chamber with a reception area and eleven work stations as well as six separate behavioral and psychophysiological testing rooms. All initial telephone and in-person screening visits will be conducted in the Sponsor's laboratory. The laboratory is easily accessible by public transportation and ample parking for research participants is provided in a parking lot immediately adjacent to the laboratory.

The Westwood/UCLA Clinical & Translational Research Center: To determine eligibility for the project, participants will have physical examinations conducted at the Westwood/UCLA Clinical & Translational Research Center (CTRC). The CTRC is divided into two separate units: an inpatient unit (3,100 square feet) that has just opened in the new hospital and an outpatient unit. The UCLA CTRC averages over 5,000 outpatient visits/year (110% of awarded), and between 1,200 and 1,400 inpatient days (100% of awarded), with more than 85% of that activity dedicated to investigator-initiated protocols. The proposed screening physical examinations as well as endotoxin/placebo administration will be conducted at the outpatient unit of the UCLA CTRC. The Sponsor currently has two studies approved and active at the UCLA CTRC, and the CTRC is walking distance from the Sponsor's laboratory.

Animals: N/A

Office: The Department of Psychology at UCLA will provide meeting space, office space, and furniture for the project investigator, research staff, and administrative staff associated with this project.

Other: The Department of Psychology at UCLA owns and operates an extensive network of facilities and services. These facilities are connected to departments through high-speed networks. UCLA has building-wide LocalTalk and Ethernet networks, which are connected to the campus network through a high-speed T1 connection and allow access to these powerful services. Full-time computer support staff is available to the research team. UCLA also has an extensive library system and photographic services for poster printing. Lastly, computers in the Sponsor's lab have access to the UCLA libraries and to electronic versions of most relevant scientific journals.

Equipment

The Sponsor's laboratory contains the following equipment for clinical addictions research: 7 desktop computers, 4 PC laptops, 3 mac laptops, 3 breathalyzers, 2 carbon monoxide monitors, 2 freezers (-20) for collection and storage of biological samples, 3 printers, 1 fax machine, and 2 heart rate monitors. In addition, the laboratory has purchased extensive software to support specialized data acquisition and analysis, such as SPSS, SAS, EQS, Matlab, Inquisit, Media Lab, Qualtrics, and E-prime.

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: First Name*: Elizabeth Middle Name Last Name*: Burnette Suffix:

Position/Title*:	Graduate Student Researcher
Organization Name*:	The Regents of the University of California, Los Angeles
Department:	Psychology
Division:	College of Letters and Science
Street1*:	UCLA Department of Psychology
Street2:	Psychology Building, Box 156304
City*:	Los Angeles
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Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	90095-1406

Phone Number*: 310-206-6756 Fax Number: E-Mail*: eburnette@g.ucla.edu

Credential, e.g., agency login: EBURNETTE

Project Role*: PD/PI Other Project Role Category:

Degree Type: BS Degree Year: 2014

	File Name
Attach Biographical Sketch*:	Bur-nette_NRSA_FINAL_Biosketch1059942796.pdf
Attach Current & Pending Support:	

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Lara Middle Name A. Last Name*: Ray Suffix:

Position/Title*:	Assistant Professor
Organization Name*:	The Regents of the University of California, Los Angeles
Department:	Psychology
Division:	College of Letters and Science
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County:	Los Angeles County
State*:	CA: California
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	90095-1563

Phone Number*: 310-206-6756 Fax Number: 310-267-1905 E-Mail*: lararay@psych.ucla.edu

Credential, e.g., agency login: LARA_RAY

Project Role*: Other (Specify) Other Project Role Category: Sponsor

Degree Type: PhD Degree Year: 2007

	File Name
Attach Biographical Sketch*:	NRSA_Burnette_Ray_Biosketch1060080077.pdf
Attach Current & Pending Support:	

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Naomi Middle Name Last Name*: Eisenberger Suffix:

Position/Title*:	Professor
Organization Name*:	The Regents of the University of California, Los Angeles
Department:	Psychology
Division:	
Street1*:	5514 Pritzker Hall
Street2:	
City*:	Los Angeles
County:	Los Angeles
State*:	CA: California
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	90095-1563

Phone Number*: 310-267-5196 Fax Number: 310-206-5895 E-Mail*: neisenbe@ucla.edu

Credential, e.g., agency login: EISENBERGER2

Project Role*: Consultant Other Project Role Category:

Degree Type: PhD Degree Year: 2005

	File Name
Attach Biographical Sketch*:	COLLABORAT-OR_Eisenberger_Biosketch1060019283.pdf
Attach Current & Pending Support:	

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Kate Middle Name Last Name*: Wassum Suffix:

Position/Title*:	Principal Investigator
Organization Name*:	The Regents of the University of California, Los Angeles
Department:	Psychology
Division:	
Street1*:	8550 Pritzker Hall
Street2:	
City*:	Los Angeles
County:	Los Angeles County
State*:	CA: California
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	90095-1563

Phone Number*: 310-825-5543 Fax Number: E-Mail*: kwassum@ucla.edu

Credential, e.g., agency login: WASSUMK2

Project Role*: Consultant Other Project Role Category:

Degree Type: PhD Degree Year: 2009

	File Name
Attach Biographical Sketch*:	COLLABORAT-OR_Wassum_Biosketch1060019282.pdf
Attach Current & Pending Support:	

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Elizabeth Mar Burnette

eRA COMMONS USER NAME (credential, e.g., agency login): EBURNETTE

POSITION TITLE: Graduate Student Researcher

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
Duke University, Durham, N.C.	B.S.	08/2014	05/2018	Neuroscience
University of California, Los Angeles, C.A.	Ph.D.	09/2018	Expected: 09/2023	Neuroscience

A. Personal Statement

The central focus of my F31 application is to advance my training in psychoneuroimmunology and the clinical neuroscience of addiction through the investigation of neuroinflammation's role in reward responsivity and negative emotionality in Alcohol Use Disorder (AUD). The proposed study will be the first human endotoxin challenge in the context of AUD, using low-dose endotoxin derived from E. Coli to provoke systemic inflammation. The study will also include assessments of reward sensitivity and negative mood, as well as proinflammatory cytokine levels. The findings from this proposal will help to elucidate the causal role that inflammation plays in modulating mood and reward response among individuals with AUD.

My undergraduate and graduate training have provided me with an excellent background in translational neuroscience. As an undergraduate at Duke University, my most important research contributions were in the study of vestibular disorders and the development of a novel rodent model of Anorexia Nervosa to study disordered eating. Throughout my time at Duke, I worked with rodents, non-human primates, and humans, but concluded when it came time to start my graduate career that working in a clinical, human setting was most fitting for my direct translational interests. I am now applying this interest in translational and clinical research toward the study of AUD and am immensely excited for this opportunity to combine my undergraduate experience in pharmacology with my graduate experience in clinical neuroscience, specifically related to AUD.

As a graduate student at UCLA, I expanded my clinical research skills through a set of three rotations in my first year as a graduate student, after which I permanently joined the lab of Dr. Lara Ray (Sponsor). With Dr. Ray's expertise in the clinical neuroscience of addiction, as well as her strong interdepartmental collaborations, successful track record with graduate students, and consistent publication record, I am confident she will be an excellent mentor in my graduate training experience. Over the past year as a student in the Ray lab, I have focused on investigating bio-behavioral markers of AUD, most recently studying the intersection between AUD and impulsive / risk-taking behavior. In the proposed project, I will continue to build on my AUD research, but will be transitioning to a psychoneuroimmunology-based approach to explore the role of neuroinflammation in negative emotionality and reward sensitivity in AUD.

My success in the classroom and the lab at UCLA and Duke, as well as my dedication to and passion for my research, make me a well-suited candidate for this F31 fellowship. This NRSA research proposal will allow me to develop my knowledge base and skills in psychoneuroimmunology and clinical addictions neuroscience with a focus on the psychobiology of reward. The training portion of the proposed NRSA will allow me to enhance my skills in conducting well planned out scientific studies, learning from coursework, colloquia, and individual meetings with mentors, and communicating my research through presentations, posters, and scientific journal articles. Together, the successful completion of my NRSA research and training application will prepare me to work towards a career as a human neuroscientist in the field of addictions research.

Most relevant publication to this proposal:

Burnette, E.M., Grodin, E.N., Lim, A.C., MacKillop, J., Karno, M., & Ray, L.A. (2019). Association between impulsivity and neural activation to alcohol cues in heavy drinkers. *Psychiatry Research: Neuroimaging, 293.* PMID: 31622796.

B. Positions and Honors

Positions and Employment

2014	High School Research Intern, Stanford University
2015-2018	Undergraduate Student Researcher, Duke University
2016	Lab Manager, Duke University
2018 -	Graduate Student Researcher, UCLA
2019 -	Graduate Teaching Assistant, UCLA

Professional Memberships

Society for Neuroscience
Sigma Xi Research Honor Society
Organization for Human Brain Mapping
APA Division 50 – Society of Addiction Psychology
Research Society on Alcoholism

Academic Honors

2014	National Merit Scholarship
2017	Duke Summer Neuroscience Program Research Fellowship
2018	Sigma Xi Research Honor Society
2018	Graduation with Distinction in Neuroscience
2018	*Cum Laude*
2019	Phi Beta Kappa

C. Contributions to Science

C.1. Undergraduate Research

I first started to pursue clinical neuroscience research at Duke, in the Duke Vestibular Disorders clinic. With Dr. Erin Piker and Dr. Dennis Frank-Ito, I studied the binaural bithermic caloric test (widely used to assess vestibulo-ocular reflex) and found that there existed considerably more inter- and intra-individual variability in test results than previously thought, but that there were no significant effects of the order of the four (left/right, cold/warm) irrigations used in the test. A first-author publication resulted from this work in 2018.

Under Dr. Cynthia Kuhn in Duke's Department of Pharmacology, I worked to develop a novel rodent model to study disordered eating, based on conditioned food aversion, to more accurately reflect human eating disorder phenotypes including gut hypersensitivity, self-imposed food restriction, female dominance, and adolescent onset. Sex and age behavioral differences found in this model have led to ongoing research in Dr. Kuhn's lab regarding possible neural mechanisms underlying these differences, and I continue to consult with a current graduate student in the Kuhn lab on her project, which builds on my work. This work resulted in a poster which I presented at the Society for Neuroscience meeting in 2017, and my undergraduate honors thesis, which earned departmental distinction, in 2018. I was the lead researcher on both projects.

Publications

Burnette, E., Piker, E.G. & Frank-Ito, D. (2018). Reevaluating order effects in the binaural bithermic caloric test. *American Journal of Audiology*, *27*(1), 104-109. PMID: 29383375

Posters

Burnette, E., Ocampo, G., Wander, R., Walker, Q., Zucker, N. & Kuhn, C. (2017). Adolescents show conditioned food aversion: A strategy to study disordered eating? Poster presented at the meeting of the Society for Neuroscience, Washington, D.C.

C.2. Graduate Rotations Research

As a first-year graduate student in UCLA's Neuroscience program, I completed three laboratory rotations (the last of which was in the Ray lab, which I joined permanently). In my first rotation, under Dr. Jamie Feusner, I was introduced to functional magnetic resonance imaging (fMRI) studies. During my rotation in the Feusner lab, I led a study on neural activity in reward and anxiety networks to predict reward and anxiety psychometric scores within a clinical sample of patients with Anorexia Nervosa (AN) as well as controls. We found that anxiety network activity may negatively impact the subjective experience of reward in both groups. Furthermore, eating disorder symptomology seemed more directly related to reward network activity, but may also be indirectly related to anxiety network activity through reward network inhibition, providing a potential

novel direction for treatments for AN focusing on reducing the effects of anxiety network activation on a patient's ability to experience reward. I presented this work as a poster at the Organization for Human Brain Mapping in June 2019.

In my second rotation, under Dr. Andrew Leuchter, I gained more clinical experience, interacting directly with Major Depressive Disorder patients in the Transcranial Magnetic Stimulation (TMS) clinic. I assessed the efficacy of repetitive TMS on depressive symptoms and cognitive control, finding that rTMS significantly reduced depressive symptoms as well as reaction time (psychomotor speed) and cognitive control on the Stroop color-word task. A manuscript resulting from this work, on which I am second author, is currently in press.

Publications

Corlier, J., **Burnette, E.,** Wilson, A., Lou, J., Minzenberg, M., & Leuchter, A.F. (2020). Effect of repetitive transcranial magnetic stimulation (rTMS) treatment of major depressive disorder (MDD) on cognitive control. *Journal of Affective Disorders, 265,* 272-277. PMID: 32090751

Posters

Burnette, E., Moody, T.D., Wu, M.S., Sheen, C., Goldbeck, J., Strober, M., & Feusner, J. (2019). Reward and anxiety network activity predicts psychometrics in anorexia nervosa and anxious controls. Poster presented at the meeting of the Organization for Human Brain Mapping, Rome, Italy.

C.3. Alcohol Use Disorder Research

I have selected to focus my PhD training in addiction science, joining the UCLA Addictions Lab under Dr. Lara Ray (Sponsor). The overarching theme of my research is addiction neurobiology in human clinical populations, with a focus on reward learning. Beginning in my rotation, I studied the neural substrates of impulsivity in Alcohol Use Disorder (AUD), finding that two different measures of impulsivity (i.e. delayed reward discounting and the sensation-seeking UPPS-P Impulsive Behavior subscale) were associated with alcohol taste cue elicited neural activation in different circuits (frontoparietal and frontostriatal regions, respectively). This association indicates that sensation seeking was associated with reward responsivity, while delay discounting was associated with recruitment of self-control circuitry in individuals with AUD. This work resulted in a first-author publication in 2019, as well as a poster given by Dr. Erica Grodin at the International Conference on Applications of Neuroimaging to Alcoholism in July 2019. I will also be presenting this work as part of a symposium at the (now-cancelled) Collaborative Perspectives on Addiction meeting in April 2020.

Related to this project, I am currently studying neural activation during risk-taking behavior (as measured by the Balloon Analog Risk Task, BART) as correlated with AUD severity, and found that participants with more severe AUD showed stronger frontal pole activation during higher-risk explosion events, possibly indicating that subjects with more severe AUD do not form logical expectations of explosion as risk level increases, so they may experience more surprise or subjective loss during an explosion event. Participants with more severe AUD also showed stronger precuneus activation during cash-out events regardless of risk level, a region previously shown to be part of a frontoparietal network involved in self-control. I plan to give a poster presentation on this work at the Research Society on Alcoholism meeting in June 2020 and am following up this study by collaborating with Dr. Edythe London to compare this AUD sample against matched controls. I am the lead researcher on both of these projects.

Publications

Burnette, E.M., Grodin, E.N., Lim, A.C., MacKillop, J., Karno, M., & Ray, L.A. (2019). Association between impulsivity and neural activation to alcohol cues in heavy drinkers. *Psychiatry Research: Neuroimaging, 293.* PMID: 31622796.

Lim, A.C., Green, R., Grodin, E.N., Venegas, A., Meredith, L.M., Donato, S., **Burnette, E.,** & Ray, L.A. (2020). Alcohol cue-induced ventral striatum activity predicts subsequent alcohol self-administration. *Under review.*

Posters and Symposia

Grodin, E.N., **Burnette, E.**, Lim, A.C., MacKillop, J., Karno, M. & Ray, L.A. (2019). Association between impulsivity and neural activation to alcohol cues in heavy drinkers. Poster presented at the International Conference on Applications of Neuroimaging to Alcoholism, New Haven, CT.

Burnette, E.M., Grodin, E.N., Lim, A.C., MacKillop, J., Karno, M., & Ray, L.A. (2020*). Association

between impulsivity and neural activation to alcohol cues in heavy drinkers. In E.N. Grodin (Chair), *Translational Studies in Alcohol Use Disorder*. Symposium accepted for the Collaborative Perspectives on Addiction Annual Meeting, San Diego, CA. *Meeting cancelled due to COVID-19.

Burnette, E.M., Grodin, E.N., & Ray, L.A. (2020). Risk taking and Alcohol Use Disorder Severity: An fMRI study. Poster to be presented at the Research Society on Alcoholism meeting, New Orleans, LA.

A full list of published works can be found in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/elizabeth.burnette.1/bibliography/public/

D. Scholastic Performance

YEAR	COURSE TITLE	GRADE	YEAR	COURSE TITLE	GRADE
		DUKE UNIVERSITY			
	SCIENCE COURSEWORK			**NON-SCIENCE COURSEWORK**	
2014	Core Concepts in Chemistry	B	2014	Intermediate Chinese I	A
2014	Languages, Lesions, and Loss	A+	2014	Law, Ethics, and Responsibility	A
2014	Special Topics in Cognitive Neuroscience and Law	S	2014	Marching Band	S
2015	Introduction to Computer Science	A	2015	Intermediate Chinese II	A-
2015	Biological Basis of Behavior	A	2015	Theory and Practice of Tonal Music I	A
2015	General Physics I	A-	2015	Academic Writing	A
2015	Data Analysis and Statistical Inference	A+	2015	Collegium Musicum	S
2015	Genetics and Evolution	B+	2016	Collegium Musicum	S
2015	Brain and Behavior	B	2016	Introduction to Jazz	A+
2015	General Physics II	B+	2016	Advanced Chinese	A
2015	Regression Analysis	B	2016	Writing Across Cultures	A+
2016	Multivariable Calculus	B	2017	Bilingualism	A+
2016	Contemporary Neuroscience Methods	A	2017	Poetic Cinema	A
2016	Research Independent Study	A	2017	Refugee Lives	A
2016	Statistical Probability	B+	2017	Film Music	A
2016	Cell and Molecular Neurobiology	A	2017	Collegium Musicum	S
2016	Medical Anthropology	A	2017	Sound, Music, and Moving Image	A
2016	Introductory Astrophysics	A	2017	Music History: Antiquity through Renaissance	A
2017	Honors Thesis Independent Study 1	A			
2017	Fundamentals of Neuroscience	A+			
2017	Neuroscience and Multilingualism	A+			
2017	Honors Thesis Independent Study 2	A			
2018	Current Research in Neuroscience	A-			
2018	Nature and Treatment of Eating Disorders	A+			
2018	Honors Thesis Independent Study 3	A			

Grading: Duke University offers half-credit courses on a Satisfactory/Unsatisfactory basis, which do not count toward GPA. S denotes a grade of C or higher.

YEAR	COURSE TITLE	GRADE
	UNIVERSITY OF CALIFORNIA, LOS ANGELES	
2018	Cellular Neurophysiology	A+
2018	Current Research Topics in Neuroimaging	S
2018	Current Literature in Neuroscience A	S
2018	Directed Individual Research	S
2018	Anatomy of the Central Nervous System	A+
2018	Systems Neuroscience	A-
2018	Current Literature in Neuroscience B	S
2018	Directed Individual Research	S
2019	Cell, Developmental, and Molecular Neurobiology	A
2019	Integrity of Scientific Investigation	S
2019	Current Literature in Neuroscience C	S
2019	Current Research Topics in Neuroimaging	S
2019	Directed Individual Research	S
2019	Data Management and Statistical Computing	A
2019	Grant Writing & Evaluation of Research Literature	S
2019	Teaching Apprenticeship Practicum	S
2019	Directed Individual Research	S

Grading: UCLA gives Satisfactory grades for work which would otherwise earn a grade of B or better in graduate/professional level classes.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Lara A. Ray

eRA COMMONS USER NAME (credential, e.g., agency login): LARA_RAY

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
San Diego State University	BA	08/2001	Psychology
University of Colorado at Boulder	MA	04/2004	Clinical Psychology
Brown University Medical School		06/2007	Clinical Internship
University of Colorado at Boulder		08/2007	Behavioral Genetics
University of Colorado at Boulder	PhD	08/2007	Clinical Psychology

A. Personal Statement

I am a licensed clinical psychologist with interdisciplinary training in behavioral genetics and neuroscience. I am a Professor in the Department of Psychology at UCLA. My program of research centers on clinical neuroscience of addiction. My laboratory combines clinical and experimental psychopharmacology with the goal of developing more effective treatments for alcohol use disorders. I have a strong publication record in areas such as human laboratory paradigms for alcoholism, pharmacological interventions development, and clinical neuroscience. I am delighted to support my trainee Elizabeth Burnette in this predoctoral NRSA application. I have worked closely with Ms. Burnette and I am proud of the application we have crafted together. I am confident that the proposed research and training plan will result in high impact science as well as a well-qualified independent clinical neuroscientist. Training bright young scientists, such as Ms. Burnette, is also a key mission of my K24 career award which establishes a solid foundation for training and mentoring young scholars in the field of alcohol research.

B. Positions and Honors

Positions

2001-2002 Professional Research Assistant, Consortium on Genetics of Alcoholism (COGA), University of California San Diego (UCSD)
2002-2007 Doctoral Student in Clinical Psychology, University of Colorado at Boulder, Department of Psychology and Institute for Behavioral Genetics
2006-2007 Clinical Psychology Internship, Brown University Psychology Training Consortium
2007-2008 Postdoctoral Fellow, Brown University Center for Alcohol and Addiction Studies
2008-2013 Assistant Professor (tenure track), University of California Los Angeles (UCLA), Department of Psychology (Clinical Area)
Oct 2008 - Licensed Clinical Psychologist, State of California, License # PSY CA 22240
Apr 2009 - Faculty, Interdepartmental Graduate Program for Neuroscience, University of California Los Angeles (UCLA)
Apr 2009 - Faculty, Brain Research Institute, University of California Los Angeles (UCLA)
Jul 2009 - Faculty, Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles (UCLA)
2013-2016 Associate Professor (with tenure), University of California Los Angeles (UCLA), Department of Psychology (Clinical Area)

Jul 2016 - Full Professor (with tenure), University of California Los Angeles (UCLA), Department of Psychology (Clinical Area)

Other Professional Experience

2010- Associate Editor, Clinical Psychology Science and Practice
2011- Ad Hoc Grant Reviewer, NIAAA Special Emphasis Panel, ZAA1 DD(03)
2011- Ad Hoc Grant Reviewer, VA SPLC/Genetics CSSEC Review Panel
2011- Field Editor, Alcoholism: Clinical and Experimental Research
2012- Ad Hoc Grant Reviewer, NIAAA, AA-2, Epidemiology, Prevention, and Behavior Research
2012- Ad Hoc Grant Reviewer, NIAAA, Work Group for Alcohol Research Centers, ZAA1 GG (60)
2012 *Member*, Consensus Panel on New Pharmacotherapies for Alcohol Use Disorders and Related Comorbidities, SAMHSA and NIAAA Cooperative Meeting
2013- Standing Member, NIAAA, AA-3, Clinical, Treatment, and Health Services Research Committee

Honors and Awards

2002 Fellowship from the National Science Foundation (NSF) and the Alliance for Graduate Education and the Professoriate (AGEP), University of Colorado at Boulder
2004 Alliance for Graduate Education and the Professoriate (AGEP) Travel Award, University of Colorado
2004 Student Merit Award, Research Society on Alcoholism Conference
2005 Alliance for Graduate Education and the Professoriate (AGEP) Travel Award, University of Colorado
2005 Finalist for the Enoch Gordis Research Award, Research Society on Alcoholism Conference
2005 Student Merit Award, Research Society on Alcoholism Conference
2007 Dossier Award for Outstanding Graduate Student Research Department of Psychology, CU Boulder
2007 NIH Loan Repayment Program Award
2007 Psychology Intern Research Poster, 2nd Place, Department of Psychiatry and Human Behavior, Brown Medical School, 11th Annual Research Symposium
2007 Recipient of the Enoch Gordis Research Award, Research Society on Alcoholism
2008 Young Investigator Award, NIAAA-sponsored Conference on Alcoholism and Stress: A framework for
2008 Early Career Presentation Award, American Psychological Association (APA), Division 50 (Addictions)
2008 Student Merit Award, Research Society on Alcoholism Conference
2009 Winter Conference on Brain Research, Young Investigator Travel Fellowship
2010 NIAAA Travel Award, International Society for Biomedical Research on Alcoholism (ISBRA)
2010 Travel Award, American College of Neuropsychopharmacology (ACNP)
Future Treatment Strategies
2013 David Shakow Early Career Award for Distinguished Scientific Contributions to Clinical Psychology, APA Division 12, Society of Clinical Psychology
2013 Early Career Award for Distinguished Scientific Contributions, APA Division 50, Society of Addiction Psychology
2014 Young Investigator Award, Research Society on Alcoholism
2015 Fellow, American Psychological Association Division 50, Society of Addiction Psychology
2017 Distinguished Scientific Award for Early Career Contribution to Psychology, American Psychological Association
2017 Eva King – Killam Research Award, American College of Neuropsychopharmacology
2019 Shirley M. Hatos Term Chair in Clinical Neuropharmacology, UCLA Department of Psychiatry

C. Contribution to Science

1. One program of research in my lab leverages experimental medicine and neuroimaging approaches to develop and optimize medications for nicotine and alcohol addiction. There is a strong positive association between cigarette smoking and alcohol use and heavy-drinking smokers constitute a sizeable and hard-to-treat subgroup of smokers. However, tailored smoking cessation therapies for this population are not yet available. We recently demonstrated that the combination of naltrexone and varenicline is superior to monotherapy and placebo for heavy drinking smokers on experimental measures of craving, high, and cigarette/alcohol use and on neural markers of cue-reactivity, particularly the bilateral anterior cingulate. These findings provide critical information for the potential efficacy of combination varenicline+naltrexone

therapy for heavy drinkers trying to quit smoking and may ultimately improve clinical care for this sizeable and treatment-resistant subgroup of smokers.

a. Roche, D.J., S. Bujarski, E. Hartwell, R. Green, and **Ray L.A.,** *Combined varenicline and naltrexone treatment reduces smoking topography intensity in heavy-drinking smokers.* Pharmacol Biochem Behav, 2015. **134**: p. 92-98. PMCID:4457679
b. **Ray, L.A.,** K.E. Courtney, D.G. Ghahremani, K. Miotto, A. Brody, and E.D. London, *Varenicline, low dose naltrexone, and their combination for heavy-drinking smokers: human laboratory findings.* Psychopharmacology (Berl), 2014. PMCID:4161630
c. **Ray, L.A.,** K.E. Courtney, D.G. Ghahremani, K. Miotto, A. Brody, and E.D. London, *Varenicline, naltrexone, and their combination for heavy-drinking smokers: preliminary neuroimaging findings.* Am J Drug Alcohol Abuse, 2015. **41**(1): p. 35-44. PMCID:4365972

2. Another line of research utilizes a behavioral genetics approach to further understand individual differences in addiction susceptibility and treatment response. We recently demonstrated the behavioral significance of a functional polymorphism of the mu opioid receptor (OPRM1) gene for alcoholism by showing that carriers of the Asp40 allele report greater subjective reward from the effects of alcohol. Furthermore, we identified a mechanism by which the Asn40Asp SNP of the OPRM1 gene may moderate responses to naltrexone for alcoholism, namely by naltrexone attenuating the reinforcing effects of alcohol more strongly among Asp40 carriers. These findings advanced the knowledge of genetic determinants of risk for alcoholism and the mechanisms of action of naltrexone and genetic moderators of response to this pharmacotherapy.

a. **Ray, L.A.** and Hutchison K.E., *A polymorphism of the mu-opioid receptor gene (OPRM1) and sensitivity to the effects of alcohol in humans.* Alcohol Clin Exp Res, 2004. **28**(12): p. 1789-95.
b. **Ray, L.A.** and Hutchison K.E., *Effects of naltrexone on alcohol sensitivity and genetic moderators of medication response: a double-blind placebo-controlled study.* Arch Gen Psychiatry, 2007. **64**(9): p. 1069-77.
c. **Ray, L.A.,** S. Bujarski, P.F. Chin, and K. Miotto, *Pharmacogenetics of naltrexone in asian americans: a randomized placebo-controlled laboratory study.* Neuropsychopharmacology, 2012. **37**(2): p. 445-55. PMCID:3242306

3. In order for neurobiologically precise research utilizing animal models to contribute optimal insights into human psychopathology, such theories must be validated in clinical samples. My research extends hypotheses from neurobiological models of addiction to clinical samples using experimental medicine and neuroimaging approaches. Specifically, we have been able to demonstrate that the positive reinforcing effects of alcohol are weaker determinants of craving for alcohol among individuals with more severe alcoholism, which is consistent with the proposed transition from positive to negative reinforcement as addiction progresses. This research further validates models of behavior used in preclinical studies, and contributes to the development of methods for direct translation from preclinical to human samples.

a. Bujarski, S. and **Ray L.A.,** *Subjective response to alcohol and associated craving in heavy drinkers vs. alcohol dependents: an examination of Koob's allostatic model in humans.* Drug Alcohol Depend, 2014. **140**: p. 161-7. PMCID:4169206
b. **Ray, L.A.,** K.E. Courtney, K.E. Hutchison, J. Mackillop, A. Galvan, and D.G. Ghahremani, *Initial evidence that OPRM1 genotype moderates ventral and dorsal striatum functional connectivity during alcohol cues.* Alcohol Clin Exp Res, 2014. **38**(1): p. 78-89. PMCID:3808494
c. Courtney, K.E., D. Ghahremani, and **Ray L.A.,** *Fronto-Striatal Functional Connectivity during Response Inhibition in Alcohol Dependence.* Addiction Biology, 2013. **18**(3): p. 593-604. PMCID:3683582

For a Complete List of Peer-Reviewed Publications, please see:
http://www.ncbi.nlm.nih.gov/pubmed/?term=lara+ray

D. Research Support

Ongoing Research Support

NIAAA R01AA026190 Ray (PI) 5/15/2018-2/28/2022
A randomized controlled clinical trial of the neuroimmune modulator ibudilast for the treatment of alcohol use disorder
The purpose of this study is to advance medication development for alcohol use disorder by conducting a 12-week, double-blind, placebo-controlled randomized trial of ibudilast.

NIAAA K24AA025704 Ray (PI) 9/15/2018-8/31/2023
Clinical neuroscience of alcoholism: integrating neuroscience and clinical trials
This is a mid-career Investigator award is comprised of projects to extend research in the areas of neuroscience, clinical trials, and advanced quantitative methods.

NIAAA R01AA026190S1 (Diversity Supplement) Ray (PI/Mentor) 5/01/2019-4/30/2022
A randomized controlled clinical trial of the neuroimmune modulator ibudilast for the treatment of AUD
The purpose of this diversity supplement is to support the research training of a PhD student from an underrepresented background and to test the effects of ibudilast on executive function.

NIAAA R21AA027180 Ray (PI) 9/20/2019-8/31/2021
A novel human laboratory model for screening medications for alcohol use disorder
This study will validate a novel clinical paradigm for testing the initial efficacy of pharmacotherapies for alcohol use disorder.

NIAAA R21 AA026006 Magill (PI)/ Ray (Co-I) 10/1/2017-8/30/2020 (NCE)
A Meta-Analysis of CBT/RP Efficacy, Moderated Efficacy, and Mediation
The purpose of this study is to conduct a state-of-the-art meta-analysis of CBT/RP efficacy, moderated efficacy, and mediating processes.

<u>Completed Research Support (past three years)</u>
NIDA R01DA041226 Ray (PI) 9/1/2015-5/31/2019
Combining varenicline and naltrexone for smoking cessation and drinking reduction
This proposal is to conduct a randomized clinical trial comparing varenicline alone to varenicline plus naltrexone for smoking cessation in heavy drinking smokers.

NIH-NIDA 3R01DA041226-02S1 (Supplement) Ray (PI) 9/1/2015-5/31/2019
Combining varenicline and naltrexone for smoking cessation and drinking reduction
The purpose of this supplement is to examine the effect of sex as a marker of medication response.

NIAAA R21 AA023669 Ray/Karno (Co-PIs) 4/1/2015-3/31/2018
Perceived alcohol reward value and risk: Neural correlates and treatment effects
This study will examine the effects of a brief intervention for alcohol use disorder on neural markers of the incentive salience of alcohol.

NIAAA R21 AA022752 Ray (PI) 9/10/2014-8/31/2017
Modeling alcohol reward and reinforcement in the human laboratory
This study will test the association between subjective measures of alcohol reward and self-administration using state-of-the-art human laboratory paradigms.

NIAAA R01 AA021744 Ray (PI) 7/1/2013-6/30/2017
Optimizing naltrexone for individuals of Asian descent
The purpose of this application is to optimize the use of naltrexone for alcoholism on the basis of pharmacogenetics.

HHSN27500003-1061-NCIG6-UCLA Ray/Shoptaw (Co-PIs) 3/1/2015-1/30/2017
Randomized, double blind, placebo-controlled trial of the safety and efficacy of gabapentin enacarbil (Horizant®) extended-release tablets for the treatment of alcohol use disorder
This project is a randomized, multisite clinical trial comparing Horizant to placebo for the treatment of alcohol use disorders.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Eisenberger, Naomi I.

eRA COMMONS USER NAME (credential, e.g., agency login): EISENBERGER2

POSITION TITLE: Professor, Department of Psychology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of California, Los Angeles, CA	B.S.	1997	Psychobiology
University of California, Los Angeles, CA	M.A.	2000	Psychology
University of California, Los Angeles, CA	Ph.D.	2005	Psychology

A. Personal Statement

My training is in social psychology and social neuroscience, with a focus on how these underlying processes relate to health. I am a nationally recognized expert on the neural correlates underlying social rejection and connection as well as how these neural responses relate to health-relevant physiological responses. I have been the PI or Co-I on many NIH-funded projects that have examined the neural underpinnings of specific social processes or the relationships between social processes and health outcomes. One line of my research has utilized neuroimaging techniques to investigate the neural correlates of social rejection and social connection. Through this line of research, I have shown that the experience of social rejection relies, in part, on physical pain-related neural regions and that the experience of social connection relies, in part, on reward-related neural regions. In another line of research, I have been examining how inflammatory processes alter neural sensitivity to social experience (increasing sensitivity to social threats, decreasing sensitivity to reward), which may increase risk for depression and other psychiatric disorders. Results from this work have shown that an experimental inflammatory challenge can lead to increases in feelings of social disconnection, in addition to depressed mood. In addition, we have shown that heightened inflammation may increase risk for depression by altering sensitivity to negative and positive experiences. For example, we have shown that greater increases in inflammatory activity (in response to an inflammatory challenge) were associated with greater increases in pain-related neural activity in response to social exclusion. In addition, we have also found that an experimental inflammatory challenge also decreased reward-related neural activity in response to a monetary reward task, suggesting that inflammatory activity may increase depression risk through reducing reward motivation.

1. Eisenberger, N.I., Inagaki, T.K., Rameson, L., Mashal, N.M., & Irwin, M.R. (2009). An fMRI study of cytokine-induced depressed mood and social pain: The role of sex differences. *Neuroimage, 47,* 881-890.
2. Eisenberger, N.I., Inagaki, T.K., Mashal, N.M. & Irwin, M.R. (2010). Inflammation and social experience: An inflammatory challenge induces feelings of social disconnection in addition to depressed mood. *Brain, Behavior, and Immunity, 24,* 558-563.
3. Eisenberger, N.I., Berkman, E.T., Inagaki, T.K., Rameson, L., Mashal, N., & Irwin, M.R. (2010). Inflammation-induced anhedonia: Endotoxin reduces ventral striatum responses to reward. *Biological Psychiatry, 68,* 748-754.
4. Moieni, M., Jevtic, I., Irwin, M.R., Breen, E., & Eisenberger, N.I. (2015). Females show greater depressive and socioemotional responses to a randomized clinical trial of endotoxin: Implications for sex differences in depression. *Neuropsychopharmacology, 40,* 1709-1716.

B. Positions and Honors

Positions and Employment

2005-2007 Post-Doctoral Fellow in Psychoneuroimmunology, UCLA, Los Angeles, CA
2007-2013 Assistant Professor in Psychology, UCLA, Los Angeles, CA
2010-2015 Jeffrey/Wenzel Term Chair in Behavioral Neuroscience, UCLA
2013-2017 Associate Professor in Psychology, UCLA, Los Angeles, CA
2017-present Full Professor in Psychology, UCLA, Los Angeles, CA

Other Experience and Professional Memberships

2005-present Associate Member, Center for Neurovisceral Sciences & Women's Health, UCLA
2006-present Consulting Editor, *Social Cognitive and Affective Neuroscience*
2008-present Affiliated Faculty, Health Psychology Training Grant, UCLA
2009-2012 Editorial Board, *Psychological Science*
2010-present Affiliated Faculty, Cousins Center for Psychoneuroimmuology, UCLA
2011-present Editorial Board, *Culture and Brain*
2011-present Network Member, National Cancer Institute's Network on Biobehavioral Pathways in Cancer
2016-present Cousins Center for Psychoneuroimmunology Internal Advisory Board
2017-2019 Associate Editor, *Emotion*

Honors

2011 American Psychosomatic Society (APS) Herbert Weiner Early Career Award
2011 Association for Psychological Science (APS) Janet Taylor Spence Award for Transformative Early Career Contributions
2012 Foundation for Personality and Social Psychology (SPSP) Sage Young Scholars Award
2012 International Union of Psychological Science (IUPS) Young Investigator Award
2013 American Psychological Association (APA) Distinguished Scientific Award for an Early Career Contribution to Psychology
2016 Neuropsychopharmacology Editors' Award for a Transformative Original Report
2017 American Psychosomatic Society (APS) 75th Anniversary Award

C. Contributions to Science

1. **Identifying similarities in the neural systems that process physical and social pain.** My most long-standing line of research has investigated the similarities in the ways in which individuals process physical and social pain. Here, I have argued that, based on the importance of social connection for mammalian survival, socially painful experiences may activate some of the same neural regions that typically process physical pain—borrowing the pain signal to prevent social disconnection. Three critical findings have emerged from this line of research, each lending support to the idea that physical and social pain processes rely on shared neural circuitry. First, we have shown that social rejection activates pain-related neural regions, specifically those typically involved in the distressing experience of physical pain (dorsal anterior cingulate cortex (dACC), anterior insula). Second, as one functional consequence of a physical-social pain overlap, we have shown that individual differences in sensitivity to one kind of pain relate to individual differences in sensitivity to the other. Finally, as a second consequence of a physical-social pain overlap, we have shown that modulating one kind of pain affects the other kind of pain in a similar manner. For example, giving subjects Tylenol, known to be a physical pain reliever, can reduce experiences of social pain as well as neural sensitivity to social exclusion.

a. Eisenberger, N.I., Lieberman, M.D., & Williams, K.D. (2003). Does rejection hurt? An fMRI study of social exclusion. *Science, 302,* 290-292. PMID: 14551436
b. Way, B.M., Taylor, S.E., & Eisenberger, N.I. (2009). Variation in the mu-opioid receptor gene (OPRM1) is associated with dispositional and neural sensitivity to social rejection. *Proceedings of the National Academy of Sciences, 106,* 15079-15084. PMCID: PMC2736434
c. DeWall, C.N., MacDonald, G., Webster, G.D., Masten, C.L., Baumeister, R.F., Powell, C., Combs, D., Schurtz, D.R., Stillman, T.F., Tice, D.M., & Eisenberger, N.I. (2010). Tylenol reduces social pain: Behavioral and neural evidence. *Psychological Science, 21,* 931-937. PMID: 20548058
d. Eisenberger, N.I. (2012). The pain of social disconnection: Examining the shared neural underpinnings of physical and social pain. *Nature Reviews Neuroscience, 13,* 421-434. PMID: 22551663

2. **Identifying the neural underpinnings of social connection.** Paralleling my work on the overlap in the neural systems underlying physical and social pain, I am interested in delineating the type of neural systems that have been co-opted to support pleasurable social experiences. One type of pleasurable social experience that we have examined is the feeling of safety and distress reduction that comes from knowing that one will receive support from others during times of need. Along these lines, we have shown that not only does viewing a picture of a close other during a time of need (receiving painful stimuli) reduce pain distress, but it also activates a neural region that is known to play a role in signaling safety and attenuating threat responding (ventromedial prefrontal cortex (VMPFC)). Moreover, greater neural activity in this region correlates with greater perceived support from the close other and greater reductions in self-reported pain distress and pain-related neural activity. In addition to examining the neural correlates associated with receiving support from others, we have also been examining the neural correlates of giving support to others. Along these lines, we have shown that giving support to loved ones activates reward-related neural regions that are involved in maternal caregiving behavior in animals (ventral striatum, septal area). Moreover, greater activity in these reward-related neural regions is associated with reduced activity in threat-related neural regions, suggesting that giving support to others may reduce physiological threat responding.

a. Eisenberger, N.I., Master, S.L., Inagaki, T.I., Taylor, S.E., Shirinyan, D., Lieberman, M.D., & Naliboff, B. (2011). Attachment figures activate a safety signal-related neural region and reduce pain experience. *Proceedings of the National Academy of Sciences, 108,* 11721-11726. PMCID: PMC3136329
b. Inagaki, T.K. & Eisenberger, N.I. (2012). Neural correlates of giving support to a loved one. *Psychosomatic Medicine, 74,* 3-7. PMID: 22071630
c. Eisenberger, N.I. (2013). An empirical review of the neural underpinnings of receiving and giving social support: Implications for health. *Psychosomatic Medicine, 75,* 545-556. PMCID: PMC3763941
d. Inagaki, T.K. & Eisenberger, N.I. (2013). Shared neural mechanisms underlying “social warmth” and physical warmth. *Psychological Science, 24,* 2272-2280. PMID: 24048423

3. **Understanding the mechanisms that link social relationships and health.** My final line of research builds on these two other lines of research to explore why social ties are consistently linked with beneficial health outcomes. To examine these mechanisms more closely, I have explored how the neural regions associated with social rejection and connection may play a role in the relationship between social ties and physiological stress responses, which have implications for health.

Social Pain and Health. Building on my work on the neural correlates of social pain, I have explored the extent to which these same neural regions mediate some of the links between negative social experiences and physiological stress responding. Thus, we have shown that individuals with less daily social support showed more social pain-related activity (dACC) to social rejection and more cortisol reactivity to a social stressor. We have also demonstrated that individuals who showed greater social pain-related neural activity to social rejection (dACC, anterior insula) showed greater inflammatory activity to a similar social stressor. In addition to the work investigating how social factors alter downstream physiological responses, we have also examined the reverse, namely how inflammatory processes can alter social experience (described in section A).

Social Connection and Health. Finally, we have also started to explore several ways in which positive experiences of social connection may relate to health. Specifically, we are examining the ways in which the receipt of social support activates safety-related neural mechanisms, which function to attenuate physiological threat responding. We are also examining the ways in which giving social support to others reduces sympathetic nervous system activation to a subsequent social stressor.

a. Eisenberger, N.I., Taylor, S.E., Gable, S.L., Hilmert, C.J., & Lieberman, M.D. (2007). Neural pathways link social support to attenuated neuroendocrine stress responses. *Neuroimage, 35,* 1601-1612. PMCID: PMC2710966
b. Slavich, G.M., Way, B.M., Eisenberger, N.I., & Taylor, S.E. (2010). Neural sensitivity to social rejection is associated with inflammatory responses to social stress. *Proceedings of the National Academy of Sciences, 107,* 14817-14822. PMCID: PMC2930449
c. Eisenberger, N.I. & Cole, S.W. (2012). Social neuroscience and health: Neurophysiological mechanisms linking social ties with physical health. *Nature Neuroscience, 15,* 669-674. PMID: 22504347
d. Inagaki T.K. & Eisenberger, N.I. (2016). Giving support to others reduces sympathetic nervous system-related responses to stress. *Psychophysiology, 53,* 427-435. PMID: 26575283

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

NICHD R01HD093823 Eisenberger, Fuligni, Galvan (co-PIs) 1/26/2018-12/31/2022
Prosocial Behavior and Neural Development During Adolescence
This project examines the neural correlates associated with developmental changes in prosocial behavior across adolescence.

NIA R21AG058893 Eisenberger (PI) 2/1/2019-1/31/2021
Can an Anti-Inflammatory Medication Reduce Loneliness?
This project will examine whether a non-steroidal anti-inflammatory drug can reduce self-reported feelings of loneliness over time as well as the psychological mechanisms that underlie these changes.

NIMH R21MH115287 Eisenberger (PI) 9/18/17-8/31/2020
Revisiting Safety Signals: Examining a Separate Safety Mechanism for Social Support Figures
This project compares social support figures as safety signals with other standard learned safety signals to examine whether different mechanisms underlie those two processes.

NSF 1626477 Eisenberger (PI) 7/1/2016-6/30/2020
An Examination of Social Support Figures as Prepared Safety Stimuli
This project uses fear conditioning techniques to examine whether social support figures serve as prepared safety stimuli, making it harder to learn fear and speeding the unlearning of fear in their presence.

NSF 1551952 Eisenberger, Fuligni, Galvan (co-PIs) 9/1/2016-8/31/2020
Giving to Others and Neural Development During Adolescence
This project examines the neural correlates associated with developmental changes in prosocial behavior across adolescence.

US-Israel BSF 2015068 Eisenberger, Shamay-Tsoory (co-PIs) 9/2016-8/2020
Brain-to-Brain Interaction During Consolation
This project examines the neural underpinnings associated with the act of consoling and the act of being consoled among couples experiencing physical and social pain.

NIMH R01MH107422 Horan (PI), Eisenberger (Co-I) 7/1/2015-6/30/2020
Social Affiliation in Psychosis: Mechanisms and Vulnerability Factors
This project examines whether disturbances in two key components of the RDoC affiliation construct, the social approach and avoidance systems of the brain, contribute to the social disability associated with psychosis.

NIA R01AG051944 Irwin (PI), Eisenberge (Co-I) 9/5/2016-8/30/2020
Experimental Model of Depression in Aging: Insomnia, Inflammation, and Affect Mechanisms
This project examines the role of insomnia in the effects of inflammation on depression. (Role: Co-I)

NIMH R01MH110470 Green (PI), Eisenberger (Co-I) 9/1/2016-6/30/2021
The Determinants of Social Disconnectedness: A Spectrum from the General Community to Severe Mental Illness.
This project uses multiple types of assessments (e.g., fMRI, behavioral) to investigate the spectrum of feelings of social disconnection.

Completed (within last 3 years)

NIA R03AG049254 Eisenberger (PI) 9/1/2015-9/30/2017
Feeling Needed: Effects of Generativity on Health in Lonely Older Adults
This project examined the effect of a generativity intervention (aimed at increasing perceptions of giving to others) on loneliness, inflammatory activity, and overall health in a sample of older lonely adults.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Kate Wassum

eRA COMMONS USER NAME (credential, e.g., agency login): Wassumk2

POSITION TITLE: Associate Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of North Carolina, Chapel Hill	B.S.	12/2004	Psychology
University of California, Los Angeles	Ph. D	12/2009	Neuroscience
University of California, Los Angeles	Postdoctoral	10/2011	Neuroscience

A. Personal Statement

Work in my laboratory is broadly aimed at exposing the psychological processes and neural mechanisms that underlie appetitive associative learning, motivation, and decision making. We take a multidisciplinary approach to our research, combining behavioral procedures rooted in the rich traditions of learning theory with advanced systems neuroscience neural recording, interference, and/or molecular methods. One aim of the lab is to expose the neural correlate of discrete aspects of motivated behavior and then, using interference methods, to test the causal role for these signals in behavior. We work to parse the precise contribution of specific brain circuits to motivated behavior. As part of this, we are assessing how neurochemical interactions within a brain region modulate circuit dynamics. Lastly, we aim to determine the mechanisms regulating the encoding of stimulus-response and action-goal associative memories and the balance of behavioral control between these habitual and goal-directed systems. We focus on cortico-striatal-limbic circuitry. All of our work is targeted at understanding the neural mechanisms underlying the maladaptive motivated behavior that marks diseases such as addiction, compulsive overeating, and depression.

Publications most relevant to the current proposal:

1. Malvaez M, Shieh C, Murphy MD, Greenfield VY, Wassum KM. (2019) Distinct cortical-amygdala projections drive reward value encoding and retrieval. Nature Neuroscience. 22 762–769. PMC6486448a.
2. Collins AL, Aitken TJ, Huang I, Shieh C, Greenfield VY, Monbouquette HG, Ostlund SB, Wassum KM. (2019) Nucleus accumbens cholinergic interneurons oppose cue-motivated behavior. Biological Psychiatry 86:5 388-396.
3. Lichtenberg NT, Pennington ZT, Holley SM, Greenfield VY, Cepeda C, Levine MS, Wassum KM. (2017) Basolateral amygdala to orbitofrontal cortex projections enable cue-triggered reward expectations. Journal of Neuroscience 45(3), 381-387. PMC5577854
4. Malvaez M, Greenfield VY, Matheos DP, Angelillis N, Murphy MD, Kennedy PJ, Wood MA, Wassum KM. (2018) Habits are negatively regulated by HDAC3 in the dorsal striatum. Biological Psychiatry, 84(5) 383-392. PMC60827929

B. Positions and Honors

Positions and Employment

2003-2005 Research Assistant, *Dr. R. Mark Wightman*, Analytical Chemistry, University of North Carolina, Chapel Hill, Chapel Hill, NC

2004-2005 Research Assistant, *Dr. Regina Carelli*, Psychology, University of North Carolina, Chapel Hill, Chapel Hill, NC

2005-2009 Graduate Student Researcher, *Dr. Nigel Maidment*, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA

2006-2009 Graduate Student Researcher, *Dr. Bernard Balleine*, Psychology, University of California Los Angeles, Los Angeles, CA

2010-2011 Postdoctoral Fellow, *Dr. Nigel Maidment*, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA

2011-2017 Assistant Professor, Psychology, University of California, Los Angeles, CA

2017- Associate Professor, Psychology, University of California, Los Angeles, CA

Affiliations and Professional Memberships

University Affiliations: Brain Research Institute (BRI); Integrative Center for Learning and Memory, Council member; Center for Study of Opioid Receptors and Drugs of Abuse; Integrative Center for Addictive Behaviors and Training Program in Translational Neuroscience of Drug Abuse; Microcircuits Training Grant Executive Committee; Biotechnology Training Program in Biomedical Sciences and Engineering Executive Committee

Professional Memberships: Society for Neuroscience; International Society for Monitoring Molecules in Neuroscience, Organizing committee 2014, Advisory board member 2014-2022; Pavlovian Society; American College of Neuropharmacology, Associate Member; International behavioral neuroscience; International drug abuse research society

Reviewing and Editorial Service

2012- Reviewing Editor, *Frontier's in Behavioral Neuroscience* and *Frontier's in Decision Neuroscience*
2014 Guest Editor, ACS Chemical Neuroscience
2014- Editorial advisory board member, *ACS Chemical Neuroscience*
2016- Editorial board member, *Scientific Reports*
2018-2019 Associate Editor, *Journal of Neuroscience*
2018-2020 Editorial Board Member, *Neuropsychopharmacology*
2018-2019 Reviewing Editor, *eLife*
2018- Consulting Editor *Journal of Experimental Psychology Animal Learning & Cognition*
2019- Senior Editor, *eLife*
2019-2021 Reviewing Editor, *Journal of Neuroscience*
2019- Consulting Editor, *Behavioral Neuroscience*

Grant review: NIH Neurobiology of motivated behavior Study Section, NSF BIO/IOS, NSF CAREER, Canada Foundation for Innovation, UCLA CTSI, Brain Canada, Swiss National Science Foundation, BBSRC UK, NIH Biobehavioral Applications on Substance Abuse and Decision-Making SEP, NIH Cellular and Molecular Biology of complex brain disorders SEP, NIH Fellowship SEP.

Journal and other review: Nature, Neuron, Nature Neurosci., J. Neurosci. (2016 most frequent reviewer), Neuropsychopharmacology, Biological, Psychiatry, PNAS, Current Biol., eLife, Proceedings B, ACS Chemical Neuroscience, American J. Physiol Regul Integer Comp Phys, Behavioral Brain Research, Beh. Neurosci., Cognitive Process, Frontiers, Jove, J. Neurochem, J. Neurosci. Research, J. Neurophysiology, J. Huntington's Disease, Psychopharmacology, Neurobio. Disease, Neuropharmacology, Neuroscience, Neurobiology of Learn. & Mem., Pharmacology, Biochemistry & Beh., PlosOne, Sci. Advances, Scientific Reports, Translational Psychiatry, Cosyne, Neuropharmacology, Analytical Chemistry

Honors

2004 Smallwood Undergraduate Research Fellowship
2005-2008 Achievement Rewards for College Scientists Grant
2007-2010 Training Grant: University of California Biotechnology Research and Training Program
2007-2010 NIH Training Grant: F31 DA023774
2008-2010 UCLA Brain Research Institute Travel Award
2008 NIDA Travel Award
2010 International Behavioral Neuroscience Travel award
2010-2011 NIH Training Grant: T32 DA024635
2010 Eva Mary Kavan Prize for Excellence in Research on the Brain
2011 UCLA Brain Research Institute Arne Schiebel Distinguished Postdoctoral Fellow

2012 Ann E. Kelley Travel Fellow, Winter Brain Conference on Brain Research
2013 Society of Biological Psychiatry Ziskind Somerfeld Research Award Nominee for "Phasic mesolimbic dopamine signaling precedes and predicts performance of a self-initiated action sequence." (1/10 selected from over 2000 articles)
2013-2014 UCLA Hellman Fellows Award

C. Contribution to Science

Italics denotes trainees

1. **Function of amygdala-cortical circuitry in reward encoding, retrieval, and decision making**. The basolateral amygdala (BLA) is thought to function in emotional learning, valence, and fear. Our data have revealed a new function for the BLA in reward pursuit and decision making. We have found that BLA signaling tracks the ability of reward-predictive cues to bias decision making (A)- a function that we found to be mediated by BLA mu-opioid-receptor-regulated microcircuitry (B) and via BLA projections to the lateral orbitofrontal cortex (C). We also recently identified a necessary and sufficient role for the BLA, via inputs from the medial and lateral OFC, respectively, in reward valuation and value-guided reward pursuit decisions (D). Our data indicate that the BLA encodes specific and dynamic reward representations and contributes to the circuit-level orchestration of reward-related decision making.
    a. *Malvaez M*, *Greenfield VY*, *Wang AS*, Yorita AM, Feng L, *Linker KE*, Monbouquette HG, **Wassum KM**. (2015) Basolateral amygdala rapid glutamate release encodes an outcome-specific representation vital for reward-predictive cues to selectively invigorate reward-seeking actions. Sci. Reports. 5:12511. PMC4648450.
    b. *Lichtenberg NT*, **Wassum KM**. (2016) Amygdala mu-opioid receptors mediate the motivating influence of cue-triggered reward expectations. European Journal of Neuroscience. 45(3):381-387. PMC5293612
    c. *Lichtenberg NT*, Pennington ZT, Holley SM, *Greenfield VY*, Cepeda C, Levine MS, **Wassum KM**. (2017) Basolateral amygdala to orbitofrontal cortex projections enable cue-triggered reward expectations. Journal of Neuroscience 45(3), 381-387. PMC5577854
    d. *Malvaez M*, *Shieh C*, *Murphy MD*, *Greenfield VY*, **Wassum KM**. (2019) Distinct cortical-amygdala projections drive reward value encoding and retrieval. Nature Neuroscience. 22 762–769. PMC6486448

2. **Regulation of motivated behavior by striatal dopamine and acetylcholine**. We have found that dopamine release in the nucleus accumbens core (NAc) is a major substrate of motivation that is regulated by cholinergic interneurons in the NAc to maintain adaptive behavior. Our data indicate that reward-predicative cues robustly elicit dopamine release in the NAc and this signal encodes the need-based motivational value that allows those cues to invigorate reward-seeking behavior when this is adaptive (A). We have found that the activity of cholinergic interneurons in the NAc opposes the motivational influence of reward-predictive cues via acetylcholine action at the nicotinic acetylcholine receptors known to be located on dopamine terminals (D) and that activity of these receptors regulates phasic cue-evoked dopamine release and associated motivation (C). We have also shown dopamine to relate to self-initiated action and have identified a new prolonged mode of dopamine release that is dynamic with learning, overtraining, task disengagement/reengagement, and expectation violation (B). Combined these works suggest that in the NAc dopamine signaling serves a motivational function by encoding the current adaptive value of available rewards and that NAc cholinergic interneurons gate the degree to which midbrain dopamine firing elicited by salient rewarding events is translated into a chemical message at the terminal.
    a. *Aitkens TJ**, *Greenfield VY**, **Wassum KM**. (2016) Nucleus accumbens core dopamine signaling tracks the need-based motivational value of food-paired cues. J. Neurochem. 136:5, 1026-1036. PMC4819964.
    b. *Collins AL*, *Greenfield VY*, Bye JK, *Linker KE*, *Wang AS*, **Wassum KM**. (2016) Dynamic mesolimbic dopamine signaling during action sequence learning and expectation violation. Sci. Reports, 6:20231. PMC4755124.
    c. *Collins AL*, *Aitken TJ*, *Greenfield VY*, *Ostlund SB*, **Wassum KM**. (2016) Nucleus accumbens acetylcholine receptors modulate dopamine and motivation. Neuropsychopharmacology. 41:12 2830-2838. PMC5061892

d. *Collins AL*, *Aitken TJ*, Huang I, *Shieh C*, *Greenfield VY*, Monbouquette HG, Ostlund SB, **Wassum KM**. (2019) Nucleus accumbens cholinergic interneurons oppose cue-motivated behavior. Biological Psychiatry 86:5 388-396.

3. **Striatal mechanisms of habit**. Humans and animals rely on two strategies for decision making, one cognitive and one habitual. The balance between these allows for adaptive and efficient behavior, but when it is disrupted can lead to the symptoms that underlie myriad neurodegenerative and psychiatric diseases. Although the gross brain structures are known, almost nothing is known about the molecular mechanisms. In a recent report (A), we identified a critical molecular regulator of the transition to habit: the epigenetic transcriptional repressor: histone deacetylase 3 (HDAC3). We found that HDAC3 functions in both the dorsolateral and dorsomedial striatum as a molecular brake over habit, remaining in place to slow the transition to habit and being removed when the conditions are ripe for habits to dominate. These results identify dorsal striatal HDAC3 as a critical molecular directive of the transition to habit and, as we discussed in (B) have implications for the understanding and treatment of diseases marked by maladaptive habits.
    a. *Malvaez M*, *Greenfield VY*, Matheos DP, Angelillis N, *Murphy MD*, Kennedy PJ, Wood MA, **Wassum KM**. (2018) Habits are negatively regulated by HDAC3 in the dorsal striatum. Biological Psychiatry, 84(5) 383-392. PMC60827929
    b. *Malvaez M*, **Wassum KM**. (2018) Regulation of habit formation in the dorsal striatum. Current Opinion in Behavioral Sciences, 20:64-74. PMC5920535

4. **Amygdala opioid involvement in normal and maladaptive reward value encoding.** The endogenous opioid system was proposed to be the brain's pleasure system and that the neural mechanisms mediating such pleasure experience were thought to be the same as those through which that experience is encoded into a reward's incentive value. We reported that the neural mechanisms mediating the emotional experience of a reward (e.g., pleasure) and those through which this hedonic information is translated into the incentive value used for decision making are doubly dissociable at the level of ventral striatal and basolateral amygdala mu-opioid receptors, respectively (A & B). This provided a potential mechanism for the inappropriate reward-related decision making that marks addiction. Indeed, we found that the opioid receptor system is required for goal-directed learning (C) and that in withdrawal following chronic opioid exposure there is a disruption in process by which reward values used for later decision making are learned such that reward seeking is inflated, out of line with the pleasure experience and need state (D).
    a. **Wassum KM**, Ostlund SB, Maidment NT, Balleine BW. (2009) Distinct opioid circuits determine the palatability and the desirability of rewarding events. PNAS, 106(30): 12512-7. PMC2718390.
    b. **Wassum KM**, *Cely IC*, Balleine BW, Maidment NT. (2011) Mu opioid receptor activation in the basolateral amygdala mediates the learning of increases, but not decreases in the incentive value of a food reward. J. Neurosci, 31(5): 1583-1590. PMC3081716.
    c. **Wassum KM**, *Cely IC*, Ostlund SB, Maidment NT, Balleine BW. (2009) Disruption of endogenous opioid activity during instrumental learning enhances habit acquisition. Neuroscience, 163(3): 770-80. PMC3065789
    d. **Wassum KM**, *Greenfield VY*, *Linker KE*, Maidment NT, & Ostlund SB. (2016). Inflated reward value in early opiate withdrawal. Addiction biology, 21:2, Epub 2014. PMC4312551.

5. **Development and application of biosensor technologies.** Tools for the real-time measurement of electroactive (e.g., dopamine) neurotransmitters have been fundamental to understanding neurochemical transmission, but neurochemical monitoring techniques for non-electroactive (e.g., glutamate, acetylcholine) of have been limited in comparison. To remedy this, I worked as part of a collaborative team to develop and advance a biosensor technology that allows online, near-real time measurement of glutamate release in freely-moving rodents (A &C) and have used this tool to measure spatially discrete, transient glutamate fluctuations in the basolateral amygdala that tracked reward seeking (B). We are now evaluating the information encoding by this signal and finding that it carries reward-specific motivational information (see #1A & D). We have also combined this tool with optogenetics and chemogenetics in vivo (#1D). We have also developed an electroenzymatic acetylcholine biosensors, which we have used to measure optically-evoked and chemogenetically modulated acetylcholine release (D, & #2D).
    a. **Wassum KM**, Tolosa VM, Wang J, Walker E, Monbouquette HG, Maidment NT. (2008) Silicon wafer-based platinum microelectrode array biosensor for near real-time measurement of glutamate in vivo. Sensors, 8: 5023-5036. PMC2699285.

b. **Wassum KM**, Tolosa VM, Tseng TC, Balleine BW, Monbouquette HG, Maidment NT. (2012) Transient extracellular glutamate events in the basolateral amygdala track reward seeking actions. J. Neurosci, 32(8): 2734-2746. PMC3548241.
c. Tolosa VM, **Wassum KM**, Maidment NT, Monbouquette HG. (2013). Electrochemically deposited iridium oxide reference electrode integrated with an electroenzymatic glutamate sensor on a multi-electrode array microprobe. Biosens Bioelectron. 42: 256-60.
d. Hersman S, Cushman J, Lemelson N, **Wassum KM**, Lotfipour S, Fanselow MS. (2017) Optogenetic excitation of cholinergic inputs to the hippocampus primes future contextual fear associations. Sci. Reports. 7:2333. PMC5443779.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/kate.wassum.1/bibliography/47644156/public/?sort=date&direction=ascending

Preprints:
No unpublished preprints at the moment.

D. Research Support

Ongoing Research Support

NIH 2R01-DA035443 Wassum (PI) 05/2013-12/2023
NIDA
"Amygdala-cortical circuitry in reward encoding, expectation, and decision making"
This project will expose the amygdala-cortical brain circuits vital for encoding and retrieving memories of rewarding events, which will enable future research on how dysfunction in these processes contributes to pathological behavior.

NIH 1R01MH106972 Wassum/Ostlund (PIs) 05/2016-04/2021
NIMH
"Cholinergic regulation of striatal neurochemistry in cue-triggered decision-making"
In this project we examine the roles of acetylcholine and dopamine in the striatum in cue-triggered behavior and decision making as well as the regulation of dopamine signaling by acetylcholine during such behaviors. There is no scientific or budgetary overlap.

NIH R01-DA046679 Wassum (PI) 04/2019-03/2024
NIDA
"Epigenetic regulation of striatal circuit function for action and habit learning"
The goal of this project is to expose the epigenetic-genomic-physiological-functional conduit to habit in medial and lateral dorsal striatal direct and indirect pathway projections.

Completed Research Support (selected, completed last 3 years)

NIH 1R01NS087494 Monbouquette/Maidment (PI) 04/2014-03/2019
NINDS
"Multifunctional Microprobe for Multiple Neurotransmitter Sensing and Optogenetics"
Role: Co-Investigator

NIH 1R01AG045380 Maidment/Murphy/Ostlund (PIs) 08/2014-05/2019
NIA
"Neurochemical bases for changes in decision-making across the lifespan"

NIH 2P50DA005010-31 Evans (Director)/Wassum Pilot PI 09/2017-08/2019
NIDA
"Hatos Center for opioid neuropharmacology- Pilot Project

PHS Fellowship Supplemental Form

OMB Number: 0925-0001
Expiration Date: 03/31/2020

Introduction

1. Introduction
(for Resubmission applications)

Fellowship Applicant Section

2. * Applicant's Background and Goals for Fellowship Training	Burnette_NRSA_FINAL_BackgroundTraini1059942809.pdf

Research Training Plan Section

3. * Specific Aims	Burnette_NRSA_FINAL_SAs1060019278.pdf
4. * Research Strategy	Burnette_NRSA_FINAL_ResearchStrat1060019826.pdf
5. * Respective Contributions	Burnette_NRSA_FINAL_RespectiveContri1059942799.pdf
6. * Selection of Sponsor and Institution	Burnette_NRSA_FINAL_Selection1060019904.pdf
7. Progress Report Publication List (for Renewal applications)	
8. * Training in the Responsible Conduct of Research	Burnette_NRSA_FINAL_ResponsibleCondu1059942811.pdf

Sponsor(s), Collaborator(s) and Consultant(s) Section

9. Sponsor and Co-Sponsor Statements	Sponsor_Info_Ray_Burnette_FINAL1060019916.pdf
10. Letters of Support from Collaborators, Contributors and Consultants	COLLABORATOR_Eisenberger_Letter1060019281.pdf

Institutional Environment and Commitment to Training Section

11. Description of Institutional Environment and Commitment to Training	NRSA_InstEnvironment_Burnette1060019905.pdf

Other Research Training Plan Section

Vertebrate Animals

The following item is taken from the Research & Related Other Project Information form and repeated here for your reference. Any change to this item must be made on the Research & Related Other Project Information form.

Are Vertebrate Animals Used? Yes ✔ No

12. Are vertebrate animals euthanized?

If "Yes" to euthanasia
Is method consistent with American Veterinary Medical Association (AVMA) guidelines?
If "No" to AVMA guidelines, describe method and provide scientific justification

13. Vertebrate Animals

PHS Fellowship Supplemental Form

OMB Number: 0925-0001
Expiration Date: 03/31/2020

Other Research Training Plan Information

14. Select Agent Research

15. Resource Sharing Plan Burnette_NRSA_FINAL_ResourceSharing1060019218.pdf

16. Authentication of Key Biological and/or Chemical Resources

Additional Information Section

17. Human Embryonic Stem Cells

Does the proposed project involve human embryonic stem cells?* Yes ✔ No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/research/registry/. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s):

18. Alternate Phone Number:

19. Degree Sought During Proposed Award:

Degree:	If "other", indicate degree type:	Expected Completion Date (MM/YYYY):
PHD: Doctor of Philosophy		09/2023

20. * Field of Training for Current Proposal: 160 Neurosciences & Neurobiology

21. * Current Or Prior Kirschstein-NRSA Support? Yes ✔ No

If yes, please identify current and prior Kirschstein-NRSA support below:

Level*	Type*	Start Date (if known)	End Date (if known)	Grant Number (if known)

22. * Applications for Concurrent Support? Yes ✔ No

If yes, describe in an attached file:

23. * Citizenship

U.S. Citizen U.S. Citizen or Non-Citizen National? ✔ Yes No

Non-U.S. Citizen With a Permanent U.S. Resident Visa

With a Temporary U.S. Visa

If you are a non-U.S. citizen with a temporary visa applying for an award that requires permanent residency status, and expect to be granted a permanent resident visa by the start date of the award, check here:

24. Change of Sponsoring Institution Name of Former Institution:*

PHS Fellowship Supplemental Form

OMB Number: 0925-0001
Expiration Date: 03/31/2020

Budget Section

All Fellowship Applicants:

25. * Tuition and Fees:

None Requested ✔ Funds Requested

Year 1	$13,342.00
Year 2	$13,742.00
Year 3	$14,154.00
Year 4	
Year 5	
Year 6 (when applicable)	
Total Funds Requested:	$41,238.00

Senior Fellowship Applicants Only:

26. Present Institutional Base Salary: Amount | Academic Period | Number of Months

27. Stipends/Salary During First Year of Proposed Fellowship:

a. Federal Stipend Requested: Amount | Number of Months

b. Supplementation from other sources: Amount | Number of Months

Type (e.g., sabbatical leave, salary)

Source

Appendix

28. Appendix

Doctoral Dissertation and Research Experience

Baccalaureate Research: I joined Dr. Erin Piker's lab, the Duke Vestibular Disorders Clinic, in my first year as an undergraduate at Duke University. As my only previous research experience had been on the molecular scale, it was a steep and exciting learning curve to make the huge leap from enzymes to human clinical research. Through my work in the clinic, I gained a deep appreciation for the importance of subject confidentiality, informed consent, safety, and documentation in human research, and studied inter- and intra-individual variability and order effects in a widely-used vestibulo-ocular reflex test, which resulted in my first paper, published in 2018 in the *American Journal of Audiology*. However, while translational clinical research interested me immensely, in the spirit of building a broad knowledge base, I wanted to gain experience in more basic animal research. In Dr. Cynthia Kuhn's lab in Duke's Department of Pharmacology, I had the opportunity to develop and carry out my undergraduate thesis project studying the development of disordered eating across age and sex in an animal model of Anorexia Nervosa. This process involved planning and troubleshooting a behavioral model in rats, extracting brains after transcardial perfusion, and performing immunohistochemistry to observe the development of c-fos response in the insular cortex, amygdala, and thalamus. Working on a project that was entirely my own for the first time brought a unique set of frustrations and challenges that pushed me to learn to troubleshoot my protocols by reading scores of methods papers, taking meticulous notes on any deviations I made, and consulting with a previous graduate student who left the lab in 2012 for histology advice. I grew immensely as a researcher during my year and a half in the Kuhn lab, and was proud to share my research as a poster at the Society for Neuroscience meeting in 2017, as well as producing my undergraduate honors thesis, which earned departmental distinction, in 2018. While I enjoyed gaining experience as an animal researcher during my time at Duke, my ultimate goal has always been to conduct research with direct translational applications, and I knew I wanted to return to clinical research.

Graduate Rotations Research: The UCLA Neuroscience Interdepartmental PhD Program is rotation-based, with students completing three quarterly rotations in their first year before joining a lab. With my goal of returning to clinical research, I exclusively rotated in clinical labs, gaining skills in human neuroimaging, neurostimulation, and behavioral assessment. My first rotation in the fall of 2018 was with Dr. Jamie Feusner, applying my undergraduate experience in eating disorder research to a human population. There, I had my first introduction to fMRI research and analysis, using neural activity in reward and anxiety networks to predict psychometrics within a clinical sample of patients with anorexia as well as controls. We found that anxiety network activity may negatively impact the subjective experience of reward. Furthermore, eating disorder symptomology seemed more directly related to reward network activity, but may also be indirectly related to anxiety network activity through reward network inhibition, providing an interesting potential direction for treatments for anorexia focusing on reducing the effects of anxiety network activation on a patient's ability to experience reward. I presented a poster on this work at the Organization for Human Brain Mapping in June 2019. In my second rotation, under Dr. Andrew Leuchter, I gained more clinical experience, interacting directly with patients in the UCLA Transcranial Magnetic Stimulation (TMS) clinic. I assessed the efficacy of repetitive TMS on depressive symptoms and cognitive control, finding that rTMS significantly reduced depressive symptoms as well as reaction time (psychomotor speed) and cognitive control as assessed by the Stroop color-word task. This research resulted in a *Journal of Affective Disorders* publication in 2020. My experience in these two clinical labs reinforced my interest in translational clinical research, allowing me to both gain experience working with fMRI and behavioral data and to work directly with clinical populations.

Doctoral Research: I permanently joined the UCLA Addictions Lab with Dr. Lara Ray (Sponsor) following my final rotation in spring 2019. I was excited to explore the field of addiction science, as addictive disorders affect so many people (over 1 billion worldwide), and thus the potential for translational clinical neuroscience research with a direct impact is incredibly high. I was, and remain, very impressed by Dr. Ray's robust research program integrating clinical psychology with medication development, neuroimaging, and pharmacology. Dr. Ray is herself a cutting-edge, well-respected scientist in the field of addiction, who understands both complex neuroscience paradigms and the clinical phenomenology of addiction. This combination of clinical science and neuroscience is a powerful driving force in Dr. Ray's work and I deeply admire how well she is able to integrate the two, with neuroscience informing her clinical research and vice-versa. This translatability aligns perfectly with my goals, and thus I am confident that training with Dr. Ray represents an ideal opportunity to develop my interest in clinical addiction neuroscience.

Additionally, Dr. Ray is an excellent mentor with a successful track record with graduate students and postdoctoral fellows, as well as an impressive and consistent publication record. Over the past year, Dr. Ray and I have fostered a strong and productive mentor-mentee relationship resulting in opportunities for collaborative and first-author posters and presentations, as well as a first-author publication. I am confident that this level of quality and productivity will be accelerated by this training award.

Beginning in my rotation and continuing through summer 2019, I worked closely with a postdoctoral fellow in the Ray lab, Dr. Erica Grodin, to gain more experience in fMRI analyses and study the intersection between Alcohol Use Disorder (AUD) and impulsivity / risk-taking behavior. We found that two different measures of impulsivity – delayed reward discounting and the sensation-seeking UPPS-P Impulsive Behavior subscale – were associated with neural activation to alcohol taste cues in different circuits, such that sensation seeking was positively associated with cue-elicited activity in frontostriatal regions while delay discounting was negatively associated with cue-reactivity in frontoparietal regions. These findings indicate that sensation seeking is associated with reward responsivity, while delay discounting is associated with recruitment of self-control circuitry. This work resulted in a *Psychiatry Research: Neuroimaging* publication in 2019, in which I am first author. I was also invited to present this work as part of a symposium at the Collaborative Perspectives on Addiction meeting in April 2020.

Relatedly, I am currently studying neural activation during risk-taking behavior (as measured by the Balloon Analog Risk Task, BART) as correlated with AUD severity, and have found that participants with more severe AUD showed stronger frontal pole activation during risk taking events, possibly indicating that subjects with more severe AUD do not form logical expectations of negative outcomes as risk level increases, so they may experience more surprise or subjective loss during a negative event. Participants with more severe AUD also showed stronger precuneus activation during reward receipt events regardless of risk level, a region previously shown to be part of a frontoparietal network involved in self-control. I will give a poster presentation on this work at the Research Society on Alcoholism meeting in June 2020 and will be following up this study by collaborating with Dr. Edythe London to compare this AUD sample against matched controls. These projects have allowed me to explore exciting behavioral aspects of AUD such as impulsivity, risk-taking, and reward learning, and to dive deeper into clinical addictions neuroscience, furthering my interest in the intersection of AUD, reward sensitivity, and the brain.

For the proposed F31 study, I will continue to build on my clinical addiction neuroscience research, but will be transitioning to a psychoneuroimmunology-based approach to explore the role of neuroinflammation in negative emotionality and reward sensitivity in AUD. I am incredibly excited for this opportunity to combine my undergraduate experience in pharmacology with my graduate experience in clinical research, specifically related to alcoholism. From my early graduate coursework in cellular and molecular neuroscience, I have become very interested in neuroinflammation and its effects on behavior and disease and will be exploring its relationship to negative mood and reward response in AUD. I aim to fill an important gap in the literature, as reward sensitivity and negative emotionality have been associated separately with both neuroinflammation and AUD, but the links between these three domains of inflammation, AUD, and behavioral outcomes have not been explored. Specifically, for the proposed project, I will provoke low-grade systemic inflammation by endotoxin infusion in a clinical sample of non-treatment-seeking, heavy-drinking individuals with AUD and a comparison group of light-drinking healthy controls, and will assess negative mood and reward responsiveness, as well as plasma levels of proinflammatory cytokines as a peripheral marker of inflammation. The proposed F31 project will allow me to develop my knowledge base and skills in psychoneuroimmunology and addiction neuroscience with a focus on the psychobiology of reward. These skills will foster my long-term career goal of becoming an independent researcher in clinical addictions neuroscience.

Training Goals and Objectives

I have been fascinated by the relationships between biology and behavior and how these interactions can go wrong since the beginning of my involvement in scientific research. My main research interest lies, therefore, in clinical and translational human neuroscience. Since joining the Ray lab, I have become deeply interested in clinical research as it pertains to addiction, specifically focusing on Alcohol Use Disorder. This award will allow me to continue along this training trajectory to achieve my ultimate goal of becoming an independent scientist in the field of addictions neuroscience, by pursuing coursework and mentorship in the following training domains.

Clinical Neuroscience of Addiction: My broad research interests involve understanding the biological mechanisms underlying the development, maintenance, and treatment of substance use disorders. To train in the clinical neuroscience of addiction, I will enroll in a course offered through the UCLA Department of Psychology, "*Behavioral and Psychophysiological Problems of Alcoholism*" (Psychology 293). This course discusses behavioral and psychophysiological characteristics of alcoholism, along with theories concerning their etiology, treatment, and experimental approaches.

Reward response is an important facet of addiction neuroscience and ties directly into the second aim of my research plan. To gain background knowledge of reward psychobiology, I plan to enroll in Psychology 205E, *"Neural Basis of Reward and Value*," an overview of neural systems underlying reward and value with an emphasis on mechanisms of reinforcement learning and cost-benefit or value-based decision making. Additionally, I will meet regularly with my proposed collaborator Dr. Kate Wassum, a well-known researcher in the field of addiction neuroscience who has carried out extensive research focusing on reward. Through these meetings as well as my weekly meetings with the Sponsor (Dr. Ray), I will gain valuable training on the clinical neuroscience of addiction.

Psychoneuroimmunology (PNI): The proposed project centers on psychoneuroimmunology, a field in which I am deeply interested but have had very little training. Therefore, I plan to develop my knowledge of PNI through coursework and mentorship. I plan to enroll in Psychology 216B, "*Psychoneuroimmunology,"* which serves as an introduction to the field of psychoneuroimmunology to develop conceptual and methodological skills necessary for interpreting and conducting research in the area. I also plan to attend Psychoneuroimmunology Research Seminars, a seminar series offered through the UCLA Department of Psychiatry, to stay abreast of developments in the field.

My proposed collaborator Dr. Naomi Eisenberger has performed extensive PNI research, including using the proposed endotoxin in a human control study that acts as preliminary data upon which the proposed project is built. Under the guidance of Dr. Eisenberger and Dr. Ray, along with the proposed coursework and selected readings (below), I will devote substantial time and effort to advance my understanding of the principles of psychoneuroimmunology.

Professional Development: This award will provide me with numerous opportunities to develop professional development skills, including scientific writing and communication, coursework, public speaking, and networking, above and beyond that which I would receive without the grant.

Specifically, I plan to write up the results of the proposed study in 1-2 first-authored manuscripts, which will further my training in scientific writing. In weekly lab meetings, I will discuss experimental design and results with lab members, as well as practice talks for upcoming conferences. I will also continue to attend and present my data in regular departmental and interdepartmental seminars and journal clubs in the fields of addiction and neuroscience. Examples of these seminars and journal clubs include a student-led research literature journal club in the translational neuroscience of drug abuse (TNDA), a Psychoneuroimmunology-focused seminar series (PNI), and seminars through the Integrative Center for Addictive Disorders (ICAD) and Joint Seminars in Neuroscience (JSN), both of which invite guest speakers from numerous institutions to present on their work, within the fields of addiction research (ICAD) and neuroscience in general (JSN). Attending these seminars and presenting in journal clubs will both expose me to a breadth of research in my field and provide opportunities to present my own research.

In order to meet the NIH requirement of undertaking instruction in the responsible conduct of research at least once every 4 years, I plan to enroll in Medicine M261 "*Responsible Conduct of Research Involving Humans*," a discussion of current issues in the responsible conduct of clinical research, including reporting of

research, basis for authorship, issues in genetic research, principles and practice of research on humans, conflicts of interest, Institutional Review Board (IRB), and related topics.

I am eager to disseminate my research and become actively engaged in the scientific community of addiction researchers. To that end, I will present my work in the form of posters, symposia, and presentations at conferences relevant to my work, such as the Society for Neuroscience (SfN), Research Society on Alcoholism (RSA), and PsychoNeuroImmunology Research Society (PNIRS). These presentations will also enhance my communication skills and allow me to form professional networking connections with fellow scientists, both of which are highly important for my future career. With the completion of these proposed training goals I will make crucial steps toward my long-term goal of becoming an independent clinical neuroscientist in the field of addiction.

<u>Selected Readings on Psychoneuroimmunology:</u>

1. Irwin, M.R. *Human psychoneuroimmunology: 20 years of discovery.* Brain Behav. Immun., 2008. **22**(2): p. 129-139.
2. Dantzer, R., *et al. From inflammation to sickness and depression: When the immune system subjugates the brain.* Nat. Rev. Neurosci., 2008. **9**(1): p. 46-56.
3. Bonneau, R.H., D.A. Padgett, and J.F. Sheridan. *Twenty years of psychoneuroimmunology and viral infections in Brain, Behavior, and Immunity*. Brain Behav. Immun., 2007. **21**(3): p. 273-280.
4. Ziemssen, T., and S. Kern. *Psychoneuroimmunology – cross-talk between the immune and nervous systems.* J. Neurol., 2007. **254**: p. II8-II11.
5. Segerstrom, S.C. *Resources, stress, and immunity: An ecological perspective on human psychoneuroimmunology.* Ann. Behav. Med., 2010. **40**(1): p. 114-125.
6. Del Giudice, M. and S.W. Gangestad. *Rethinking IL-6 and CRP: Why they are more than inflammatory biomarkers and why it matters.* Brain Behav. Immun., 2018. **70**: 61-75.
7. Lopez, R.B. *et al. Neural mechanisms of emotion regulation and their role in endocrine and immune functioning: A review with implications for treatment of affective disorders.* Neurosci. Biobehav. Rev., 2018. **95**: 508-514.
8. Dooley, L.N. *et al. The role of inflammation in core features of depression: Insights from paradigms using exogenously-induced inflammation*. Neurosci. Biobehav. Rev., 2018. **94**: p. 219-237.
9. Kiecolt-Glaser, J.K., H.M. Derry, and C.P. Fagundes. *Inflammation: depression fans the flames and feasts on the heat.* Am. J. Psychiatry, 2015. **172**(11): p. 1075-1091.
10. Lieberman, A.C. *et al. Neuroimmune and inflammatory signals in complex disorders of the central nervous system.* Neuroimmunomodulation, 2018. **25**(5-6): p. 246-270.
11. Crews, F.T., *et al. The role of neuroimmune signaling in alcoholism.* Neuropharmacology, 2017. **122**: p. 56-73.
12. De Timary, P. *et al. A role for the peripheral immune system in the development of alcohol use disorders?* Neuropharmacology, 2017. **122**: 148-160.
13. Coleman, L.G. and F.T. Crews. *Innate immune signaling and alcohol use disorders.* Handb. Exp. Pharmacol., 2018. **248**: p. 369-396.
14. Loftis, J.M and M. Huckans. *Substance use disorders: Psychoneuroimmunologicalmechanisms and new targets for therapy.* Pharmacol. Ther., 2013. **139**(2): p. 289-300.
15. Erikson, E.K., *et al. Neuroimmune signaling in alcohol use disorder.* Pharmacol. Biochem. Behav., 2019. **177**: p. 34-60.

Activities Planned Under This Award

Summary of planned activities under each year of the award period (% time):

Funding Year	Calendar Year	PhD Year	*Research & Writing*	*Coursework & Seminars*	*Professional Development*
1	2020-21	3	70%	20%	10%
2	2021-22	4	70%	20%	10%
3	2022-23	5	80%	10%	10%

As described in the Research Strategy section, I am requesting three years of funding for optimal execution of the proposed study and training plan. Throughout this period, I will meet weekly with the Sponsor (Dr. Ray) and monthly with the collaborators (Drs. Eisenberger and Wassum) to discuss issues pertinent to my training and execution of the proposed study, including participant recruitment and retention, methodological problem-solving, and data analysis and interpretation. The experiments discussed in my research plan will take place over the requested award period (three years). During that time, I will be involved in data collection, data analysis, manuscript writing and dissertation writing, as well as attending courses, seminars, and journal clubs, meeting with my Sponsor, our collaborators, and members of my dissertation committee, performing community outreach (detailed below), and preparing for and attending conferences. If funded by this award, I will not need to devote time to teaching assistantships and will therefore be able to reallocate that time toward research, coursework, and professional development.

While most of my time will be spent conducting, analyzing, and disseminating my research, I plan to complete the remainder of my coursework – as discussed above in my Training Goals – throughout the course of the award period. As I have completed all required core courses for the UCLA Neuroscience Interdepartmental PhD program, I will use my elective course units to take classes that complement my research plan in the fields of psychoneuroimmunology, reward neuroscience, and alcohol addiction, as well as attending regular journal clubs and seminars in the fields of addiction and general neuroscience. Participating in these seminars and journal clubs will both expose me to a breadth of research in my field and provide opportunities to present my own research. Specific coursework, seminars, and journal clubs are detailed in Training Goals.

I will also spend time on professional development, including improving my science communication and teaching skills through neuroscience outreach events and attending and presenting my research at journal clubs and conferences. I am passionate about community involvement and have been participated in science-related community outreach for over a decade, starting in high school. Currently, my involvement takes the form of organizing and running workshops to communicate neuroscience topics to elementary- and middle-school students through Brain Awareness Week, an annual event sponsored by the UCLA Brain Research Institute. These workshops strengthen my teaching and science communication skills and allow me to encourage younger generations of students to explore and get excited about science.

Finally, I plan to attend conferences relevant to my work, such as the Society for Neuroscience (SfN), Research Society on Alcoholism (RSA), PsychoNeuroImmunology Research Society (PNIRS), and other national and international meetings. Presenting my work in the form of posters, symposia, and presentations at these conferences will also enhance my communication skills and allow me to form professional networking connections with fellow scientists, both of which are highly important for my future career.

Details of planned research, coursework, and professional development for each year under the funding cycle:
Year 1 Funding Cycle: September 2020-August 2021
70% Time: Research – In the first year of the award period, I will pilot all study procedures and will begin recruiting participants. After data collection is underway, I will regularly conduct detailed reviews of study procedures and data quality. In the first funding year, I will also propose my dissertation, using the research strategy of this application as the basis for the proposal.
20% Time: Coursework – I will enroll in Psychology 216B, "Psychoneuroimmunology" and Psychology 205E, "Neural Basis of Reward and Value," as well as regularly attending seminars (see summary table).
10% Time: Professional Development – I will attend and present at the RSA conference. I will participate in monthly meetings on the proposed project with the Sponsor and collaborators. I will attend the Translational Neuroscience of Drug Abuse (TNDA) journal club, as well as the Psychoneuroimmunology (PNI) seminar course, and talks through the Integrative Center for Addiction Disorders (ICAD) and Joint Seminars in Neuroscience (JSN).

Year 2 Funding Cycle: September 2021-August 2022
70% Time: Research – The second year under this award will be spent continuing to recruit subjects, collect data, and conduct data pre-processing. I will also analyze preliminary results and submit them for presentation at the RSA and SfN conferences.
20% Time: Coursework – I will enroll in Psychology 293, "Behavioral and Psychophysiological Problems of Alcoholism" as well as regularly attending seminars (see summary table).
10% Time: Professional Development – I will present preliminary results at journal clubs and as a poster at RSA and SfN. I will continue to participate in monthly meetings on the proposed project with the Sponsor and collaborators. I will also continue to attend PNI, ICAD, and JSN monthly seminars.

Year 3 Funding Cycle: September 2022-August 2023
80% Time: Research – Data collection will be completed within the first three months of the third year of the award period. The results will be analyzed and submitted for presentation at the RSA and PNIRS conferences. Furthermore, findings from this study will be written up and submitted for a peer-reviewed publication, targeting Neuropsychopharmacology or Biological Psychiatry, which will also comprise the basis of my dissertation.
10% Time: Coursework – In order to meet the NIH requirement of completing bioethics instruction at least once every 4 years, I will enroll in Medicine M261 "Responsible Conduct of Research Involving Humans," according to course availability. I will also continue to regularly attend seminars (see summary table).
10% Time: Professional Development – I will present the results of this study at RSA and PNIRS conferences and will work towards my dissertation defense. I will continue to participate in monthly meetings on the proposed project with the Sponsor and collaborators. I will also continue to attend PNI, ICAD, and JSN monthly seminars.

Summary of planned research, coursework, and professional development by funding year:

	Year 1 2020-2021	**Year 2 2021-2022**	**Year 3 2022-2023**
Research	• Pilot all study procedures • Review study procedures and data quality	• Continue subject recruitment and data collection • Analyze and present preliminary results	• Complete data collection • Analyze final results • Write up final results for manuscript/dissertation
Coursework and Seminars	• Psychology 216B (PNI) • Psychology 205E (Reward) • PNI Seminar Series (weekly) • ICAD Seminars (monthly) • Joint Seminars in Neuroscience (weekly) • TNDA Journal Club (weekly)	• Psychology 293 (Alcoholism) • PNI Seminar Series (weekly) • ICAD Seminars (monthly) • Joint Seminars in Neuroscience (weekly)	• Medicine 261 (Responsible Conduct of Research) • PNI Seminar Series (weekly) • ICAD Seminars (monthly) • Joint Seminars in Neuroscience (weekly)
Professional Development	• Propose dissertation • Attend RSA conference	• Present preliminary results at RSA / SfN conferences	• Present final results at RSA / PNIRS conferences • Write manuscript / dissertation and defend

Specific Aims

Chronic alcohol consumption is thought to produce a sustained inflammatory state, such that individuals with alcohol use disorder (AUD) have increased inflammation throughout the brain[1]. Alcohol-induced neuroinflammation is implicated in chronic alcohol seeking, as well as the behavioral and neurotoxic effects of alcohol in preclinical studies[2]. Neuroimmune factors implicated in addiction mediate neuro-inflammation and modulate a wide range of brain functions[3,4], with alcohol exposure increasing both neural and systemic markers of inflammation. In animal models, induced inflammation increases alcohol consumption[5], while knocking out inflammatory signaling genes attenuates alcohol preference and self-administration[6]. While neuroinflammation appears to be a key component of AUD, the existing literature is overwhelmingly preclinical[8] and findings in humans have been largely correlational, while experimental approaches that establish a causal link between inflammation and AUD phenotypes are lacking.

Addiction has been conceptualized as a reward deficit disorder[34], with reward threshold heightening after substance use acting as a reinforcer for continued use[35]. Preclinical studies show that neuroinflammation alters reward sensitivity in mice[15,16]. The relationship between AUD and negative mood is also well-established[36]. Alcohol inhibits the regulation of negative emotion[56], and sadness, anxiety and anhedonia[45] are well-associated with alcohol addiction, such that individuals with AUD demonstrate higher levels of overall low mood[46,47]. Neuroinflammation has also been associated with the emergence of negative emotionality[37], such that cytokines have been shown to play a causal role in the onset of negative mood in previous human studies[41-44]. Human studies indicate that brain activation in response to reward is also decreased after endotoxin infusion[14]. To our knowledge, the associations between inflammation, negative mood, and reward responsivity have not been studied previously in the context of AUD. Elucidating these relationships will provide novel insight into the biological mechanisms underlying AUD.

The current NRSA predoctoral proposal will examine the role of inflammation in reward responsivity and mood in a clinical sample of non-treatment-seeking heavy drinkers and light-drinking healthy controls. This proposal is a supplementary study to a clinical trial of endotoxin led by the Sponsor, Dr. Lara Ray. We propose to conduct an inflammatory challenge in a sample of 38 individuals with AUD and a comparison group of 38 light-drinking healthy controls to examine the effects of experimentally-induced inflammation on negative mood and reward sensitivity. The study consists of a randomized, double-blind, placebo-controlled trial of low dose endotoxin. We will experimentally provoke a systemic inflammatory response, measurable by plasma proinflammatory cytokine levels, using low-dose endotoxin derived from E. coli (E. coli group O:113:BB-IND 12948 to MRI), delivered intravenously. This endotoxin provides a safe, effective, and well-tolerated inflammatory challenge[10-13]. The low dose endotoxin challenge induces a transient "phasic" inflammatory response with normalization of cytokine levels within 4 hours, offering a time-limited yet robust inflammatory challenge that is distinct from chronic ("tonic") levels of inflammation that may be present with AUD. Participants will be randomly assigned (stratified by sex and baseline depression symptoms) to receive an IV infusion of endotoxin (0.8 ng/kg of body weight) or placebo (same volume of 0.9% saline solution) in the laboratory. Mood and cytokine levels will be assessed at baseline and hourly for 4 hours post-infusion, while reward responsiveness will be assessed at baseline and at hour 2 post-infusion (peak cytokine levels[11,12]).

Aim 1: Examine the effects of inflammation on negative mood in Alcohol Use Disorder.
Approach: Participants will complete the Profile of Mood States (POMS) questionnaire[38] at baseline and hourly for 4 hours post-infusion. Hypothesis: Endotoxin will produce greater increases in negative mood than placebo infusion, and heavy drinkers will experience greater endotoxin-induced negative mood.

Aim 2: Examine the effects of inflammation on reward response in Alcohol Use Disorder.
Approach: Participants will complete the Reward Response Scale (RRS)[31] and Probabilistic Reward Task (PRT)[32,33] at baseline and at time of peak cytokine levels (2 hours post-infusion[11,12]). Hypothesis: Endotoxin will produce decreased reward response compared to placebo infusion, and heavy drinkers will experience a greater reduction in endotoxin-induced reward response compared to controls.

Exploratory Aim: Test associations between proinflammatory cytokine levels, negative mood, and reward sensitivity. Approach: Blood samples will be collected at baseline and hourly for 4 hours post-infusion. We will test for correlations between plasma levels of proinflammatory cytokines (IL-6 and TNF-α) with both negative mood and reward sensitivity. Hypothesis: Higher cytokine levels will correlate with increased negative mood and decreased reward sensitivity. These correlations will be stronger in heavy drinkers than controls.

Training Aim: Develop expertise in psychoneuroimmunology and clinical addictions neuroscience with a focus on reward learning. By working closely with my Sponsor and Collaborators, as well as through coursework and training activities, I will gain experience in clinical addictions neuroscience, reward learning, and psychoneuroimmunology, preparing me for a career as a human neuroscientist in the addictions field.

RESEARCH STRATEGY

A. SIGNIFICANCE

A.1. Inflammatory signaling is significantly implicated in alcohol use disorder.

Molecular and behavioral studies suggest a central role for the innate immune system in mediating the acute and chronic effects of alcohol and generally support an inflammatory hypothesis of alcohol use disorder[17]. Neurotrophins, including glial (GDNF) and brain derived neurotrophic factor (BDNF), are essential for basic cell signaling, including midbrain dopamine transmission[18,19]. In rodent models of AUD, reductions in GDNF and BDNF expression underlie dysfunctional striatal dopamine signaling, increased motivation to consume alcohol, and heightened alcohol reward[20-23]. In preclinical studies, lipopolysaccharide (LPS)-induced inflammation produces prolonged increases in alcohol consumption[5], while knocking out immune-signaling genes attenuates alcohol preference and self-administration[6]. Chronic alcohol exposure produces long-lasting increases in systemic inflammation, which in turn is associated with cognitive and behavioral impairment and brain damage[24]. Furthermore, inflammation increases vulnerability to stress-induced drug seeking and relapse[25].

Overall, alcohol consumption produces a sustained inflammatory state, and in turn, this alcohol-induced neuroinflammation contributes to the behavioral and neurotoxic effects of alcohol[4]. Individuals with AUD are thought to have increased neuroinflammation throughout the brain[3], and elevated peripheral levels of proinflammatory cytokines have been proposed as a biomarker for AUD[26]. Specifically, individuals with AUD have been shown to have increased plasma levels of proinflammatory cytokines, including the cytokines of interest in this study, Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)[58,59]. These cytokines have been shown to cross the blood-brain barrier[57], therefore possibly contributing to central nervous system effects. Nevertheless, there are contrasting findings such that a recent imaging study reported that individuals with AUD exhibit less activated microglia in the brain and blunted peripheral proinflammatory response than controls[27]. In sum, the role of inflammation in AUD remains unclear and has been largely unexplored in human/clinical populations.

A.2. The literature on inflammatory signaling and AUD is overwhelmingly preclinical and translation to human clinical samples is sorely needed.

To date, the vast majority of the research implicating alcohol and inflammation has been preclinical. Therefore, it is crucial for the field to progress to experimental models that can effectively probe the role of neuroinflammation in AUD phenotypes in humans. This is particularly relevant given recent evidence that genomic responses to inflammation and inflammatory disease in mouse models cannot be extrapolated to humans[8], which “supports higher priority to focus on the more complex human conditions rather than rely on mouse models to study human inflammatory diseases.”

A.3. Reward Sensitivity is correlated with alcohol use disorder and neuroinflammation.

Addiction has been shown to be a reward deficit disorder[34], with reward threshold heightening after substance use acting as a major reinforcing effect of substance abuse[35]. Reward sensitivity is a marker of initial risky drinking, such that individuals with baseline higher reward sensitivity are at increased risk of problematic alcohol use[50-52]. However, in the transition from early abuse to AUD, continued alcohol use eventually impairs neuronal circuits that are involved in reward sensitivity, thereby shifting alcohol use from an innately rewarding activity into drinking to relieve withdrawal and negative symptoms[49]. Reward responsiveness is also correlated with neuroinflammation. Preclinical studies show that lipopolysaccharide-induced inflammation alters reward sensitivity in mice[15,16], and in humans, neuroinflammation has been implicated in reward processing impairments in Major Depressive Disorder[53]. Additionally, previous studies in human control populations carried out by our collaborators indicate that brain activation in response to reward stimuli is decreased after endotoxin infusion[14].

A.4. Negative Mood is correlated with both AUD and neuroinflammation.

There is a well-established relationship between AUD and negative mood[36]. While negative mood can induce alcohol seeking due to its effects on craving[54,55], alcohol use also inhibits negative emotion regulation, i.e. the ability to alleviate negative mood states through one’s own efforts[56]. Negative emotionality, a comprehensive set of emotional states related to unpleasant feelings or a lack of feelings (e.g. sadness, anxiety, malaise, anhedonia)[45] are well-associated with alcohol addiction, such that individuals with AUD demonstrate higher levels of overall low mood[46,47]. Neuroinflammation has been associated with the emergence of negative emotionality[37], such that cytokines have been shown to play a causal role in the onset of negative mood in previous human studies[41-44].

Taken together, reward sensitivity and negative mood have both been associated with AUD and with inflammation, but separately. The link between AUD, inflammation, and these behavioral outcomes has not yet been explored.

The overall significance of the proposed F31 application hinges on the premise that while evidence is accumulating that the innate immune system and inflammation contribute to AUD, the evidence is largely preclinical and translation to human clinical samples is necessary. Findings in humans have been mostly correlational while experimental approaches that can establish a causal link between inflammation and AUD phenotypes are lacking. The proposed study fills an important gap in the literature by examining the role of inflammation in mood and reward responsiveness in a clinical sample of non-treatment-seeking heavy drinkers and light drinking healthy controls. The successful completion of the proposed study will advance the field by experimentally probing the role of neuroinflammation in mood and reward response in AUD. This study may inform future medication development applied to novel neuroimmune modulators with therapeutic potential for AUD[7,28]. Notably, this approach has been successful in the psychoneuroimmunology field[29,30] and has yet to be applied to the field of AUD.

A.5. Innovation of the Proposal

The proposed research is highly innovative in using an experimental model of inflammation to develop a framework for elucidating the link between inflammation, mood, and reward sensitivity in alcohol use disorder (AUD), by integrating behavioral (i.e. reward and mood), and biologic (i.e. inflammatory signaling responses) mechanisms. This research provides a meaningful translation of basic science findings to clinical samples. Further, the present study leverages resources and expertise, including a reference endotoxin provided by the NIH Clinical Center[9], which has demonstrated safety[10] and has been successfully administered at UCLA by the investigative team[11,12]. This will result in a safe, effective, and well-tolerated inflammatory challenge that offers an experimental probe of the role of inflammation in mood and reward sensitivity in AUD. A recent review of human endotoxin studies concluded that this model is safe, provides consistent and reproducible data, and can interrogate inflammation-behavior relationships[13]. To our knowledge, this is the first application of an endotoxin challenge to the study of AUD in humans. Lastly, this study is innovative in its inclusion of a light-drinking healthy control sample to assist with integrating previous findings from inflammatory challenges in non-AUD samples. In sum, we expect that the outcomes of the proposed research will add to our understanding of the causal role that inflammation plays in modulating mood and reward response among individuals with AUD.

B. APPROACH

B.1. Design Overview: The study design consists of a randomized, double-blind, placebo-controlled study of low dose endotoxin (see **Figure 1)**. A total of 76 participants (38 non-treatment seeking heavy drinkers and 38 light drinking healthy controls) will be randomly assigned (stratified by sex and baseline depression symptomology) to receive an I.V. infusion of either low dose endotoxin (0.8 ng/kg of body weight) or placebo (same volume of 0.9% saline solution) in the laboratory. Peripheral levels of proinflammatory cytokines [i.e. Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)], as well as mood (assessed by the Profile of Mood States, detailed below) will be assessed at baseline and hourly for four hours post infusion, while trait reward sensitivity (assessed by the Reward Response Scale and Probabilistic Reward Task, detailed below) will be assessed at baseline and at hour 2. Previous studies have shown that cytokine response peaks at 2 hours post infusion, as shown in **Figure 2** (from our collaborator Dr. Eisenberg's work[11,12]). All participants will receive a follow-up phone call by the study physician the day after the endotoxin challenge.

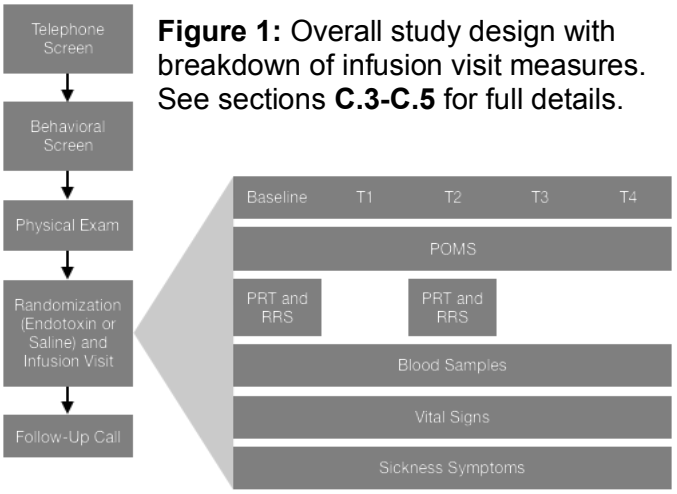

Figure 1: Overall study design with breakdown of infusion visit measures. See sections **C.3-C.5** for full details.

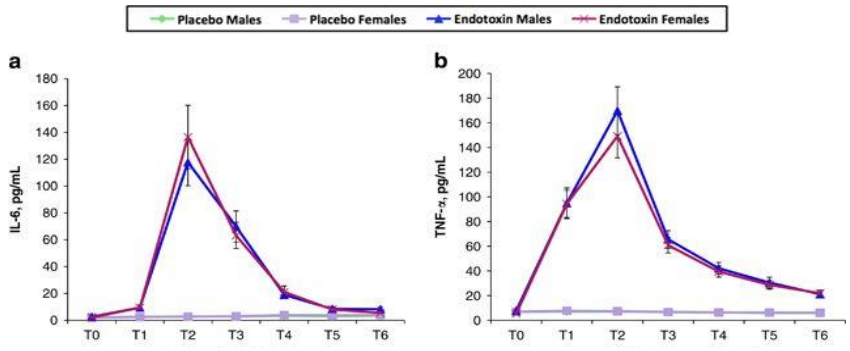

Figure 2: Plasma levels of proinflammatory cytokines IL-6 (a) and TNF-α (b) peak at approximately 2 hours post-infusion.

B.2. Participants: Inclusion criteria for non-treatment-seeking heavy drinkers are: (1) Alcohol Use Disorder Identification Test (AUDIT) score ≥ 8; and (2) report drinking at binge levels at least 1 time in the past month (5+ drinks/day for men, 4+

drinks/day for women). Inclusion criteria for light-drinking controls are: (1) AUDIT score < 4; and (2) report no occasions of binge drinking in the past month. Inclusion criteria for all participants are: (1) age between 21 and 45; and (2) non-treatment seeking for AUD. Exclusion criteria for all participants are: (1) a current (last 12 months) DSM-5 diagnosis of substance use disorder for any psychoactive substances other than alcohol and nicotine; (2) a lifetime DSM-5 diagnosis of major depressive disorder, schizophrenia, bipolar disorder, or any psychotic disorder; (3) current moderate to severe depression as indicated by a score of ≥ 21 on the Beck Depression Inventory-II (BDI-II); (4) current suicidal ideation or lifetime history of suicide attempt as reported on the Columbia-Suicide Severity Rating Scale (C-SSRS); (5) positive urine screen for drugs other than cannabis; (6) clinically significant alcohol withdrawal symptoms as indicated by a score ≥ 10 on the Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar); (7) an intense fear of needles or history of any adverse reactions to needle puncture; (8) pregnancy, nursing, or refusal to use reliable method of birth control (if female); (9) a medical condition that may interfere with safe study participation (e.g., unstable cardiac, renal, or liver disease, uncontrolled hypertension or diabetes); (10) abnormal electrocardiogram (EKG) or clinical labs; (11) ≥ Grade 2 laboratory abnormalities, based on FDA Guidance Document "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials; or (12) other circumstances that, in the opinion of the investigators, compromises participant safety.
Participants who, on arrival to the experimental visit, show any of the following will *not* be allowed to complete the endotoxin challenge: (a) Breath Alcohol Content (BrAC) > 0.0 g/dl; (b) clinical withdrawal (CIWA-Ar) score ≥ 10; (c) blood pressure ≤ 90/60 or ≥ 160/120; (d) pulse ≤ 50 beats/minute; (e) temperature ≥ 99.5°F, (f) recent (past 2 weeks) acute illness or vaccination; or (g) score of ≥ 10 on Physical Sickness Symptoms Assessment.
B.3. Recruitment and Enrollment Procedures: Participants will be recruited from the community through campaigns in radio, TV, local buses, social media, and print publications. After a telephone interview, eligible individuals will come in for an in-person screening visit in which they provide written informed consent after receiving a detailed explanation of the study. At this visit, we will administer the clinical diagnostic interview for DSM-5 (SCID-5) and collect individual differences measures and a urine sample for toxicology. Eligible participants will complete a physical exam, including EKG and laboratory tests. The study physician will obtain written informed consent for the medical exam and endotoxin challenge. Participants who pass the physical exam will then be urn randomized to an experimental condition (i.e. endotoxin vs. placebo). Urn randomization will be used to balance the groups by sex and trait depression (BDI-II) scores. Participants will receive $20 for the in-person screening session, $30 for the physical exam, and $100 for the intravenous infusion visit. All study procedures have been reviewed and approved by the UCLA Institutional Review Board (IRB) for Human Subjects research. In addition, an IND has been obtained. The project has received funding from a pilot/seed grant from the UCLA Cousins Center for Psychoneuroimmunology (see Sponsor pages).
B.4. Inflammatory Challenge (Endotoxin): Upon arrival to the UCLA Clinical and Translational Research Center (CTRC), a nurse, who will be blind to condition, will insert a catheter with a heparin lock into the dominant forearm for hourly blood draws and one into the non-dominant forearm for a continuous saline flush and for drug administration. Ninety minutes after arrival to the CTRC, each participant will receive either low-dose endotoxin (0.8 ng/kg of body weight administered) or placebo (same volume of 0.9% saline), which will be administered by the nurse as an intravenous bolus. This low dose has been shown to result in an increase in cytokine levels without significant changes in vital signs, in order to safely and briefly mimic low-grade inflammatory response[48]. The endotoxin will be derived from *Escherichia coli (E. Coli* group O:113: BB-IND 12948 to M.R.I) and will be provided by the NIH Clinical Center as a reference endotoxin for studies of experimental inflammation in humans[9]. This endotoxin preparation has been used in many human challenge studies and remains the World Health Organization standard for endotoxin assays used in the pharmaceutical industry[48]. The endotoxin drug fact sheet, certificate of analysis, and letter from NIH/NIDA regarding the use of *E. coli O:113* endotoxin in human challenge studies are provided as supplementary materials.

A computer generated stratified randomization scheme be used to balance the groups by sex and depression scores (BDI-II). The UCLA Research Pharmacy will manage the blind. The treatment conditions will not be different in appearance or method of administration. However, it is possible that participants undergoing the endotoxin challenge who feel very symptomatic may suspect that they are in the active condition. For this reason, we will exclude individuals who experience severe sickness symptoms during the challenge (which is expected to be less than 5% of the sample). The study physician will be on-call and will consult with the research team as needed to manage adverse events. In the event that significant medical problems are encountered, the blind will be broken and appropriate medical treatment will be provided. All participants will receive a follow-up phone call by the study physician the day after the endotoxin challenge.
B.5. Assessments during the Challenge: Participants will be assessed at baseline and for 4 hours post-

infusion, based on cytokine level time frames as shown in **Figure 2**. This time frame allows for us to fully capture the dose response curve from initial infusion to onset of inflammatory response to return to baseline. The following measures will be administered at the time points indicated:

(a) The Profile of Mood States (POMS) is a standard, validated psychological rating scale that measures dimensions of transient mood states by asking subjects to indicate how well each item describes their mood on a 5-point Likert scale (i.e. Not at All, A Little, Moderately, Quite a lot, Extremely).The assessment has four dimensions; positive mood, negative mood, vigor, and tension[38]. The negative mood subscale will be used to assess negative mood resulting from endotoxin administration, which is consistent with previous work by the investigative team[39]. This assessment will be completed electronically at 5 timepoints during the experimental visits (at baseline, 1, 2, 3, and 4 hours post-infusion).

(b) A Probabilistic Reward Task (PRT), depicted schematically in **Figure 3**[32,33], will be completed electronically at 2 timepoints during the experimental visits (at baseline and at time of peak cytokine levels, e.g. 2 hours post-infusion[11,12]). The task has been validated in multiple independent samples[33] and allows for the objective assessment of a subject's propensity to modulate behavior as a function of reward-based reinforcement. In each trial, the subject is asked to determine (via button press) whether a short or long mouth is presented on a previously mouthless cartoon face. Within each block (1 block = 100 trials; task = 3 blocks), an equal number of short and long mouths are presented. Importantly, the difference between mouth lengths is small and therefore difficult to determine. To elicit a response bias, an asymmetric reinforcer ratio is introduced: correct identification of one mouth length is rewarded ("Correct!! You won 5 cents") three times more frequently (rich stimulus) than correct identification of the other mouth length (lean stimulus), counterbalanced across subjects. Participants are told that the goal of the task is to win as much money as possible, and that not all correct responses will be rewarded.

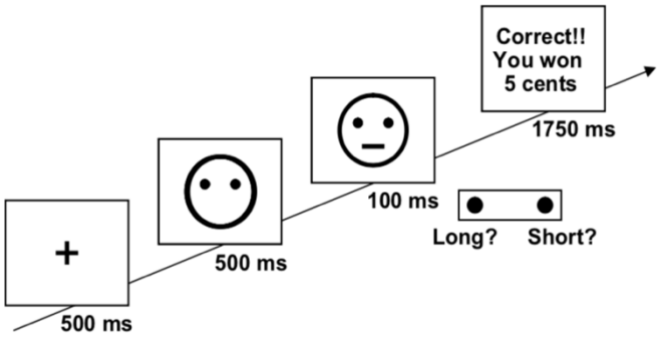

Figure 3: Schematic diagram of probabilistic reward task. Participants are asked to determine whether a short or long mouth is presented. The two mouth lengths have differential reward frequencies.

The outcome variable of interest is response bias, which indexes the participant's systematic preference for the response paired with the more frequent reward (rich stimulus), or the extent to which behavior is modulated by reinforcement history. Response bias is calculated as $log\ bias = \frac{1}{2}\ log\ (Rich_{correct} * Lean_{incorrect}) / (Rich_{incorrect} * Lean_{correct})$. The degree of response bias toward the more frequently reinforced response can be used to objectively determine reward responsiveness.

(c) The Reward Responsiveness Scale (RRS) is a self-report questionnaire that measures trait reward responsiveness by asking subjects to rate their agreement with various statements on a 4-point Likert scale (i.e. Strong Disagreement, Mild Disagreement, Mild Agreement, Strong Agreement)[31]. This assessment will also be completed electronically at the same 2 timepoints during the experimental visits. The RRS measures tonic reward responsiveness, while the PRT measures transient, behavioral reward responsiveness. The RRS will be collected at the same two timepoints as the PRT, i.e. baseline and T2 (peak).

(d) Whole blood samples will be collected in EDTA tubes at 5 timepoints during the experimental visit (baseline, T1, T2, T3, and T4). After collection, the samples will be stored in a -70 °C freezer until the completion of the study. Plasma TNF-α and IL-6 concentrations (assay ranges 0.8-31000 pg/mL and 0.2-38000 pg/mL, respectively) will be determined using a Bio-Plex 200 (Luminex) Instrument and a high sensitivity bead-based multiplex immunoassay, as described in previous studies[11,39]. All plasma samples from each subject will be assayed on the same 96-well plate. It should also be noted that the endotoxin used in the proposed study has been shown to lead to a coordinated pattern of increases across several different proinflammatory cytokines. Therefore, we are not suggesting that the effects of this endotoxin are primarily or uniquely related to IL-6 or TNF-α levels. We have chosen to assay IL-6 and TNF-α levels, as these markers of inflammation have previously been shown to correlate with measures of depression[44] and to map with other peripheral inflammatory markers such as IL-1 receptor antagonist[42], therefore allowing us to consider IL-6 and TNF-α to be representative indicators of systemic inflammation. Furthermore, these cytokines have been shown by our collaborator in a study of human controls to track with the endotoxin challenge[11,12] proposed for use in this study.

(e) Vital signs (i.e. pulse, blood pressure, temperature, respiration rate) will be collected at baseline and hourly for 4 hours post-infusion.
(f) Self-reported physical sickness symptoms (i.e. headaches, muscle pain, shivering, nausea, shortness of breath, fatigue) will be assessed on a scale from 0 (no symptoms) to 4 (very severe) and will be collected at baseline and hourly for 4 hours post-infusion.

B.6. Power Analysis and Data Analytic Plan:

Power Analysis: A power analysis was conducted for the proposed study based on results from a previous human endotoxin challenge carried out in a control sample by our collaborators[12]. Effect size was calculated based on Eisenberger et al.'s reported sample size of N = 39 and F-statistic of 8.13 for increase in negative mood at T2 after endotoxin infusion, yielding Cohen's *d* = 0.4687. Power analysis was conducted according to Cohen's guidelines to determine the sample size needed to achieve a power ≥ 0.80 (i.e. 80%) at an alpha level of .05. Using the program G*Power version 3.1 and selecting the repeated measures ANOVA, within-between interactions design, where alpha = .05, effect size f = 0.234, we arrived at a total N = 76 completers (38 heavy drinkers and 38 healthy controls). Specifically, we powered the study to detect differences from baseline to peak (T2) inflammatory response, given that the remaining data points post-peak tend to be similar and may obscure the effects of the inflammatory challenge. Individuals who experience severe sickness symptoms will be excluded (expected to be <5% of the sample). To account for an anticipated drop-out rate of 15%, including exclusion of individuals experiencing sickness symptoms, we aim to randomize approximately 90 participants in order to ensure we reach 76 completers.

Aim 1: Negative Mood. We will conduct a series of multilevel models (Proc Mixed in SAS Software) in which Group (heavy drinker versus light drinker) will be a two level between-subjects factor, Treatment (endotoxin vs. placebo) is a two level between-subjects factor, Time is a within-subjects factor, and the outcome measure is negative mood compared to baseline (captured by the POMS). Sickness symptoms and drinking history (i.e. drinks per day and drinks per drinking day in past year) will be used as covariates.

Aim 2: Reward Responsivity. As in Aim 1, a series of multilevel models (Proc Mixed in SAS Software) will be conducted. Specifically, in the repeated measures ANOVA models, Group (Heavy drinking versus light drinking) will be a two level between-subjects factor, and Treatment (endotoxin vs. placebo) will be a two level within-subjects factor. The dependent measures will be response bias in the PRT and score on the RRS compared to baseline. Sickness symptoms and drinking history (i.e. drinks per day and drinks per drinking day in past year) will be used as covariates in these analyses.

Exploratory Aim: Cytokines. Multilevel models will be used to capture the effects of Treatment (endotoxin vs. placebo) by Time for the proposed planned outcomes (i.e. proinflammatory cytokines, reward responsiveness, and negative mood). As with the first two aims, sickness symptoms and drinking history will be entered in these models as covariates.

B.7. Potential Pitfalls and Alternative Approaches

During the development of this proposal, several alternative designs and potential pitfalls were considered.

- **Follow-up period.** We considered a longer period of follow-up than the proposed 4 hours post-infusion. However, we decided that the existing literature on endotoxin challenge showed a robust response peaking within 2 hours and returning to near-baseline cytokine levels by 4 hours[11,12]. Therefore, we believe that participants can be safely discharged at 4 hours post-infusion. As always, the study physician will decide on discharge of participants who report any adverse events during the protocol.
- **Inflammatory biomarkers used.** Alternative peripheral inflammatory biomarkers were considered (e.g. C-reactive protein, IL-1 receptor antagonist); however, we chose to build on our collaborators' work with IL-6 and TNF-α due to their shown compatibility with the endotoxin challenge proposed[11,12] as well as previously-shown correlations with depression measures[44]. Furthermore, IL-6 and TNF-α have also been shown to map along with other markers of inflammation (IL-1 receptor antagonist) in response to inflammatory challenge[42], therefore, we can confidently consider the cytokines used to be representative of peripheral inflammation in general.
- **Between-subjects model.** We considered using a within-subjects model, such that each subject would experience both the endotoxin and the placebo infusions, separated by a washout period. However, we were concerned about participants' ability to easily discern between the two treatments, as well as possible attrition from participants completing the first visit but not the second (especially if they received endotoxin as their first infusion). Therefore, we selected a between-subjects model.
- **Sickness symptoms as a confound.** It is a consideration that individuals who feel extremely symptomatic might assume their treatment condition (i.e. assume they are receiving endotoxin) and

thus present a confound. In response, we plan to exclude participants who experience severe sickness symptoms (expected to be about 5% of the sample based on previous endotoxin challenge results[11,12]).

- **Sex differences.** Emerging literature suggests that there may be sex differences in endotoxin-based inflammatory response[14,40]. However, we are not currently powered to conduct a thorough investigation of sex differences as a primary aim of the study. Therefore, our best approach is to balance each cohort of participants on sex, and potentially examine sex differences as another exploratory aim.
- **Translational value of endotoxin model.** While there is a great deal of interest in the role of neuroinflammation in psychiatric disorders, and addiction in particular, there are few models that allows for experimental manipulations of inflammation in humans. The selection of an endotoxin "challenge" model as a probe for inflammatory responses in this sample was based on its successful application in mood disorders. In particular, we were compelled by the reliable effect of endotoxin on peripheral biomarkers of inflammation and its association with mood. Having the opportunity to collaborate with the UCLA-based team that conducted the pioneer endotoxin work in mood disorders and social neuroscience[11,12] has shaped our belief that this is a valid and worthwhile experimental model which should be employed to address AUD-related questions.

B.8. Study Timeline and Feasibility

The proposed analyses and training plan have been designed to span a three-year award period. Recruitment will take place over the first two years, with analysis, interpretation, and writing spanning the third year. No start-up period is planned as initial recruitment will have already begun by the beginning of the award period, funded by a pilot/seed grant from the UCLA Cousins Center for Psychoneuroimmunlogy. The projected recruitment is approximately 3-4 participants per month, consistent with observed enrollment in previous studies conducted in Dr. Ray's laboratory.

Projected Participant Flow, Males/Females (Total)

Year	0-3 mo.	4-6 mo.	7-9 mo.	10-12 mo.	Yearly Total
1	08/03 (11)	07/04 (11)	07/04 (11)	08/04 (12)	30/15 (45)
2	08/04 (12)	07/04 (11)	07/04 (11)	08/03 (11)	30/15 (45)
					Total: 60/30 (90)*

*Based on power analysis and drop-out rate described above.

Overall Study Timeline	Year 1			Year 2			Year 3		
Funding Month	**1-4**	**5-8**	**9-12**	**1-4**	**5-8**	**9-12**	**1-4**	**5-8**	**9-12**
Pilot / Finalize Study Procedures									
Data Collection									
Data Analysis									
Data Interpretation									
Preliminary Poster Preparation									
Manuscript Preparation									
Manuscript Submission / Revision									

B.9. Non-Clinical Trial Human Subjects Research

The current F31 proposal is a supplementary study to a pilot trial of endotoxin led by the Sponsor. The proposed study includes the abovementioned behavioral measures of reward responsiveness and negative mood, as well as peripheral cytokine markers, but I am not independently leading the trial of endotoxin itself.

B.10. Implications and Future Directions

The proposed study will fill an important gap in the literature pertaining to bio-behavioral interactions in AUD, specifically the modulation of negative mood and reward sensitivity by neuroinflammation, which has not been previously studied in a clinical AUD sample. Outcomes of the proposed research will add to our understanding of the causal role that inflammation plays in modulating mood and reward response among individuals with AUD. In the future, while this is beyond the scope of the currently study, I hope to follow up the proposed project by adding a neuroimaging component in order to more thoroughly explore the mechanisms through which endotoxin-induced neuroinflammation modulates reward response and negative emotionality in AUD. The proposed NRSA study sets the stage for my training as a human neuroscientist in addiction.

Respective Contributions

This training grant, including all experiments and specific aims, was developed in close collaboration with my Sponsor, Dr. Lara Ray. I joined Dr. Ray's laboratory with the goal of becoming a clinical neuroscientist, and this application stems from that goal. Weekly meetings with Dr. Ray provided me with invaluable opportunities for collaboration, and her constructive feedback and expertise in addiction and clinical neuroscience were instrumental in the proposal generation and development process. Additional feedback during the writing process was provided informally by Dr. Erica Grodin, a postdoctoral fellow in the Ray lab, and formally by Dr. Nigel Maidment, Dr. Christopher Colwell, and fellow graduate students in a grant-writing course offered through the Neuroscience program. Frequent discussions with Dr. Ray and Dr. Grodin helped me to tailor experiments to appropriately address the research questions of interest. For example, Drs. Ray and Grodin suggested I add a task-based measure of reward responsiveness rather than relying on the self-report scale alone, which I believe strengthens my second aim significantly.

I will continue to meet with Dr. Ray formally in one-on-one meetings on a weekly basis, as well as attending weekly lab meetings at which I will receive informal feedback from lab members on the progress of my experiments. I will continue to have access to Dr. Grodin and will discuss the project on a regular basis with her as well in individual and lab meetings. Additionally, Dr. Naomi Eisenberger, an expert in the field of psychoneuroimmunology, and Dr. Kate Wassum, an expert in the field of addiction neuroscience and reward learning, have both agreed to serve as Collaborators on this project. I will meet with Drs. Eisenberger and Wassum on a monthly basis to discuss the execution and results of the proposed project, as well as interpretation of results and the direction and progress of my research. I will take primary responsibility for most aspects of the research, including data acquisition, preprocessing, analysis, and dissemination, and will be responsible for ensuring that all study procedures are in accordance with the UCLA Office of Human Research Protection Program. I will also take the lead on any presentations or publications that emerge from this research application. Consistent with the opportunities I have had thus far for first-authored and collaborative publications with Dr. Ray and lab members, I am confident this training will be productive and will set the stage for my independent research career.

Selection of Sponsor and Institution

As a neuroscientist with a background in animal research but an interest in clinical and translational human research, I was very impressed by Dr. Lara Ray's (Sponsor) robust research program integrating clinical psychology with medication development, neuroimaging, and pharmacology. Dr. Ray is herself a cutting-edge, well-respected scientist in the field of addiction, who understands both complex neuroscience paradigms and the clinical phenomenology of addiction. This combination of clinical science and neuroscience is a powerful driving force in Dr. Ray's work and I deeply admire how well she is able to integrate the two, with neuroscience informing her clinical research and vice-versa. This translatability aligns perfectly with my goals, and thus I am confident that training with Dr. Ray represents an ideal opportunity to develop my interest in clinical addiction neuroscience.

Dr. Ray has also established herself in the Department of Psychology, and UCLA as a whole, as a prominent faculty member with strong connections across departments including psychiatry and neuroscience. Dr. Ray has had multiple cross departmental grants from NIAAA and NIDA with Co-Investigators from the fields of pharmacology, psychiatry, and neuroscience. Moreover, Dr. Ray is highly motivated and an excellent mentor, which is reflected by her successful track record with graduate students and postdoctoral fellows. Dr. Ray also has an impressive and consistent publication record, ensuring that this project and its manuscripts will be completed in a timely manner. Dr. Ray is committed to providing the applicant with all necessary training and research resources necessary to successfully complete this project (see Sponsor Statement). Dr. Ray currently holds a K24 midcareer award that protects her time to provide expert mentoring to junior scientists like myself. Over the past year, Dr. Ray and I have fostered a strong and productive mentor-mentee relationship resulting in opportunities for collaborative and first-author posters and presentations, as well as a first-author publication. I am confident that this level of quality and productivity will be accelerated by this training award.

As an institution, UCLA provides a world-class research and training environment across a range of disciplines. It is ranked #1 among U.S. public universities and #12 worldwide, largely due to UCLA's extraordinary research program. UCLA ranks #10 in research productivity (measured by number of publications) in the US (US News & World Report, 2017) and receives approximately $1 billion annually in research funds. UCLA specifically documents a strong, well-established research program in the clinical neuroscience of addiction, my area of interest. UCLA's Brain Research Institute (BRI) is a neuroscience research collective with over 300 faculty members representing 30 departments. The central mission of the BRI is to advance interdisciplinary basic and clinical neuroscience research. Within the BRI is the UCLA Integrative Center for Addictive Disorders, a state- of-the art, multidisciplinary research and treatment consortium with efforts devoted toward basic science research and clinical treatment interventions. The Integrative Center for Addictive Disorders provides regular seminars through the academic year with lectures by leading experts in addiction. These lectures are in addition to weekly Joint Seminars in Neuroscience lectures hosted by the Brain Research Institute, which feature world leaders in neuroscience research.

Conducting the proposed research and training program at UCLA will afford me the opportunity to pursue my training and research interests within a prolific interdisciplinary environment. The research atmosphere at UCLA fosters intra- and inter-departmental collaboration, with easy access to clinical support (see Facilities and Other Resources), thus providing the necessary structural support for the proposed research training. In addition, UCLA nurtures student research and training, which has enabled me to work on projects with faculty from various backgrounds and expertise, including Dr. Jamie Feusner, Dr. Andrew Leuchter, Dr. Adriana Galván, and Dr. Edythe London, in addition to my identified Sponsor and collaborators. Therefore, the intellectual and material resources available at UCLA render it the ideal institution for the advancement of my research training.

UCLA's collaborative environment has allowed me to find collaborators for the proposed project who will aid in my training in their areas of expertise. The two Collaborators on this project, Dr. Kate Wassum and Dr. Naomi Eisenberger, will provide training with respect to the pharmacology of addiction, clinical neuroscience, psychoneuroimmunology, and reward (see Letters of Collaboration). Combined, these resources make UCLA an outstanding environment for the proposed award with multiple mechanisms of support available to me while I perform the proposed research. Under the guidance of Dr. Ray, and with support from Drs. Eisenberger and Wassum, I will advance my knowledge of psychoneuroimmunology and addiction neuroscience with a focus on the psychobiology of reward. In sum, the institution and sponsor of this application are well-suited to foster my development as a clinical and translational addictions neuroscientist.

Responsible Conduct of Research

When conducting human research in a clinical setting – and even more so for a project involving administering endotoxin to participants – responsible ethical research is of the utmost importance. I completed a course offered and required by the UCLA Neuroscience program (Neuroscience 207), entitled "Integrity of Scientific Investigation: Education, Research, and Career Implications" in the spring of 2019. The class met for two hours per week throughout the 10-week quarter and included lectures, student-led presentations, and group discussions of assigned readings from *Scientific Integrity: Text and Cases in Responsible Conduct of Research* (Francis L. Macrina) and additional case studies from recent news. Students were graded on a "Satisfactory / Unsatisfactory" basis, and I received a "Satisfactory" grade. Grading was based on attendance and active class participation, presentations, and completion of writing assignments, including a final paper evaluating the ethics of a number of case studies. This course covered a range of topics in science ethics, including data ownership and intellectual property, competing interests, authorship, peer review, collaboration, mentorship, academic appointments, animal and human research, scientific record keeping and data management, responsible scientific communication, and overall scientific ethical behavior.

As indicated in my Training Plan, in order to meet the NIH requirement of undertaking instruction in the responsible conduct of research at least once every 4 years, I plan to complete additional training in human clinical research by enrolling in a course offered through the UCLA Department of Medicine (Medicine M261) entitled "Responsible Conduct of Research Involving Humans." This course discusses current issues in responsible conduct of clinical research, including reporting of research, basis for authorship, issues in genetic research, principles and practice of research on humans, conflicts of interest, Institutional Review Board (IRB), and related topics.

Additionally, through UCLA's Department of Environmental Health and Safety (EHS) and the Collaborative Institutional Training Initiative (CITI), I have participated in a number of required in-person and online courses focusing on safe and ethical research. These courses included topics such as fundamentals in laboratory safety, working with bloodborne pathogens, medical waste management, ethical principles in human subjects research, assessing risk in the social and behavioral sciences, informed consent, good clinical practice for clinical trials, and HIPAA confidentiality/privacy training. UCLA requires that most of these courses be retaken or refreshed every 1-3 years. I comply with these requirements and will continue to do so during the planned award period.

In the Ray lab's weekly lab meetings, lab members also informally discuss experimental designs and compliance with ethical research practices. For example, during a recent lab retreat with our collaborators at the University of Southern California, we spent part of the day discussing scientific ethics, talking through a case study involving a collaboration and authorship dispute. Dr. Ray actively facilitates and participates in such discussions and will continue this instruction throughout the planned award period. Dr. Ray and I also have discussions about day-to-day responsible conduct of research during our weekly individual meetings. Common topics range from IRB protocol preparations to ensuring safety, confidentiality, and comfort for all our subjects. Finally, I plan to enhance my understanding of ethical issues related to my specific project by researching these topics in my own free time and actively engaging in discussions about ethics with fellow students and faculty during the proposed award period and throughout my career.

SECTION II – SPONSOR INFORMATION

(a) Research Support Available

PI	Project Number	Title	Dates	Total Direct Cost
Ray	R01AA026190	A randomized controlled clinical trial of ibudilast for the treatment of AUD	05/15/2018-4/30/2022	$1,892,000
Ray	K24AA025704	Clinical neuroscience of AUD: integrating neuroscience and clinical trials	9/15/2018-8/31/2023	$851,575
Ray	R21AA027180	A novel human laboratory model for screening medications for AUD	9/20/2019-8/31/2021	$262,500
Ray	R01AA026190S1	Diversity Supplement	5/01/2019-4/30/2022	$141,661
Magill (PI) Ray (Co-I)	R21AA026006	A Meta-Analysis of CBT/RP efficacy, moderated efficacy, and mediation	8/01/2017-07/31/2020 (NCE)	$313,147
Ray	Seed Grant from UCLA Cousins Center for PNI	Endotoxin challenge to probe inflammatory mechanisms in alcohol use disorder	3/17/2020-3/30/2022	$20,000
Ray/Grodin	R21AA028444	Development of a selective ALDH2 inhibitor for the treatment of AUD	Pending (Priority Score=20)	$275,000

(b) Sponsor's/Co-Sponsor's Previous Fellows/Trainees

Dr. Lara Ray is the primary mentor of Ms. Burnette as well as 5 graduate students in the UCLA Psychology doctoral program in Clinical Psychology and 2 postdoctoral fellows in neuroscience. Dr. Ray has served on 25 dissertation and/or master's committees for doctoral students, and has served as a clinical supervisor for doctoral students at UCLA. She has mentored over 60 UCLA undergraduates, including 5 UCLA undergraduate honor's thesis students. Over the past 5 years, Dr. Ray has mentored two predoctoral NRSAs (Spencer Bujarski and Kelly Courtney) and two postdoctoral NRSAs (Megan Yardley and Erica Grodin). She is the primary mentor on a K01 award (Daniel Roche) and has 2 predoctoral trainees funded by the California Tobacco Related Disease Research Program (TRDRP) (Aaron Lim and ReJoyce Green). Students who have graduated with Dr. Ray hold a host of research-oriented positions, including: Anita Cservenka (Assistant Professor at Oregon State University), Kelly Courtney (Assistant Professor of Psychiatry at UCSD), Daniel Roche (Assistant Professor, University of Maryland School of Medicine, Department of Psychiatry), Guadalupe Bacio (Assistant Professor at Pomona College), and Emily Hartwell (Postdoctoral Fellow at Philadelphia VA and University of Pennsylvania). Dr. Ray's current graduate student and postdoctoral trainees are:

Trainee	Training Institution	Present Position
Erica Grodin, PhD	Postdoctoral Fellow (with F32 support)	Postdoctoral Fellow
Steven Nieto, PhD	Postdoctoral Fellow (with T32 support)	Postdoctoral Fellow
Aaron Lim, MA	UCLA, Clinical Psychology PhD Program	5th year PhD student
ReJoyce Green, MA	UCLA, Clinical Psychology PhD Program	4th year PhD student
Alex Venegas, BA	UCLA, Clinical Psychology PhD Program	3rd year PhD student
Lindsay Meredith, MA	UCLA, Clinical Psychology PhD Program	2nd year PhD student
Suzanna Donato, BA	UCLA, Clinical Psychology PhD Program	1st year PhD student

Trainees mentored by Dr. Ray 2010-present

Name	Position as Trainee	Areas of Mentorship	Dates	Current Position
Daniel Roche, Ph.D.	Postdoctoral Fellow	Medications development; human laboratory models for AUD	03/13 – 02/18	Assistant Professor, University of Maryland Psychiatry Dept

Megan Yardley, Ph.D.	Postdoctoral Fellow	Medications development for alcoholism	08/14 – 02/16	Senior Clinical Research Scientist, Biosense Webster
Anita Cservenka, Ph.D.	Postdoctoral Fellow	fMRI for medications development; psychopharmacology	08/15 – 08/16	Assistant Professor of Psychology, Oregon State University
James Ashenhurst, Ph.D.	PhD Student in Neuroscience	Experimental psychopharmacology and behavioral genetics	08/09 – 06/14	Product Scientist, 23andMe
Guadalupe Bacio, Ph.D.	PhD Student in Clinical Psychology	Experimental psychopathology, multiculturalism	09/12 – 06/14	Assistant Professor of Psychology, Pomona College
Nathasha (Moallem) Correa, Ph.D.	PhD Student in Clinical Psychology	Experimental psychopharmacology, neuropsychology	08/10 – 06/16	Staff Psychologist, San Diego VA CBOC Clinic
Vincent Allen, Ph.D.	PhD Student in Clinical Psychology	Experimental psychopathology, multiculturalism	08/10 - 06/16	Postdoctoral Fellow, Georgia State University
Kelly Courtney, Ph.D.	NSRA fellow PhD Student in Clinical Psychology	fMRI for medications development; psychopharmacology	08/10 - 06/16	Assistant Professor, UCSD Psychiatry Department
Spencer Bujarski, Ph.D.	NSRA Fellow, PhD Student in Clinical Psychology	Experimental psychopathology, clinical neuroscience of addiction	08/11 – 05/18	Senior data scientist, Hulu
Emily Hartwell, Ph.D.	PhD Student in Clinical Psychology	Experimental psychopharmacology, behavioral genetics	08/12 – 8/2018	Postdoctoral Fellow, Philadelphia VA and Univ of Pennsylvania
Erica Grodin, Ph.D.	Postdoctoral Fellow	fMRI for medications development; psychopharmacology	1/19-present	Postdoctoral Fellow (F32 Recipient)
Steven Nieto, Ph.D.	Postdoctoral Fellow	Translational neuroscience	1/20-present	Postdoctoral Fellow (NIDA T32 Recipient)
Aaron Lim, M.A.	PhD Student in Clinical Psychology	fMRI for medications development; clinical psychopharmacology	08/15 – present	PhD Student in Clinical Psychology
ReJoyce Green, M.A.	Diversity Fellowship Recipient	Psychopharmacology, multiculturalism	09/13-present	PhD Student in Clinical Psychology
Alexandra Venegas, B.A.	PhD Student in Clinical Psychology	Behavioral pharmacology of alcoholism	08/16-present	PhD Student in Clinical Psychology
Michael Mirbaba, M.D., Ph.D.	Psychiatry Resident, UCLA	Medications development	07/14 – 06/17	Staff Psychiatrist, UCLA
Hee-Sang Lyu, M.D.	Psychiatry Resident, UCLA	Medications development	07/14 – 06/17	Staff Psychiatrist, UCLA
Artha Gillis, M.D.	Psychiatry Resident, UCLA	Addiction Science, NIH Loan Repayment Program	08/17 – present	Assistant Professor, UCLA Psychiatry

(c) Training Plan, Environment, Research Facilities

Training Plan

Ms. Burnette and I have been in close contact in crafting a plan to ensure her success during the award period and towards the goal of developing her independent research skills. With this goal in mind, we have planned a training program that would provide Ms. Burnette with a strong foundation to ask insightful questions about how alcohol and drugs interact with the central nervous system, and the technical knowledge and

experience to select and incorporate the best techniques to answer those questions. Together we decided on a program that would cover a three-year training period (described in Activities Planned under This Award).

The goal for Ms. Burnette's training program is to build expertise in clinical neuroscience of addiction and in psychoneuroimmunology. The proposed training plan will result in a highly skilled and well-rounded clinical neuroscientist who can have a successful independent career in translational science of addiction. These goals will be reached through a combination of direct mentoring by the sponsor and collaborators, course work, and selected training opportunities. The proposed research project will also support the training goals by allowing Ms. Burnette to carry out a cutting-edge research study using an endotoxin challenge to provoke inflammation under controlled laboratory conditions. This work is also supported by a Seed Grant awarded to me by the UCLA Cousins Center for Psychoneuroimmunology, a leading research center on PNI.

I will meet with Ms. Burnette individually on a weekly basis to monitor her progress in the proposed research and training plans. In addition, I will meet with Ms. Burnette in a group format during our weekly lab meeting and in weekly staff meeting when we review study progress. Importantly, I see my trainees, including Ms. Burnette, on a near daily basis in my research laboratory and I conduct informal mentoring on a regular basis through these daily interactions about ongoing studies in my laboratory. Ms. Burnette will also meet at least monthly with the collaborators on this project, Drs. Naomi Eisenberger and Kate Wassum. I have an excellent working relationship with Drs. Wassum and Eisenberger and I am delighted that they can contribute to Ms. Burnette's training. They are both outstanding female scientists at different career stages who can provide fantastic scientific input as well as serve as role models to Mrs. Burnette.

The following are the primary areas of training identified by Ms. Burnette and myself as critical to her development as a translational scientist in addiction.

1. Clinical Neuroscience of Addiction: The main goal of Ms. Burnette's proposal is to develop her skill set as a clinical and translational researcher. To accomplish this goal, a critical component of her training will involve developing expertise in designing and executing experimental medicine studies in clinical samples. Ms. Burnette will take coursework on the Neural Basis of Reward and Value (by Dr. Kate Wassum) to increase her understanding of the principles of reward learning. Through selected readings, meetings with me and Dr. Wassum, and attendance of local and national conferences, she will develop expertise in the clinical neuroscience of AUD. These training experiences will provide Ms. Burnette with the foundation and knowledge necessary to design and execute studies that elucidate the pathophysiology of addiction in humans, including neuroimmune determinants. As the sponsor in this application, I will ensure that Ms. Burnette has ample access to readings and discussions about the design of experimental medicine studies that can advance translational science of AUD. I am eager to engage our collaborators in these discussions, particularly Dr. Kate Wassum who is a well-respected preclinical scientist in the field of reward learning and addiction. The combination of basic and clinical expertise in the mentoring team is designed to provide Mrs. Burnette with a rich set of opportunities and scientific methods/viewpoints.

2. Psychoneuroimmunology: Ms. Burnette is committed to gaining expertise in the field of PNI and she will do so through a combination of coursework, seminar series, and individual meetings and select readings (see list of select readings provided). This training goal is a great match for Ms. Burnette's overall training program in human neuroscience and is supported by the fact that I currently have multiple research grants examining neuroinflammatory processes in AUD (including two studies on ibudilast and a seed grant to support an endotoxin challenge). Ms. Burnette will enroll in Psychology 216B, "*Psychoneuroimmunology,"* which serves as an introduction to the field of psychoneuroimmunology. This will allow Ms. Burnette to develop conceptual and methodological skills necessary for interpreting and conducting research in the area. Ms. Burnette will also attend Psychoneuroimmunology Research Seminars, a seminar series offered through the UCLA Department of Psychiatry, to stay abreast of developments in the field. As with the clinical neuroscience training goal, we have enlisted an expert collaborator to support Ms. Burnette's training. Dr. Naomi Eisenberger is a leading expert in the field of social and affective neuroscience. She has performed extensive PNI research, including using the proposed endotoxin challenge in a sample of 140 healthy controls. Dr. Eisenberger's preliminary data conducting endotoxin studies at UCLA have supported the study design and feasibility. Ms. Burnette will meet monthly with Dr. Eisenberger to review the study progress and discuss other opportunities for research training in PNI. I am confident that we have allocated sufficient resources to ensure that Ms. Burnette will be able to deepen her understanding of the principles of psychoneuroimmunology and apply them to the study of alcohol use disorder.

Professional Development

In addition to the substantive areas of training described above, I will work to ensure that Ms. Burnette receives outstanding professional development training. As a mid-career scientist who is deeply committed to training the new generation of alcohol scientists, I am delighted to support Ms. Burnette's professional development in a very active and engaged fashion. Of note, I am currently on the second year of my K24 award, a mechanism which allows me to focus sharply on mentoring. Regarding specific goals for professional development, Ms. Burnette and I have identified the following two critical areas of focus:

(a) Communication and Writing Skills. Equally important to training in the content areas and technical aspects of the work, is the acquisition of the skills needed to communicate well in order to present and publish scientific findings effectively. To achieve this goal, Ms. Burnette will work closely with me on manuscript preparation, conference presentations, and even some exposure to grant writing. I deeply value scientific communication through peer-reviewed papers and conference presentations. I am active in both areas with over 180 peer-reviewed publications and a very active schedule of scientific lecturing. I am eager to involve Ms. Burnette in a wide host of manuscripts relevant to her interests and training goals. I will also make sure that Ms. Burnette is able to present and discuss her findings with the scientific community through scientific talks and lectures. Specifically, I will support Ms. Burnette in attending both national and international meetings of high relevance to her goals, such as the Research Society on Alcoholism, The American College on Neuropsychopharmacology, the Society for Neuroscience, and the International Society for Biomedical Research on Alcoholism. These opportunities will allow Ms. Burnette to interact with trainees and senior investigators in the field to share scientific ideas and to network. I believe that the setting at specialized conferences will facilitate the development of professional relationships with national and international scientists. This level of exposure will allow Ms. Burnette to select an excellent postdoctoral training program at the conclusion of her PhD training at UCLA.

(b) Responsible Conduct of Research. At each step of the research process, I educate trainees and staff on ethical research practices. Anytime we establish new protocols, all laboratory members learn how to properly recruit participants, collect data, and enter it into our databases in order to safeguard patient confidentiality. Ms. Burnette and I will meet weekly to discuss the conduct of her research project as well as the Seed Grant project (from the UCLA Cousins Center for Psychoneuroimmunology) that supports her application. This will allow Ms. Burnette to have regular and meaningful discussions about good clinical practice in research context and the ethical conduct of clinical studies. Furthermore, Ms. Burnette will participate in the UCLA Clinical Translational Science Institute seminar series which cover critical topics, such as scientific misconduct, data ownership and authorship. I have enjoyed participating in this training myself over the past year, as part of my own K24 training.

(c) Work-life Balance in Academia. As a midcareer scientist with three young children, I recognize that young scientists need support with regard to the ever-evolving topic of work-life balance. I find that scientific careers can often be intimidating to outstanding young scientists due to concerns about whether they can effectively balance their personal and professional lives. I take an active role in discussing life outside of academia and to convey aspects of my personal life and past experiences that allow my trainees to engage in open discussions about self-care, family life, women in science, and issues of race and ethnicity. I firmly believe these issues are central to the development of a balanced and supportive work environment, which in turn can nurture young scientists in their professional and personal lives.

Research Environment and Facilities

The Department of Psychology at the Univervisty of California, Los Angeles (UCLA) provides an ideal environment with ample resources for the proposed training and research plan. UCLA has a large and world-renowned psychology and neuroscience community. Specifically, Ms. Burnette will benefit from the strong scientific community of addiction scientists (e.g., Drs. Edythe London, Chris Evans, Steve Shoptaw, Keith Heinzerling, and Walter Ling) and PNI experts (e.g., Drs. Michael Irwin, Steve Cole, Naomi Eisenberger, and Julie Bower). Further, the UCLA Clinical Psychology Doctoral Program in which I am appointed as a Full Professor, has been ranked by US News and World Report as the top program in the nation for over 20 years. Ms. Burnette is enrolled in the UCLA Interdepartmental Neuroscience Program (IDP), a highly-rank PhD program that draws resources and faculty from across the medical and life sciences campus. Further, UCLA offers extensive coursework, seminars, workshops, and conferences on addiciton, clinical science, pharmacology, clinical trials, and psychoneuroimmunology. In brief, the rich availability of experts in addiction, neuroscience, and psychoneuroimmunology adds substantially to the training opportunities available to Ms. Burnette. Based on her training trejectory thus far, I expect Ms. Burnette to make the most of these opportunities, particularly with the support of an NRSA predoctoral award.

In addition to my appointment in the Psychology Department at UCLA, I have an appointment in the Department of Psychiatry and Biobehavioral Sciences and I am very active in the Psychiatry and Neuroscience communities at UCLA. Ms. Burnette will benefit from the resources of the UCLA Department of Psychiatry, including its multiple centers and world-class faculty. In particular, I am affiliated with the UCLA Brain Research Institute (BRI) which is an umbrella organization that integrates the neuroscience reseach community at UCLA. Within the BRI, I have leardership responsibilities in the UCLA Integrative Center for Addictive Disorders, where I routinely host speakers, organize meetings, and select applicants for various training and faculty positions. I also actively mentor students in the NIDA Translational Neuroscience of Drug Abuse (TNDA; PI: London). I serve on the executive committee for the TNDA T32, which I hope will provide funding for Ms. Burnette before her NRSA can be considered for extramural support. I am delighted that Ms. Burnette may benefit from the resources of the TNDA Training Grant such as scientific writing workshops and university-wide meetings and lectures on addiction science.

To complement the outstanding intellectual resources available to Ms. Burnette at UCLA, she will have access to the state-of-the-art facilities for clinical trials and neuroscience research. These facilities include the UCLA Clinical and Translational Research Center (CTRC) and the Staglin Center for Cognitive Neuroscience (CCN). Of note, the medical screening and biological samples for the Seed Grant in PNI (that is supporting the proposed experiments) are fully supported by the UCLA CTRC. The UCLA CTRC is an active and newly remodelled facility with many active clinical trials and a large staff of research nurses and technicians who are well-qualified to support the clinical research enterprise. The proposed endotoxin challenge sessions will be conducted at the outpatient facilities of the UCLA CTRC. As a member of my lab, Ms. Burnette has her own office space, telephone, computer, and high-speed access to the Ray Lab server as well as the CCN's server where neuroimaging data are stored (Hoffman2). My newly renovated and expanded laboratory environment includes two large chambers, each with a reception area and eleven work stations as well as six separate behavioral and psychophysiological testing chambers. All the screening of research participants will be conducted in my laboratory.

In summary, Ms. Burnette will be part of a rich and very active research environment that will provide ample support for her research and training plans. The NRSA Individual Predoctoral Fellowship award would allow Ms. Burnette to devote her efforts fully to developing expertise in clinical neuroscience of addiction and psychoneuroimmunology, as outlined in the training plans in this application. Ms. Burnette will also be able to conduct an exciting research project that was designed to support her training goals and to leverage existing resources from my laboratory in order to produce high-impact science.

Importantly, a Seed Grant from the UCLA Cousins Center for Psychoneuroimmunology was obtained to cover the costs of the experimental procedures proposed. In addition, a voucher from the UCLA CTRC was obtained to offset the costs of nursing staff. An IRB protocol has been approved for the project. The endotoxin has been acquired from NIDA and an IND has been obtained from the FDA. All of these important regulatory and funding support documents serve to demonstrate both the high feasibility of the proposed study and the high level of commitment from myself and my laboratory to ensure the proposed study gets executed with the highest scientific rigor. Together, the research and training goals of this proposal will result in novel findings about neuroinflammatory processes in AUD while training a promising neuroscientist who will be poised to have a successful independent career in translational science of addiction.

(d) Number of Trainees to be Supervised during the Fellowship

As of September 2020 (start date), Dr. Ray will supervise the following trainees, in addition to the applicant:

1.	Erica Grodin, PhD	Postdoctoral Fellow (with F32 support)	Postdoctoral Fellow
2.	Steven Nieto, PhD	Postdoctoral Fellow (with T32 support)	Postdoctoral Fellow
3.	Aaron Lim, MA	UCLA, Clinical Psychology PhD Program	5th year PhD student
4.	ReJoyce Green, MA	UCLA, Clinical Psychology PhD Program	4th year PhD student
5.	Alex Venegas, BA	UCLA, Clinical Psychology PhD Program	3rd year PhD student
6.	Lindsay Meredith, MA	UCLA, Clinical Psychology PhD Program	2nd year PhD student
7.	Suzanna Donato, BA	UCLA, Clinical Psychology PhD Program	1st year PhD student

(e) Applicant's Qualifications and Potential for a Research Career

I am delighted to write this letter of support for Elizabeth (Libby) Burnette's application to the NRSA Predoctoral Research Fellowship. Simply put, Libby is an ideal candidate for a predoctoral NRSA. She is completing her second year in the UCLA Neuroscience Interdepartmental Program and is deeply committed to clinical neuroscience of addiction. I met Libby approximately one year ago when she did a 3-month rotation in

my laboratory. I was stunned when Libby published an excellent manuscript during her quarter-long rotation. I have never seen a student produce such high-quality work in such a timely fashion. I was delighted when Libby selected my lab for the remainder of her PhD training and she has not disappointed. Few students are as ambitious and productive as Libby. I am confident she will have an outstanding training experience at UCLA, which will set the stage for her continued career success.

Let me tell you more about Libby and why I believe she is an outstanding candidate for an NRSA predoctoral fellowship. Libby completed her Bachelor's Degree in neuroscience at Duke University before joining the UCLA Interdepartmental Neuroscience PhD program. She was highly recommended by her mentors at Duke who clearly recognized her talent, ambition, and determination. At UCLA, Libby conducted three rotations during her first year of training in the Interdepartmental Neuroscience Program. She focused all three rotations on human neuroscience broadly, and psychiatric populations in particular. Libby was quite skilled when she joined my laboratory for her third rotation and was quickly able to hit the ground running. She wrote an excellent paper on the link between impulsivity and neural activation to alcohol cues in heavy drinkers: https://www.ncbi.nlm.nih.gov/pubmed/31622796 I could not have been prouder of Libby's work during her rotation in my lab. She took feedback exceedingly well. She also forged a strong relationship with an outstanding postdoctoral fellow in my laboratory, Dr. Erica Grodin. I expect they will continue to work together during their time in my laboratory.

In the study conducted during her first-year rotation, Libby found that self-reported sensation seeking was positively associated with alcohol taste cue-elicited activation in frontostriatal regions, such that individuals who reported higher sensation seeking displayed greater neural response to alcohol taste cues. Conversely, delay discounting was negatively associated with activation in frontoparietal regions, such that individuals who reported greater discounting showed less cue-elicited activation. Libby's results indicate that sensation seeking is associated with reward responsivity, while delay discounting is associated with recruitment of self-control circuitry. I am excited to see Libby continue to pursue these interests as she advances her training. In particular, Libby is currently collaborating with Dr. Edythe London's lab to examine differences in impulsivity, measured by the Balloon Analog Risk Task (BART), between healthy controls and individuals with alcohol use disorder. As this work unfolds, I am sure Libby will continue to grow as a neuroscientist in the field of addiction.

Central to this NRSA application, while Libby is skilled in functional neuroimaging methods, she clearly identified clinical neuroscience and psychoneuroimmunology as the core areas in which she wants to train. Libby is currently writing a review of the literature on human studies implicating neuroinflammatory process in alcohol use disorder. This review paper is of the highest quality and I expect it to be well-received in peer-review and to become a highly cited summary of the literature on PNI and AUD. In sum, I am confident that Libby's background, current interests/training, and goals are an excellent fit for the proposed predoctoral NRSA. I would love to see Libby benefit from protected research time (through the NRSA mechanism) so that she can take full advantage of the rich academic environment at UCLA. I urge you to give Libby's application for this NRSA fellowship your highest consideration based on the strength of her academic record as well as her cutting-edge research and training plans.

In closing, I give Libby my strongest and most enthusiastic recommendation. A predoctoral NRSA award would make a major difference in Libby's career trajectory and I am confident that if given this opportunity, Libby will thrive. As I hope you can see in this application, I am deeply committed to training Libby and to making sure she completes the proposed research plan with the highest scientific rigor. We have taken ample steps to ensure the feasibility and funding support for the costs associated with this project. I am doing so because I have every confidence this will be a highly impactful study. I am also confident that this NRSA will set up the stage for Libby to become a highly productive and successful clinical neuroscientist of addiction. Please do not hesitate to contact me should you have any further questions.

Lara A. Ray, PhD
Shirley M. Hatos Term Chair in Clinical Neuropharmacology
Professor, Department of Psychology
Department of Psychiatry and Biobehavioral Sciences
Brain Research Institute
University of California Los Angeles

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NAOMI I. EISENBERGER
DEPARTMENT OF PSYCHOLOGY
5514 PRITZKER HALL
LOS ANGELES, CALIFORNIA 90095-1563

March 20, 2020

Elizabeth Burnette
Neuroscience Interdepartmental Ph.D. Program
Department of Psychology
1285 Franz Hall, Box 951563
Los Angeles, CA 90095-1563

Re: "Probing Inflammation and Reward Sensitivity in Alcohol Use Disorder"

Dear Elizabeth:

I am happy to serve as a Collaborator with you on your National Research Service Award Predoctoral Fellowship (F31) application entitled "Probing Inflammation and Reward Sensitivity in Alcohol Use Disorder." Given my expertise in psychoneuroimmunology and your interest in the clinical neuroscience of addiction, I am confident of fruitful synergy and productive collaborations. Your proposed project addresses a critical gap in the literature by using an endotoxin challenge to investigate the effects of neuroinflammation on negative mood and reward sensitivity, which will help to elucidate the mechanisms underpinning AUD.

My expertise and background in the relationships between neuroimmunology and affective outcomes make me uniquely suited to serve as a Collaborator on this project. As you know, I am a Professor in Social Psychology at the University of California, Los Angeles, the director of the Social and Affective Neuroscience Laboratory and the co-director of the Social Cognitive Neuroscience Laboratory. Additionally, my work has used the human endotoxin challenge that you will be employing in your proposed study to experimentally manipulate immune system activity. Given my expertise in psychoneuroimmunology, I am delighted to provide you with training and support for your proposed study.

I am excited to offer your application my strongest support and I look forward to working with you as a Collaborator on this project. Your research background, scientific productivity, and supportive mentor make you an excellent candidate for this F31 award.

Sincerely,

Naomi Eisenberger, Ph.D.
UCLA Professor of Psychology

UCLA College | Life Sciences Psychology

KATE M. WASSUM, PH.D.
ASSOCIATE PROFESSOR OF PSYCHOLOGY
UNIVERSITY OF CALIFORNIA, LOS ANGELES
BOX 951563
LOS ANGELES, CA 90095-1563

March 11, 2020

Elizabeth Burnette
Neuroscience Interdepartmental Ph.D. Program
Department of Psychology
University of California, Los Angeles

RE: F31 Letter of Support

Dear Elizabeth,

I would be delighted to serve as a Collaborator with you on your National Research Service Award Predoctoral Fellowship (F31) application, entitled "Probing Inflammation and Reward Sensitivity in Alcohol Use Disorder." I am in full support of your identified research and training goals in the fields of clinical neuroscience of addiction, reward learning, and psychoneuroimmunology.

I would like to express my commitment to supporting these goals. Specifically, my expertise and background in addictions neuroscience and reward learning provide me with the required skills to contribute to your training and research goals. On this project, I will serve as a Collaborator to offer the value of my expertise and knowledge regarding reward learning within the context of addiction neuroscience. I will aid with issues related to study design, measurement, analysis, theoretical conceptualization, and interpretation. You are always welcome at my lab meetings to discuss your work with my group. Moreover, as we've discussed, we will meet monthly to discuss your progress on your project.

Additionally, I will be available to provide feedback and guidance to support your professional development and we will use our monthly meetings for this as well. Of course I'll also be available to you on an as needed basis and available to chat more informally at the regular seminars and colloquia we both routinely attend.

As an affiliate of the Neuroscience Interdepartmental Ph.D. Program, I am also familiar with the quality of the early graduate training you have received and am confident that it will aid you in successfully carrying out your proposed research.

I look forward to our collaboration on your proposed study and offer your F31 application my full support. Your passion for research, background in neuroscience, and supportive mentor make you an outstanding candidate for this award.

Kate M. Wassum, Ph.D.

Additional Educational Information

Elizabeth Burnette, the current F31 fellowship applicant, is in good standing with the Neuroscience Interdepartmental Graduate Program, University of California, Los Angeles. PhD program details are:

Graduate Program Description

UCLA's Neuroscience Interdepartmental Program (NSIDP) is a PhD program within the David Geffen School of Medicine at UCLA. UCLA's academic calendar is on a 3-quarter system (Fall, Winter & Spring). The first year of the program is comprised of core courses in Cellular Developmental Molecular Neurobiology, Cellular Neurophysiology, Neuroanatomy and Neural Systems. In addition to the core courses, there are literature-based seminars that are part of the first-year program. These seminars include: literature review, presentation skills, neuroscience methods, scientific ethics, presentation skills and attendance is required at a weekly Joint Seminars in Neuroscience series, where experts in the fields present their research and interact with graduate students from across different disciplines interested in Neuroscience related research topics. Students are also required to complete 2-3 research rotations in their first year. By the end of the Spring Quarter term, students are required to formally join a research lab.

In subsequent years, students are required to complete the following courses to meet PhD program requirements: a grant-writing course, complete two pre-approved elective courses related to Neuroscience at the graduate level, at least one quarter of a biostatistics course, attendance of at least five journal club formatted seminars on a specific Neuroscience topic (i.e. Addiction, Learning & Memory, Neural Development, Degeneration, and Repair, Neurogenetics, Neuroimaging, Synapses, Cells and Circuits, and Neuroendocrinology).

One quarter minimum of teaching experience is required in the program. General teaching assignments are in undergraduate courses in the undergraduate Neuroscience Interdepartmental Program. Examples of these courses are Cellular and Systems Neuroscience, Molecular and Developmental Neuroscience, Behavioral and Cognitive Neuroscience, Introduction to Functional Anatomy of Central Nervous System. A typical teaching assignment involves leading a Discussion section or Laboratory section under the supervision of a primary faculty lecturer and faculty course coordinator.

Advising: The Neuroscience program provides a comprehensive system of advising for students throughout their graduate studies. During orientation the advising committee and program chair meet with new students to review the first-year requirements in general terms. Throughout the term, students are expected to meet individually with the chair or other members of the advising committee to identify faculty whose research is closest to their own interests and who would be most appropriate for laboratory rotations. At the end of the fall term, the entire advising committee meets informally with the first-year students to field questions that have come up after their initial entry into the program. In subsequent quarters, students' enrollment and performance in core courses and laboratory rotations are closely monitored and, as the need arises, students are counseled individually by the advising chair. At the end of Spring Quarter of the first year, students are required to submit a Faculty Mentor Approval Form (co-signed by the mentor) to the advising committee, which meets to consider the choice of mentor and the ability of the faculty to serve in this capacity.

The advising program continues after each student has chosen a faculty research mentor. Every year students receive a memorandum outlining current requirements (for example, course electives, the written and oral qualifying examinations and midstream seminar). The advising committee also meets every year to discuss the progress of all students and identify potential problems. The committee then sends each student a letter that assesses their current progress in the program and makes specific recommendations as needed. An overall assessment of student progress is also made annually to the neuroscience committee. In addition to the formal advising procedures outlined above, students are repeatedly encouraged to seek advice on career development from faculty members in the UCLA neuroscience community. Finally, an annual retreat serves the purpose of allowing informal and organized contacts between faculty and students, which provides further opportunity for advising.

Written and Oral Qualifying Examinations:
A written qualifying examination is required following completion of the core requirements, generally by the beginning of the second year. The objective of this examination is to test basic knowledge and ability to relate knowledge in different neuroscience areas, to locate and interpret literature, and to apply research problems.

After passing the written qualifying examination, and after completion of a degree audit, students, in consultation with the adviser, choose the doctoral committee to administer the University Oral Qualifying Examination. For the examination students are expected to write a research proposal and orally present the outline of the proposal to their doctoral committee. This presentation usually takes between one-and-one-half and three hours. The eight- to 10-page proposal should follow the basic format of an NIH grant proposal focusing on an important question pertinent to the student's field of study, with well-defined *Specific Aims, Methods, and Experimental Design*. Students should not have completed significant portions of the dissertation project at the time of the examination. Instead, the purpose of the exercise is for students to 1) formulate their plans in their own words; (2) become acquainted with the faculty committee; and (3) familiarize the committee with their projects at an early stage. The written qualifying exam generally takes place during the third year.

Doctoral Committee Meetings: Students also are expected to hold doctoral committee meetings each year after the University Oral Qualifying Examination. The yearly doctoral committee meetings provide additional interaction between the committee and the student and serve as an important barometer for the progress of the student's research proposal since the University Oral Qualifying Examination. Each yearly meeting requires a written progress report (prepared jointly by the doctoral committee chair and the student) to monitor and track the student's progress in their dissertation research and time-to-degree. Furthermore, at least one of these yearly meetings is required to include a formal presentation of the student's research before the final defense. This presentation also helps to identify the critical experimental areas that students need to complete prior to the final defense of the dissertation.

Advancement to Candidacy: Students are advanced to candidacy upon successful completion of the written and oral qualifying examinations.

Doctoral Dissertation: Every doctoral degree program requires the completion of an approved dissertation that demonstrates the student's ability to perform original, independent research and constitutes a distinct contribution to knowledge in the principal field of study.

Final Oral Examination (Defense of Dissertation): Required for all students in the program.

Time-to-Degree: In general, overall progress toward the degree is accomplished with completion of the written qualifying examination by the beginning of the second year. It is recommended that students complete the University Oral Qualifying Examination by the end of Fall Quarter of the third year, and the examination must be completed no later than Spring Quarter of the third year. Students must hold doctoral committee meetings each year after the University Oral Qualifying Examination and before the Final Oral Examination (defense of the dissertation). The approved normative time-to-degree is 18 quarters or 6 years. The average time to degree over the past 10 years has been 5.97 years.

Applicant Progress/Status in the Program:
The applicant, Elizabeth Burnette is in her second-year of the PhD portion of her program. She entered the program in September 2018. Elizabeth has completed her 1st year course requirements and completed and passed the Written Qualifying Exam on September 2019. This is one of three exam requirements for the graduate program. She plans on completing and passing her Oral Qualifying Exam by December 2020. She is making normal progress towards her degree and program requirements.

This information has been provided by Prof. Felix E. Schweizer, Chair – Interdepartmental Graduate Program in Neuroscience, UCLA. Vice Chair of Education – Neurobiology Department, UCLA David Geffen School of Medicine.

Resource Sharing Plan

All human data collected in this project will be shared (after appropriate de-identification) with the scientific community in a timely manner, in accordance with NIH policy. The dataset will be made available to the community upon request, and a data application will be required.

PHS Assignment Request Form

Funding Opportunity Number: PA-19-195

Funding Opportunity Title: Ruth L. Kirschstein National Research Service Award (NRSA) Individual Predoctoral Fellowship (Parent F31)

Awarding Component Assignment Request *(optional)*

If you have a preference for an awarding component (e.g., NIH Institute/Center) assignment, use the link below to identify the appropriate short abbreviation and enter it below. All requests will be considered; however, assignment requests cannot always be honored.

Awarding Components: https://grants.nih.gov/grants/phs_assignment_information.htm#AwardingComponents

	First Choice	Second Choice	Third Choice
Assign to Awarding Component:	NIAAA		
Do Not Assign to Awarding Component:			

Study Section Assignment Request *(optional)*

If you have a preference for study section assignment, use the link below to identify the appropriate study section (e.g., NIH Scientific Review Group or Special Emphasis Panel) and enter it below. Remove all hyphens, parentheses, and spaces. All requests will be considered; however, assignment requests cannot always be honored.

Study Sections: https://grants.nih.gov/grants/phs_assignment_information.htm#StudySection

	First Choice	Second Choice	Third Choice
Assign to Study Section: *(only 20 characters allowed)*			
Do Not Assign to Study Section: *(only 20 characters allowed)*			

PHS Assignment Request Form

List individuals who should not review your application and why *(optional)* *Only 1000 characters allowed*

Identify scientific areas of expertise needed to review your applications *(optional)*

Note: Please do not provide names of individuals

	1	2	3	4	5
Expertise: *Only 40 characters allowed*					

PHS Human Subjects and Clinical Trials Information

Are Human Subjects Involved	●Yes		❍No					
Is the Project Exempt from Federal regulations?	❍Yes		●No					
Exemption Number	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6	❑ 7	❑ 8
Other Requested Information								

Human Subject Studies

Study#	Study Title	Clinical Trial?
1	Probing Inflammation and Reward Sensitivity in Alcohol Use Disorder	No

Delayed Onset Studies

Delayed Onset Study#	Study Title	Anticipated Clinical Trial?	Justification
The form does not have any delayed onset studies			

Section 1 - Basic Information (Study 1)

1.1. Study Title *

Probing Inflammation and Reward Sensitivity in Alcohol 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

2.1. Conditions or Focus of Study

- Alcohol Use Disorder

2.2. Eligibility Criteria

Inclusion criteria for non-treatment-seeking heavy drinkers are: (1) Alcohol Use Disorder Identification Test (AUDIT) score # 8; and (2) report drinking at binge levels at least 1 time in the past month (5+ drinks/day for men, 4+ drinks/day for women). Inclusion criteria for light-drinking controls are: (1) AUDIT score < 4; and (2) report no occasions of binge drinking in the past month. Inclusion criteria for all participants are: (1) age between 21 and 45; and (2) non-treatment seeking for AUD. Exclusion criteria for all participants are: (1) a current (last 12 months) DSM-5 diagnosis of substance use disorder for any psychoactive substances other than alcohol and nicotine; (2) a lifetime DSM-5 diagnosis of major depressive disorder, schizophrenia, bipolar disorder, or any psychotic disorder; (3) current moderate to severe depression as indicated by a score of # 21 on the Beck Depression Inventory-II (BDI-II); (4) current suicidal ideation or lifetime history of suicide attempt as reported on the Columbia-Suicide Severity Rating Scale (C-SSRS); (5) positive urine screen for drugs other than cannabis; (6) clinically significant alcohol withdrawal symptoms as indicated by a score # 10 on the Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar); (7) an intense fear of needles or history of any adverse reactions to needle puncture; (8) pregnancy, nursing, or refusal to use reliable method of birth control (if female); (9) a medical condition that may interfere with safe study participation (e.g., unstable cardiac, renal, or liver disease, uncontrolled hypertension or diabetes); (10) abnormal electrocardiogram (EKG) or clinical labs; (11) # Grade 2 laboratory abnormalities, based on FDA Guidance Document "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials; or (12) other circumstances that, in the opinion of the investigators, compromises participant safety.
Participants who, on arrival to the experimental visit, show any of the following will not be allowed to complete the endotoxin challenge: (a) Breath Alcohol Content (BrAC) > 0.0 g/dl; (b) clinical withdrawal (CIWA-Ar) score # 10; (c) blood pressure # 90/60 or # 160/120; (d) pulse # 50 beats/minute; (e) temperature # 99.5#F, (f) recent (past 2 weeks) acute illness or vaccination; or (g) score of # 10 on Physical Sickness Symptoms Assessment.

2.3. Age Limits	Min Age: 21 Years Max Age: 45 Years
2.4. Inclusion of Women, Minorities, and Children	Burnette_NRSA_FINAL_WomMinChild1060019825.pdf
2.5. Recruitment and Retention Plan	Burnette_NRSA_FINAL_Recruitment1060019275.pdf
2.6. Recruitment Status	Not yet recruiting
2.7. Study Timeline	Burnette_NRSA_FINAL_StudyTimeline1060019276.pdf
2.8. Enrollment of First Subject	09/01/2020 Anticipated

Inclusion Enrollment Reports

Entry#	Enrollment Location Type	Enrollment Location
IER 1	Domestic	University of California, Los Angeles

Section 3 - Protection and Monitoring Plans

3.1. Protection of Human Subjects

Burnette_NRSA_FINAL_PHS1060019824.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

3.4. Will a Data and Safety Monitoring Board be appointed for this study? ❍ Yes ❍ No

3.5. Overall Structure of the Study Team

Section 4 - Protocol Synopsis

4.1. Brief Summary
4.2. Study Design
4.2.a. Narrative Study Description
4.2.b. Primary Purpose
4.2.c. Interventions

Type	Name	Description

4.2.d. Study Phase
Is this an NIH-defined Phase III Clinical Trial? ❍ Yes ❍ No

4.2.e. Intervention Model
4.2.f. Masking ❍ Yes ❍ No

❑ Participant ❑ Care Provider ❑ Investigator ❑ Outcomes Assessor

4.2.g. Allocation
4.3. Outcome Measures

Type	Name	Time Frame	Brief Description

4.4. Statistical Design and Power
4.5. Subject Participation Duration

4.6. Will the study use an FDA-regulated intervention? ❍ Yes ❍ No

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

Section 5 - Other Clinical Trial-related Attachments

5.1. Other Clinical Trial-related Attachments

Inclusion Enrollment Report 1

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

Enrollment Location Type* : ●Domestic ❍Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): University of California, Los Angeles

Comments:

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	1	2	0	0	3
Asian	3	4	0	0	7
Native Hawaiian or Other Pacific Islander	1	2	0	0	3
Black or African American	5	10	3	5	23
White	6	12	4	8	30
More than One Race	2	3	2	3	10
Total	18	33	9	16	76

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Re-ported	Female	Male	Unknown/ Not Re-ported	Female	Male	Unknown/ Not Re-ported	
American Indian/Alaska Native										0
Asian										0
Native Hawaiian or Other Pacific Islander										0
Black or African American										0
White										0
More than One Race										0
Unknown or Not Reported										0
Total	0	0	0	0	0	0	0	0	0	0

Inclusion of Women, Minorities, and Children

We expect, based on the Sponsor's studies, is that approximately two-thirds of our community samples of non-treatment-seeking-participants with AUD are male (i.e. 51 male and 25 female participants for our total of 76). We also anticipate the following racial and ethnic demographics for our 76 participants:

Racial Categories	Non-Hispanic/Latina Female	Non-Hispanic/Latino Male	Hispanic/Latina Female	Hispanic/Latino Male	Total
Native	1	2			3
Asian	3	4			7
Hawaiian/ Pacific Islander	1	2			3
African American	5	10	3	5	23
White	6	12	4	8	30
Multiracial	2	3	2	3	10
Total	18	32	9	17	76

These estimates are based on previous studies conducted in the UCLA addictions lab among healthy controls and non-treatment-seeking participants with AUD. Los Angeles County includes approximately 50% ethnic minorities as reported in the 2010 US Census. The ethnic diversity of the proposed sample is consistent with the diversity of LA County and the observed diversity of our previous studies of AUD.

Participants will be recruited from the community through radio, TV, local bus, social media, and newspaper advertisements. The recruitment efforts proposed been successful at the Sponsor's site in previous studies and have yielded diverse study cohorts in the past.

Women and minorities will be encouraged to participate. No participants will be excluded on the basis of gender, race, or ethnicity. No individuals under the age of 21 will be recruited to participate.

Recruitment and Retention Plan

Recruitment

Initial Recruitment: Accounting for our expected attrition rate, we aim to initially recruit 90 participants in order to have at least 76 completers, i.e. 38 non-treatment-seeking heavy-drinking individuals and 38 light-drinking controls. Participants will be recruited from the community through campaigns in radio, TV, local buses, social media, and print publications.

Telephone Screen: Individuals who call the lab (in response to advertisements) expressing interest in the study will receive detailed information about the study procedures, and if they remain interested, they will complete a telephone screen performed by a trained research assistant for self- reported inclusion and exclusion criteria. Those who appear eligible will be invited to the laboratory for an initial in-person screening session.

Initial Screening Visit: Prior to conducting any research related procedures, research staff will conduct the informed consent process, which details the procedures to take place during the screening visit. Informed consent will be a three-part process. First, participants will be asked to read and provide verbal consent for breathalyzer. If the breathalyzer is above 0.000 g/dl, the visit will be stopped, and the participant will not be compensated. The participant will be given an opportunity to reschedule the visit for another day. If the breathalyzer test is negative, the written informed consent form will be reviewed and signed by the participant and study staff outlining procedures for the initial screening visit. A second written consent form will be reviewed and signed in the presence of the study physician at the medical screening visit if the participant is found eligible to continue to that visit. At the initial screening visit, subjects will be asked to provide a urine sample to test for drugs of abuse and pregnancy (if female) and will complete a series of individual differences measures (described in detail below). This visit should take approximately 2 hours. Following the initial in-person screening, participants who appear to be eligible based on study inclusion/exclusion criteria will be invited to continue to the medical screening visit.

Medical Screening Visit: Eligible participants will complete a physical exam, including EKG and laboratory tests. The study physician will obtain written informed consent for the medical exam and endotoxin challenge. This visit will be conducted by the study physician and will start with a breathalyzer test. If the breathalyzer is above 0.000, the visit will be stopped and the participant will not be compensated. The participant will be given an opportunity to reschedule the visit for another day. If the breathalyzer test is negative, the physician will conduct the second written (experimental) consent; medical history interview and physical exam. In addition, a urine drug screen test will be repeated. The participant will then be accompanied by research personnel to the CTRC for blood specimen collection including Comprehensive Metabolic Panel and Complete Blood Count to evaluate overall health; and EKG to screen for medical conditions that could make study participation medically unsafe. The study physician will review each participant's medical history, vital signs, weight, review of systems, and laboratory tests, including liver function tests (LFTs), drug screen, chemistry screen, and urine pregnancy screen to determine if it is medically safe for the participant to take the study medication.

Inclusion and Exclusion Criteria: The inclusion and exclusion criteria for the proposed study are as follows.
Inclusion criteria for non-treatment-seeking heavy drinkers are: (1) Alcohol Use Disorder Identification Test (AUDIT) score ≥ 8; and (2) report drinking at binge levels at least 1 time in the past month (5+ drinks/day for men, 4+ drinks/day for women).
Inclusion criteria for light-drinking controls are: (1) AUDIT score < 4; and (2) report no occasions of binge drinking in the past month.
Inclusion criteria for all participants are: (1) age between 21 and 45; and (2) non-treatment seeking.
Exclusion criteria for all participants are: (1) a current (last 12 months) DSM-5 diagnosis of substance use disorder for any psychoactive substances other than alcohol and nicotine; (2) a lifetime DSM-5 diagnosis of major depressive disorder, schizophrenia, bipolar disorder, or any psychotic disorder; (3) current moderate to severe depression as indicated by a score of ≥ 21 on the Beck Depression Inventory-II (BDI-II); (4) current suicidal ideation or lifetime history of suicide attempt as reported on the Columbia-Suicide Severity Rating Scale (C-SSRS); (5) positive urine screen for drugs other than cannabis; (6) clinically significant alcohol withdrawal symptoms as indicated by a score ≥ 10 on the Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar); (7) an intense fear of needles or history of any adverse reactions to needle puncture; (8)

pregnancy, nursing, or refusal to use reliable method of birth control (if female); (9) a medical condition that may interfere with safe study participation (e.g., unstable cardiac, renal, or liver disease, uncontrolled hypertension or diabetes); (10) abnormal electrocardiogram (EKG) or clinical labs; (11) ≥ Grade 2 laboratory abnormalities, based on FDA Guidance Document "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials; or (12) other circumstances that, in the opinion of the investigators, compromises participant safety.

Participants who, on arrival to the experimental visit, show any of the following will *not* be allowed to complete the endotoxin challenge: (a) Breath Alcohol Content (BrAC) > 0.000 g/dl; (b) clinical withdrawal (CIWA-Ar) score ≥ 10; (c) blood pressure ≤ 90/60 or ≥ 160/120; (d) pulse ≤ 50 beats/minute; (e) temperature ≥ 99.5°F, (f) recent (past 2 weeks) acute illness or vaccination; or (g) score of ≥ 10 on Physical Sickness Symptoms Assessment. Participants meeting any of the above criteria will be invited to reschedule their visit when the symptom(s) resolve.

Projected Participant Flow, Males/Females (Total)

Year	0-3 mo.	4-6 mo.	7-9 mo.	10-12 mo.	Yearly Total
1	08/03 (11)	07/04 (11)	07/04 (11)	08/04 (12)	30/15 (45)
2	08/04 (12)	07/04 (11)	07/04 (11)	08/03 (11)	30/15 (45)
					Total: 60/30 (90)*

*Based on power analysis and drop-out rate described in Research Plan.

A Start-up period is not reflected as preliminary recruitment will begin prior to the award period, funded by a pilot study grant from the UCLA Cousins Center for PNI. Analysis and write-up will occur in year 3.

Participant recruitment will be tracked by study staff and discussed in weekly meetings. During the initial phone screen for participant eligibility, study staff will obtain information regarding how participants heard about the study. This information will be logged and tracked to further optimize participant recruitment and retention.

Retention

The following considerations have been made to increase participant retention for the proposed study. Parking fees (or bus tokens) will be covered by the study to decrease travel-related burden for participants. Participants will be compensated for each successfully completed study visit, with compensation amounts increasing for visits later in the study ($20 for initial screening visit, $30 for medical screening visit, $100 for inflammatory challenge (experimental) visit). Study staff will send out appointment reminders to participants by phone (text and calls) and email. Study staff will also build rapport with participants by having the same study staff member interact with the participant throughout the entire study. We provide an inviting laboratory environment for participants by providing coffee, water, and snacks as needed. While the five-hour experimental visit is quite long, the UCLA CTRC environment is also very comfortable and participants will have access to food and drink as well. In sum, the retention plan for this study was designed to be highly feasible and has proven successful in other studies in the Sponsor's lab.

Study Timeline

	Year 1			Year 2			Year 3		
Funding Month	**1-4**	**5-8**	**9-12**	**1-4**	**5-8**	**9-12**	**1-4**	**5-8**	**9-12**
Pilot / Finalize Study Procedures									
Data Collection									
Data Analysis									
Data Interpretation									
Preliminary Poster Preparation									
Manuscript Preparation									
Manuscript Submission / Revision									

Protection of Human Subjects

1. Risks to Human Subjects

1.A. Human Involvement and Characteristics: Participants will be 76 total individuals: 38 non-treatment-seeking heavy-drinking individuals and 38 light-drinking controls. In order to ensure 76 completers, we aim to recruit 90 participants. These participants will be recruited from the Los Angeles community through advertisements.

Inclusion and exclusion criteria for the proposed study are as follows:

Inclusion criteria for non-treatment-seeking heavy drinkers are: (1) Alcohol Use Disorder Identification Test (AUDIT) score ≥ 8; and (2) report drinking at binge levels at least 1 time in the past month (5+ drinks/day for men, 4+ drinks/day for women).

Inclusion criteria for light-drinking controls are: (1) AUDIT score < 4; and (2) report no occasions of binge drinking in the past month.

Inclusion criteria for all participants are: (1) age between 21 and 45; and (2) non-treatment seeking.

Exclusion criteria for all participants are: (1) a current (last 12 months) DSM-5 diagnosis of substance use disorder for any psychoactive substances other than alcohol and nicotine; (2) a lifetime DSM-5 diagnosis of major depressive disorder, schizophrenia, bipolar disorder, or any psychotic disorder; (3) current moderate to severe depression as indicated by a score of ≥ 21 on the Beck Depression Inventory-II (BDI-II); (4) current suicidal ideation or lifetime history of suicide attempt as reported on the Columbia-Suicide Severity Rating Scale (C-SSRS); (5) positive urine screen for drugs other than cannabis; (6) clinically significant alcohol withdrawal symptoms as indicated by a score ≥ 10 on the Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar); (7) an intense fear of needles or history of any adverse reactions to needle puncture; (8) pregnancy, nursing, or refusal to use reliable method of birth control (if female); (9) a medical condition that may interfere with safe study participation (e.g., unstable cardiac, renal, or liver disease, uncontrolled hypertension or diabetes); (10) abnormal electrocardiogram (EKG) or clinical labs; (11) ≥ Grade 2 laboratory abnormalities, based on FDA Guidance Document "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials; or (12) other circumstances that, in the opinion of the investigators, compromises participant safety.

Participants who, on arrival to the experimental visit, show any of the following will *not* be allowed to complete the endotoxin challenge: (a) Breath Alcohol Content (BrAC) > 0.000 g/dl; (b) clinical withdrawal (CIWA-Ar) score ≥ 10; (c) blood pressure ≤ 90/60 or ≥ 160/120; (d) pulse ≤ 50 beats/minute; (e) temperature ≥ 99.5°F, (f) recent (past 2 weeks) acute illness or vaccination; or (g) score of ≥ 10 on Physical Sickness Symptoms Assessment.

1.B. Study Procedures, Materials, and Potential Risks: The materials for this study will be collected from participants. Of primary interest are blood samples collected during the experimental visit to assay for cytokine levels, as well as task and self-report assessments of reward responsiveness and negative mood. All materials will be gathered only for research purposes.

As part of the screening process, subjects will provide a urine sample for pregnancy test and toxicology screen. A blood sample will be required during the physical exam, for the purpose of safety-related laboratory tests (i.e., comprehensive metabolic panel, complete blood count). The physical exam also includes an EKG, vital signs, and weight. These samples will be used solely to exclude subjects who are unsafe to participate or who do not meet study criteria and not for research data purposes.

Subject identification (ID) numbers will be assigned to each participant; no personally identifying information will be collected on the questionnaires, interviews, or other scoring sheets thus assuring confidentiality. All information will be kept anonymous and participants' names will be present in their consent forms. A subject assignment sheet will contain the subjects' ID number, first name and last initial, and date of birth. The assignment sheet will be kept for the duration of the data collection phase of the study and then destroyed one year after the completion of the study. All assessment packets and subject assignment sheet will be kept in locked cabinets and all identifiable information will be kept separate from the assessment packets, which will contain a subject number only. Consent forms will be kept separately in a locked file cabinet. Only the applicant, the Sponsor, and the trained research assistants on the project will have access to the data and codes. No data with subject identifiers will be released.

Potential Risks: The risks of this study include breach of confidentiality, risk of coercion, and possible adverse events from the endotoxin challenge.

(1) The risk of breach of confidentiality is low, with numerous safeguards for confidentiality that are outlined in

the “Protection against Risks” section below.
(2) The risk of coercion arises in the context of payments that subjects can earn from participating. Coercion is not likely because subject fees are reasonable for the amount of time and effort required and comparable with studies in this locale, and there will be no other inducements.
(3) Endotoxin Adverse Events: The reference endotoxin (E. coli group O:113:BB-IND 12948 to MRI) is provided by the NIH Clinical Center, has demonstrated safety, and has been successfully administered previously at UCLA by our collaborators. A recent review of human endotoxin studies concluded that this model is safe, provides consistent and reproducible data, and can interrogate inflammation-behavior relationships. The dose used (0.8 ng/kg body weight) has been shown to result in an increase in cytokine levels without significant changes in vital signs, in order to safely and briefly mimic low-grade inflammatory response. Additionally, this endotoxin preparation has been used in many human challenge studies and remains the World Health Organization standard for endotoxin assays used in the pharmaceutical industry. The endotoxin drug fact sheet, certificate of analysis, and letter from NIH regarding the use of *E. coli O:113* endotoxin in human challenge studies are provided as supplementary materials.

In summary, we do not anticipate the endotoxin challenge to produce any adverse events. However, the study physician will be on-call and will consult with our research team as needed to manage adverse events. In the event that significant medical problems are encountered, the blind will be broken, and appropriate medical treatment will be provided. Individuals who meet the following stopping criteria will discontinue study-related data collection procedures: (a) ≥ 1 serious adverse event (SAE) at least possibly related to endotoxin administration; (b) ≥2 Grade 3 (severe) adverse events at least possibly related to endotoxin administration, based on the FDA Guidance Document “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.”

2. Adequacy of Protection Against Risk

2.A. Informed Consent and Assent: Participants will be recruited from the community through radio, TV, local bus, social media, and newspaper advertisements. The recruitment efforts proposed been successful at the Sponsor’s site in previous studies. Individuals who call us about the study will undergo a telephone screening for self-reported inclusion and exclusionary criteria and the nature of the study will be further explained. Those who appear eligible will be scheduled for an appointment with our staff for an in-person screening session. A separate consent form will be used for the medical screening and this consent will be administered and signed by the study physician. If after completing the initial screening visit, the potential participant still appears eligible, the study will be fully explained including all aspects of procedures, potential side effects, and those who continue to be interested will have blood drawn and urine collected for laboratory tests. An appointment will be made with the study physician for a physical exam, clinical labs, and EKG. After the physical exam, the study physician will review each participant’s lab test results and if those preclude participation, the individual will be called and the reason why s/he cannot continue in the study will be explained.
Incentives: Participants will receive $100 for the completion of the experimental (endotoxin challenge) component of the protocol. This compensation is in addition to the compensation participants receive from the screening visits ($20 for initial screen, $30 for medical screen), totaling $150 if they complete all parts of the study. Participants will have parking fees covered by the study (or bus tokens provided). These incentives have been successful in previous studies at UCLA.

2.B. Protections Against Risk: (1) Breach of confidentiality is highly unlikely. The risk of breach of confidentiality will be handled by emphasizing that information obtained during assessments is confidential and will be used solely for research purposes. All records will be kept in a locked file and will be available to research personnel who have been trained in human subjects’ protection guidelines. A cross-index of identity information will be kept in a separate locked location. In addition, all data will contain only a numeric code, all assessment procedures will be closely supervised by the applicant and the Sponsor. Staff will be trained and reminded of the need to keep all information confidential. No names will be used in presenting data in lectures, seminars, and papers. Information will be released only with the written consent of the subject.
(2) Coercion is not likely because participation fee is reasonable for the amount of time/effort required and is comparable to other studies in this locale. There may be no other inducements. Furthermore, participants are free to discontinue at any time and will receive the weekly compensation for the amount of time that they participated, so that they will be fairly compensated for their time and effort.

(3) Endotoxin Adverse Events are expected to be mild based on the low dose (0.8ng/kg body weight) used, which has been shown to result in an increase in cytokine levels without significant changes in vital signs, in order to safely and briefly mimic low-grade inflammatory response. Participants will be monitored by staff through the CTRC throughout the experimental visit. The study physician will be available to all study participants for the duration of the study and will assess for possible AEs and SAEs. Adverse events will be monitored at each study visit and reported; any serious adverse events will be reported immediately to the UCLA IRB.

Medical Monitoring and Stopping Rules: The study physician and study site staff are responsible for the detection, documentation, classification, reporting, and follow up of events meeting the definition of an AE or SAE. Adverse Events will be assessed at the two experimental visits. However, SAEs will be collected from the time of informed consent onward. General symptoms will be collected via an open-ended question: "How have you been feeling since your last visit or the last time we spoke?"
Adverse Events will be recorded on the AE Log using accepted medical terms and/or the diagnoses that accurately characterize the event. When a diagnosis is known, the AE term recorded on the eCRF will be the diagnosis rather than a constellation of symptoms. The study physician will assess all AEs for seriousness, relationship to study medication, and severity. When an event has not resolved by study closure, it will be documented on the AE Log as "ongoing".
If a woman has a positive or borderline pregnancy test after enrollment, the pregnancy will be recorded as an AE. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been terminated or completed. The outcome of the pregnancy (e.g., normal birth, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn) will be recorded.
All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study physicians until satisfactory resolution (the event either resolved or stabilized and is not expected to resolve in the near term). All SAE's will be reported per requirements.
The study physician will be on-call and will consult with our research team as needed to manage adverse events. In the event that significant medical problems are encountered, the blind will be broken, and appropriate medical treatment will be provided. Individuals who meet the following stopping criteria will discontinue study-related data collection procedures: (a) ≥ 1 serious adverse event (SAE) at least possibly related to endotoxin administration; (b) ≥2 Grade 3 (severe) adverse events at least possibly related to endotoxin administration, based on the FDA Guidance Document "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials."

3. Potential Benefits of Proposed Research to Subjects and Others
There are no direct benefits to subjects other than receiving compensation for their participation, as our population is not seeking treatment for AUD. We believe that the risk/benefit ratio justifies the conduct of this study, given the need to understand the association between neuroinflammation and AUD and its related behaviors.

4. Importance of the Knowledge to be Gained
This project will be the first to explore the associations between inflammation, negative mood, and reward response in the context of AUD. Therefore, elucidating the relationships between inflammation, negative mood, and reward response in AUD has significant implications, including opportunities for the development of novel and potentially more effective therapeutics for AUD. Individuals with AUD will benefit from the knowledge that will be gained from the proposed study. Given the low risks to subjects and the possibility of great benefits to persons with AUD in the future, the risk/benefit ratio is favorable.

Data Sharing Plan
After all data have been collected and the results of the study have been published, de-identified data will be made available to other qualified researchers on request, on a USB memory stick or other electronic means that is compatible with our systems and the investigator's system. The request will be evaluated by the applicant and the Sponsor to ensure that it meets reasonable standards of scientific integrity and has the potential to make a reasonable scientific contribution. Since this funding period will have expired, the requesting investigator will be expected to cover the costs incurred in providing the data. The UCLA-IRB approved consent form asks participants to give permission to have their de-identified data shared with other scientists. Only data from participants who agree to data sharing will be used in the procedures outlined above.