

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

			3. DATE RECEIVED BY STATE	State Application Identifier
			4.a. Federal Identifier	
<input type="radio"/> Pre-application <input type="radio"/> Application <input checked="" type="radio"/> Changed/Corrected Application			b. Agency Routing Number	
2. DATE SUBMITTED 2019-10-03	Application Identifier 265806		c. Previous Grants.gov Tracking Number GRANT12944603	
5. APPLICANT INFORMATION				
Legal Name*: Temple University - Of The Commonwealth System of Department: CLA:PSYCHOLOGY (18110) Division: Street1*: 1801 North Broad Street, Street2: City*: Philadelphia County: Philadelphia State*: PA: Pennsylvania Province: Country*: USA: UNITED STATES ZIP / Postal Code*: 19122-6003				
Person to be contacted on matters involving this application				
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Position/Title: GRANTS AND CONTRACTS SPECIALIST				
Street1*: 1852 North 10th Street (TASB)				
Street2:				
City*: Philadelphia County: Philadelphia State*: PA: Pennsylvania Province: Country*: USA: UNITED STATES ZIP / Postal Code*: 19122-6003				
Phone Number*: 215-707-3106		Fax Number: 215-204-7486	Email: tue53587@temple.edu	
6. EMPLOYER IDENTIFICATION NUMBER (EIN) or (TIN)* 1231365971A1				
7. TYPE OF APPLICANT* X: Other (specify)				
Other (Specify): Public, Nonprofit, State-related Inst of Higher Ed				
Small Business Organization Type <input type="radio"/> Women Owned <input type="radio"/> Socially and Economically Disadvantaged				
8. TYPE OF APPLICATION*		If Revision, mark appropriate box(es).		
<input checked="" type="radio"/> New <input type="radio"/> Resubmission <input type="radio"/> Renewal <input type="radio"/> Continuation <input type="radio"/> Revision		<input type="radio"/> A. Increase Award <input type="radio"/> B. Decrease Award <input type="radio"/> C. Increase Duration <input type="radio"/> D. Decrease Duration <input type="radio"/> E. Other (specify):		
Is this application being submitted to other agencies?* <input type="radio"/> Yes <input checked="" type="radio"/> 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* Integrated Reward-Inflammation Model of First Onset of Major Depression in Adolescence				
12. PROPOSED PROJECT Start Date* 07/01/2020			13. CONGRESSIONAL DISTRICTS OF APPLICANT Ending Date* 06/30/2025 PA-002	

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE**14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION**

Prefix: DR First Name*: LAUREN Middle Name: B Last Name*: ALLOY Suffix:
 Position/Title: PROFESSOR
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 Department: CLA:PSYCHOLOGY (18110)
 Division:
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 City*: Philadelphia
 County:
 State*: PA: Pennsylvania
 Province:
 Country*: USA: UNITED STATES
 ZIP / Postal Code*: 19122-6011
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15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	\$3,764,229.00
b. Total Non-Federal Funds*	\$0.00
c. Total Federal & Non-Federal Funds*	\$3,764,229.00
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:

19. AUTHORIZED REPRESENTATIVE

Prefix: MS. First Name*: KAREN Middle Name: D. Last Name*: MITCHELL Suffix:
 Position/Title*: ASSISTANT VICE PRESIDENT
 Organization Name*: Temple University - Of The Commonwealth System of
 Department: RESEARCH: EXECUTIVE LEADERSHIP
 Division:
 Street1*: Temple University Services Bldg
 Street2: 1852 North 10th street
 City*: Philadelphia
 County:
 State*: PA: Pennsylvania
 Province:
 Country*: USA: UNITED STATES
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Signature of Authorized Representative*

MS. KAREN D. MITCHELL

Date Signed*

10/04/2019

20. PRE-APPLICATION File Name:**21. COVER LETTER ATTACHMENT** File Name:

424 R&R and PHS-398 Specific

Table Of Contents

SF 424 R&R Cover Page.....	1
Table of Contents.....	3
Performance Sites.....	4
Research & Related Other Project Information.....	5
Project Summary/Abstract(Description).....	6
Project Narrative.....	7
Facilities & Other Resources.....	8
Equipment.....	12
Research & Related Senior/Key Person.....	14
Research & Related Budget Year - 1.....	47
Research & Related Budget Year - 2.....	50
Research & Related Budget Year - 3.....	53
Research & Related Budget Year - 4.....	56
Research & Related Budget Year - 5.....	59
Budget Justification.....	62
Research & Related Cumulative Budget.....	74
Research & Related Budget - Consortium Budget (Subaward 1).....	75
Total Direct Costs Less Consortium F&A.....	93
PHS398 Cover Page Supplement.....	94
PHS 398 Research Plan.....	96
Specific Aims.....	97
Research Strategy.....	98
PHS Human Subjects and Clinical Trials Information.....	110
Study 1: Integrated Reward-Inflammation Model of First Onset of Major Depression in Adolescence.....	112
Inclusion Enrollment Reports.....	120
Multiple PD/PI Leadership Plan.....	143
Bibliography & References Cited.....	145
Consortium/Contractual Arrangements.....	169
Letters of Support.....	172
Resource Sharing Plan(s).....	173
Authentication of Key Biological and/or Chemical Resources.....	174

Project/Performance Site Location(s)

Project/Performance Site Primary Location

I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Temple University - Of The Commonwealth System of
Duns Number: 0571231920000
Street1*: 1701 N. 13th Street
Street2: Weiss Hall
City*: Philadelphia
County: Philadelphia
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 19122-6011
Project/Performance Site Congressional District*: PA-002

Project/Performance Site Location 1

I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Northwestern University
DUNS Number: 1600794550000
Street1*: 229 Sheridan Road
Street2:
City*: Evanston
County:
State*: IL: Illinois
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 60208-0855
Project/Performance Site Congressional District*: IL-009

Additional Location(s)

File Name:

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: — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8

If NO, is the IRB review Pending? Yes No

IRB Approval Date:

Human Subject Assurance Number 00004964

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 this project have an actual or potential 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?

4.d. If yes, please explain:

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

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* Yes No

6.a. If yes, identify countries:

6.b. Optional Explanation:

Filename

7. Project Summary/Abstract* 7. Project Summary_MD.pdf

8. Project Narrative* 8. Project Narrative_MD.pdf

9. Bibliography & References Cited 9. References Cited.pdf

10. Facilities & Other Resources 10. Facilities Other Resources.pdf

11. Equipment 11. Equipment.pdf

7. Project Summary/Abstract

Adolescence is an “age of risk” for emergence of 1st onset of major depressive disorder (MD). Despite its prevalence and public health significance, major unanswered questions exist regarding the mechanisms involved in vulnerability to MD. Depression (Dep) is associated with a reduced sensitivity to rewards and low reward-related brain function in cortico-striatal circuitry. However, little work has tested whether low reward responsivity (RR) or attenuated RR development during adolescence predicts 1st onset of MD. A separate literature documents elevated peripheral inflammation in Dep. Yet, research also has not examined the development of peripheral inflammation across adolescence and whether chronically elevated inflammation or increases in inflammation during adolescence predicts 1st onset of MD. Further, research on inflammation and RR mostly has proceeded in parallel. Recently, however, we and others have proposed neuroimmune network models of Dep. These models draw on research indicating that peripheral inflammatory mediators (e.g., cytokines) access the brain, where they lower RR. When dysregulated, this immune-to-brain signaling can lead to chronic reductions in RR, which is reflected in anhedonia and dysphoria. This low RR is proposed to initiate unhealthy behaviors (substance use, poor diet), as well as sleep disruption and stress generation, which further heighten inflammation. Over time, dysregulation in RR and immune signaling may synergize in a positive feedback loop, whereby dysregulation in each system exacerbates dysregulation in the other. We propose that reward-immune dysregulation is a two-hit vulnerability for the 1st onset of MD and increases in Dep symptoms (Sxs) during adolescence. Moreover, early adversity and recent stressors influence both RR and inflammation, and may set the foundation for reward-immune dysregulation. This proposal is the first systematic test of these hypotheses. We will use an innovative biobehavioral high-risk design to examine bidirectional relationships between peripheral inflammation and multiple indices of RR and their joint prediction of risk for 1st onset of MD and increases in Dep Sxs. Three hundred 14-15 year old participants (Ps) will complete a prospective 3-year longitudinal study. Ps with no prior history of MD will be selected along the entire dimension of self-reported RR, with oversampling at the low tail of the dimension in order to increase the likelihood of MD onsets. At Time 1 (T1), T3, and T5, each a year apart, Ps will complete blood draws to quantify inflammation, self-report and behavioral measures of RR, and fMRI scans of reward neural activity and functional connectivity. At T1-T5 (with T2 and T4 6 mo. between the yearly sessions), Ps also will complete diagnostic interviews, and measures of Dep Sxs, reward-relevant life events, and behaviors that increase inflammation. Childhood adversity history will be assessed at T1 only. This proposal is an innovative integration of research on reward and inflammatory signaling in understanding 1st onset of MD in adolescence. It has the potential to facilitate novel neuroimmune interventions to treat, and ideally prevent, MD.

8. Project Narrative

Adolescence is an “age of risk” for the emergence of major depressive disorder (MD), a major public health problem. Using an innovative biobehavioral high-risk approach with a prospective longitudinal design, this application will examine bidirectional relationships between peripheral inflammation and multimodal reward function and their joint prediction of first onset of MD and increases in depression symptoms. It will provide critical tools for the early identification of adolescents at risk for MD, integrate two separate research traditions to increase our understanding of specific etiological pathways underlying MD, and contribute to development of behavioral and biological interventions for ameliorating reward processing and inflammatory abnormalities.

10. Facilities & Other Resources

Research will be conducted at Temple University's main campus, at Northwestern University's main campus, and at Northwestern University's Foundations of Health Research Center (located a few blocks from the main campus).

Temple University

Laboratory:

MPI Dr. Alloy's Mood and Cognition Laboratory is located on the 7th floor of Weiss Hall on the main campus of Temple University. The initial screening and all components of the Time 1 - 5 sessions (except for the fMRI scans) will be conducted in the Mood and Cognition Laboratory. The Lab consists of 1,920 square feet of renovated, electronically secure, temperature controlled research space, which includes four interview rooms, a conference room, a large file room, a phlebotomy room, and a computer laboratory. Two rooms are dedicated to psychophysiological studies, with equipment to monitor EEG, heart rate, blood pressure, and skin conductance. The psychophysiology laboratory provides a sound-attenuated, light- and temperature-controlled test environment for optimal recording. EEG is acquired using a 32-channel Neuroscan Synamps I amplifier; signal processing and analysis is accomplished with Scan v 4.3 software. Heart rate and skin conductance are recorded using a Psylab Stand Alone Monitor. DMDX software is used for stimulus presentation and recording behavioral responses. All recording equipment is housed in an adjacent room. The Phlebotomy room adheres to Bio-Safety Level 2 standards, with universal precautions, and is adapted to avoid exposure to pathogenic agents. The Phlebotomy room has an adjustable venipuncture chair and will store and maintain all blood draw, blood draw site preparation, and blood specimen storage supplies to be used during the project. All blood procedures, handling, and disposal in Dr. Alloy's lab meet all Environmental Health and Radiation (EHRS) standards. In disposing of blood collection materials, any contaminated waste (gauze, gloves, etc.) is placed in a biohazard bag opened with a foot pedal. A sharps container is used for unused blood collection tubes, capped needles, and their plastic covers. The waste is dropped off in the designated area for department hazardous waste to be collected, and is picked up by EHRS.

Dr. Alloy's Lab also includes two rooms on the 9th floor of Weiss Hall that house a centrifuge (Thermo Scientific Benchtop Centrifuge Sorvall ST 16R, with 4 x 400mL capacity, RCF 15,200 rpm/25,830 x g maximum speed and 120 V 60 Hz of electrical power), and a -80°C freezer (Thermo Fisher Scientific Revco RLE30086A ultra-cold (-80°C) freezer with the capacity to hold 300 standard 2" boxes within 14.9 cu.ft., 115V, 60 Hz of electrical power, and 12.6 AMP of rated current) for the storage of blood specimens prior to overnight shipment to Co-I Miller's Laboratory at Northwestern University for immunological assay.

Computer:

The computer laboratory, interview rooms, psychophysiology, and phlebotomy rooms, and all project staff and graduate student offices have desktop computers (see description of computers in Section 11, Equipment, Other Project Information Form). The computers are connected via a HIPAA compliant Ethernet Local Area Network (LAN) to a Dell Power Edge 4600 file/print server with dual 2.8 GHz processors, 4.0 GB RAM, and 2 TB hard disk space, running the Windows HPC 2008 R2 network operating system. The HIPAA-compliant secure computer network provides data entry, word processing, graphics, and statistical analysis capabilities. For additional security, the LAN interfaces through a firewall and proxy server to the campus-wide network, which offers mainframe, library, and internet access. For off-campus field interviews, the Mood and Cognition Laboratory also has 3 laptop computers, each equipped with a 2.5GHz processor, 8 RAM GB, M.2 256 GB SATA Class 20 Solid State Hard Drive, and the Windows 10 operating system. In addition, services such as the design of computer based tasks, creation and maintenance of specialized programs, graphic and desktop publishing services are available. Statistical software packages and other programs (SPSS, MPlus, Matlab, EPrime, Microsoft Word, Excel, PowerPoint) necessary for experimental paradigms and data analyses are also available.

Office:

Nine offices at a total of 1,035 square feet are available on the 7th floor of Weiss Hall for MPI Alloy and all project staff. Four interview rooms (320 additional square feet) are also available for the project.

Temple University Brain Research & Imaging Center (TUBRIC):

TUBRIC provides much of the major equipment (and related support personnel) to be used for the MRI scans in this project, including a research-dedicated MRI scanner that is located in the lower level of Weiss Hall, the same building as MPI Alloy's Mood and Cognition Lab. TUBRIC houses a newly acquired Siemens MAGNETOM Prisma 3-Tesla whole-body MRI scanner, supporting a collection of structural MRI, fMRI, and DWI/DTI sequences (see description of MRI Scanner in Section 11, Equipment, Other Project Information Form). TUBRIC is a 3,400 square foot fully functional research-dedicated facility with immediately adjacent participant preparation, testing, and interview space, furnished with a range of integrated and supplemental research instruments to complement basic imaging work. Integrated tools include MRI compatible stimulus delivery (e.g., visual projection, audio, liquid delivery, electric shock delivery), response collection, physiological monitoring, phlebotomy, and eye-tracking devices. The Center also houses facilities for brain electrophysiology (EEG), additional offline eye-tracking, and brain stimulation (tDCs) equipment, along with a host of other project-specific devices. The facility is staffed by a director (Dr. Jason Chein), a MRI physicist, a neuroimaging supervisor, and administrative and IT support personnel. TUBRIC also provides some centralized computing and data archiving resources, including the PACS (Picture Archiving and Communications Systems) medical image data archiving system. University researchers work in concert with TUBRIC staff to coordinate and carry out research protocols. Dr. Jason Chein, Director of TUBRIC, will serve as a Consultant on this project and will insure that we can scan Ps at Times 1, 3, and 5 (each a year apart) of the 3-year protocol at approximately the same time of day. He has provided a letter of support (see Section 9, Letters of Support, Research Plan Form).

Other Resources:

A machine and electronics shop is located in the lower level of Weiss Hall. A full-time computer support/IT staff person is available to Psychology department faculty. In addition, audiovisual support services and library facilities are readily available, which allows remote, online access to the library catalogue, journal collections, and major databases including MEDLINE, PsychInfo, Current Contents, CINAHL, and Health.

Temple University is a Research I University with a full array of support services available as needed to the research team to complete the proposed project aims. The Department of Psychology, housed in the College of Liberal Arts, excels as a regional and national leader in psychological research and in the training of psychology professionals, and fosters interdisciplinary research and collaboration with the Temple University Hospital and Neuroscience program. Federal and state funding for research in the Department ranks in the top 25 of psychology departments nationally. Research, administrative, and clerical personnel from the Department of Psychology may draw upon other resources of the institution including the Office of Public Relations composed of communication experts and science writers, Center for Information Services, Office of Clinical Research, Office of the Vice President for Research & Graduate Studies, and the Managed Care Office. Administrative services in the College of Liberal Arts also are available for grant management. In addition to having an internal structure that is conducive to research, Temple is uniquely situated to pursue translational research, evaluating the real-world impact of intellectual advances. Set in an urban neighborhood with which it maintains strong ties, the University conducts population-based studies to determine how changes in the understanding and treatment of disease affect average people. Moreover, Temple's urban environment will facilitate our ability to recruit a racially and ethnically diverse sample of 14-15 year old high school freshmen for this project.

Northwestern University

All MRI related data for this proposal will be collected and prepared at the Temple University Brain Research & Imaging Center (TUBRIC). This strategy insures identical scanner parameters for all participants. Once collected and prepared, MRI related data will be securely transferred to MPI Nusslock's laboratory at Northwestern University for processing and analysis using the Extensible Neuroimaging Archive Toolkit (XNAT). An archive of all MRI data collected for this proposal will be stored on TUBRIC's server.

Laboratory:

MPI Dr. Nusslock's Affective & Clinical Neuroscience Laboratory is located on the 3rd floor of Cresap Hall and on the 5th floor of Maple Hall on the main campus of Northwestern University. Dr. Nusslock's laboratory has all of the equipment, software, and resources for processing and conducting advanced analyses of MRI data. The lab is over 1,400 square feet and includes five testing rooms, a phlebotomy room, three offices (including Dr.

Nusslock's office), and two EEG/MRI data processing rooms. Two rooms are dedicated to psychophysiological studies, with equipment to monitor electroencephalography (EEG), electromyography (EMG), heart rate, skin conductance, and startle. The psychophysiology laboratory is copper shielded and includes a sound and electrically shielded data collection chamber. Psychophysiology data are acquired with a 64-channel Neuroscan Synamps amplifier. The laboratory has sixteen Dell Optiplex computers each featuring an Intel-dual core processor, 16 GB RAM, 500 GB Hard Drive, and a 17" flat-panel display. Data are stored on a 50 terabyte server maintained by Northwestern University Information Technology (NUIT). MRI preprocessing pipelines for each imaging type (BOLD, Structural) will be conducted through Northwestern University Neuroimaging Data Archive (NUNDA), described below. MRI data will be preprocessed and analyzed on Northwestern University's high-performance Computing cluster known as QUEST, also described below. All facilities and equipment are securely protected both physically and electronically.

Neuroimaging:

Dr. Nusslock's laboratory is fully integrated with the MRI facilities at the Center for Translational Imaging (CTI, www.CTI.northwestern.edu), which is associated with the Department of Radiology at the Feinberg School of Medicine at Northwestern University. CTI is directed by Dr. Todd Parrish who will be available to provide on-site technical support and consultation to Dr. Nusslock and his research team on all aspects of MRI data processing and analysis. Neuroimaging is a primary research focus at CTI. Unique to Northwestern University is its extensive collaborative agreement with Siemens Medical Systems. Since 1997, Siemens has housed 5 PhD scientists at CTI, which has kept CTI researchers at the forefront of neuroimaging methods. Siemens has an onsite engineer at Northwestern from 6 AM-10 PM 5 days a week.

CTI occupies approximately 6,000 square feet of space in the Feinberg School of Medicine at Northwestern University. Equipment currently dedicated to research at CTI includes: two 3T Siemens Prisma scanners, IR navigated TMS from Magventure, a Brain Products 32 channel MRI compatible EEG. CTI's day to day operations are overseen by a neuroimaging operations manager, Jennie Chen, PhD. She is responsible for technical issues and imaging quality assurance. CTI employs three MR technologists with more than 15 years of experience each.

The Northwestern MPI and his research team are members of the Northwestern Cognitive Brain Mapping Group (CBMG). The CBMG involves the PIs and research teams from more than 10 neuroimaging laboratories at Northwestern University across multiple departments. Members of the CBMG meet weekly to discuss neuroimaging issues ranging from task development, methodology, MRI physics, data processing and analysis, and connectivity analyses. The combination of CTI and CBMG provide a cohesive neuroimaging community for the Northwestern Co-I and his research team and enables cross-fertilization and insightful discussions about all aspects of neuroimaging and related research.

Secure Data Transfer from TUBRIC to Northwestern University:

MRI data will be transferred from TUBRIC to the Northwestern MPI's laboratory using the Extensible Neuroimaging Archive Toolkit (XNAT). XNAT is an open source software platform designed to facilitate management and exploration of neuroimaging and related data. XNAT provides methods for data validation and integrity checking and the ability to export data into a number of convenient formats with maximal security for maintaining data confidentiality and integrity. The XNAT system is already functional at Temple University and will allow the investigative team to effortlessly transfer data back and forth between Temple University and Northwestern University in a completely secure and confidential manner. Drs. Nusslock, Alloy, and Chein have successfully used this system for data transfer between Temple University and Northwestern University for the past six years as part of another NIH R01 grant (MH077908).

Northwestern University Neuroimaging Data Archive – NUNDA:

MPI Nusslock's research team will use well established and supported pipelines through Northwestern University Neuroimaging Data Archive (NUNDA) for preprocessing and archiving each imaging type (BOLD, Structural). Dr. Nusslock's team has been successfully using NUNDA for the past six years to preprocess and archive MRI data for another NIH R01 grant (MH077908) with Drs. Alloy and Chein. NUNDA was developed jointly by the Departments of Psychiatry and Radiology (Drs. Lei Wang and Todd Parrish) to integrate neuroimaging research data (multi-modal imaging, demographic, and behavioral) and efficiently process and securely store data (currently 253 projects with 11,538 participants and 17,617 imaging sessions (>75Tb of raw imaging data)). Data are archived using XNAT. It includes a secure database backend and a rich web-based user interface. XNAT uses an XML data model from which a relational database is generated. Non-

imaging data are entered via web-based forms, spreadsheet uploads, or XML. Newly entered data are placed in a virtual quarantine until an authorized user validates the integrity of the data. Once the data have been validated, they are moved into a secure archive. Archived data are made available to data-specific automated processing pipelines. All data arriving in NUNDA can have automatic Quality Assurance pipelines run. The results are visible to the user and stored in a project-wide spreadsheet. Furthermore, processing pipelines for each imaging type (BOLD, Structural) can be automatically launched with the user specific options utilized providing reproducible analysis. Preprocessed data then will be analyzed using standard MRI analysis software (e.g., SPM, FreeSurfer) within the NUNDA infrastructure. Members of the investigative team for the current proposal will be given passwords so they can remotely log into NUNDA and MPI Nusslock's laboratory server. This will allow our investigative team to work with the MRI data for this proposal in a seamless manner and coordinate our efforts across sites.

High Performance Computing Systems at Northwestern University:

We will run preprocessing scripts and analyses on Northwestern's high-performance computing cluster known as QUEST. This is a secure Data Center that has a Data Storage component known as the Vault. QUEST's computing resources and Data Storage have been integrated to support the operations of NUNDA in a seamless environment. QUEST currently has more than 8,000 cores online with access to over a Petabyte of disk storage. Dr. Nusslock's laboratory has 50 TB of processing space and storage on QUEST, which will be available for the proposed research.

Inflammation Assay Facilities: Blood samples for inflammation analyses will be collected in MPI Alloy's phlebotomy room at Temple University. Blood samples will be centrifuged, and the serum will be harvested, divided into aliquots, then frozen and stored at -80°C, until shipped to Co-I Dr. Miller's Foundations of Health Research Center at Northwestern University for assays.

Foundations of Health Research Center:

This 3800-square foot research facility is directed by Co-I Dr. Miller. It is located in Evanston's main commercial district, just a few blocks from the Northwestern University main campus, and is easily accessed from across Greater Chicago. Commuting participants can make use of public parking just across the street or mass transit stops located within a block. The research center has five spacious rooms used for psychosocial assessment. All are furnished with comfortable furniture suitable for children, adults, and families. There is a separate room dedicated to physiological monitoring; it contains equipment for electrocardiography, continuous blood pressure measurement, and spirometry. The center also has a dedicated room for phlebotomy and anthropometry. It contains an adjustable venipuncture chair, a medical-grade scale with height rod, and a body-composition analyzer. Adjacent to the phlebotomy room is 2000-square feet of wet-lab space, outfitted for sample processing, cell separation, tissue culture, tissue homogenization, nucleic acid extraction, plus immunoassay, qPCR, and flow cytometry applications. For tissue homogenization, the lab uses a Miltenyi gentleMACS Dissociator. This benchtop instrument does high-throughput, semi-automated dissociation of tissues into homogenates. For tissue culture, the lab has 2 biosafety cabinets, an air-jacketed CO₂ incubator, and multiple benchtop centrifuges and microfuges. A Miltenyi autoMACS instrument is used for automated cell separation. For immunoassays, the lab houses a MesoScale Sector Imager 2400A and a microplate reader and washer from Tecan. There is also a Guava EasyCyte 6HT-2L for automated flow cytometry and an Eppendorf Mastercycler for qPCR. For specimen storage, the lab has 3 standard (-30°C) and 2 ultra-cold (-80° C) freezers. All freezers have backup systems that preserve specimens during electrical or mechanical failures. Blood collection and assay materials will be placed in a biohazard sharp bin or bag and disposed of according to Northwestern University's Environmental Health and Safety Guidelines (or NU Office for Research Safety Guidelines).

Computer:

The lab is equipped with multiple tablet computers that enable participants to complete study measures online, using finger-swipe motions akin to an iPad. Project staff can access more than a half-dozen laptop and desktop computers across the research center, all with word processing, statistical analysis, and web browsing software, as well as access to the file server where study materials are stored. This server is compliant with federal HIPPA standards for protecting personally identifiable information. Its contents are backed up hourly to multiple data warehouses. The server is maintained by Northwestern's Weinberg College of Arts and Sciences.

11. Equipment

Computers and Data Storage

MPI Dr. Alloy's Mood and Cognition Laboratory is located on the 7th floor of Weiss Hall on the main campus of Temple University. The laboratory, interview rooms, and all project staff and graduate student offices have Dell Optiplex and HP desktop computers. Each of the 20 systems features an Intel dual-core processor, 16 GB RAM, 250 GB Hard Drive, and a 17" flat-panel display. They are connected via a HIPAA compliant Ethernet Local Area Network (LAN) to a Dell Power Edge 4600 file/print server with dual 2.8 GHz processors, 4.0 GB RAM, and 2 TB hard disk space, running the Windows HPC 2008 R2 network operating system. The HIPAA-compliant secure computer network provides data entry, word processing, graphics, and statistical analysis capabilities. For additional security, the LAN interfaces through a firewall and proxy server to the campus-wide network, which offers mainframe, library, and internet access. For off-campus field interviews, the Mood and Cognition Laboratory also has 3 laptop computers, each equipped with a 2.5GHz processor, 8 RAM GB, M.2 256 GB SATA Class 20 Solid State Hard Drive, and the Windows 10 operating system. In addition, services such as the design of computer based tasks, creation and maintenance of specialized programs, graphic and desktop publishing services are available. The Mood and Cognition Lab also possesses statistical software packages and other programs (SPSS, MPlus, Matlab, EPrime, Microsoft Word, Excel, PowerPoint) necessary for experimental paradigms and data analyses.

MPI Dr. Nusslock's Affective & Clinical Neuroscience Laboratory is located on the 3rd floor of Cresap Hall and on the 5th floor of Maple Hall on the main campus of Northwestern University. The laboratory has sixteen Dell Optiplex computers each featuring an Intel-dual core processor, 16 GB RAM, 500 GB Hard Drive, and a 17" flat-panel display. Local data are stored on a 50 terabyte server maintained by Northwestern University Information Technology (NUIT). MRI data will be collected at Temple University and transferred to Northwestern University for processing and analysis, using the Extensible Neuroimaging Archive Toolkit (XNAT). MRI preprocessing pipelines for each imaging type (BOLD, Structural) will be conducted through Northwestern University Neuroimaging Data Archive (NUNDA) (for details, see Section 10, Facilities & Other Resources, Other Project Information Form). Preprocessed data then will be analyzed using standard MRI analysis software (e.g., SPM, FSL, FreeSurfer) within the NUNDA infrastructure. We will run preprocessing scripts and analyses on Northwestern's high-performance computing cluster known as QUEST. This is a secure Data Center that has a Data Storage component known as the Vault. QUEST's computing resources and Data Storage have been integrated to support the operations of NUNDA in a seamless environment. QUEST currently has more than 8,000 cores online with access to over a Petabyte of disk storage. Dr. Nusslock's laboratory has 50 TB of processing space and storage on QUEST, which will be available for the proposed research. Dr. Nusslock's laboratory also possesses additional neuroimaging and statistical/programing software (e.g., SPSS, Matlab, R, Python) necessary to carry out the proposed research. All facilities and equipment are securely protected both physically and electronically.

Co-I Dr. Miller's Foundations of Health Research Center is equipped with multiple tablet computers that enable participants to complete study measures online, using finger-swipe motions akin to an iPad. Project staff can access more than a half-dozen laptop and desktop computers across the research center, all with word processing, statistical analysis, and web browsing software, as well as access to the file server where study materials are stored. This server is compliant with federal HIPPA standards for protecting personally identifiable information. Its contents are backed up hourly to multiple data warehouses. The server is maintained by Northwestern's Weinberg College of Arts and Sciences.

MRI Scanner

Scanning will be conducted on a newly acquired Siemens MAGNETOM Prisma 3-Tesla whole-body MRI scanner, supporting collection of structural MRI, functional MRI (fMRI), and diffusion weighted sequences. This instrument provides the strongest commercially available gradient field (80mT/m) in combination with the fastest available gradient switching rate (200mT/m/s). The magnet is equipped with advanced active shielding capabilities, using Siemen's MRITimTX TrueForm, to overcome B1 inhomogeneities at 3T, providing a maximally stable and linearly uniform imaging field of view. The magnet's coil uses an ultra-high-performance cooling and force-compensated design to reduce vibrations, which results in a minimization of eddy currents and acoustic noise. The advanced fully-dynamic parallel transmit RF technology in this system integrates all transmit and receive components within the magnet housing, providing industry leading signal-to-noise performance and high image stability with minimal RF noise artifact. The complete system is equipped with a

64-channel phased-array parallel transmit and receive RF head/neck coil, providing maximal image quality with exceptionally high spatial and temporal resolution for all brain imaging pulse sequences.

The scanner is housed within the Temple University Brain Research & Imaging Center (TUBRIC), a 3,400 square foot, multi-modal, research imaging center serving the neuroimaging research community on Temple's main campus. TUBRIC is a fully functional research-dedicated facility with immediately adjacent participant preparation, testing, and interview space, furnished with a range of integrated and supplemental research instruments to complement basic imaging work. Integrated tools include MRI compatible stimulus delivery (e.g., visual projection, audio, liquid delivery, electric shock delivery), response collection, physiological monitoring, and eye-tracking devices. The Center also houses facilities for brain electrophysiology (EEG), additional offline eye-tracking, and brain stimulation (tDCs) equipment, along with a host of other project-specific devices. The facility is staffed by a director (Consultant Dr. Jason Chein), a MRI physicist, a neuroimaging supervisor, and administrative and IT support personnel. TUBRIC is located in the lower level of Weiss Hall, the same building as the Mood and Cognition Lab.

Centrifuge

Blood specimens will be obtained via antecubital venipuncture by a certified phlebotomist at Time 1, Time 2, and Time 3 in MPI Alloy's Mood and Cognition Lab. The Lab is equipped with a Thermo Scientific Benchtop Centrifuge Sorvall ST 16R, with 4 x 400mL capacity, RCF 15,200 rpm/25,830 x g maximum speed and 120 V 60 Hz of electrical power, which will be used to centrifuge the blood specimens prior to freezing.

-80°C Freezer for Storage of Blood Samples

Blood specimens will be stored in a Thermo Fisher Scientific Revco RLE30086A ultra-cold (-80°C) freezer in MPI Alloy's Lab, with the capacity to hold 300 standard 2" boxes within 14.9 cu.ft., 115V, 60 Hz of electrical power, and 12.6 AMP of rated current for the storage of blood specimens until they are shipped to Co-I Dr. Miller's lab at NU for immunological assays. The ultra-cold freezer will have a backup system that preserves specimens during electrical or mechanical failures.

Immunological Assays

Co-I Miller's lab is outfitted for sample processing, cell separation, tissue culture, tissue homogenization, nucleic acid extraction, plus immunoassay, qPCR, and flow cytometry applications. For immunoassays, the lab houses a MesoScale Sector Imager 2400A and a microplate reader and washer from Tecan. There is also a Guava EasyCyte 6HT-2L for automated flow cytometry and an Eppendorf Mastercycler for qPCR. For tissue homogenization, the lab uses a Miltenyi gentleMACS Dissociator. This benchtop instrument does high-throughput, semi-automated dissociation of tissues into homogenates. For tissue culture, the lab has 2 biosafety cabinets, an air-jacketed CO₂ incubator, and multiple benchtop centrifuges and microfuges. A Miltenyi autoMACS instrument is used for automated cell separation. For specimen storage, the lab has 3 standard (-30°C) and 2 ultra-cold (-80°C) freezers. All freezers have backup systems that preserve specimens during electrical or mechanical failures.

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator				
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PROFILE - Senior/Key Person				
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State*:	IL: Illinois			
Province:				
Country*:	USA: UNITED STATES			
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Phone Number*:	847-467-4148		Fax Number:	
E-Mail*:	nusslock@northwestern.edu			
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Project Role*:	PD/PI		Other Project Role Category:	
Degree Type:	Degree Year:			
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Attach Current & Pending Support:	File Name:			

PROFILE - Senior/Key Person				
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PROFILE - Senior/Key Person			
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	Other Project Role Category: Other Significant Contributor		
Degree Type:	Degree Year:		
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Attach Current & Pending Support:	File Name:		

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: Lauren B. Alloy, Ph.D.

ERA COMMONS USER NAME (credential, e.g., agency login): LAURENA

POSITION TITLE: Laura H. Carnell Professor of Psychology; Joseph Wolpe Distinguished Faculty

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 Pennsylvania, Philadelphia, PA	B.A.	05/1974	Psychology
University of Pennsylvania, Philadelphia, PA	Ph.D.	08/1979	Clin. & Expt. Psychol.
University of Pennsylvania, Philadelphia, PA		1978-1979	Clinical Internship

A. Personal Statement

The goal of this application is to examine bidirectional relationships between multilevel reward system function and inflammatory signaling and their separate and joint prediction of risk for developing 1st onset of major depression and increases in depression symptoms in adolescence. As MPI, I will oversee all aspects of the proposed research, including conducting a prospective high-risk study design, recruitment and retention of a longitudinal adolescent sample, theoretical model development, assessment of reward-related and immune system constructs, analyses and writing of project findings, and administering a large R01 project. I have the appropriate expertise and leadership abilities to carry out this work with the assistance of my esteemed MPI, Co-Is, and Consultant. I have a documented, long-standing record of expertise and experience in studying reward sensitivity/processing, cognitive vulnerabilities, life stress, emotion regulation, and developmental precursors (e.g., childhood adversity) in both depression and bipolar spectrum disorders, for over 40 years. I am in the top 1% of most cited authors in psychology, with over 350 publications, and am the recipient of multiple lifetime/career scientific achievement awards from multiple professional societies for my work on the etiology and course of mood disorders. Specifically relevant to this application, I have published extensively on the role of reward sensitivity/processing in the bipolar spectrum and inflammation in depression and am currently conducting several grant-funded studies of inflammation in mood disorders. I am PI of three NIMH R01 grants and a PA CURE grant that examine: 1) reward sensitivity (including reward-related brain function) in first onset of adolescent bipolar spectrum pathology, 2) the interaction of the reward and circadian rhythm systems in onset and course of bipolar spectrum disorders, 3) cognitive, emotion regulation, developmental, and psychosocial stress risk factors in combination with inflammation as vulnerabilities to adolescent depression, and 4) associations between inflammatory biomarkers and neural reward responsivity in adolescents with or at familial or environmental risk for depression. In addition to these grants, I also have an extensive record of external funding since 1974, including prior R01s on first onset of major depression.

As MPI, I have assembled an outstanding team of scientists who have collaborated previously, who have worked together on the design and writing of this proposal, and who will actively collaborate on the proposed research and bring to bear their relevant areas of expertise. Specifically, the team includes scientists with expertise on mood disorders (MPIs Drs. Alloy and Nusslock, Co-Is Drs. Ellman, Miller and Olino), prospective longitudinal designs (Alloy, Ellman, Nusslock, Olino), reward-related neuroimaging (Nusslock, Olino, Consultant Chein), psychoneuroimmunology (Ellman, Miller), inflammation in mood disorders (Alloy, Ellman, Miller, Nusslock), biostatistics and sophisticated statistical modeling (Olino) and symptom, diagnostic, life event, reward, and sleep assessments (Alloy, Nusslock, Olino). Moreover, MPI Nusslock and I have been joint investigators on a previous NIMH R01 grant (MH077908). In summary, I have a long-standing and continuing record of successful and productive research on topics directly relevant to this proposal, I have assembled a team of outstanding collaborators, and I have the expertise and leadership skills necessary to implement and oversee the research strategy outlined in the present proposal. I will devote 33% effort academic year and 50% effort summer to this project for 5 years.

B. Positions and Honors**Positions and Employment**

1974-1977	NSF Predoctoral Fellowship, Dept. of Psychology, Univ. of Pennsylvania, Phila, PA
1977-1978	University of Pennsylvania Dissertation Year Fellowship
1977-1979	NIMH Predoctoral NRSA (F31) Fellowship, Dept. of Psychology, Univ. of Pennsylvania
1979-1983	Assistant Professor of Psychology, Northwestern University, Evanston, IL
1983-1986	Associate Professor of Psychology, Northwestern University, Evanston, IL
1986-1989	Professor of Psychology, Northwestern University, Evanston, IL
1989-present	Professor of Psychology, Temple University, Philadelphia, PA
2004-present	Joseph Wolpe Distinguished Faculty in Psychology, Temple Univ., Phila., PA
2007-2016	Director of Clinical Training, Department of Psychology, Temple University, Phila., PA
2015-present	Laura H. Carnell Professor of Psychology (Endowed professorship), Temple Univ.

Selected Other Experience and Professional Memberships

1982-1986	NIMH Psychopathology and Clinical Biology Review Panel
1982-1987	PI, MacArthur Foundation Grant, "Depression, Meaning, and Inference"
1988-1993	Member of DSMIV Work Group on GAD and Mixed Anxiety-Depression
1990-2004	PI, NIMH R01, "Negative Cognition Depression: Etiology and Course"
1997-2000	PI, NIH, "HIV Prevention: Role of Optimism, Stress, and Support"
1997-2002	PI, NIMH R01, "Course of Cyclothymia: Role of Cognition and Stress"
2001-2002	Appointed to NIMH Workgroup on Neural and Behavioral Substrates of Mood Regulation
2002-2008	NIMH R01, "BAS and Bipolar Spectrum: Biopsychosocial Integration"
2007-2013	NIMH R01, "BAS and Bipolar Disorder: Prospective Biobehavioral High Risk Design"
2008-2014	NIMH R01, "Depression Surge in Adolescence & Gender Differences: Biocognitive Mechanisms"
2013-2019	NIMH R01, "Risk for Bipolar Disorder: Reward-related Brain Function & Social Rhythms"
2013-2019	NIMH R01, "Risk for Adolescent Depression: Stress, Cognitive Vulnerability, & Inflammation"
2013-2018	NIMH R01, "Social and Circadian Rhythms, Reward Sensitivity, and Risk for Bipolar Disorder"
2017-2020	PA CURE, "Neural Reward Responsivity, Inflammatory Biomarkers, and Risk for Adolescent Depression"

Fellow of APS, APPA, APA Divs. 3, 12; APPA Board ('06-'10); Member: ABCT; ADAA; SRP; ISBD; SSCP
 Editorial Board of JCCP, '96-'98; CTAR, '81-'01; JAP, '89-'94, '14-'pres.; JSCP, '82-'85, '02-pres.; JPSP, '84-'85; CP:SP, '03-pres.; JCP: AIQ, '99-pres.; P&P, '05-pres.; JCCAP, '07-'16; IJCP, '08-pres.

Guest Editor for JAP, CTAR, JCP:AIQ, JSCP, IJCP.

Selected Honors

1974	B.A. Summa Cum Laude, Phi Beta Kappa
1974-1977	National Science Foundation Predoctoral Fellowship
1977-1979	National Institute of Mental Health Predoctoral Fellowship (NRSA/F31)
1977-1978	University of Pennsylvania Dissertation Year Fellowship
1984	American Psychological Association "Young Psychologist" Award
1988	Northwestern University CAS Great Teacher Award
1996	Finalist, NARSAD Established Investigator Award
2001	Paul W. Eberman Faculty Research Award, Temple University
2002	American Psychological Association Master Lecturer in Psychopathology Award
2002	Finalist for Grawemeyer Award for Best Theoretical Idea in Psychology
2003	Amer. Psychol. Assoc. Division 12 Distinguished Scientific Contribution Award
2003	Society for a Science of Clinical Psychology Distinguished Scientist Award
2004	Joseph Wolpe Distinguished Faculty in Psychology, Temple University
2009	APS James McKeen Cattell Award for Lifetime Achievement in Applied Psychol. Research
2014	SRP Joseph Zubin Award for Lifetime Achievement in Psychopathology Research
2014	Association for Behavioral and Cognitive Therapies Career/Lifetime Achievement Award
2015	Laura H. Carnell Professor of Psychology, Temple University – Endowed Chair
2015	Top 1% of Most Cited Authors in Psychology – Thomson Reuters' Essential Science Indicators
2017	Temple University Faculty Research Award (TU's highest research award)
2018	Society for Research in Psychopathology John Neale Award for Outstanding Mentorship

C. Contributions to Science (From earlier to more recent contributions; *current or former advisee)

1. Depressive Realism/"Sadder but Wiser" Effect: In collaboration with Lyn Abramson, my early provocative theory and empirical work on depressive realism and nondepressive optimistic illusions was creative and highly original. Since the publication of our initial article on depressive realism in *JEP: General* (2,242 citations), this idea has captured the attention of scientists and the lay public alike. First, this work showed that, contrary to both scientific and lay assumptions, cognitive distortion is not exclusively associated with psychopathology, nor is accurate reality testing the sole province of mental health. Our work showed that depressed people sometimes are more accurate than nondepressed people in making judgments about themselves and their control over events. Second, this work provided a fundamental challenge to the conceptual underpinnings of cognitive therapy for depression. It suggested that cognitive therapy may work by training depressed clients to engage in the sort of optimistic biases that nondepressed individuals typically construct for themselves. Third, the depressive realism work built a bridge between clinical and experimental psychology. Our study of cognitive errors and their absence in depressive mood states as well as the mechanisms underlying this phenomenon led to an understanding that normal human cognition is characterized by self-enhancing biases and revealed some of the normal psychological processes underlying these biases. Finally, our work was provocative because of its practical implications; it suggests that optimistic cognitive illusions have adaptive consequences and evolutionary significance, including positive affect, high self esteem, behavioral persistence, improved stress coping, and decreased vulnerability to depression, suicide, and physical illness.

- a. Alloy, L.B., & Abramson, L.Y. (1979). The judgment of contingency in depressed and nondepressed students: Sadder but wiser? *Journal of Experimental Psychology: General*, 108, 441-485.
- b. Alloy, L.B., Abramson, L.Y., & *Viscusi, D. (1981). Induced mood and the illusion of control. *Journal of Personality and Social Psychology*, 41, 1129-1140.
- c. Alloy, L.B., & Abramson, L.Y. (1982). Learned helplessness, depression, and the illusion of control. *Journal of Personality and Social Psychology*, 42, 1114-1126.
- d. Alloy, L.B., & *Clements, C.M. (1992). Illusion of control: Invulnerability to negative affect and depressive symptoms after laboratory and natural stressors. *Journal of Abnormal Psychology*, 101, 234-245.

2. Cognitive Vulnerability and the Hopelessness Theory of Depression: In 1989, developments in descriptive psychiatry, cognitive and social psychology, and cumulative results from tests of the earlier learned helplessness model led Abramson and me to propose the hopelessness theory of depression (4,283 citations). This theory has had huge impact and ignited an explosion of research. Indeed, it is featured in virtually every Abnormal Psychology and Introductory Psychology textbook. Whereas psychopathologists typically focus on symptom-based definitions of disorders, we proposed a theory-based, etiologically-defined subtype of depression. In testing our highly influential theory, we pioneered prospective behavioral high-risk study designs and longitudinal, naturalistic methods to test complex, theoretically guided predictions about the unfolding of depressive reactions to negative events over time, and these study designs have been widely adopted by other researchers testing vulnerability-stress models of other forms of psychopathology. In addition, we provided the first methodologically adequate tests of cognitive vulnerability theories of depression (hopelessness theory and Beck's theory). Our empirical work testing hopelessness theory in a wide variety of samples (psychiatric patients, community samples, undergraduates, children, adolescents) suggests that hopelessness depression does exist in nature. For example, results from our NIMH-funded Cognitive Vulnerability to Depression project (referred to as "the most important study on depression in the 1990s") provide the first empirical demonstration that negative cognitive styles indeed confer vulnerability for full-blown clinically significant depressive disorders. Negative cognitive styles are stable over years and increase vulnerability for first lifetime onsets as well as subsequent recurrences of depressive episodes, a more pernicious course of depression, and suicidality. Our work also has contributed to understanding the basis of the sex difference in depression, the role of cognitive vulnerabilities in stress generation and emotion regulation, and the mechanisms involved in cognitive therapy and preventive interventions for depression. Finally, more recently, we have integrated the hopelessness theory with neurobiological models of depression that emphasize blunted reward system activation and pro-inflammatory states in this disorder.

- a. Alloy, L.B., Abramson, L.Y., Whitehouse, W.G., et al. (2006). Prospective incidence of first onsets and recurrences of depression in individuals at high and low cognitive risk for depression. *JAP*, 115, 145-156.
- b. *Mac Giollabhui, N., *Hamilton, J.L., ... & Alloy, L.B. (2018). Negative cognitive style interacts with negative life events to predict first onset of a major depressive episode in adolescence via hopelessness. *Journal of Abnormal Psychology*, 127, 1-11. Lead article.
- c. *Moriarity, D.P., *Mac Giollabhui, N., Ellman, L.M., ... & Alloy, L.B. (2019). Inflammatory proteins predict change in depressive symptoms in male and female adolescents. *Clinical Psychological Science*, 7, 754-767.

d. *Kautz, M.M., ..., Ellman, L.M., Abramson, L.Y., & **Alloy, L.B.** (in press). Longitudinal changes of inflammatory biomarkers moderate the relationship between recent stressful life events and prospective symptoms of depression in a diverse sample of urban adolescents. *Brain, Behavior, and Immunity*.

3. Developmental Origins of Cognitive Vulnerability and Depression: In collaboration with Abramson and my students, I found that cognitive risk for depression may have its origins, in part, in a developmental history of adversity and maltreatment, peer victimization, negative inferential feedback, and negative parenting practices. Our prospective findings in children and adolescents are provocative in suggesting that emotional abuse may be particularly virulent in contributing to cognitive vulnerability to depression. Our work on this topic places the hopelessness theory in a developmental context and increases its scope.

a. **Alloy, L.B.**, Abramson, L.Y., ..., & *Morocco, A. (2001). Developmental origins of cognitive vulnerability to depression: Parenting, cognitive, and inferential feedback styles of the parents of individuals at high and low cognitive risk for depression. *Cognitive Therapy and Research*, 25, 397-423.

b. *Liu, R.T., **Alloy, L.B.**, ..., & Whitehouse, W.G. (2009). Emotional maltreatment and depression: Prospective prediction of depressive episodes. *Depression and Anxiety*, 26, 174-181.

c. *Hamilton, J.L., *Stange, J.P., Abramson, L.Y., & **Alloy, L.B.** (2015). Stress and the development of cognitive vulnerabilities to depression explain sex differences in depressive symptoms during adolescence. *Clinical Psychological Science*, 3, 702-714.

d. **Alloy, L.B.**, *Hamilton, J.L., et al. (2016). Pubertal development, emotion regulatory styles, and the emergence of sex differences in internalizing disorders and symptoms in adolescence. *CPS*, 4, 867-881.

4. Reward Hypersensitivity Model of Bipolar Spectrum Disorders (BSDs): In collaboration with Abramson, Nusslock, and others, we further developed and empirically tested the Behavioral Approach System (BAS)/reward hypersensitivity theory of BSDs. According to this model, individuals with or vulnerable to bipolar disorders have a hypersensitive reward system, which can become overactivated in response to reward activation events (e.g., goal-striving or attainment, rewards, anger-inducing events) leading to hypomanic/manic symptoms, or too strongly deactivated in response to reward deactivation events (irreversible failures, losses) leading to depressive symptoms. This model not only integrates psychological, neurobiological, and environmental processes in BSD, but it also can explain both poles of the disorder with a single theme – approach motivation/reward hypersensitivity. Consistent with the model, we have found that high BAS/reward sensitivity measured via self-report, behavioral tasks, or with neurobiological indices (greater left frontal cortical activation on EEG) distinguish BSD from control individuals and predict prospective onsets of hypomanic/manic and depressive episodes, first lifetime onset of BSD in adolescents with no prior history of bipolar disorder, and progression to more severe bipolar disorders. In addition, we found that reward-relevant cognitive styles uniquely characterize individuals with BSDs and predict prospectively episodes of depression and hypomania/mania alone and in combination with relevant life events in individuals with BSDs. Finally, BAS/reward-activation life events (e.g., goal-striving events) predict onsets of hypomanic episodes. This work provides an innovative biopsychosocial approach to understanding bipolar disorder, has major implications for screening, prevention and treatment, and is routinely covered in Abnormal Psychology textbooks.

a. **Alloy, L.B.**, *Bender, R.E., ..., & Abramson, L.Y. (2012). High Behavioral Approach System (BAS) sensitivity, reward responsiveness, and goal-striving predict first onset of bipolar spectrum disorders: A prospective behavioral high-risk design. *Journal of Abnormal Psychology*, 121, 339-351.

b. Nusslock, R., & **Alloy, L.B.** (2017). Reward processing and mood disorder symptoms: An RDoC and translational neuroscience perspective. *Journal of Affective Disorders*, 216, 3-16. Lead article.

c. **Alloy, L.B.**, & Nusslock, R. (2019). Future directions for understanding adolescent bipolar spectrum disorders: A reward hypersensitivity perspective. *JCCAP*, 48, 669-683.

d. *Ng, T.H., **Alloy, L.B.**, & Smith, D.V. (in press). Meta-analysis of reward processing in major depressive disorder reveals distinct abnormalities within the reward circuit. *Translational Psychiatry*.

5. Social/Circadian Rhythm Model and Integration with Reward Hypersensitivity Model of BSDs: My colleagues and I also have further developed and empirically tested a second major biopsychosocial theory of bipolar disorder, the social and circadian rhythm disruption model. According to this theory, the occurrence of certain life events can disturb social zeitgebers ("time givers") by impacting daily social rhythms, which in turn disrupt circadian rhythms, resulting in manic and depressive symptoms. We demonstrated that individuals with BSDs have more irregular social rhythms than matched healthy controls and that social rhythm irregularity predicts prospective onsets of hypomanic/manic and major depressive episodes, as well as first lifetime onset of BSD. In addition, we found that social rhythm disruption (SRD) events precipitated major depressive episodes in individuals with BSDs and that bipolar individuals experience more SRD than healthy controls in response to experiences of equivalent positive and negative life events. Finally, we developed a novel

integration of the reward hypersensitivity and social/circadian rhythm models of BSD. We found that adolescents at risk for BSD based on exhibiting reward hypersensitivity also experience greater SRD from reward-relevant life events than do moderate reward sensitivity adolescents and that the SRD from these reward-relevant events predicts bipolar mood symptoms prospectively. This integrated Reward and Circadian Rhythm (RCR) model of BSD should lead to a better understanding of the pathophysiological mechanisms underlying bipolar disorders.

- a. **Alloy, L.B.**, Nusslock, R., & *Boland, E.M. (2015). The development and course of bipolar spectrum disorders: An integrated reward and circadian rhythm dysregulation model. *ARCP*, 11, 213-250.
- b. **Alloy, L.B.**, et al. (2015). Low social rhythm regularity predicts first onset of bipolar spectrum disorders among at risk individuals with reward hypersensitivity. *Journal of Abnormal Psychology*, 124, 944-952.
- c. *Boland, E.M., *Stange, J.P., ..., & **Alloy, L.B.** (2016). Affective disruption from social rhythm and behavioral approach system (BAS) sensitivities: A test of the integration of the social zeitgeber and reward theories of bipolar disorder. *Clinical Psychological Science*, 4, 418-432.
- d. **Alloy, L.B.**, *Ng, T.H., *Titone, M.K., & *Boland, E.M. (2017). Circadian rhythm dysregulation in bipolar spectrum disorders. *Current Psychiatry Reports*, 19: 21, 1-10.

Complete List of Recent Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/lauren.alloy.1/bibliography/40586669/public/?sort=date&direction=asc>
ending

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

Ongoing Research Support

PA Dept. of Health PA261083 (Alloy, PI) 01/01/17 – 12/31/20
“Neural Reward Responsivity, Inflammatory Biomarkers, and Risk for Adolescent Depression”
This project examines associations between inflammatory biomarkers and neural reward responsiveness in adolescents with depression or at familial or environmental (childhood adversity) risk for depression. Role: PI

NIMH R01 MH107495 (Olino, PI) 04/01/16 – 01/31/21
“Developmental Changes in Reward Responsivity: Associations with Depression Risk Markers”
This project examines the roles of parental history of depression and the development of reward responsivity (self-report, behavioral, neural) during the pubertal transition on the emergence of youth depression. Role: Co-I

NIMH R01 MH118545 (Ellman, PI) 07/01/19 – 06/30/24
“Maternal Inflammation During Pregnancy: Clinical and Neurocognitive Outcomes in Adult Offspring”
This project examines how maternal inflammation during pregnancy contributes to clinical, neurocognitive, and neural outcomes among late middle-aged offspring. Role: Co-I.

NIDA I/START R03 DA046733 (Smith, PI) 05/01/19 – 04/30/20
“Aberrant Reward Sensitivity: Mechanisms Underlying Drug Abuse”
This project examines the association between drug use and striatal activation and functional connectivity in response to monetary and social rewards in three groups varying in reward sensitivity. Role: Co-I

Recently Completed

NIMH R01 MH077908-06 (Alloy, PI) 07/05/13 – 04/30/19
“Risk for Bipolar Disorder: Reward-related Brain Function & Social Rhythms”
This project uses a biobehavioral high-risk design to examine reward sensitivity and activation of a fronto-striatal “reward-related” neural network on social rhythm disruption and bipolar mood pathology. Role: PI

NIMH R01 MH101168 (Alloy, PI) 07/01/13 – 03/31/19
“Risk for Adolescent Depression: Stress, Cognitive Vulnerability, & Inflammation”
This project examines the role of proinflammatory states in combination with cognitive vulnerabilities, stress, and childhood adversity in depression among a large urban sample of diverse adolescents. Role: PI

NIMH R01 MH102310 (NCE) (Alloy, PI) 12/09/13 – 11/30/18
“Social and Circadian Rhythms, Reward Sensitivity, and Risk for Bipolar Disorder”
This project uses a biobehavioral high-risk design to examine bidirectional influences of reward sensitivity and social and circadian rhythm disruption as risk factors for bipolar mood symptoms and episodes. Role: PI

BIOGRAPHICAL SKETCH

NAME: Lauren M. Ellman

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

POSITION TITLE: Associate Professor of Psychology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	Completion Date MM/YYYY	FIELD OF STUDY
Tulane University, New Orleans, LA	B.A.	1998	Psychology & Philosophy
Sepulveda VA Ambulatory Care Center, North Hills, CA	Internship	2007	Clinical Psychology
University of California-Los Angeles, Los Angeles, CA	Ph.D.	2007	Clinical Psychology
Columbia University, New York, NY	Postdoc	2009	Schizophrenia Research

A. Personal Statement

This project is designed to examine bidirectional relationships between reward sensitivity/processing and inflammation and their joint prediction of first onset of major depression in adolescence. My expertise and research focus are perfectly suited for the proposed project. Specifically, my lab investigates developmental risk factors for major mental disorders, with an emphasis on schizophrenia and depression. A number of the major findings linking maternal inflammation during pregnancy to neurodevelopmental sequelae in schizophrenia samples have come from my lab, and findings from my recent R01 link maternal infection and inflammation during pregnancy to increased risk of adolescent depression, cognitive problems throughout childhood and adolescence, and emotional/behavioral difficulties in childhood. These latter findings will be the first results linking maternal inflammation during pregnancy to disorders other than schizophrenia and autism. In addition to having a longstanding history of examining immunological contributions to psychotic disorders and depression, I received specialized training in psychoneuroimmunology (PNI) from the Cousins Center of Psychoneuroimmunology at UCLA, one of the world's most prominent PNI centers. Further, I currently am PI on two R01s and Co-I on another R01 that just ended (PI: Lauren Alloy), two of which center on inflammatory processes in major mental disorders. In addition, Dr. Alloy was a Co-I on my previous R01 grant linking maternal inflammation during pregnancy and adolescent depression. Thus, Dr. Alloy and I already have a strong and fruitful collaboration over the last 10 years. My role as Co-I on the current study will be to serve as an on-site PNI expert who will assist with all aspects of the study related to PNI, including issues pertaining to study methods, data collection, and interpretation of results.

B. Positions and Honors**Positions and Employment**

- 1996 Research Assistant (Dr. Beatrice Beebe, PI), New York State Psychiatric Institute
- 1996-1998 Research Assistant (Dr. Jeffrey Lockman, PI), Tulane University
- 1999-2001 Research Coordinator (Dr. Catherine Monk, PI), New York State Psychiatric Institute
- 2001-2007 Doctoral Student (Dr. Tyrone Cannon, advisor), University of California-Los Angeles
- 2006-2007 Psychology Intern, Sepulveda VA Ambulatory Care Center
- 2007-2009 Postdoctoral Research Fellow (Dr. Alan Brown, advisor), Columbia University
- 2009-2015 Assistant Professor, Temple University, Psychology Department
- 2015-present Associate Professor, Temple University, Psychology Department

Honors

Dean's list, Tulane University

Departmental honors in psychology, Tulane University

Awards & Fellowships

2001-2002	Regent's Award, UCLA
2004	Departmental Summer Graduate Student Research Mentorship Award, UCLA
2004	NRSA Incentive Award, UCLA
2004-2005	Graduate Student Research Mentorship Award, UCLA
2005-2006	Fishbaugh Pollack/Affiliates Fellowship, UCLA
2005-2006	NIMH predoctoral fellowship, Health Psychology Training Grant (MH15750), UCLA
2008	Society of Biological Psychiatry's Travel Scholarship
2009	International Congress on Schizophrenia Research Young Investigator Award
2007-2009	NIMH Postdoctoral fellowship in Schizophrenia Research (5 T32 MH018870-20), Columbia University
2009	Early Life Programming and Neurodevelopmental Conference Travel Award

C. Contributions to Science

My research program uses a multidisciplinary approach to 1) identify developmental risk factors for schizophrenia, depression, and related disorders during two vulnerable periods of development, the prenatal period and adolescence/young adulthood, and to 2) delineate developmental trajectories towards these disorders. This research is a crucial first step to developing effective intervention and prevention strategies.

*denotes student projects in my lab, where I am the corresponding author

1. Immune Processes in the Etiology of Schizophrenia, Depression, and Related Disorders

My lab focuses on understanding how infection and changes in immune processes during pregnancy, as well as throughout development, increase risk for schizophrenia and depression, and related disorders. I have found that maternal infection/inflammation during pregnancy is related to increased risk of schizophrenia in offspring, poorer cognitive functioning premorbidly, more severe brain abnormalities in cases, and more severe symptom profiles (the latter in preparation). Further, I have found that these results are not specific to schizophrenia, but rather that inflammation/infection during pregnancy also increases risk for offspring internalizing/externalizing symptoms and depression (the latter in preparation). In addition, I have published noteworthy reviews that highlight the gaps in the literature aimed at examining abnormalities in immune processes in risk for schizophrenia. My work has important implications for understanding the role of immune processes in risk for schizophrenia and depression, as I have found that inflammation and infection influence the courses of these disorders at various stages of development and that these early insults are more likely to affect those who have liability for the disorders. I also have proposed developmental models of how immune functioning operates within the course of schizophrenia, and I have identified key gaps in the literature in immune-psychosis investigations, all of which could have important implications for the development of early intervention and treatment strategies. Finally, I have a currently funded R-01 to examine pre- and postnatal inflammation and offspring symptoms, cognitive functioning, and multi-modal indicators of brain abnormalities in mid-life, which is a follow up study of my previous R-01 examining similar questions in adolescent offspring.

- a. Mac Giollabhui, N.*., Murphy, S.K., Maxwell, S.D., & **Ellman, L.M.** (2019). Maternal inflammation during pregnancy and risk for offspring externalizing and internalizing symptoms: Fetal sex and timing matters. *Journal of Psychiatric Research*, 111, 96-103.
- b. Murphy, S.K.,* Fineberg, A.M., Maxwell, S.D., Alloy, L.B., Zimmerman, L., Krigbaum, N.Y., Cohn, B.A., & **Ellman, L.M.** (2017) Maternal infection and stress during pregnancy and depressive symptoms in adolescent offspring. *Psychiatry Research*, 257, 102-110.
- c. Fineberg, A.M.* & **Ellman, L.M.** (2013). Inflammatory cytokines and neurological and neurocognitive alterations in the course of schizophrenia. *Biological Psychiatry*, 73(10), 951-966.
- d. **Ellman, L.M.**, Deicken, R.F., Vinogradov, S., Kremen, W.S., Poole, J.H., Kern, D.M., Tsai, W.Y., Schaefer, C.A., & Brown, A.S. (2010). Structural brain alterations in schizophrenia following fetal exposure to the inflammatory cytokine interleukin-8. *Schizophrenia Research*, 121(1-3), 46-54.

2. Obstetric Complications and Schizophrenia

My work also has shown that a history of obstetric complications (OCs, e.g., fetal hypoxia and infection/immune processes during pregnancy) are associated with decreased fetal growth, difficulties during the premorbid period, a more severe course of the disorder, more severe brain abnormalities, and more pronounced neuromotor and neurocognitive difficulties. OCs in these studies were not related to compromise among controls, suggesting that liability associated with schizophrenia is necessary for OCs to result in increased risk for the disorder and associated neurodevelopmental sequelae. This work holds the potential for major contributions to the development of early intervention and prevention strategies, as my findings suggest that OCs lead to observable changes in behavior and growth that are detectable as early as infancy in people who later develop schizophrenia, and that liability for the disorder may be necessary in order for the fetus to be vulnerable to these OCs. My research also is aimed at determining whether OCs depend on (gene-environment interaction), covary with (gene-environment covariation), are independent of (phenocopy), and/or act additively (additive influences) with genetic factors in the etiology of schizophrenia. In two population-based, genetic high-risk studies in Finland that utilize national prenatal/perinatal and psychiatric registries, I have found support for gene-environment covariation for two OCs (decreased fetal growth and fetal hypoxia), as well as results limiting the possibility of gene-environment covariation for a number of other OCs. My initial article from my first study was the first to incorporate maternal experiences during pregnancy into interpretations of the gene-environment covariation model of OCs and schizophrenia; this article was recognized in the book, the "Year in Schizophrenia," as among the most cutting-edge studies to address how environmental factors play a role in the course of schizophrenia in 2007 (Brown, 2007). This study was the basis for a March of Dimes grant that I wrote with my graduate school mentor, Dr. Tyrone Cannon, which collects data on OCs for offspring of all fathers and mothers in Finland who were diagnosed with schizophrenia, and detailed information on maternal health-risk behaviors during pregnancy. Findings from this second study provide compelling evidence that liability associated with schizophrenia overlaps with liability for fetal hypoxia and decreased fetal growth, and, therefore, bolster my previous findings that fetal hypoxia leads to decreases in fetal growth among newborns who later develop schizophrenia, but not among control newborns (Ellman et al., in preparation). More importantly, these findings provide preliminary evidence that, in combination, fetal hypoxia and decreased fetal growth may be particularly important markers for future risk of schizophrenia. I also was the first (to my knowledge) to write about how the aforementioned gene-OC models are not mutually exclusive (as has been assumed in previous publications), but rather likely operate simultaneously; this theoretical modification has changed some schizophrenia researchers' views of how OCs operate in the course of schizophrenia.

- a. Forsyth, J.K., **Ellman, L.M.**, Tanskanen, A., Mustonen, U., Huttunen, M.O., Suvisaari, J., & Cannon, T.D. (2013). Genetic risk for schizophrenia, obstetric complications, and adolescent school outcome: Evidence for gene-environment interaction. *Schizophrenia Bulletin*, 39(5), 1067-1076.
- b. **Ellman, L.M.**, Vinogradov, S., Kremen, W.S., Poole, J.H., Kern, D.M., Deicken, R.F., & Brown, A.S. (2012). Low maternal hemoglobin during pregnancy and diminished neuromotor and neurocognitive performance in offspring with schizophrenia. *Schizophrenia Research*, 138(1), 81-87.
- c. **Ellman, L.M.**, Yolken, R.H., Buka, S.L., Torrey, E.F., & Cannon, T.D. (2009). Cognitive functioning prior to the onset of psychosis: The role of fetal exposure to serologically determined influenza infection. *Biological Psychiatry*, 65(12), 1040-1047.
- d. **Ellman, L.M.**, Huttunen, M., Lönnqvist, J., & Cannon, T.D. (2007). The effects of genetic liability for schizophrenia and maternal smoking during pregnancy on obstetric complications. *Schizophrenia Research*, 93(1-3), 229-236.

3. Maternal Stress/Emotional States During Pregnancy and Offspring Outcomes

My research and my work with colleagues have demonstrated that maternal stress and other emotional states during pregnancy are related to fetal and newborn changes in physiology and growth, as well as to risk for schizophrenia and depression among offspring in both community-based and epidemiological samples. In a series of studies, we have found sex differences in fetal responses to maternal stress during pregnancy. Specifically, male fetuses seem to be particularly vulnerable to maternal stress during pregnancy, showing reduced maturation at birth and risk for schizophrenia later in life. Interestingly, female offspring seem to be relatively spared at birth, but, like male offspring, show increased risk of depression in adolescence—although some of our findings suggest that the influence of stress on later risk of depression only occurs when infection is also present, which would suggest that stress moderates the relation between infection during pregnancy and offspring risk of depression (Murphy et al., 2017).

- a. **Ellman, L.M.**, Murphy, S.K., Maxwell, S.D., Calvo, E.M., Cooper, T., Schaefer, C.A., Bresnahan, M.A., Susser, E.S., Brown, A.S. (in Press). Maternal cortisol during pregnancy and offspring schizophrenia: Influence of fetal sex and timing of exposure. *Schizophrenia Research*.
- b. Maxwell, S.D., * Fineberg, A.M., Drabick, D.A., Murphy, S. K., & **Ellman, L.M.** (in press). Maternal prenatal stress and other developmental risk factors for adolescent depression: Spotlight on sex differences. *Journal of Abnormal Child Psychology*.
- c. Fineberg, A.M.* **Ellman, L.M.**, Schaefer, C.A., Maxwell, S.D., Shen, L., Chaudhury, N., Cook, A.L., Bresnahan, M.A., Susser, E.S., & Brown, A.S. (2016). Fetal exposure to maternal stress and risk for schizophrenia spectrum disorders among offspring: Differential influences of fetal sex. *Psychiatry Research*, 236, 91-97.
- d. **Ellman, L.M.**, Schetter, C.D., Hobel, C.J., Chicz-Demet, A., Glynn, L.M., & Sandman, C.A. (2008). Timing of fetal exposure to stress hormones: Effects on newborn physical and neuromuscular maturation. *Developmental Psychobiology*, 50(3), 232-241.

4. Risk Factors for Psychotic Disorders and the Extended Psychosis Phenotype among Young Adults

I am leading a series of studies aimed at identifying risk factors for psychosis that are proximal to the onset of the disorder, as well as risk factors for the extended psychosis phenotype, given findings that psychotic symptoms occur on a continuum. These studies use non-treatment-seeking young adults from the community. I also am PI on a collaborative R01, on which I am the coordinating PI, to develop a psychosis-risk screener for adolescents and young adults in non-treatment seeking samples. These studies are novel, in that the preponderance of investigations exploring clinical high risk for psychosis have used clinically referred samples, which may limit generalizability to non-clinical samples in the general population. We have a number of findings linking subthreshold psychotic symptoms to risk factors for psychosis, including cannabis use, nicotine use, and a variety of clinical variables (e.g., trauma history, sleep disturbances, etc.). Further, initial DTI and fMRI results indicate that those with a high number of psychotic-like experiences exhibit similar brain abnormalities to those observed in schizophrenia and clinical high risk samples (Cooper et al, in press). I also have collaborated with Dr. Deidre Anglin at City College in New York to investigate how race, ethnicity, and discrimination are associated with psychotic-like experiences and risk for psychosis. We found that discrimination and rejection sensitivity are associated with psychotic-like experiences among ethnic minority undergraduates (Anglin et al., 2014a, Anglin et al, 2014b). Ultimately, these results could be used to identify young adults who may be at particular risk for developing psychotic disorders during periods (e.g., college) in which supervision and monitoring may be limited. Similarly, understanding the shared causes and expressions of disorders across the greater psychosis phenotype likely has major implications for treatment of a number of mental disorders.

- a. Ered, A.,* Gibson, L.E., & **Ellman, L.M** (2017). Coping mediates the relationship between stress and attenuated positive psychotic symptoms. *European Psychiatry*, 43, 9-13.
- b. Gibson, L.E.,* Cooper, S., Reeves, L.E., & **Ellman, L.M.** (2017) The association between traumatic life events and psychological symptoms from a conservative, transdiagnostic perspective: does specificity exist? *Psychiatry Research*, 252, 70-74.
- c. Wolfe, R.M.,* Reeves, L.E., Gibson, L.E., Cooper, S., & **Ellman, L.M.** (2017). Attenuated positive psychotic symptoms in relation to cigarette smoking in a non-clinical population. *Nicotine & Tobacco Research*, 19(1), 124-128.
- d. Cooper, S.* , Klugman, J., Heimberg, R.G., Anglin, D.M., & **Ellman, L.M.** (2016). Attenuated positive psychotic symptoms and social anxiety: Along a psychotic continuum or different constructs? *Psychiatry Research*. 235, 139-147.

Complete List of Published Work in My Bibliography:

<https://www.ncbi.nlm.nih.gov/myncbi/lauren.ellman.1/bibliography/public/>

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

ACTIVE SUPPORT

NIMH R01 MH112613

(Ellman, PI)

09/01/17 – 06/30/22

“1/3 - Psychosis risk screening: A multi-site instrument development study”

The aims of the project are to develop a psychosis-risk screener for non-treatment seeking adolescents and young adults, as well as to estimate the prevalence and correlates of psychotic-like experiences in the community.

Role: Coordinating PI

NIMH R01 MH118545 (Ellman, PI) 07/01/19 – 03/31/24

Title: Maternal Inflammation During Pregnancy: Clinical and Neurocognitive Outcomes in Adult Offspring

To investigate how maternal inflammation during pregnancy contributes to clinical, neurocognitive, and neural outcomes among late middle-aged offspring.

Role: PD/PI

CBCRP (Cohn, PI) 01/01/18 – 12/31/21

“Linking neighborhood and individual ACEs to breast cancer”

The aims of this project are to determine early life adverse events that increase risk for breast cancer in adulthood, such as individual and neighborhood-level stress.

Role: Co-Investigator (Temple Site PI)

Start-Up Award (Ellman, PI) 2009 – present

Temple University

The goals of this award are to assist in developing a laboratory at Temple University in any capacity.

Role: PI

COMPLETED SUPPORT (within last 3 years)

NIMH R01 MH101168 (Alloy, PI) 07/01/13 – 03/31/19

“Risk for Adolescent Depression: Stress, Cognitive Vulnerability, & Inflammation”

The aims of this project are to investigate the relation between inflammation and the development of adolescent depression symptoms and episodes.

Role: Co-Investigator

NIMH R01 MH096478 (Ellman, PI) 04/01/12 – 12/31/17

“Fetal Exposure to Maternal Stress and Inflammation: Effects on Neurodevelopment”

The project aims to investigate how maternal stress and inflammation during pregnancy influence the risk of symptoms of depression during adolescence in offspring.

Role: PI

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: Gregory E. Miller

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

POSITION TITLE: Louis W. Menk 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 <i>(if applicable)</i>	Completion Date MM/YYYY	FIELD OF STUDY
University of California, Los Angeles, CA	BA	05/1993	Psychology
University of California, Los Angeles, CA	PhD	05/1998	Clinical Psychology
Carnegie Mellon University, Pittsburgh, PA	Post-Doc	08/2000	Health Psychology

A. Personal Statement

There is a growing recognition of the role that neuroimmune signaling plays in the pathophysiology of mental and physical illness. To help facilitate this research, MPI Dr. Nusslock and I recently published a Neuroimmune Network (NIN) model as a heuristic framework for organizing knowledge from disparate literatures and as a springboard for generating integrative research. This model proposes that early-life adversity amplifies crosstalk between peripheral inflammation and neural circuitries subserving threat-, reward-, and executive control-related processes. This crosstalk results in chronic low-grade inflammation and dysregulated neuroimmune signaling in a manner that contributes to predisease states. The proposed research in this application extends this model to the investigation of neuroimmune signaling in the emergence of major depression in adolescence. All immune data will be collected at Temple University and sent to my laboratory at Northwestern University for assay and analysis. As a Co-Investigator, my roles will be to (a) provide input on the conceptual and mechanistic basis for links between early adversity, neural reward, and inflammatory data, (b) oversee the assay and analysis of inflammatory data, and (c) actively participate in analysis and interpretation of data, and co-author manuscripts that result. I'm in an excellent position to serve in these roles. As is evident from the papers below, my team has been actively involved in this research. In a handful of early studies, we highlighted the role of elevated inflammation in depression. More generally, our work has identified patterns of immune dysfunction as likely mechanisms through which chronic stressors, particularly related to low SES, bring about mental and physical health problems across the lifecourse. We also are in the midst of two R01s that explore related questions about the effect of early adversity and life stress on neuroimmune signaling in risk for mental and physical illness. In our work, we do thorough assessments of the inflammatory biomarkers proposed here, so I'm well versed in the nuances of sample collection, analysis, and interpretation. Furthermore, I have a strong working relationship with MPIS Nusslock and Alloy. I have published papers with Dr. Nusslock on inflammation's role in mental and physical health, and have ongoing projects and manuscripts under review with both Drs. Nusslock and Alloy.

B. Positions and Honors**Academic Positions**

- 2000-2003 Washington University, Assistant Professor, Dept of Psychology.
- 2003-2012 University of British Columbia, Assistant, Associate, Full Professor, Dept of Psychology.
- 2012-2017 Northwestern University, Professor of Psychology; Faculty Fellow, Institute for Policy Research
- 2017 - Northwestern University, Louis W Menk Professor; Faculty Fellow, Institute for Policy Research

Professional Memberships

American Psychosomatic Society; Division of Health Psychology of APA; Psychoneuroimmunology Research Society; Society for Behavioral Medicine; Academy of Behavioral Medicine Research

Awards & Honors

President, Academy of Behavioral Medicine Research (2015-2016)
Highly Cited Researcher, Clarivate Analytics (citations in top 1% of psychology/psychiatry 2004-14; 2006-16)
George A. Miller Award for best paper in general psychology (2016)
Fellow, Academy of Behavioral Medicine Research (2008), Society of Behavioral Medicine (2008)
Herbert Weiner Early Career Award, American Psychosomatic Society, 2005
Distinguished Scientific Early Career Contribution to Health Psychology, Amer Psychol Assoc, 2004
Young Investigator Award, Society of Behavioral Medicine, 2003
Associate Editor, *Psychological Bulletin*, 2010 - 2014
Associate Editor, *Psychosomatic Medicine*, 2008 - 2011
Consulting Editor: *Brain, Behavior, & Immunity* (2005-) *Psychological Bulletin* (2014-), *Clinical Psychological Science* (2012-) *Psychosomatic Medicine* (2004-08) *Journal of Consulting and Clinical Psychology* (2002-08)

C. Contributions to Science

1. Much of my research has focused on understanding how chronic stress affects functions of the immune system, which resists or mediates most of the diseases that seriously threaten the well-being of humans. By studying healthy adults who are caring for a family member with cancer, we helped identify two broad changes in immune function that occur with chronic stress. First, activated monocytes bring about a mild systemic inflammatory response. This pattern is important because it suggests a plausible mechanism linking stress with diseases whose pathogenesis involves persistent, excessive inflammation (e.g., heart disease, rheumatoid arthritis). Second, stress leads to a decrement in the capacity of monocytes and lymphocytes to respond to invading pathogens, which explains why it is also associated with susceptibility to common infectious diseases. Using tools from molecular biology like transcriptional microarrays, we've begun to unravel the signaling pathways underlying these changes. Briefly, chronic stress reduces the capacity of the glucocorticoid receptor to transduce cortisol-mediated signals. This blunting allows the transcription factor NF- κ B to become overactive, and switch on genes that orchestrate chronic inflammation. Chronic stress also downregulates expression of genes involved with Type-1 interferon signaling, which are critical to anti-viral defenses.

A. Cohen, S., Janicki-Deverts, D., Doyle, W.J., **Miller, G.E.**, Frank, E., Rabin, B.S., & Turner, R.B. (2012). Chronic stress, glucocorticoid receptor resistance, inflammation and disease risk. *Proceedings of the National Academy of Sciences of the United States of America*, 109, 5995-5999. (PMC3341031)

B. **Miller, G.E.**, Chen, E., Sze, J., Marin, T.J., Doll, R., Ma, R., & Cole, S.W. (2008). A functional genomic fingerprint of chronic stress in humans: Blunted glucocorticoid and increased NF- κ B signaling. *Biological Psychiatry*, 64, 266-272. (PMC2581622)

C. Rohleder, N., Marin, T.J., Ma, R., & **Miller, G.E.** (2009). Biologic cost of caring for a cancer patient: Dysregulation of pro- and anti-inflammatory signaling pathways. *Journal of Clinical Oncology*, 27, 2909-2915. (No PMCID; funded by Canadian Institutes of Health Research)

D. Powell, N.D., Sloan, E.K., Bailey, M.T., Arevalo, J.M.G., **Miller, G.E.**, Chen, E., Kobor, M.S., Reader, B.F., Sheridan, J.F., & Cole, S.W. (2013). Social stress up-regulates inflammatory gene expression in the leukocyte transcriptome via β -adrenergic induction of myelopoiesis. *Proceedings of the National Academy of Sciences of the United States of America*, 110, 16574-16579. (PMC3799381)

2. Children of low socioeconomic status (SES) are at risk for multiple health problems across the lifespan. But little is known about the behavioral and biological mechanisms that are responsible for these disparities. To fill this gap, we've spent much of the past 15 years doing theoretical and empirical work on children's SES, family relationships, and immune development. Using tools from clinical immunology, we've shown that children exposed to material hardship and family harshness develop a pro-inflammatory phenotype. As a consequence, their monocytes show especially aggressive inflammatory responses to microbial stimuli, and are relatively insensitive to glucocorticoid signals, which normally terminate those responses. While inflammation is essential for survival, it must be tightly regulated. Otherwise, it can accelerate the pathogenesis of many common health problems. With molecular tools, we have begun to characterize the epigenetic and transcriptional processes that underlie this phenotype. In recent years we've expanded this research to the gestational period, showing that low-SES pregnant women have greater inflammatory activity at the maternal-fetal interface, as reflected in both transcriptional patterns and histologically-documented lesions.

A. **Miller, G.E.**, Borders, A.E., Crockett, A.H., Ross, K.M., Qadir, S., Keenan-Devlin, L. et al. (2017). Maternal socioeconomic disadvantage is associated with transcriptional indications of greater immune activation and slower tissue maturation in placental biopsies and newborn cord blood. *Brain, Behavior, and Immunity*, 64, 276-84 (PMC5493326).

B. **Miller, G.E.**, Chen, E., & Parker, K.J. (2011). Psychological stress in childhood and susceptibility to the chronic diseases of aging: Moving towards a model of behavioral and biological mechanisms. *Psychological Bulletin*, 137, 959-997. (PMC3202072)

C. **Miller, G.E.**, & Chen, E. (2010). Harsh family climate in early life presages the emergence of a proinflammatory phenotype in adolescence. *Psychological Science*, 21, 848-856. (PMC3207635)

D. **Miller, G.E.**, Chen, E. Fok, A., et al. (2009). Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. *Proceedings of the National Academy of Sciences of the United States of America*, 106, 14716-14721. (PMC2732821)

3. Of course, not all low-SES children go on to develop this phenotype and the medical problems to which it contributes. Thus, we've also focused on identifying sources of and pathways to resilience, particularly in the family. In four distinct studies, we've found evidence suggesting that parental nurturance operates as a buffer, protecting low-SES youth from subsequent health risks. Reinforcing the importance of family relationships, we also found evidence in a randomized controlled trial that a parenting intervention reduces inflammation 8 years later. In a related line of inquiry, we're trying to understand the psychological resources that nurturant parents instill in low-SES youth, and how they might protect against health problems. We have identified a coping strategy called "shift-and-persist" that promotes resilience in low-SES youth. It prioritizes shifting oneself – that is, accepting stress for what it is and adapting through reappraisal - and persisting – that is, enduring life with strength by holding on to meaning and optimism. The combination of shift-and-persist seems to protect children against some common health problems that pattern by SES (asthma, cardiovascular risk.)

A. **Miller, G.E.**, Brody, G.H., Yu, T., & Chen, E. (2014). A family oriented psychosocial intervention reduces inflammation in low-SES African-American youth. *Proceedings of the National Academy of Sciences of the United States of America*, 111, 11287-11292. (PMC4128159)

B. Chen, E., **Miller, G.E.**, Kobor, M.S., & Cole, S. (2011). Maternal warmth buffers the effects of low early-life socioeconomic status on pro-inflammatory signaling in adulthood. *Molecular Psychiatry*, 16, 729-737. (PMC2925055)

C. Chen, E., Strunk, R.C, Trethewey, A., Schreier, H.M.C., Maharaj, N., & **Miller, G.E.** (2011). Resilience in low socioeconomic status children with asthma: Adaptations to stress. *Journal of Allergy and Clinical Immunology*, 128, 970-976. (PMC3205307)

D. Chen, E., & **Miller, G.E.** (2013). Socioeconomic status and health: Mediating and moderating factors. *Annual Review of Clinical Psychology*, 9, 723-749. (No PMCID; funded by Canadian Institutes of Health Research)

4. Many of us intuitively believe upward mobility is the best "antidote" for protecting children from the health problems associated with poverty. While mobility undoubtedly has its benefits, our research has identified some unanticipated costs, too. They are particularly evident in the physical health of African-Americans attempting to rise from poverty. In multiple studies we have observed a pattern called "skin-deep resilience," where upwardly mobile Blacks display outward signs of achievement and competence, but worse physical health. These apparent "costs" of success manifest in greater cardiometabolic risk, faster epigenetic aging, and higher risks of Type 2 diabetes and upper respiratory infection. These findings challenge the conventional view of what it means to be resilient. Current thinking suggests that if low-SES youth do well in school and stay out of trouble, they have overcome disadvantage. As our work shows, that is only partially accurate.

A. Brody, G.H., Yu, T., Chen, E., **Miller, G.E.**, Kogan, S.M., & Beach, S.R. (2013). Is resilience only skin deep?: Rural African Americans' socioeconomic status-related risk and competence in preadolescence and psychological adjustment and allostatic load at age 19. *Psychological Science*, 24, 1285-1293. (PMC3713113)

B. Gaydosh, L., Schorpp, K., Chen, E., **Miller, G.E.**, & Harris, K.M. (2018). College completion predicts lower depression but higher metabolic syndrome among disadvantaged minorities in young adulthood. *Proceedings of the National Academy of Sciences of the USA*, 115, 109-114. (PMC5776811)

C. **Miller, G.E.**, Yu, T., Chen, E., & Brody, G.H. (2015). Self-control forecasts better psychosocial outcomes but faster epigenetic aging in low-SES youth. *Proceedings of the National Academy of Sciences of the USA*, 112, 10325-10330. (PMC4547243)

D. Miller, G.E., Cohen, S., Janicki-Deverts, D., Brody, G.H., & Chen, E. (2016). Viral challenge reveals further evidence of skin-deep resilience in African Americans from disadvantaged backgrounds. *Health Psychology*, 35, 1225-1234. (PMC5067971)

D. Research Support

Ongoing Support

P30DA027827 (Brody)

07/14-06/30/20

NIH/NIDA (via University of Georgia)

Vulnerability to Drug Use & HIV: Advancing Prevention for Rural African Americans

This Center focuses on the prevention of substance use among rural African-Americans as they make the transition from adolescence to adulthood. It brings together expertise, resources, and methods from psychology, neuroscience, immunology, and prevention science.

Role: Co-Investigator, Subaward PI

R01HD030588 (Brody)

07/14-06/30/20

NIH/NICHD (via University of Georgia)

Rural African American Young Adults' Pathways to Psychosocial and Physical Health

This project will investigate a longitudinal cohort of rural African American youth as they transition into young adulthood in order to understand the impact of SES and race-related stressors on physiological function, and to test psychosocial protective mechanisms of this relationship.

Role: Co-Investigator, Subaward PI

1R01HL122328 (Miller)

12/14-11/30/19 (NCE)

NIH/NHLBI

Childhood Origins of CHD Disparities: Neural & Immune Pathways

People who spend the early years of their lives in poverty are more likely to develop heart disease when they reach adulthood, and this project attempts to identify the mechanisms that underlie this process. We study teenagers over a two-year period, asking whether brain development, immune functioning, and heart disease risk depend on their family's economic situation. By studying these processes, we may be able to identify targets for early prevention.

Role: PI

1R01CA20645601A1RE (Penedo)

07/16-06/30/21

National Cancer Institute

Culturally Adapted Cognitive Behavioral Stress and Self-Management (C-CBSM) Intervention for PC

This study will fill several critical gaps in our knowledge on the incremental efficacy of culturally adapted EBTs, relative to standard linguistic translations, on improving symptom burden and HRQoL in Hispanic men with localized PC, and map sociocultural, psychosocial and molecular mechanisms involved in the efficacy of CBSM, and therefore help guide targeted treatments for this critically understudied population and other Spanish monolingual cancer survivors.

Role: Co-Investigator

1R01MD011749-01 (Miller)

09/26/17-05/31/22

NIH/NIMHD

Understanding Socioeconomic Disparities in Perinatal Risk: The Role of Epigenetic and Transcriptional Regulation in the Placenta

There are marked disparities in perinatal outcomes by SES, but little is known about the underlying mechanisms. This project examines the contribution of gene regulation at the maternal-fetal interface to these disparities. With a multilevel approach, it also seeks to understand how factors at the neighborhood, family, and individual operate together to bring about perinatal risks.

Role: PI

96-18-01 (Miller)

12/1/17-11/30/19 (NCE)

Russell Sage Foundation

Socioeconomic and Racial Gaps in Schools: Implications for Health and Employment

The proposed research will use a large, nationally representative sample to test whether people who are African-American or Latino or who are from lower SES backgrounds and who attend schools with greater racial and socioeconomic academic inequality have greater health risk and health impairment at work as adults.

Role: PI

R01HD092446 (Borders) 04/1/18-03/31/23
NIH/NICHD (via Northshore)

Psychosocial Intervention, Maternal Inflammation, and Birth Outcomes: Comparison of Centering vs. Routine Prenatal Care

This project examines whether a psychosocial intervention during pregnancy can alter profiles of inflammation at the maternal-fetal interface, and mechanisms through which this happens.

Role: Co-Investigator, Subaward PI

R01HD091235 (Valentino) 03/1/18-02/28/23
NIH/NICHD (via University of Notre Dame)

Pathways Linking Early Adversity and Support to Behavioral and Physical Health

This project prospectively examines the potentiating effect of early adversity on children's mental and physical health. It also evaluates potential explanatory mechanisms linking adversity to child health, and experimentally considers the protective effects of maternal support on child health via analysis of a parenting intervention for maltreated preschool-aged children and their parents.

Role: Co-Investigator

R01MH113883 (Luby) 04/1/18-03/31/23
NIH/NICHD (via Washington University St. Louis)

Early Life Adversity, Biological Embedding, and Risk for Developmental Precursors of Mental Disorders

This prospective study examines how maternal stress during pregnancy relates to newborn inflammation and neurodevelopment.

Role: Co-Investigator

R01HD093718 (Chen) 09/1/17-08/31/22
NIH/NICHD

Understanding Diverging Profiles of Academic and Physical Health Outcomes in African American Youth

The same factors that help youth to succeed academically may be exacting a toll on them physically, resulting in resilience that is only 'skin-deep.' Here we use an accelerated longitudinal design to clarify why skin-deep resilience develops, when in development it emerges, and whether early-warning signs can be detected.

Role: Co-Investigator

R01HL136676 (Chen) 09/1/17-08/31/22
NIH/NHLBI

An Interpersonal Relationships Intervention for Improving Cardiovascular Health in Youth

This project implements a mentoring intervention, where low-income minority college students serve as mentors to low-income minority elementary students. It examines the effects on the cardiovascular health.

Role: Co-Investigator

R01HD091046 (Brody, PI) 09/1/2017 – 08/31/2020
NIH/NICHD

Origin of Chronic Diseases of Aging among Rural African American Young Adults

In this proposal, we examine exposure to multidimensional SES- and race-related stressors during the transition to adulthood, and how they relate to changes in biological weathering among rural African Americans.

Role: Co-Investigator, Subaward PI

Scientific Overlap: None

Commitment Overlap: None

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: Robin Nusslock

ERA COMMONS USER NAME (credential, e.g., agency login): Nusslock

POSITION TITLE: Associate Professor of Psychology and AT&T Research Chair

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 <i>(if applicable)</i>	Completion Date MM/YYYY	FIELD OF STUDY
University of Wisconsin-Madison, Madison, WI	B.A.	05/1999	Psychology
University of Wisconsin-Madison, Madison, WI	Ph.D.	08/2009	Clinical Psychology
University of Pittsburgh Medical Center, Western Psychiatric Institute and Clinic, Pittsburgh, PA	Internship	08/2009	Clinical Psychology
University of Pittsburgh Medical Center, Western Psychiatric Institute and Clinic, Pittsburgh, PA	Post-Doc	08/2010	Neuroimaging

A. Personal Statement

This project aims to use an innovative biobehavioral high-risk approach to examine the relationship between reward system functioning and inflammatory signaling as separate, and joint, determinants of risk for first onset of major depression in adolescence. As MPI, I will oversee the processing and analysis of MRI data in close collaboration with our investigative team. I also will work with MPI Dr. Alloy to oversee theoretical model development, the assessment of reward and immune system constructs, and the analysis and writing of project findings. MRI data for this proposal will be collected and prepared at Temple University and transferred to my laboratory at Northwestern University for processing and analysis. In addition to my laboratory's resources, I also will have full access to the resources associated with Northwestern University's Center for Translational Imaging (CTI), a world-renowned neuroimaging facility. My training, successful scientific track record, and collaborative relationships with the investigative team make me confident in my ability to serve as an MPI on this project and in our research team's ability to carry out the proposed research.

I am an Associate Professor of Psychology and a Faculty Fellow at the Institute for Policy Research at Northwestern University, where I also hold appointments in Neuroscience, Psychiatry, Neurobiology, and Medical Social Sciences. The research proposed in the current grant is a very strong match with my research program and expertise, which focuses on abnormalities in reward-processing and reward-related brain function in mood disorders. Dr. Alloy and I have collaborated for 17 years in examining the Behavioral Approach System (BAS)/reward sensitivity theory of bipolar disorder and depression, and we have numerous joint publications. Furthermore, I successfully served as a Co-I on one of Dr. Alloy's NIMH R01 grants (MH077908), for which I oversaw the processing and analysis of MRI data. Thus, our team already has established the mechanism for transferring MRI data between Temple and Northwestern University and we will employ identical procedures in the proposed research. I have multiple publications using the proposed fMRI monetary reward paradigm and we have well-established preprocessing and analytic pipelines for managing the MRI data in the proposed research. I also have considerable experience managing large-scale neuroimaging studies and I am currently PI on a multi-site NIMH R01 grant using MRI to examine the relationship between reward-related neural circuitry and mood disorder symptoms (MH100117). Finally, I have a close working relationship with Co-I Dr. Miller, who is also at Northwestern University. Dr. Miller and I published a neuroimmune network model in *Biological Psychiatry* (2016) on the bidirectional relationship between reward-related brain function and peripheral inflammation in risk for mental and physical illness. The current proposal is a novel extension of this model to the investigation of onset of major depression in adolescence.

B. Positions and Honors

Academic Employment

2008-2009	Clinical Psychology Intern, Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center
2009-2010	Postdoctoral Research Fellow, Clinical and Translational Affective Neuroscience Program, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center
2010-2016	Assistant Professor, Department of Psychology, Northwestern University
2016-present	Associate Professor (with tenure), Department of Psychology, Northwestern University

Other Academic Appointments

2010-2016	Adjunct Assistant Professor, Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center
2010-Present	Faculty Affiliate, Interdepartmental Neuroscience Program (NUIN), Northwestern University
2010-Present	Professor, Department of Psychiatry, Northwestern University (Secondary)
2014-Present	Professor, Department of Neurobiology, Northwestern University (Secondary)
2016-Present	Professor, Department of Medical Social Sciences, Northwestern University (Secondary)
2016-2018	Faculty Associate, Institute for Policy Research, Northwestern University
2016-2018	AT&T Research Chair, Northwestern University (awarded to top tenure cases in College of Arts & Science)
2018-Present	Faculty Fellow, Institute for Policy Research, Northwestern University

Honors

1999	Devereux Foundation Institute of Clinical Training and Research Fellowship
2002-2004	NIMH Emotion Research Training Grant recipient, University of Wisconsin-Madison
2009	NIMH Postdoctoral Clinical Neuroscience Fellowship, University of Pittsburgh Medical Center
2010	NIMH Career Development Institute in Bipolar Disorder Awardee
2011	International Society for Bipolar Disorders Samuel Gershon Junior Investigator Award
2013	Association for Psychological Science (APS) Rising Star Award
2013	Northwestern University Undergraduate Psychology Association Excellence in Teaching Award
2016	Northwestern University Associated Student Government "Faculty Honor Roll"
2017	Fellow, Association for Psychological Science

C. Contributions to Science

1. *Neuroimmune Network Model of Emotional and Physical Health:* My work on neuroimmune mechanisms in the pathophysiology of depression and anxiety is the most recent development in my research program. To facilitate this research, we recently published a Neuroimmune Network (NIN) model in *Biological Psychiatry* as a heuristic framework for organizing knowledge from disparate literatures and as a springboard for generating integrative research (1). This hypothesis argues that early-life adversity amplifies crosstalk between peripheral inflammation and neural circuitries subserving threat-, reward-, and executive control-related processes. This crosstalk results in chronic low-grade inflammation, thereby contributing to adiposity, insulin resistance, and other predisease states. In the brain, we propose that inflammatory mediators act on these same threat-, reward-, and executive control-related brain systems in a manner that predisposes individuals to self-medicating behaviors like smoking, drug use, and consumption of high-fat diets. Acting in concert with inflammation, these behaviors are proposed to accelerate the pathogenesis of emotional and physical health problems. In line with this perspective, we recently reported that heightened peripheral inflammation is associated with lower functional connectivity in the brain's emotion regulation and central executive networks (2). We also report that executive control-related brain function moderates the effect of stress exposure (neighborhood violence) on cardiometabolic health (3) and that supportive parenting strengthens executive control neural circuitry in the face of early life adversity (4).

1. **Nusslock, R., & Miller, G.E.** (2016). Early-life adversity and physical and emotional health across the lifespan: A neuro-immune network hypothesis. *Biological Psychiatry*, 80, 23-32. PMCID: PMC4670279

2. **Nusslock, R.**, Brody, G.H., Armstrong, C.C., Carroll, A.L., Sweet, L.H., Yu, T., Barton, Hallowell, E., A.W., Chen, E., Higgins, J., Parrish, T.B., Wang, L., & Miller, G.E. (2019). Higher peripheral inflammatory signaling associated with lower resting state functional brain connectivity in emotion regulation and central executive networks. *Biological Psychiatry*, 86, 153-162. PMCID: PMC31054766
 3. Miller, G.E., Chen, E., Armstrong, C.C., Carroll, A.L., Ozturk, S., Rydland, K.J., Brody, G.H., Parrish, T.B., & **Nusslock, R.** (2018). Functional connectivity in central executive network protects youth against cardiometabolic risks linked with neighborhood violence. *Proceedings of the National Academy of Sciences*, 115, 12063-12068. PMCID: PMC30397136
 4. Brody, G.H., Yu, T., **Nusslock, R.**, Barton, A.W., Miller, G.E., Chen, E., & Sweet, L.H. (2019). Effect of supportive parenting on the relationship between adolescent poverty and resting state functional brain connectivity during adulthood. *Psychological Science*, 30, 1040-1049. PMCID: PMC6657149
2. *Reward Hypersensitivity Model of Bipolar Disorder:* My colleagues and I have played a central role in developing and refining the Reward Hypersensitivity Model of bipolar disorder. This model proposes that a core mechanism underlying risk for bipolar disorder is a hypersensitivity to reward cues, which can lead to excessive approach-motivation in response to reward-relevant events. In the extreme, this motivation is reflected in hypo/manic symptoms. In line with this perspective, we have shown that elevated trait reward sensitivity prospectively predicts a greater likelihood of developing a bipolar spectrum diagnosis and progressing to more severe bipolar diagnoses (e.g., bipolar I) (1). Using fMRI, we reported that increased approach motivation is associated with elevated reward-related brain function (2) and that individuals with bipolar I disorder exhibit greater reward-related brain function compared to healthy controls (3). Using diffusion tensor imaging (DTI), we reported that individuals at elevated risk for bipolar disorder display increased white matter structural connectivity between the nucleus accumbens (NAcc) and the medial orbitofrontal cortex (mOFC) (4). This latter finding suggests that risk for bipolar disorder may be characterized by a cortico-striatal amplification circuit in which at risk individuals engage the cortex in a manner to amplify or up-regulate sub-cortical reward processing.
1. Alloy, L.B., Urosevic, S., Abramson, L.Y., Jager-Hyman, S., **Nusslock, R.**, Whitehouse, W.G., & Hogan, M.E. (2012). Progression along the bipolar spectrum: A longitudinal study of predictors of conversion from bipolar spectrum conditions to bipolar I and II disorders. *Journal of Abnormal Psychology*, 121, 16-27. PMCID: PMC3192298
 2. Young, C.B., & **Nusslock, R.** (2016). Positive mood enhances reward-related neural activity. *Social Cognitive and Affective Neuroscience*, 11, 934-944. PMCID: PMC4884311
 3. **Nusslock, R.**, Almeida, J.R.C., Forbes, E.E., Versace, A., LaBarbara, E.J., Klein, C., & Phillips, M.L. (2012). Waiting to win: Elevated striatal and orbitofrontal cortical activity during reward anticipation in euthymic bipolar adults. *Bipolar Disorders*, 14, 249-260. PMCID: PMC3826255
 4. Damme, K., Young, C.B., & **Nusslock, R.** (2017). Elevated nucleus accumbens structural connectivity associated with proneness to hypomania: A reward hypersensitivity perspective. *Social Cognitive and Affective Neuroscience*, 12, 928-936. PMCID: PMC5472153
3. *Mapping the Relationship between Threat/Reward Neural Circuitry and Symptom Dimensions of Mood and Anxiety Disorders.* A central goal of my research program is to use fMRI to examine the relationship between threat- and reward-related brain function and specific symptom dimensions of mood and anxiety disorders. We have reported that whereas risk for unipolar depression (without a history of hypo/mania) is characterized by abnormally blunted reward-related brain activity (1, 2), bipolar disorder is characterized by abnormally elevated reward-related brain function in the cortico-striatal circuit (3, 4). This suggests that risk for unipolar depression and bipolar disorder are characterized by distinct and opposite profiles of reward-related brain function. This work has implications for identifying biomarkers of differential risk for depression versus bipolar disorder, which can inform our understanding of pathophysiology and help identify targets for treatment. To move beyond considering psychiatric illnesses as unitary constructs or

homogenous disorders, my colleagues and I are currently testing the hypothesis that elevated threat-related brain function is associated with symptoms of General Distress that are common across mood and anxiety disorders, whereas reduced reward-related brain function is uniquely associated with depressive anhedonia. In line with this prediction, we recently reported that reduced functional connectivity within the cortico-striatal reward circuit is associated with anhedonia, but not general distress, among depressed participants (1). This work is in line with the goals of the RDoC initiative to map specific circuits to specific symptoms.

1. Young, C.B., Chen, T., **Nusslock, R.**, Keller, J., Scatzberg, A.F., & Menon, V. (2016). Anhedonia and general distress associated with dissociable connectivity of ventromedial prefrontal cortex in major depressive disorder. *Translational Psychiatry*, 6, e810. PMCID: PMC5070048
2. **Nusslock, R.**, Shackman, A.J., Coan, J.A., Harmon-Jones, E., Alloy, L.B., & Abramson, L.Y. (2011). Cognitive vulnerability and frontal brain asymmetry: Common predictors of first prospective depressive episode. *Journal of Abnormal Psychology*, 120, 497-503. PMCID: PMC3130533
3. **Nusslock, R.**, & Alloy, L.B. (2017). Reward processing and mood-related symptoms: An RDoC and translational neuroscience perspective. *Journal of Affective Disorders*, 216, 3-16. PMCID: PMC28237133
4. Glazer, J.E., Kelley, N.J., Pornpattananangkul, N., & **Nusslock, R.** (in press). Hypomania and depression associated with distinct neural activity for immediate and future rewards. *Psychophysiology*. PMCID: PMC30443957
4. *Integrating Research on Reward/Threat Processing with Circadian and Self-Regulatory Perspectives*. My colleagues and I have recently extended our work on threat/reward processing in important and novel directions. First, we proposed an integrated Reward/Circadian Rhythm Dysregulation model of bipolar disorder that highlights relationships between reward-related neural circuitry and both social and circadian rhythm disruption in the pathophysiology of bipolar disorder (1, 2). This model argues that the tendency of bipolar individuals to engage in excessive goal pursuit and experience excessive approach motivation in response to rewarding life events is incompatible with maintaining regular social rhythms or circadian rhythms, which is critical for managing bipolar symptoms. Second, we have begun examining abnormalities in threat/reward processing in mood and anxiety disorder symptoms from a self-regulatory perspective. This involves examining the extent to which individuals with mood and anxiety disorders have difficulty disengaging from positive or rewarding stimuli (3), and the role of threat/reward-related neural activity in modulating impulsive decision-making (4).
1. Alloy, L.B., **Nusslock, R.**, & Boland, E.M. (2015). The development and course of bipolar spectrum disorders: An integrated reward and circadian rhythm dysregulation model. *Annual Review of Clinical Psychology*, 11, 213-250. PMCID: PMC4380533
2. Levenson, J.C., **Nusslock, R.**, & Frank, E. (2013). Life events, sleep disturbances, and mania: An integrated model. *Clinical Psychology: Science and Practice*, 20, 195-210.
3. Pornpattananangkul, N., Hu, X., & **Nusslock, R.** (2016). Threat/reward-sensitivity and hypomanic personality modulate cognitive-control and attentional neural processes to emotional stimuli. *Social, Cognitive, and Affective Neuroscience*, 11, 1525-1536. PMCID: PMC4631148.
4. Pornpattananangkul, N., Grogans, S., Yu, R., & **Nusslock, R.** (2019). Single-trial EEG dissociates motivation and conflict processes during decision-making under risk. *Neuroimage*, 188, 483-501. PMCID: PMC5110616.

Complete List of Recent Published Work in MyBibliography:

<https://www.ncbi.nlm.nih.gov/sites/myncbi/107aphbpu97QV/bibliography/51525852/public>

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

Ongoing Research Support

Independent Investigator Award	Nusslock, R. (PI)	01/15/19 – 01/14/21
Ryan Licht Sang Bipolar Foundation & Chauncey and Marion D. McCormick Family Foundation		
<i>Reward-Related Brain Function and Inflammatory Signaling in Bipolar Disorder.</i>		
The goal of this project is to examine the relationship between reward-related brain function and peripheral inflammatory signaling in generating risk for bipolar disorder onset.		
Role: Principal Investigator		
R01MH100117	Nusslock, R. (PI)	02/01/14 – 01/31/20
NIMH		
Symptom Dimensions of Threat- and Reward-Related Neurocircuitry		
This grant examines the commonalities and differences in threat and reward-related neural circuitry underlying the hierarchical structure of depressive and anxiety symptoms.		
Role: Principal Investigator		

Completed Research Support

R21MH110374	Mittal, V. (PI)	04/01/17 – 03/31/19
NIMH		
Neural Habituation in Ultra High-Risk Youth		
This grant examines the relationship between neural habituation, defined as a decrease in neural response to repeated visual stimuli, and social processing deficits in youth at risk for psychosis.		
Role: Co-Investigator		
R01MH077908-06	Alloy, L.B. (PI)	07/05/13 – 04/30/19
NIMH		
Risk for Bipolar Disorder: Reward-Related Brain Function & Social Rhythms		
The major goal of this project is to use a biobehavioral high-risk design to examine two interrelated processes: 1) heightened activation of a fronto-striatal “reward-related” neural network involving the ventral striatum and orbitofrontal cortex (measured by fMRI); and 2) influences of reward sensitivity and activation (measured by multiple indices) on social rhythm dysregulation.		
Role: Co-Investigator and P.I. of Northwestern Subcontract		
Independent Investigator Award	Nusslock, R. (PI)	08/01/14 – 07/31/19
Ryan Licht Sang Bipolar Foundation & Chauncey and Marion D. McCormick Family Foundation		
Multi-Modal Investigation of Reward-Related Brain Function and Bipolar Disorder Symptoms		
The major goal of this project is to examine the relationship between indices of structural connectivity (diffusion tensor imaging) and functional connectivity in the cortico-striatal reward circuit.		
Role: Principal Investigator		
Young Investigator Award	Nusslock, R. (PI)	09/01/13 – 08/31/15
Ryan Licht Sang Bipolar Foundation		
Reward-Related Brain Activity in Bipolar Disorder and Depression: A Quest for the Test		
The major goal of this project is to examine reward-related brain function as biomarker of differential risk for bipolar disorder versus unipolar depression.		
Role: Principal Investigator		

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: Thomas M. Olino

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

POSITION TITLE: Associate Professor 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
Queens College – CUNY, Queens, NY		1998	
Cornell University, Ithaca, NY	B.S.	1999-2002	Human Development
Stony Brook University, Stony Brook, NY	M.A.	2002-2003	Psychology
Stony Brook University, Stony Brook, NY	Ph.D.	2002-2008	Clinical Psychology; Minor: Quantitative Methods
Western Psychiatric Institute and Clinic, Pittsburgh, PA	Intern	2007-2008	Clinical Psychology
University of Pittsburgh	Post-doc	2008-2010	Clinical Psychology/ Affective Neuroscience

A. Personal Statement

The goal of the proposed study is to investigate bidirectional associations between the reward and immune systems and their joint prediction of the emergence of major depression during adolescence. As Co-I, I will be involved in the design, collection, analysis, and interpretation of results from the project, particularly, the multimodal assessment of reward functioning component of the study, as well as serve as the PhD level biostatistician on the project. My research interests lie in the developmental trajectories that lead youth towards developing unipolar depression. In particular, I am interested in the role of abnormal trajectories of reward-related brain functioning and approach motivational systems as risk factors for depression. I have investigated risk for first onset of depression in young children, adolescents, and adults. My graduate training was completed under the mentorship of Dr. Daniel Klein when I worked on the original pilot study of preschool temperament and the follow-up, larger study. Across both studies, there has been supportive evidence for positive emotionality and approach motivational systems being involved in risk for depression. I was supported by K01 MH092603 to examine neural substrates of this appetitive motivational disturbance observed in youth at high-risk for depression by virtue of having a mother with a history of chronic and/or recurrent major depression. Moreover, I am currently the PI of a research grant (R01 MH107495; Developmental changes in reward responsiveness: Associations with depression risk markers) that examines developmental processes leading to depression in adolescence. In addition, I am the recipient of a NARSAD Independent Investigator Award that is supporting the collection of blood to permit assays of immune function. Thus, my research interests and expertise dovetail well with the goals of this proposal. Since arriving at Temple, Dr. Alloy and I have been Co-Is on several of each other's R01 grants and we have successfully collaborated on multiple projects.

In addition to a strong coherence between the substantive questions raised in this proposal and my ongoing interests, I also have extensive expertise in the data analytic methods that are optimal for examining the questions raised in this proposal. My doctoral training included a comprehensive minor in Quantitative Psychology, and I pursued additional training in sophisticated quantitative data analysis using latent variable and multilevel models. These methods have been used in over half of my 143 publications. In addition to my publishing record using advanced statistical methods, I have multiple experiences in training others in the use of latent variable models. I regularly teach doctoral level courses in multivariate statistics, structural equation modeling, and hierarchical linear modeling at Temple, and I also have taught workshops in latent variable

modeling four times. Moreover, I have served as the PhD level biostatistician in either a Co-I or Consultant role on other funded NIH grants (R01 MH069942; PI: Klein; R15 MH106885; PI: Bufferd; R01 MH104418; PI: Forbes; R01 MH112545; PI: Ellman) and on my own NIMH funded R01 (MH107495). Thus, I will be able to conduct analyses of primary interest to the present proposal, as well as facilitate Dr. Alloy's students having focused learning experiences in the analytic methods employed in this proposal.

B. Positions and Honors

Positions and Employment

2007-2008	Clinical Psychology Intern; Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA; Program Directors: Paul A. Pilkonis, Ph.D., Marsha Marcus, Ph.D., Jill Cyranowski, Ph.D. & Melissa Kalarchian, Ph.D.
2008-2010	Postdoctoral Scholar; Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA; Primary Mentor: Erika E. Forbes, Ph.D.
2010-2013	Assistant Professor; Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA
2013-2018	Adjunct Assistant Professor; Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA
2013-2018	Assistant Professor; Department of Psychology, Temple University, Philadelphia, PA
2018-	Associate Professor; Department of Psychology, Temple University, Philadelphia, PA

Academic and Professional Honors

2008-	SSCPNet Listserv Manager
2010	Western Fellow, University of Western Ontario
2013	Association for Psychological Science <i>Rising Star</i>
2014-2016	Association for Psychological Science Conference Committee, Co-Chair Clinical Track
2016	David Shakow Early Career Award for Contributions to Clinical Psychology, Society of Clinical Psychology, Division 12 of the American Psychological Association
2016	Susan Nolen-Hoeksema Early Career Award from the Society for a Science of Clinical Psychology
2017	Early Career Award from the Society for Research in Psychopathology

C. Contributions to Science

Full bibliography of works are available at:

<http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/41198150/?sort=date&direction=ascending>

Role of positive affect and reward functioning in risk for depression

There is a long history of examining the role of temperamental positive affect in prediction of onset, course, and outcome of depression. However, most of this work is built on self-report methods. My work has emphasized the use of behavioral observations and functional MRI in furthering this line of inquiry. In my work I have shown that there is a complex interplay between youth positive and negative affectivity in relating to parental depression. Yet, in youth with a strong familial loading for depression (i.e., offspring of mothers with childhood onset depression), there are direct influences of maternal depression on attenuated positive affect in offspring that are persistent across childhood. Further, I have reported that offspring of depressed parents demonstrate reduced reward responsiveness to monetary *and* social incentives, beyond the influence of their own experience of depressive symptoms. Each of these findings adds to the literature implicating positive affect and underlying neural correlates in risk for depression.

Olino, T.M., Klein, D.N., Dyson, M.W., Rose, S.A., & Durbin, C.E. (2010). Temperamental emotionality in preschool-aged children and depressive disorders in parents: Associations in a large community sample. *Journal of Abnormal Psychology*, 119, 468-478. PMCID: PMC2989334

Olino, T.M., Lopez-Duran, N., Kovacs, M., George, C., Gentzler, A., & Shaw, D.S. (2011). Developmental trajectories of positive and negative affect in children at high and low familial risk for depressive disorder. *Journal of Child Psychology and Psychiatry*, 52, 792-799. PMCID: PMC3419431

Olino, T.M., McMakin, D.L., Morgan, J.K., Silk, J.S., Birmaher, B., Axelson, D.A., Williamson, D.E., Dahl, R.E., Ryan, N.D., & Forbes, E.E. (2014). Reduced reward anticipation in youth at high-risk for unipolar depression: A preliminary study. *Developmental Cognitive Neuroscience*, 8, 55-64. PMCID: PMC3960320

Olino, T.M., Silk, J.S., Osterriitter, C., & Forbes, E.E. (2015). Social reward in youth at-risk for depression: A preliminary investigation of subjective and neural differences. *Journal of Child and Adolescent Psychopharmacology*, 25, 711-721. PMCID: PMC4653819

Assessment and measurement of positive emotionality in relation to other temperamental traits

Developmental, personality, clinical, and neuroscientific psychologists generally agree that there are between three and five broad organizational domains of functioning. In the developmental, personality, and clinical literatures the understanding of the interrelationships among these factors has relied nearly exclusively on self-reports of adult personality/temperament and parent-reports of youth temperament. My work has extended this work by focusing on observed temperament. My first (ever) publication was the first investigation of the structure of extraversion in children using behavioral observation methods. This study has important implications for conceptualizing the positive valence systems described in the RDoC and helps place the RDoC into a developmental framework. I have also been centrally involved in projects examining the broader collection of temperament traits in young children. Across these studies, we find that there are interrelationships between dimensions of temperament that remain relatively consistent across development.

Olino, T.M., Klein, D.N., Durbin, C.E., Hayden, E.P., & Buckley, M.E. (2005). The structure of extraversion in preschool aged children. *Personality and Individual Differences*, 39, 481-492.

Dyson, M.W., **Olino, T.M.**, Durbin, C.E., Goldsmith, H.H., & Klein, D.N. (2012). The structure of temperament in preschoolers: A two-stage factor analytic approach. *Emotion*, 12, 44-57. PMCID: PMC3526001

Kotelnikova, Y., **Olino, T.M.**, Mackrell, S.V.M., Jordan, P.L., & Hayden, E.P. (2013). Structure of observed temperament in middle childhood. *Journal of Research in Personality*, 47, 524-532. PMCID: PMC3840535

Dyson, M.W., **Olino, T.M.**, Durbin, C.E., Goldsmith, H.H., Bufferd, S.J., Miller, A.R., & Klein, D.N. (2015). The structural and rank-order stability of temperament in young children based on a laboratory-observational measure. *Psychological Assessment*, 27, 1388-1401. PMCID: PMC4615267

Longitudinal relationships between depression and anxiety

Depression and anxiety are highly comorbid conditions. Conceptual models were developed (e.g., tripartite model) and tested in cross-sectional studies, which demonstrated validity of these hypotheses. Yet, only recently have investigations of the relationships between these disorders been examined in longitudinal studies. I presented one of the first longitudinal structural models of the relationships between depression and anxiety and found that the structure was best defined by a general internalizing factor and independent anxiety and depression factors. However, in follow-up examinations, I relied on mixture models (i.e., latent class; growth mixture models) to investigate whether there are different patterns of depression and anxiety across time. These studies, which relied on very different samples and assessment strategies, yielded surprisingly similar results. Results of these studies also highlighted specificity of course, such that offspring with greater familial loading for depression had more chronic courses of depression, whereas offspring with greater familial loading for anxiety had more chronic courses of anxiety. Collectively, these results provide greater understanding of the complex relationships of depression and anxiety over an extended period of development.

Olino, T.M., Klein, D.N., Lewinsohn, P.M., Rohde, P., & Seeley, J.R. (2008). Longitudinal associations between depressive and anxiety disorders: A comparison of two trait models. *Psychological Medicine*, 38, 353-363. PMCID: PMC2771643

Olino, T.M., Klein, D.N., Lewinsohn, P.M., Rohde, P., & Seeley, J.R. (2010). Latent trajectory classes of depressive and anxiety disorders: Descriptions of classes and associations with risk factors. *Comprehensive Psychiatry*, 51, 224-235. PMCID: PMC2857532

Olino, T.M., Stepp, S.D., Keenan, K., Loeber, R., & Hipwell, A. (2014). Trajectories of symptoms of depression and anxiety in adolescent girls: A comparison of parallel trajectory approaches. *Journal of Personality Assessment*, 96, 316-326. PMCID: PMC4225067

Hamilton, J.L., Potter, C.M., **Olino, T.M.**, Abramson, L.Y., Heimberg, R.G., & Alloy, L.B. (2016). The temporal sequence of social anxiety and depressive symptoms following interpersonal stressors during adolescence. *Journal of Abnormal Child Psychology*, 44, 495-509. PMCID: in progress.

Assessment of internalizing symptoms in youth

Many of the instruments developed to assess internalizing problems in youth rely on classical test theory to evaluate their reliability. However, application of modern psychometric methods (e.g., item response theory [IRT], longitudinal confirmatory factor analysis) can provide further guidance for how to best assess these

symptoms in youth and how measurement of these symptoms may change over the course of development. I was the first to apply IRT linking methods to items from multiple measures of depressive symptomatology. In two separate studies, I demonstrated that we can match instruments to research and clinical areas based on how items from distinct instruments better assess information at low versus high symptom trait levels. Further, we also examined whether symptoms of anxiety and depression are uniformly assessed across adolescence. This investigation found that, indeed, the items functioned similarly across development; thus, scale scores are comparable across the ages sampled. However, if items functioned differently, it would not have been possible to determine whether the observed changes in symptoms were due to development or psychometric functioning. Collectively, this work highlights the need to assess symptom functioning using modern methods to better evaluate instruments.

Klein, D.N., Dougherty, L.R., & **Olino, T.M.** (2005). Toward guidelines for evidence-based assessment of depression in children and adolescents. *Journal of Clinical Child and Adolescent Psychology*, 34, 412-432.

Olino, T.M., Yu, L., Klein, D.N., Rohde, P., Seeley, J.R., Pilkonis, P.A. & Lewinsohn, P.M. (2012). Measuring depression using item response theory: An examination of three measures of depressive symptomatology. *International Journal of Methods in Psychiatric Research*, 21, 76-85. PMCID: PMC3302969

Mathyssek, C.M., **Olino, T.M.**, Hartman, C.A., Ormel, J., Verhulst, F.C., & van Oort, F.V.A. (2013). Does the Revised Child Anxiety and Depression Scale (RCADS) measure anxiety symptoms consistently across adolescence? The TRAILS study. *International Journal of Methods in Psychiatric Research*, 22, 27-35. PMCID: PMC3801212

Olino, T.M., Yu, L., McMakin, D.L., Forbes, E.E., Seeley, J.R., Lewinsohn, P.M., & Pilkonis, P.A. (2013). Comparisons across depression assessment instruments in adolescence and young adulthood: An IRT study using two linking methods. *Journal of Abnormal Child Psychology*, 41, 1267-1277. PMCID: PMC3795839

Longitudinal prediction of psychopathology course from brain function

I have had central roles in examinations of predicting change in depression and BMI in diverse samples. This work has found that reward-related brain function predicts depressive symptoms across a two-year period in a naturalistic follow-up study; reward-related brain function predicts depressive symptoms across a naturalistic treatment study; and resting state functional connectivity is associated with acute weight change in behavior weight loss treatment.

Forbes, E.E., **Olino, T.M.**, Ryan, N.D., Birmaher, B., Axelson, D., Moyles, D.L., Ronan, K.A., & Dahl, R.E. (2010). Reward-related brain function as a predictor of improvement with treatment in adolescents with major depressive disorder. *Cognitive, Affective, and Behavioral Neuroscience*, 10, 107-118. PMCID: PMC2841787

Morgan, J.K., **Olino, T.M.**, McMakin, D.L., Ryan, N.D., Forbes, E.E. (2013). Neural response to reward as a predictor of rise in depressive symptoms in adolescence. *Neurobiology of Disease*, 52, 66-74. PMCID: PMC3430834

Chen, E.Y., **Olino, T.M.**, Conklin, C.J., Mohamed, F.B., Hoge, W.S., Foster, G.D., & the Genetic and Neural Biomarkers of Obesity (GN-BO) study group. (2017). Genetic and neural predictors of behavioral weight loss treatment: A preliminary study. *Obesity*, 25, 66-75. PMCID: PMC5381816

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

Ongoing Research Support

R01 MH118545-01A1 Ellman (PI) 07/01/19-06/30/24

NIH/NIMH

Maternal Inflammation During Pregnancy: Clinical and Neurocognitive Outcomes in Adult Offspring

To investigate how maternal inflammation during pregnancy contributes to clinical, neurocognitive, and neural outcomes among late middle-aged offspring.

R01 AA024433-01 Hicks/Heitzeg (MPI) 07/01/17-06/30/22

NIH/NIAAA

Developmental and peer effects on the neurobiology of cognitive control and reward processes

The goal is to examine the role of development and sensitivity to peer context as factors in adolescent alcohol use disorders.

Role: Co-I

R01MH112613 NIH/NIMH	Ellman (PI)	09/01/17-08/31/22
1/3-Community psychosis risk screening: An instrument development study This collaborative, multi-site proposal aims to develop a valid psychosis-risk screening tool using non-clinical samples across 3 large, diverse, US catchment areas.		
Role: Co-I		
R01 MH107495 NIH/NIMH	Olino (PI)	04/01/16-01/31/21
Developmental changes in reward responsiveness: Associations with depression risk markers The goal of this study is to examine predictors and outcomes of developmental trajectories in reward responsiveness in adolescence.		
Role: PI		
23UB-9452 CBCRP	Cohn (PI)	12/01/17-11/30/20
“Linking neighborhood and individual ACEs to breast cancer” This project aims to investigate whether neighborhood segregation in childhood is an independent predictor of risk for breast cancer.		
Completed Support		
K01 MH092603 Reward-related Brain Functioning as an Endophenotype for Depression	Olino (PI)	12/01/10-11/30/15
The goal of this study is to examine differences between youth at high- and low-familial risk for depression on neural indices of appetitive motivation.		
Role: PI		
Independent Investigator Award NARSAD	Olino (PI)	09/01/17-08/31/19
Blood biomarkers and developmental changes in reward responsivity This study examines markers of inflammation of mechanisms linking experience of stressful life events to developmental changes in reward function in adolescence.		
Role: PI		
R01 MH101168 NIH/NIMH	Alloy (PI)	07/01/13 – 03/31/19
Risk for Adolescent Depression: Stress, Cognitive Vulnerability, & Inflammation The major goal of this project is to determine the role of proinflammatory states in combination with cognitive vulnerabilities, stress, and childhood adversity in contributing to high rates of depression among a large urban sample of adolescents, just reaching the critical age when the increase in depression should begin.		
Role: Co-I		
R01 MH102310 NIH/NIMH	Alloy (PI)	12/09/13 – 11/30/18
Social and Circadian Rhythms, Reward Sensitivity, and Risk for Bipolar Disorder The major goal of this project is to use a biobehavioral high-risk design to examine bidirectional influences of reward sensitivity and social and circadian rhythm disruption as risk factors for bipolar spectrum disorder mood symptoms and episodes.		
Role: Co-I		

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: Chein, Jason

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

POSITION TITLE: Professor of Psychology, Temple University

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
Temple University	B.A.	05/1997	Psychology, Comp. Sci.
University of Pittsburgh	M.S.	05/2001	Cognitive Psychology
University of Pittsburgh	Ph.D.	04/2004	Cognitive Neuroscience
Princeton University	Postdoc	01/2006	Cognitive Neuroscience

A. Personal Statement

The goal of this study is to investigate the independent and potentially synergistic involvement of reward function and inflammatory signaling as determinants of risk for the development of 1st onset of major depression in adolescence, using a prospective longitudinal design that includes MRI-based measures. I am a cognitive neuroscientist with over 20 years of experience conducting neuroimaging research with a focus on working memory and cognitive control. Over the last 15 years I have added a substantial developmental component to my work, and have been exploring the development of reward function and control, and the neural circuits that undergird these processes as they mature from adolescence into young adulthood. The key reward-related psychological constructs and procedures described in the present proposal parallel those used in my ongoing, grant funded, research investigating the behavioral and neural correlates of age-related differences in reward processing and decision-making. As the recently appointed Director of the Temple University Brain Research & Imaging Center (TUBRIC), in which the proposed neuroimaging studies will be enacted, I am also in a position to facilitate logistical aspects of the proposal. In sum, I have a wealth of experience with many of the techniques, tasks, and constructs that are a focus of the present proposal, have experience conducting research in closely related populations, and will be positioned to support the execution of the proposed project. Moreover, I recently served as a Co-I on one of Dr. Alloy's NIMH R01 grants (MH077908), and thus, we have already collaborated on research investigating reward-related brain function. As a consultant on this project, I will be involved in the design, planning, and execution of the neuroimaging components of the project, and will contribute to interpretation of the experimental findings.

B. Positions and Honors**Positions**

- 2002 Adjunct Faculty Member, Department of Biology, Chatham College
- 2004-06 Postdoctoral Fellow, Princeton University, Princeton, NJ
- 2006-10 Collaborating Researcher, Princeton University Neuroimaging Institute
- 2006-12 Assistant Professor, Temple University, Dept. of Psychology
- 2012-18 Associate Professor, Temple University, Dept. of Psychology
- 2015- Director, Temple University Brain Research & Imaging Center
- 2018- Professor, Temple University, Dept. of Psychology

Selected Honors

- | | |
|---------|--|
| 1997 | College of Arts & Sciences Graduation Ceremony Speaker (Temple University) |
| 1997 | President's Scholar (Temple University) |
| 1997 | Phi Beta Kappa National Honor Society |
| 1997 | General Alumni Award For Academic Achievement (Temple University) |
| 1998 | Center for the Neural Basis of Cognition Fellowship (National Science Foundation) |
| 1998 | National Science Foundation Graduate Student Fellowship, Honorable Mention |
| 2001 | Tim Post Award for Research Excellence (University of Pittsburgh) |
| 2001 | Temple University Alumni Gallery of Success (Temple University) |
| 2013-16 | Network Scholar of the MacArthur Foundation Research Network on Law & Neuroscience |
| 2014 | Lindback Award for Distinguished Teaching |

C. Contributions to Science

Complete List of Published Work May Be Reviewed at:

[http://www.ncbi.nlm.nih.gov/pubmed/?term=\(Chein+J%5BAuthor%5D+OR+Chein+JM%5BAuthor%5D\)](http://www.ncbi.nlm.nih.gov/pubmed/?term=(Chein+J%5BAuthor%5D+OR+Chein+JM%5BAuthor%5D))

(Note: * denotes a current or former student or fellow under my supervision)

1. Brain Development and Decision Making. As people mature from pre-adolescence into adulthood, the brain systems that support working memory and cognitive control undergo important changes. These changes result in behavioral improvements in the ability to control impulses and to behave in a deliberative, goal-directed manner. Around the time of puberty, brain regions that process emotions and rewards (affective processing) also undergo substantial reorganization, causing changes in the way that emotionally arousing and potentially rewarding events are perceived. A major focus of my research over the last eight years has been to understand how the asynchronous development of cognitive control and affective processing systems impacts the mental calculus of decision making, with a particular focus on how psychosocial context affects the interaction between these systems. Across a series of experiments using behavioral and neuroimaging methods, my colleagues and I have demonstrated that adolescents take more risks, and are more reward seeking, when in the company of their peers, and this phenomenon is specifically linked to the relative engagement of interacting brain networks. The initial neuroimaging study in this series, published in 2011, is among the top 5 most read articles in the journal *Developmental Science*. In follow-up work, my colleagues and I have shown that this phenomenon cannot be explained as the result of explicit or implicit peer pressure, and is even evident in rodents, suggesting that it likely reflects an evolutionarily conserved process through which the presence of age-mates increases appetitive, exploratory, and risky behaviors.

*Sherman, LE; Steinberg, L., & **Chein, JM** (2018). Connecting Brain Responsivity and Real-World Risk-Taking: Strengths and Limitations of Current Methodological Approaches. *Developmental Cognitive Neuroscience*. DOI: 10.1016/j.dcn.2017.05.007

*Smith, A., *Rosenbaum, G., *Botdorf, M., Steinberg, L., & **Chein, J.** (2018). Peers Influence Adolescent Reward Processing, But Not Response Inhibition. *Cognitive Affective Behavioral Neuroscience*, 18(2), 284-295. DOI 10.3758/s13415-018-0569-5

*Botdorf, M., *Rosenbaum, G., *Patrianakos, J., Steinberg, L., & **Chein, J.** (2017). Adolescent Risk-Taking is Predicted by Individual Differences in Cognitive Control over Emotional, but Not Non-Emotional, Response Conflict. *Cognition & Emotion*, 31(5), 972-979.

Chein, J., *Albert, D., *O'Brien, L., *Uckert, K., & Steinberg, L. (2011). Peers increase adolescent risk taking by enhancing activity in the brain's reward circuitry. *Developmental Science*, 14, F1–F10.

2. Links between mobile technology habits, self-regulatory control, and reward. Smartphones and related mobile technologies are recognized as flexible and powerful tools that can augment human cognition, but there is also a growing perception that habitual involvement with these devices may have a negative and lasting impact on users' ability to think, remember, pay attention, and regulate emotion. A current direction for research in my lab is to explore the potential cognitive impacts of smartphone-related habits. Our findings from thus far demonstrate links between patterns of mobile technology use, self-regulatory control, reward and

sensation seeking, and the ability to delay gratification, as well as associations between mobile technology habits and the specific neural pathways that subserve reward and self-regulatory processing. These findings, along with our 2017 review of research on the potential cognitive impacts of mobile technology habits has attracted a very wide readership, and has been featured in a number of media pieces.

*Wilmer, H.H., *Hampton, W., Olino, T., Olson, I., & **Chein, J.M.** (in press) Wired to be connected? Links Between Mobile Technology Engagement, Intertemporal Preference, and Frontostriatal White Matter Connectivity. *Social Cognitive Affective Neuroscience*.

*Wilmer, HH, †Sherman, LE, & **Chein, JM.** (2017). Smartphones and Cognition: A review of research exploring the links between mobile technology habits and cognitive functioning. *Frontiers in Psychology*, 8, 605. DOI: 10.3389/fpsyg.2017.00605

*Wilmer, H. & **Chein, J.** (2016). Mobile Technology Habits – Patterns of Association Among Device Usage, Intertemporal Preference, Impulse Control, and Reward Sensitivity. *Psychonomic Bulletin & Review*, 23(5), 1607-1614.

3. Basic mechanisms of working memory and cognitive control. My earliest contributions to the fields of cognitive psychology and cognitive neuroscience focused on the mental machinery supporting two related constructs: working memory – the mental workspace in which we maintain, update, and manipulate information in the service of ongoing cognitive performance, and cognitive control – the ability to maintain and flexibly update mental representations in the service of goal-directed behavior. I continue to use a combination of convergent and complementary techniques, including traditional behavioral experiments, psychometric (individual differences) methods, and functional magnetic resonance imaging (fMRI), to advance an understanding of these important cognitive capacities, and to adjudicate between alternative theoretical models. I have also conducted influential research on the relationship between working memory and cognitive control, on the involvement of these capacities in the broader landscape of higher-order cognition (e.g., problem solving, decision-making), and on the diminishing recruitment of working memory and cognitive control as one becomes more proficient, and automatic, in executing a task. My work on these topics has been cited over 1500 times.

*Duell, N., *Icenogle, G., *Silva, K., **Chein, J.**, Steinberg, L., Banich, M., et al. (2018). A Cross-Sectional Examination of Response Inhibition and Working Memory on the Stroop Task. *Cognitive Development*. 47, 19-31.

*Morrison, A.M., *Rosenbaum, G.R., Fair, D.A., & **Chein, J.M.** (2016). Variation in Strategy Use Across Measures of Verbal Working Memory. *Memory & Cognition*, 44, 922-936.

*Morrison, A., Conway, A., & **Chein, J.** (2014). Primacy and Recency Effects as Indices of the Focus of Attention. *Frontiers in Neuroscience*, 24(8), 6. doi: 10.3389/fnhum.2014.00006.

Chein, J.M., Moore, A.B., & Conway, A.R.A. (2011). Domain general mechanisms of complex working memory span. *Neuroimage*, 54, 550-559.

4. Training working memory and control to improve cognitive functioning. Over the last decade, I have also been a central participant in a field of research exploring the ability to improve general cognitive functioning by using training to increase the capacity of working memory and the ability to control the focus of one's attention. While prior research had suggested that people tend to improve only on the very specific tasks that they practice, my lab has conducted instrumental research adding weight to the notion that repeated working memory and attention control "workouts" can produce more far reaching, and generalizable, gains. In my lab we have developed novel, theory-driven, techniques for training central cognitive faculties, and have investigated the efficacy and scope of generalization from different forms of training. One of the working memory training procedures that I developed, based on a complex working memory span task, has become one of the major training paradigms in the field. In 2011, my student and I published a highly influential review of the literature on working memory training, which has already been cited nearly 250 times.

*Rosenbaum, G., *Botdorf, MA., Steinberg, L., & **Chein, JM.** (2017). Working Memory Training in Adolescents Decreases Laboratory Risk Taking in the Presence of Peers. *Journal of Cognitive Enhancement. Enhancement*, 1(4), 513-535.

*Richmond, L., Wolk, D., **Chein, J.**, Olson, I. (2014). Transcranial Direct Current Stimulation (tDCS) Enhances Verbal Working Memory Performance Over Time and Near Transfer Outcomes. *Journal of Cognitive Neuroscience*, 26(11), 2443–2454.

*Morrison, A.B. & **Chein, J.M.** (2011). Does working memory training work? The promise and challenges of enhancing cognition by training working memory. *Psychonomic Bulletin & Review*, 18(1), 46-60.

Chein, J.M. & *Morrison, A.B. (2010). Expanding the mind's workspace: Training and transfer effects with a complex working memory span task. *Psychonomic Bulletin & Review*, 17(2), 193-199.

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

Ongoing Support

TU OVPR Targeted Grant Program **Chein** **03/1/18-02/28/20**

Individual and age difference in the D-E gap

This study investigates how information acquired through description (instruction) and experience produce disparate neural and behavioral decision outcomes across development from pre-adolescence into young adulthood.

Role: Co-Principal Investigator

R01MH107495-01 **Olino (PI)** **04/01/16-01/31/21**

Improving Adolescent Decision Making Through Cognitive Control Training (NIDA)

This study examines the impact of cognitive control training on adolescents' ability to resist peer influence on risky decision-making.

Role: Co-Investigator

R01AA024433 **Hicks (PI)** **07/01/17-6/30/22**

Developmental and peer effects on the neurobiology of cognitive control and reward processes

This study explores reward and control processing in adolescents who are at risk for the development of alcohol use disorders.

Role: Co-Investigator

R03DA046733 **Smith (PI)** **05/01/19 – 04/30/20**

Aberrant Reward Sensitivity: Mechanisms Underlying Substance Use

Study examines the disruption of reward system processes as a predictor of substance use

Role: Co-Investigator

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS*: 0571231920000

Budget Type*: ● Project ○ Subaward/Consortium**Enter name of Organization:** Temple University - Of The Commonwealth System of

Start Date*: 07-01-2020

End Date*: 06-30-2021

Budget Period: 1

A. Senior/Key Person												
	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . DR	LAUREN	B	ALLOY		PD/PI	192,300.00		1.53	1.5	48,556.00	8,199.00	56,755.00
2 . DR.	LAUREN	M	ELLMAN		Co-Investigator	192,300.00			0.5	8,013.00	649.00	8,662.00
3 .	THOMAS		OLINO		Co-Investigator	121,675.00			1	10,140.00	821.00	10,961.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:										Total Senior/Key Person		76,378.00

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
1	Graduate Students	12			27,109.00	6,641.00	33,750.00
	Undergraduate Students						
	Secretarial/Clerical						
3	Research Assistants	8.4			67,731.00	5,486.00	73,217.00
1	Data Manager	6			27,522.00	7,018.00	34,540.00
1	Program Manager	6			26,423.00	6,738.00	33,161.00
1	Project Coordinator	6			16,733.00	4,267.00	21,000.00
7	Total Number Other Personnel					Total Other Personnel	195,668.00
					Total Salary, Wages and Fringe Benefits (A+B)		272,046.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1**ORGANIZATIONAL DUNS*:** 0571231920000**Budget Type*:** Project Subaward/Consortium**Organization:** Temple University - Of The Commonwealth System of**Start Date*:** 07-01-2020**End Date*:** 06-30-2021**Budget Period:** 1**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item**Funds Requested (\$)*****Total funds requested for all equipment listed in the attached file****Total Equipment****Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)***

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

3,000.00

2. Foreign Travel Costs

Total Travel Cost**3,000.00****E. Participant/Trainee Support Costs****Funds Requested (\$)***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees**Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1**ORGANIZATIONAL DUNS*:** 0571231920000**Budget Type*:** ● Project ○ Subaward/Consortium**Organization:** Temple University - Of The Commonwealth System of**Start Date*:** 07-01-2020**End Date*:** 06-30-2021**Budget Period:** 1

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	41,700.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	63,683.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Other Costs	67,705.00
9 . Tuition	2,522.00
10 . Non-MTDC	72,717.00
Total Other Direct Costs	248,327.00

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	523,373.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	58.5	409,451.00	239,529.00
Cognizant Federal Agency				239,529.00
DHHS, Ernest Kinneer, (214) 767-3261 (Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	762,902.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	762,902.00

L. Budget Justification*	File Name: Budget Justification.pdf (Only attach one file.)
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RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS*: 0571231920000

Budget Type*: ● Project ○ Subaward/Consortium**Enter name of Organization:** Temple University - Of The Commonwealth System of

Start Date*: 07-01-2021

End Date*: 06-30-2022

Budget Period: 2

A. Senior/Key Person												
	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . DR	LAUREN	B	ALLOY		PD/PI	192,300.00		1.53	1.5	48,556.00	8,199.00	56,755.00
2 . DR.	LAUREN	M	ELLMAN		Co-Investigator	192,300.00			0.5	8,013.00	649.00	8,662.00
3 .	THOMAS		OLINO		Co-Investigator	121,675.00			1	10,140.00	821.00	10,961.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:										Total Senior/Key Person		76,378.00

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
1	Graduate Students	12			27,109.00	6,641.00	33,750.00
	Undergraduate Students						
	Secretarial/Clerical						
3	Research Assistants	8.4			67,731.00	5,486.00	73,217.00
1	Data Manager	6			27,522.00	7,018.00	34,540.00
1	Program Manager	6			26,423.00	6,738.00	33,161.00
1	Project Coordinator	6			16,733.00	4,267.00	21,000.00
7	Total Number Other Personnel					Total Other Personnel	195,668.00
					Total Salary, Wages and Fringe Benefits (A+B)		272,046.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2**ORGANIZATIONAL DUNS*:** 0571231920000**Budget Type*:** Project Subaward/Consortium**Organization:** Temple University - Of The Commonwealth System of**Start Date*:** 07-01-2021**End Date*:** 06-30-2022**Budget Period:** 2**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
Total funds requested for all equipment listed in the attached file	<hr/>
	Total Equipment

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*	
3,000.00	
<hr/>	
Total Travel Cost	3,000.00

E. Participant/Trainee Support Costs

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other:

Number of Participants/Trainees	Total Participant Trainee Support Costs
	<hr/>

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2**ORGANIZATIONAL DUNS*:** 0571231920000**Budget Type*:** ● Project ○ Subaward/Consortium**Organization:** Temple University - Of The Commonwealth System of**Start Date*:** 07-01-2021**End Date*:** 06-30-2022**Budget Period:** 2

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	13,550.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	95,459.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Other Costs	92,146.00
9 . Tuition	2,522.00
10 . Non-MTDC	56,314.00
Total Other Direct Costs	259,991.00

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	535,037.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	58.5	380,742.00	222,734.00
Cognizant Federal Agency				222,734.00
DHHS, Ernest Kinneer, (214) 767-3261 (Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	757,771.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	757,771.00

L. Budget Justification*	File Name: Budget Justification.pdf (Only attach one file.)
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RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS*: 0571231920000

Budget Type*: ● Project ○ Subaward/Consortium**Enter name of Organization:** Temple University - Of The Commonwealth System of

Start Date*: 07-01-2022

End Date*: 06-30-2023

Budget Period: 3

A. Senior/Key Person												
	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . DR	LAUREN	B	ALLOY		PD/PI	192,300.00		1.53	1.5	48,556.00	8,199.00	56,755.00
2 . DR.	LAUREN	M	ELLMAN		Co-Investigator	192,300.00			0.5	8,013.00	649.00	8,662.00
3 .	THOMAS		OLINO		Co-Investigator	121,675.00			1	10,140.00	821.00	10,961.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:										Total Senior/Key Person		76,378.00

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
1	Graduate Students	12			27,109.00	6,641.00	33,750.00
	Undergraduate Students						
	Secretarial/Clerical						
3	Research Assistants	8.4			67,731.00	5,486.00	73,217.00
1	Data Manager	6			27,522.00	7,018.00	34,540.00
1	Program Manager	6			26,423.00	6,738.00	33,161.00
1	Project Coordinator	6			16,733.00	4,267.00	21,000.00
7	Total Number Other Personnel					Total Other Personnel	195,668.00
					Total Salary, Wages and Fringe Benefits (A+B)		272,046.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3**ORGANIZATIONAL DUNS*:** 0571231920000**Budget Type*:** Project Subaward/Consortium**Organization:** Temple University - Of The Commonwealth System of**Start Date*:** 07-01-2022**End Date*:** 06-30-2023**Budget Period:** 3**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item**Funds Requested (\$)*****Total funds requested for all equipment listed in the attached file****Total Equipment****Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)***

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

3,000.00

2. Foreign Travel Costs

Total Travel Cost**3,000.00****E. Participant/Trainee Support Costs****Funds Requested (\$)***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees**Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3**ORGANIZATIONAL DUNS*:** 0571231920000**Budget Type*:** ● Project ○ Subaward/Consortium**Organization:** Temple University - Of The Commonwealth System of**Start Date*:** 07-01-2022**End Date*:** 06-30-2023**Budget Period:** 3

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	22,250.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	95,459.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Other Costs	120,151.00
9 . Tuition	2,522.00
10 . Non-MTDC	19,609.00
Total Other Direct Costs	259,991.00

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	535,037.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	58.5	417,447.00	244,206.00
Cognizant Federal Agency				244,206.00
DHHS, Ernest Kinneer, (214) 767-3261 (Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	779,243.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	779,243.00

L. Budget Justification*	File Name: Budget Justification.pdf (Only attach one file.)
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RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

ORGANIZATIONAL DUNS*: 0571231920000

Budget Type*: ● Project ○ Subaward/Consortium**Enter name of Organization:** Temple University - Of The Commonwealth System of

Start Date*: 07-01-2023

End Date*: 06-30-2024

Budget Period: 4

A. Senior/Key Person												
	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . DR	LAUREN	B	ALLOY		PD/PI	192,300.00		1.53	1.5	48,556.00	8,199.00	56,755.00
2 . DR.	LAUREN	M	ELLMAN		Co-Investigator	192,300.00			0.5	8,013.00	649.00	8,662.00
3 .	THOMAS		OLINO		Co-Investigator	121,675.00			1	10,140.00	821.00	10,961.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:										Total Senior/Key Person		76,378.00

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
1	Graduate Students	12			27,109.00	6,641.00	33,750.00
	Undergraduate Students						
	Secretarial/Clerical						
3	Research Assistants	8.4			67,731.00	5,486.00	73,217.00
1	Data Manager	6			27,522.00	7,018.00	34,540.00
1	Program Manager	6			26,423.00	6,738.00	33,161.00
1	Project Coordinator	6			16,733.00	4,267.00	21,000.00
7	Total Number Other Personnel					Total Other Personnel	195,668.00
					Total Salary, Wages and Fringe Benefits (A+B)		272,046.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4**ORGANIZATIONAL DUNS*:** 0571231920000**Budget Type*:** Project Subaward/Consortium**Organization:** Temple University - Of The Commonwealth System of**Start Date*:** 07-01-2023**End Date*:** 06-30-2024**Budget Period:** 4**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item**Funds Requested (\$)*****Total funds requested for all equipment listed in the attached file****Total Equipment****Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)***

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

3,000.00

2. Foreign Travel Costs

Total Travel Cost**3,000.00****E. Participant/Trainee Support Costs****Funds Requested (\$)***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees**Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4**ORGANIZATIONAL DUNS*:** 0571231920000**Budget Type*:** ● Project ○ Subaward/Consortium**Organization:** Temple University - Of The Commonwealth System of**Start Date*:** 07-01-2023**End Date*:** 06-30-2024**Budget Period:** 4

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	15,650.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	95,459.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Other Costs	56,835.00
9 . Tuition	2,522.00
10 . Non-MTDC	89,525.00
Total Other Direct Costs	259,991.00

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	535,037.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	58.5	347,531.00	203,306.00
Cognizant Federal Agency				203,306.00
DHHS, Ernest Kinneer, (214) 767-3261 (Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	738,343.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	738,343.00

L. Budget Justification*	File Name: Budget Justification.pdf (Only attach one file.)
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RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

ORGANIZATIONAL DUNS*: 0571231920000

Budget Type*: ● Project ○ Subaward/Consortium**Enter name of Organization:** Temple University - Of The Commonwealth System of

Start Date*: 07-01-2024

End Date*: 06-30-2025

Budget Period: 5

A. Senior/Key Person												
	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . DR	LAUREN	B	ALLOY		PD/PI	192,300.00		1.53	1.5	48,556.00	8,199.00	56,755.00
2 . DR.	LAUREN	M	ELLMAN		Co-Investigator	192,300.00			0.5	8,013.00	649.00	8,662.00
3 .	THOMAS		OLINO		Co-Investigator	121,675.00			1	10,140.00	821.00	10,961.00
Total Funds Requested for all Senior Key Persons in the attached file												
Additional Senior Key Persons: File Name:										Total Senior/Key Person		76,378.00

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
1	Graduate Students	12			27,109.00	6,641.00	33,750.00
	Undergraduate Students						
	Secretarial/Clerical						
3	Research Assistants	8.4			67,731.00	5,486.00	73,217.00
1	Data Manager	6			27,522.00	7,018.00	34,540.00
1	Program Manager	6			26,423.00	6,738.00	33,161.00
1	Project Coordinator	6			16,733.00	4,267.00	21,000.00
7	Total Number Other Personnel					Total Other Personnel	195,668.00
					Total Salary, Wages and Fringe Benefits (A+B)		272,046.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5**ORGANIZATIONAL DUNS*:** 0571231920000**Budget Type*:** Project Subaward/Consortium**Organization:** Temple University - Of The Commonwealth System of**Start Date*:** 07-01-2024**End Date*:** 06-30-2025**Budget Period:** 5**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
Total funds requested for all equipment listed in the attached file	<hr/>
	Total Equipment

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*
3,000.00
<hr/>
Total Travel Cost

E. Participant/Trainee Support Costs

Funds Requested (\$)*
1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other:
Number of Participants/Trainees
Total Participant Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5**ORGANIZATIONAL DUNS*:** 0571231920000**Budget Type*:** ● Project ○ Subaward/Consortium**Organization:** Temple University - Of The Commonwealth System of**Start Date*:** 07-01-2024**End Date*:** 06-30-2025**Budget Period:** 5

F. Other Direct Costs	Funds Requested (\$)*
1. Materials and Supplies	7,950.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	104,631.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Other Costs	37,655.00
9 . Tuition	2,522.00
10 . Non-MTDC	110,585.00
Total Other Direct Costs	263,343.00

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	538,389.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	58.5	320,651.00	187,581.00
Cognizant Federal Agency				187,581.00
DHHS, Ernest Kinneer, (214) 767-3261 (Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	725,970.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	725,970.00

L. Budget Justification*	File Name: Budget Justification.pdf (Only attach one file.)
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RESEARCH & RELATED Budget {F-K} (Funds Requested)

BUDGET JUSTIFICATION

Data collection for the proposed project will be conducted entirely at Temple University (TU). We are requesting total direct costs of \$2,499,961 for our entire budget period from 07/01/20 to 06/31/25. The total direct costs requested for Year 1, 07/01/20 to 06/31/21 are \$499,996. The F & A cost rate at TU is 58.5% in 2020 and subsequent years of the project.

Please note that in determining whether our yearly direct costs are under \$500,000, we are not including the F & A costs for the subcontract to Northwestern University (NU) in our calculation of our direct costs, as directed in the NIH document located at http://grants.nih.gov/grants/developing_budget.htm

The budget justification for the subcontract to NU appears below after the Personnel section.

SENIOR KEY PERSONNEL:

All salaries and fringe benefits were determined by TU's Personnel Department. Fringe benefit rates for project personnel at TU, with a few exceptions, are 25.5%, including the proportion of MPI Dr. Alloy's academic year salary requested. Part-time personnel (Technical RAs) and Dr. Alloy's summer salary have a fringe benefit rate of 8.1%. The Graduate Student Research Assistant (RA) on a 12-month appointment has a fringe benefit rate of 24.5%. Tuition remission for the advanced Graduate Student RA (only taking 1 credit per semester) is included in our direct costs.

Additional senior key personnel are included under the subcontract to NU.

Personnel salaries do not increase across years of the project, in compliance with NIH Notice NOT-OD-13-064 (<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-13-064.html>).

Multiple Principal Investigator -- Lauren B. Alloy, Ph.D., Laura H. Carnell Professor and Joseph Wolpe Distinguished Faculty in Psychology in the Clinical Psychology Program, TU: 33% (3.0 person-months) effort for the 9-month academic year and 50% (1.5 person-months) effort for 3 summer months for 5 years. Although Dr. Alloy will devote 33% effort to this project during the academic year, we are only requesting 17% (1.53 person-months) salary support in order to keep the total direct costs below \$500,000 per year. Please note that we have already imposed the PHS salary cap of \$192,300 on Dr. Alloy's salary for all 5 years. Dr. Alloy is the Director of the Mood and Cognition Laboratory at TU. She has over 40 years of experience conducting research on mood disorders (both unipolar depression and bipolar spectrum disorders), including multiple NIMH-funded and other externally-funded prospective, longitudinal studies of unipolar depression and bipolar spectrum disorders. These include being PI on two R01 grants studying reward processes in bipolar spectrum disorders (MH077908, MH102310), one R01 grant studying cognitive, emotion regulation, childhood adversity, and psychosocial stress risk factors in combination with inflammation as vulnerabilities to 1st onset of adolescent depression (MH101168), and a study of associations between inflammatory biomarkers and neural reward responsivity in adolescents with unipolar depression or with familial or environmental (child adversity history) risk for unipolar depression (PA CURE grant). Relevant to this grant, Dr. Alloy has specific expertise and an extensive publication record on reward sensitivity in mood disorders and multiple recent publications on inflammation in mood disorders.

Dr. Alloy will be responsible for the overall scientific conduct and administration of the project at TU. She will hire, train, and have ultimate responsibility for supervising all project staff. She will be responsible for coordinating with Dr. Robin Nusslock (MPI at NU), Dr. Lauren Ellman (Co-I at TU), Dr. Gregory Miller (Co-I at NU), Dr. Thomas Olino (Co-I at TU), and conferring with Consultant Dr. Jason Chein (TU). She also will meet regularly with the Senior Staff (Project Coordinator, Program Manager, and Data Manager/Statistician), and with the Research Assistants about diagnostic and life events interviewing, reward and immune assessments, and childhood adversity and inflammation-enhancing behavior assessments, and conduct weekly grant staff meetings (which MPI Nusslock will attend by video conferencing). Dr. Alloy also will implement assessment procedures for the study (with the assistance of MPI Nusslock and Co-Is Ellman, Miller, and Olino), oversee the recruitment and screening procedures, oversee all project assessments, plan procedures for diagnostic and life event interview training and reliability, standardize diagnostic procedures, help with reliability ratings, listen to recordings of diagnostic and life events interviews, and plan data analyses

with the MPI and Co-Is. Finally, Dr. Alloy will share responsibility for all progress reports, publications, and presentations resulting from the project with MPI Nusslock.

Co-Investigator – Lauren Ellman, Ph.D., Associate Professor of Psychology in the Clinical Psychology Program, TU: 17% (0.5 person-month) effort for 3 summer months for 5 years. Please note that we have already imposed the PHS salary cap of \$192,300 on Dr. Ellman's salary for all 5 years. Dr. Ellman will assist MPI Alloy with onsite activities related to inflammation and immune system assessments. She has a long-standing history of examining the roles of stress and immune functioning in the etiologies and courses of serious mental disorders, such as schizophrenia and unipolar depression. In addition to a longstanding research and publication record studying the influences of fetal exposure to maternal stress, prenatal infection, and inflammation in the course of schizophrenia, she recently completed a funded R01 investigating the influences of fetal exposure to maternal inflammation and maternal stress on risk for adolescent depression and has a new R01 on the influence of fetal exposure to maternal inflammation on clinical, neurocognitive, and neural outcomes among late middle-aged offspring, on both of which Dr. Alloy is a Co-I. Moreover, Dr. Ellman was a Co-I on Dr. Alloy's R01 grant (MH101168) on cognitive, emotion regulation, childhood adversity, and psychosocial stress risk factors in combination with inflammation as vulnerabilities to 1st onset of adolescent depression. Thus, Dr. Ellman and MPI Alloy already have a track record of collaborating together successfully and have multiple manuscripts from their R01 grants published and under review as joint authors. Further, Dr. Ellman had extensive training in psychoneuroimmunology (PNI), including during her time as a health psychology doctoral fellow at UCLA, as well as training in PNI from the Cousins Center for Psychoneuroimmunology during her doctoral studies at UCLA. Given her research background and training, she will be able to contribute greatly to the proposed study. She has been directly involved in the writing of this grant application. As Co-I, Dr. Ellman will assist with the design, implementation, analysis, and interpretation of inflammation data, as well as with writing progress reports, publications, and presentations resulting from the project.

Co-Investigator – Thomas Olino, Ph.D., Associate Professor of Psychology in the Clinical Psychology Program, TU: 33% (1.0 person-month) effort for 3 summer months for 5 years. Dr. Olino will serve as the Biostatistician. Dr. Olino's research program and expertise is concerned with diminished anticipation of and responses to rewards (i.e., anhedonia) as a potential marker of risk for unipolar depression. This work is informed through the use of multiple measurement strategies, including self-report, behavioral assessments, and functional MRI methods and he has multiple publications on this topic. Dr. Olino was trained in clinical affective science and quantitative methods during his graduate training at Stony Brook University under the mentorship of Dr. Daniel Klein and in neuroscience and neuroimaging during his postdoctoral fellowship with Dr. Erika Forbes at Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center. He was supported by K01 MH092603 to examine neural substrates of appetitive motivational disturbance observed in youth at high-risk for unipolar depression by virtue of having a mother with a history of chronic and/or recurrent major depression. In addition, he is currently the PI of a research grant (R01 MH107495) that examines developmental changes in reward responsiveness leading to unipolar depression in adolescence. Since arriving at Temple, Drs. Olino and Alloy have been Co-Is on several of each other's R01 grants and have successfully collaborated on multiple projects and publications. These include two grants investigating associations between reward sensitivity and inflammation in risk for unipolar depression. Moreover, Dr. Olino has expertise in the fMRI tasks and methods to be used in the proposed study and in the data analytic methods that are optimal for examining the questions raised in this proposal. He has advanced training in sophisticated quantitative data analysis using latent variable and multilevel models, methods he has used in over half of his publications. In addition, Dr. Olino regularly teaches doctoral level courses in multivariate statistics, structural equation modeling, and hierarchical linear modeling at Temple, and workshops in latent variable modeling. Moreover, he has served as the PhD level biostatistician in either a Co-I or Consultant role on other funded NIH grants (R01 MH069942; PI: Klein; R15 MH106885; PI: Bufferd; R01 MH104418; PI: Forbes; R01 MH112545; PI: Ellman) and his own NIMH funded R01 (MH107495). He has been directly involved in the writing of this grant application. As Co-I, Dr. Olino primarily will be responsible for conducting analyses of primary interest to the present proposal, as well as supervising the Graduate Student RAs in conducting planned secondary data analyses. In addition, Dr. Olino will assist MPI Nusslock with the design, implementation, analysis, and interpretation of data from the fMRI scans. Finally, he will assist with writing progress reports, publications, and presentations from the project.

OTHER PERSONNEL:

Project Coordinator – Angelique Frazier, B.A.: 50% (6 person-months) salary support for 12 months/year is requested for 5 years. Ms. Frazier has served as Project Coordinator in Dr. Alloy's lab for the past 4 years, and was a Research Assistant for another 3 years prior to her promotion to the Project Coordinator position. She has extensive expertise and experience in structured diagnostic interviewing, life event interviewing, research administration, and is a nationally certified phlebotomist with extensive experience in blood collection. She has worked closely with Dr. Alloy on 3 prior NIMH-funded prospective, longitudinal studies of bipolar spectrum disorders and unipolar depression, including MH101168 and a PA CURE grant involving peripheral inflammation measures. Ms. Frazier will have primary responsibility for the day-to-day clinical and research aspects of the project, including screening and recruitment of participants (Ps), scheduling Ps for Time 1 - 5 sessions, the 3 fMRI scans (at T1, T3, T5), the five 1 wk. periods of actigraphy, monitoring of P flow throughout the project and working with Dr. Alloy to minimize P attrition. She also will coordinate sending blood specimens to Co-I Dr. Miller at NU for c-reactive protein (CRP) and cytokine assays and sending fMRI data to MPI Nusslock at NU for preprocessing. She will assist in training and supervising new Technical and Graduate Student RAs on all structured diagnostic and life event interviews. Ms. Frazier will work with Dr. Alloy to develop research materials and appropriate study procedures. Along with Dr. Alloy and Dr. Alloy's postdoctoral fellow, she will provide ongoing individual feedback to the project interviewers (Graduate Student and Technical RAs) to maintain quality control and prevent interviewer drift. Ms. Frazier will help insure the completeness and accuracy of all data collected from Ps. She will do the final checking of all questionnaire, interview, and behavioral task data collected in the study. She will help run the weekly staff meetings. In addition, Ms. Frazier will serve as the major contact person for Ps.

In the Project Coordinator role, Ms. Frazier also will be responsible for the daily coordination of the project. This will include organizing the recruiting advertisements and initial screenings of community high-school freshmen to identify potential Ps, centralizing the scheduling of Time 1 - 5 sessions, the fMRI scans, and the five 1 wk. periods of actigraphy, tracking and contacting Ps who do not meet scheduled appointments, and maintaining and updating the computer-based participant tracking system.

Program Manager – Jeneen Bryant, B.A.: 50% (6 person-months) salary support for 12 months/year is requested for 5 years. Ms. Bryant has served as Program Manager in Dr. Alloy's lab for the past 4 years, and was a Research Assistant for another 4 years prior to her promotion to the Program Manager position. She has extensive expertise and experience in research administration, budgeting and accounting, as well as the specific research methods used in Dr. Alloy's lab. She has worked closely with Dr. Alloy on 3 prior NIMH-funded and 1 other externally-funded prospective, longitudinal studies of unipolar depression and bipolar spectrum disorders, including MH101168 and a PA CURE grant involving peripheral inflammation measures. Ms. Bryant will have primary responsibility for the day-to-day financial and regulatory aspects of the project, including developing and maintaining budgets and accounting records, insuring compliance with all NIMH and TU regulatory requirements, and developing, maintaining, updating, and renewing Institutional Review Board (IRB) protocols and monitoring compliance with IRB regulations. Ms. Bryant also will coordinate all project staff hiring (including advertising, interviewing, hiring, and coordination with TU's Personnel, Hospital and Human Resources departments), project staff salary payments, employee hours/timekeeping, payments to Ps, travel coordination and accommodation for graduate students, postdoctoral fellow and PI, and purchases of equipment, project supplies, and needed services (e.g., cytokine assays).

Data Manager/Statistician – Jasmine Lam, M.A.: 50% (6 person-months) salary support for 12 months/year is requested for Years 1-5. Ms. Lam's M.A. is in psychology and she has expertise and experience in database creation and management, programming, and multivariate statistical analysis techniques (e.g., ANOVA, multiple and logistic regression, structural equation modeling, hierarchical linear modeling, survival analysis). She has served as Data Manager/Statistician in Dr. Alloy's lab for the past 4 years. Ms. Lam has worked closely and collaborated extensively with Dr. Alloy on 3 previous NIMH-funded prospective, longitudinal studies of unipolar depression and bipolar spectrum disorders. She will be responsible for creating, updating, and managing the complex databases and for controlling data coding and entry into the databases. As such, she will train and directly supervise RAs on all data coding and entry, and verification of the accuracy and completeness of data. She will do all computer programming for the study

including for the computers that are used for data entry and data analysis, for the laptop computers for questionnaire, behavioral task, and interview administration to Ps, and for administration of the reward tasks during the fMRI scans. She will monitor the lab's HIPAA secure network and the online questionnaire system. She will be in charge of overall data computer storage, data organization, and back-ups. She also will oversee the initial processing of the actigraphy data. In addition, in consultation with Drs. Alloy and Nusslock and under the supervision of Co-I Dr. Olino (Biostatistician), she will conduct some of the statistical analyses for the project and will produce graphics for publications and presentations of project findings.

Please note that the Project Coordinator, Program Manager, and Data Manager/Statistician positions each have unique responsibilities and are each absolutely essential to the conduct of the project. We have learned from the experience of conducting multiple previous NIMH-funded projects that these three positions are necessary for the successful completion of a complex, prospective longitudinal study of this kind.

Research Assistants/Interviewers: The Graduate Student and Technical RA positions described below are mostly identical. We will need the equivalent of 3 full-time RAs in Years 1 - 5. Our estimates are based on start-up activities, recruitment activities, the initial screenings, phone interview screenings, Time 1 - 5 sessions, including 3 fMRI scans, and the five 1 wk. periods of actigraphy on a sample of 300 Ps.

We are proposing to hire one of the RAs as a full-time (12 person-months, 20 hrs/wk) Graduate Student RA for the following reasons: 1) The TU Psychology department requires faculty members to support Ph.D. graduate students on grants; 2) an advantage of Graduate Student RAs is that they typically have more relevant scientific background, clinical experience, and statistical knowledge than a Technical RA; but 3) given that the Graduate RAs are more expensive; and 4) the Technical RAs have more flexibility in being able to interview and complete other sessions with Ps at times convenient to the Ps as opposed to the Graduate Student RAs who have to work around classes and other responsibilities, we have found that a mixture of Graduate Student and Technical RAs provides the optimal strategy from both scientific and budgetary perspectives.

Technical Research Assistants (Interviewers/Experimenters)-- 3 to be named; 70% (8.4 person-months) salary support for the Technical RAs for 12 months/year for 5 years. The Technical RAs will conduct project interviews (diagnostic, life event, child adversity) and administer all other assessments to Ps (questionnaires, behavioral tasks, fMRI scans, blood draws, actigraphy). They also will be trained as phlebotomists, nationally certified in phlebotomy, and will conduct all blood draws on Ps at Times 1, 3, and 5. In addition, the Technical RAs will process the initial screening data from the BIS/BAS and SPSRQ questionnaires and contact potential Ps and conduct the further phone screening interviews. The Technical RAs will participate in weekly case conferences and staff meetings and will aid in diagnostic decision-making for the study. They also will participate in diagnostic and life event interview reliability check procedures. All Technical RAs will complete our intensive diagnostic and life event interviewer training program. In addition, they will receive extensive oral and written feedback about their interviews from Dr. Alloy, the Project Coordinator, and Dr. Alloy's postdoctoral fellow. They will meet individually with Dr. Alloy, the Project Coordinator, or postdoctoral fellow whenever they have interviewing questions and to receive feedback about interviews. All Technical RAs also will complete extensive training from Drs. Nusslock and Olino on instructing Ps in completing the fMRI procedures and from Dr. Chein on running the fMRI scans at TUBRIC.

Graduate Student Research Assistants -- 1 to be named in Years 1 - 5: 50% time for 12 months/year is requested for Years 1 - 5. Funds are needed for the Graduate Student RA stipend as well as for 2 credits of tuition support for the full-time calendar year advanced Graduate Student RA. The duties of the Graduate Student RA are identical to those of the Technical RAs except that he/she also will aid in training on diagnostic interviewing, conducting data analyses, and writing of project publications and presentations, but generally will not serve as phlebotomists.

In addition to the 50% salary and tuition support for the Graduate Student RA, MPI Alloy will have 2 Ph.D. graduate students (to be named) funded on university fellowships who will make the equivalent of a 50% commitment to assist with data collection, analyses, and manuscript writing during Years 1 – 5 of the project. These 2 graduate student appointments are funded by Temple University fellowships. Data collection for this project is very labor-intensive and the assistance of these two additional Graduate Student RAs, not actually funded on this grant, will insure that we can successfully complete the project. Working on this project

will provide these 2 doctoral students with an outstanding training experience and the opportunity to further their career through collaborations and publications.

SUBCONTRACT COSTS:

Northwestern University (NU)

The subcontract to NU consists of funds to pay 15% (1.35 person-months) of the academic year salary and associated fringe benefits for MPI, Dr. Robin Nusslock, for Years 1-5, 8% (0.71) Year 1 and 7% (0.6 person-months) of the academic year salary and associated fringe benefits for Co-I, Dr. Gregory Miller, for Years 2-5, and one Technical RA at 31.75% effort (3.8 person-months) for Years 2-4 and at 40% effort (4.8 person-months) for Year 5.

Multiple Principal Investigator – Robin Nusslock, Ph.D., Associate Professor of Psychology and AT&T Research Chair, NU: 15% (1.35 person-months) academic year effort for 12 months/year for 5 years. Dr. Nusslock's research program and expertise is in abnormalities in reward processing and reward-related brain function in unipolar and bipolar mood disorders. His publications have examined abnormalities in reward processing in mood disorders using psychosocial, neurophysiological (EEG), and neural (fMRI/DTI) indices. Dr. Nusslock was trained in clinical affective neuroscience and neuroimaging during his graduate training with Dr. Richard Davidson at the University of Wisconsin-Madison and his postdoctoral fellowship with Dr. Mary Phillips at Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center. He also has a 17-year collaboration and many joint publications with MPI Alloy on reward sensitivity in unipolar and bipolar spectrum disorders. In addition, he was Co-I on one of Dr. Alloy's NIMH R01 grants (MH077908) on reward-related brain function in the onset and course of bipolar spectrum disorders, for which he is managing all the MRI data. Thus, he has already established the mechanism for transferring MRI data between Temple and Northwestern University and will employ identical procedures in the proposed research. Dr. Nusslock has multiple publications using one of the proposed fMRI reward paradigms and methods to examine the cortico-striatal reward circuit. He also has considerable experience managing large-scale neuroimaging studies and is currently PI on a multi-site NIMH R01 grant using MRI to examine the relationship between reward-related neural circuitry and mood disorder symptoms (MH100117). As MPI on this proposal, Dr. Nusslock, with the assistance of Co-I Dr. Olino and Consultant Dr. Chein, will assist with the design, implementation, analysis, and interpretation of data from the MRI scans. He will be responsible for preprocessing MRI data, with the assistance of Co-I Dr. Olino, and he will be involved in analyzing MRI data generated from this project. As MPI at Northwestern University, Dr. Nusslock will be responsible for managing personnel and resources and ensuring overall quality control related to the aforementioned data. In addition, he will assist in the preparation of reports and scientific publications with Dr. Alloy, the other MPI.

Co-Investigator – Gregory E. Miller, Ph.D., Louis M. Menk Professor of Psychology, NU: 8% (0.71 person-months) in Year 1 and 7% (0.6 person-months) academic year effort for 12 months/year for Years 2-5. As Co-I, Dr. Miller will be responsible for conducting all immune system assays from blood specimens collected at TU. Dr. Miller is a world leader in the field of behavioral medicine and psychoneuroimmunology. He has particular expertise in the relationship between early life adversity, peripheral inflammation, and risk for mental and physical illness. He has made important contributions to understanding how stress gets under the skin to alter immune functioning in a manner that elevates risk for illness, as well as the effect of intervention programs on inflammatory signaling and stress biology. He runs a laboratory at Northwestern University that is fully equipped to process and analyze systemic and genomic inflammatory signaling, as well as hormonal, and epigenetic data. Moreover, Dr. Miller has published with MPI Nusslock on a neuroimmune network model of the relationship between inflammation and reward/threat-related brain function and risk for mental and physical health. The present proposal reflects an empirical investigation of some of the ideas proposed in this publication. Dr. Miller also has co-authored manuscripts under review with MPI Alloy from one of Dr. Alloy's R01 grants (MH077908). Thus, Dr. Miller already has been collaborating with both MPIs and has made important contributions to the design of the project and the writing of the grant application. As a Co-I, he will a) provide input on the conceptual and mechanistic linkages between early life adversity, inflammatory signaling, and risk for unipolar depression and bipolar disorder, (b) oversee the immunologic assays of systemic inflammation, and (c) actively participate in the analysis and interpretation of neuroimmune data, and co-author manuscripts that result.

Technical Research Assistant – To be named; 31.75% (3.8 person-months) for Years 2-4 and 40% (4.8 person-months) for Year 5 calendar year salary support plus fringe benefits are requested. The Technical RA primarily will assist Dr. Nusslock with the preprocessing and analysis of the fMRI data. He/she also may assist Dr. Miller with conducting the CRP and cytokine assays from the blood specimens. Effort for this Technical RA is increased in Year 5, when all of the fMRI and inflammation data will be collected and there is the highest need for data processing and analysis.

In addition to the 31.75% salary support for an MRI Technical Research Assistant for Years 2-4 and 40% salary support for Year 5 of the proposed research, the Northwestern MPI will have 2 Ph.D. graduate students funded on university fellowships who will make the equivalent of a 50% commitment to assist with MRI data processing and analysis for all 5 years of the proposed research. These 2 graduate student appointments are funded by Northwestern University fellowships and thus guaranteed. Both of these Ph.D. students have extensive experience in functional and structural MRI processing and analysis. For example, Casey Young, one of the Ph.D. students who will be working on the project, served as a post-baccalaureate MRI RA for 5 years at UCLA before starting graduate school. She worked closely with Dr. Susan Bookheimer at UCLA, a leader in the field of cognitive neuroscience, and has first authored papers on the application of graph theory to resting state functional data. The second Ph.D. student who will work on this proposal is Ann Carroll, who served as Dr. Joshua Buckholtz's full-time MRI data analyst at Harvard for 2 years before graduate school. Both Casey and Ann already have experience with the MRI data preprocessing and analysis from Dr. Alloy's previous R01 project with Dr. Nusslock (MH077908). Working on this project will provide Casey and Ann with an outstanding training experience and the opportunity to further their career through collaborations and publications. The 31.75% salary support (40% in Year 5) for the MRI Technical RA combined with Casey and Ann's effort makes us confident in our ability to successfully complete the proposed MRI processing and analysis plan.

EQUIPMENT (Year 1 Only):

Dr. Alloy's lab already has a Thermo Scientific Benchtop Centrifuge Sorvall ST 16R, with 4 x 400mL capacity, RCF 15,200 rpm/25,830 x g maximum speed and 120 V 60 Hz of electrical power and, thus, we do not need to purchase one for this project. In addition, Dr. Alloy's lab also has access to a Thermo Fisher - 80°C freezer with the capacity to hold 300 standard 2" boxes within 14.9 cu.ft., 115V, 60 Hz of electrical power, and 12.6 AMP of rated current for the storage of blood specimens until they are shipped to Co-I Dr. Miller's lab at NU for immunological assays. Thus, no equipment purchases over \$5,000 are included.

TRAVEL (Years 1 – 5):

Travel expenses are needed for the MPIs and Co-Is to attend professional conferences to stay abreast of relevant new scientific developments and to present project findings. Each conference trip is budgeted at \$1,500 and we budgeted for 2 such trips at \$3,000 in Years 1 - 5.

PARTICIPANT/TRAINEE SUPPORT COSTS:

There are no participant/trainee support costs.

OTHER DIRECT COSTS:

MATERIALS and SUPPLIES:

Computers (Years 1 - 5):

Desktop and laptop computers are needed for multiple purposes: 1) to be used directly by Ps in the performance of computerized behavioral tasks and the completion of online research questionnaires when they come to the lab for Time 1 - 5 sessions; 2) for running the reward tasks in the TUBRIC MRI scanner (laptops); 3) for database management, participant tracking throughout the protocol, and data entry; and 4) for data analyses and manuscript, presentation, and progress report preparation. Several of the computers in Dr. Alloy's lab are no longer functional and additional computers fail and become non-functional each year.

Thus, replacements are needed. We will purchase Dell – Standard Optiplex 7450 All-In-One desktops with i7-7700 3.6 GHz, RAM 16 GB, 2.5 inch 512GB SATA Class 20 Solid State Hard Drive and monitors @ \$1,300 for each computer system and the Dell Latitude 5480 laptops with i5-7200U, 2.5Ghz up to 3.1 GHz, RAM 8 GB, M.2 256 GB SATA Class 20 Solid State Hard Drive @ \$1,000 each. We have budgeted for the purchase of 3 new desktop computers in Year 1, 1 in Years 2 – 4, and 2 in Year 5. We budgeted for 2 laptops in Year 1, 0 in Year 2, and 1 in Years 3 - 5. Thus, total computer costs are \$5,900 in Year 1, \$1,300 in Year 2, \$2,300 in Years 3 - 4, and \$3,600 in Year 5.

Printer (Year 1 Only):

A multifunction printer and copier that also includes scanning and fax capabilities is needed for printing and duplicating consent and assent forms, project questionnaires and interviews, rating forms and coding packets, and preparing project reports and presentations. It is also often necessary to scan project materials. We have budgeted for the purchase of a multifunction printer in Year 1 @ \$900.

Computer Software and Supplies (Years 1 - 5):

Supplies are needed for the computer systems and printers: Flashdrives, toner cartridges and printer paper, and for computer software (e.g., statistical packages, database management packages, programming software for online questionnaire administration, software license fees). We have budgeted \$750 in Year 1 when our need is greatest and \$250 in Years 2 - 5 for computer software and supplies.

Actiwatches (Years 1 Only):

Actiwatches are needed to objectively assess Ps' sleep and activity levels continuously throughout 1 week (7 days) at each of the Time 1 – 5 assessment periods. Actigraphy provides an objective, reliable, and valid method for assessing sleep/wake cycles with minimal restriction on Ps' normal routines. We will purchase Spectrum Pro Actiwatches from the Philips Respironics Healthcare Company of Bend, OR. We already have the dock/charger and software needed to download activity data collected from the instrument. Each Actiwatch costs \$960. Given that Dr. Alloy's lab already has some Actiwatches from a previous R01 project (MH102310), we plan to purchase 20 actiwatches in Year 1 only @ \$19,200.

Blood Draw Supplies (Year 1 Only):

Supplies are needed to conduct the blood draws at the Time 1, Time 3, and Time 5 sessions. We are budgeting to purchase all of these needed supplies for the entire project period in Year 1 to take advantage of savings by buying in larger quantities. These supplies include 10 mL vacutainer tubes and blood collection kits (needles), as well as a heating pad to help make veins more accessible, and ammonia inhalants (smelling salts) in case a participant (P) becomes light-headed or faint from a blood draw. The heating pad is \$15 and the ammonia inhalants are \$11. Vacutainer tubes are \$200.28 for a box of 100 and blood collection kits are \$23.24 for a box of 48. Across the project, 300 Ps will each complete 3 blood draws for a total of 900 blood draws. Thus, we have budgeted \$4,826 for these supplies in Year 1.

Blood Draw Site Preparation Supplies (Years 1 Only):

Sterile gloves, sharps containers, tourniquets, alcohol pads, gauze, surgical tape/bandaids, cleaning wipes, and EMLA cream are needed for working with the blood draw kits and for preparing the P's inner arm for venipuncture. Again, we will purchase all of these supplies in Year 1 at \$ 5,394.

Blood Specimen Storage and Shipping Supplies (Years 1 Only):

Funds are needed for storage racks, vacutainer tube holders, and cryogenic labels for labeling and storing the blood specimens. In addition, dry ice and Sarstedt shipping boxes are needed for shipping the blood specimens to Dr. Miller's lab at NU for immunological assays. We have budgeted \$2,610 for these supplies in Year 1.

Nitrogen Tanks (Years 1 – 5):

Four nitrogen tanks @ \$41.09 each are needed each year for the maintaining and backing up the -80°C ultra-cold freezer. Thus, we have budgeted \$820 in Year 1 for the nitrogen tanks.

Food Supplies (Years 1 – 5):

When Ps come to the lab for their scheduled assessments (Time 1 - 5 sessions, including fMRI scans at the Time 1, 3, and 5 sessions), they are interviewed and/or complete questionnaires and tasks for several hours at a time. Thus, we will give Ps short breaks throughout each assessment procedure and we will provide them with snacks (beverages such as bottled water, juice, etc. and food such as fruit, cheese & crackers, chips, cookies, etc.). We believe that the provision of snacks is considerate and shows Ps that we appreciate their time and efforts, and is part of the reason we have been able to maintain a low attrition rate in our prior longitudinal studies (MH077908, MH102310, MH101168). Based on the number of Ps to be run through the various sessions each year, we have budgeted \$1,000 in Year 1, \$2,000 in Years 2 and 4, \$3,000 in Year 3, and \$900 in Year 5 for the purchase of food.

General Supplies (Years 1 – 5):

Basic office and other general supplies (e.g., folders for storing P data, manila envelopes, clips, letterhead stationery, etc.) are also needed during each year of the project. Based on our expenditures for similar previous projects, we have budgeted \$250 in Years 1 – 5 for general supplies.

OTHER EXPENSES:

Consultant:

Consultant - Jason Chein, Ph.D., Professor of Psychology in the Cognition and Neuroscience Program, TU, will contribute his expertise and assistance at no cost to the project. Dr. Chein is Director of the Temple University Brain Research & Imaging Center (TUBRIC). Dr. Chein is a cognitive neuroscientist with more than 20 years of experience examining the development of reward function and control, and the neural circuits that undergird these processes as they mature from adolescence into young adulthood. His ongoing, grant funded, research investigating the behavioral and neural correlates of age-related differences in reward processing and decision-making is directly relevant to the reward-related behavioral and neural constructs and procedures described in the current proposal. Dr. Chein has extensive training in the use of fMRI and employs this technique in combination with traditional behavioral measures to pursue his research. Furthermore, Dr. Chein served as a Co-I on one of Dr. Alloy's NIMH R01 grants (MH077908), and thus, he already collaborates with Dr. Alloy on research investigating reward-related brain function. As a Consultant, Dr. Chein will advise and collaborate on the design, planning, and execution of the neuroimaging components of the project, and will contribute to interpretation of the fMRI findings. He will work closely with MPI Nusslock and his research team on implementing preprocessing and analysis pipelines for both structural and functional MRI data. In addition, as Director of TUBRIC, he will facilitate logistical aspects of the project, including insuring that Ps in this project can be scanned at Times 1, 3, and 5 (each a year apart) at approximately the same time of day. A Biographical Sketch and Letter of Support for Dr. Chein are included in this application.

Phlebotomy Training and Certification (Years 1 and 3):

The 3 Technical RAs will complete a full course in phlebotomy techniques and specimen processing, including a practicum, at one of the local community colleges. This course will qualify them to sit for the standardized national phlebotomy certification exam and will insure that they are adequately trained to safely conduct blood draws with Ps. We have budgeted \$3,000 in Year 1 to cover tuition and examination fees for 3 Technical RAs. We also budgeted \$1,000 for this purpose in Year 3 in case one of the Technical RAs leaves the project and we have to train and certify new RAs in their place.

Immunological Assay Costs (Years 1 – 5):

All immune assays will be conducted in Co-I Dr. Miller's lab. Five biomarkers will be measured in circulation to index low-grade inflammation: C-reactive protein (CRP), interleukins (IL-), 6, 8, 10, and tumor necrosis factor- α (TNF- α). Blood will be drawn into Serum Separator Tubes (Becton-Dickinson) and centrifuged at 1000 x g for 15 minutes, after which serum will be harvested, divided into aliquots, and frozen at -80°C. At study completion, biomarkers will be measured in a single batch. For CRP, thawed samples will be centrifuged to remove all solid material. Specimens will be plated in duplicate into the wells of a commercially available immunoassay kit (Quantikine hsCRP; R&D Systems) and read at 450 nm on a Tecan Sunrise instrument, with wavelength correction at 540 nm. The high-sensitivity CRP assay kit Dr. Miller will use has a detection threshold of 0.04 pg/mL, and in our prior work, had intra- and inter-assay coefficients of variation < 5%. Cytokines will be measured by electrochemiluminescent immunoassay on a SECTOR Imager 2400A (MesoScale Discovery). As above, thawed samples will be centrifuged to remove solid material, and serum will be plated in duplicate into the wells of a V-PLEX Pro-Inflammatory FourPlex assay kit (MesoScale Discovery). In our prior work, this kit's detection thresholds have been .10 pg/ml, and the intra-assay and inter-assay coefficients of variation have been < 4.3% and < 7.5%, respectively.

Dr. Miller has quoted us a price of \$70 per blood specimen, which covers the costs of the assay kits, preparation of the specimens for assay, and personnel time to conduct the assays. Each P will complete 3 blood draws at their Time 1, 3, and 5 sessions. We anticipate that 80 Ps will complete their first blood draw (Time 1 session) in Year 1, another 110 Ps will complete their first blood draw in Year 2 (Time 1 session), and the final 110 Ps will complete their first blood draw in Year 3 (Time 1 session). Each P will complete 2 more blood draws yearly following Time 1. Thus, based on this P flow, there will be 80 blood draws in Year 1, 190 in Year 2, 300 in Year 3, 220 in Year 4, and 110 in Year 5. Thus, @ \$70 per blood specimen, we have budgeted \$5,600 in Year 1, \$13,300 in Year 2, \$21,000 in Year 3, \$15,400 in Year 4, and \$7,700 in Year 5 for immunological assay costs, totaling \$63,000 across all 5 years.

fMRI Scan Costs (Years 1 – 5):

Costs associated with conducting fMRI scans include magnet time, personnel costs, and data acquisition costs. At the TUBRIC, where the scans for this project will be conducted, these costs equal \$425 per one-hour scan session during peak hours and \$350 per one-hour scan during off-peak hours. Each P will complete 3 one-hour fMRI scans (at Time 1, 3, and 5, each a year apart). Thus, one scan will occur during the year the P begins the study and the other 2 scans will occur during the following 2 years. We plan to start 80 Ps in the study in Year 1 and 110 Ps in each of Years 2 and 3. This yields 80 scans in Year 1, 190 in Year 2, 300 in Year 3, 220 in Year 4, and 110 in Year 5, for a total of 900 scans across the project. Given that our Ps will be high school students, many of them will be available to do their scans during TUBRIC's off-peak hours. Thus, we have estimated that half of the 900 scans will be during peak hours and the other half during off-peak hours, providing some savings in scanning costs. Thus, actual scanning costs are \$31,000 in Year 1, \$73,625 in Year 2, \$116,250 in Year 3, 85,250 in Year 4, and \$42,625 in Year 5, for a total of \$348,750 across all years. However, in order to fit under the \$500,000 direct costs budget cap per year, we have redistributed costs of scans across budget years. Thus, we have actually budgeted \$72,717 in Year 1, \$56,314 in Year 2, \$19,609 in Year 3, \$89,525 in Year 4, and \$110,585 in Year 5 for the scanning costs.

Duplicating (Years 1 - 5):

Large amounts of duplicating of consent and assent forms, project interviews, questionnaires, rating forms, coding packets, etc. are needed for the project. We have budgeted \$475 in each of Years 1–4 and \$300 in Year 5.

Postage and Overnight Delivery (Years 1 - 5):

Postage costs are associated with occasionally mailing questionnaire packets (for Ps who are unable to complete a scheduled assessment in person, we must conduct these assessments by phone and mail when appropriate). Therefore, postage costs are associated with sending and receiving questionnaire

packets, etc. through the mail. In addition, we will use overnight shipping/delivery via Fed Ex to ship the blood specimens to Dr. Miller's lab for assay. We budgeted \$100 for postage costs in each of Years 1 - 5.

Telecommunications (Years 1 - 5):

Telecommunications costs include monthly charges on the project's office phones, as well as a multi-line phone service for the lab in order to recruit Ps, conduct phone screenings to determine study eligibility, schedule Ps for appointments, to remind Ps about appointments, and to check with them about unclear or inconsistent responses on the project instruments. In addition, some Ps must be administered interviews over the phone when they are not in the Philadelphia area at the time of a scheduled session. We have budgeted \$1,000 per year for Years 1 – 5 to cover the costs of the monthly charges for office phones and the lab multi-line phone service.

Data Sharing Costs (Year 5 Only):

Given that data collection will be completed in Year 5, we have budgeted \$10,000 for data preparation and sharing costs in Year 5. These funds will be used to share the neuroimaging data from this project via the NIMH Data Archive (NDA). We used the data sharing cost calculator on the NDA website to estimate these data sharing costs.

Advertising Costs for Participant Recruitment:

We plan to recruit a community sample of 300, 14-15 year old high school freshmen Ps. One primary means of recruitment will be via Facebook ads and flyers posted throughout Philadelphia and surrounding neighborhoods. Specifically, we have budgeted funds to place ads on newsfeeds on Facebook and relevant community pages on Facebook (e.g., High School Class of 20xx, vocational school groups, [Philly locals](#), [Philly summer events](#), [Philly foodies](#)) that target 14-15 yr. olds. In addition, we will place ads on the Philadelphia Craig's list for free. Finally, flyers advertising the study will be posted in local coffee shops, food stores, sports centers, community recreation centers, religious organizations, etc. throughout Philadelphia and surrounding neighborhoods. MPI Nusslock (MH100117) and Co-Is Ellman (MH112613) and Olino (MH107495) have used these methods for recruiting community adolescents and young adults in their ongoing R01 grants with much success. Facebook ads cost \$2,000 per month and we have budgeted for 10 months of Facebook ads (\$20,000) in Years 1 - 3.

Participant Reimbursement for Travel/Parking (Years 1 – 5):

Expenses are needed to reimburse a subset of participants (Ps) for travel costs and/or parking to come to Dr. Alloy's laboratory to complete the Time 1 - 5 sessions, fMRI scans, and blood draws. Some Ps will live close to the TU campus and will not require travel or parking reimbursements; however, some high school students may require reimbursement for travel or parking. Based on our plan to start 80 Ps on their Time 1 sessions in Year 1 and 110 Ps each on their Time 1 sessions in Years 2 and 3, and that 50% of Ps visits to the lab will require travel/parking reimbursement @ \$17, we budgeted \$2,380 in Year 1, \$5,021 in Year 2, \$8,226 in Year 3, \$5,610 in Year 4, and \$2,805 in Year 5 for travel/parking reimbursement.

Subject Payments (Years 1 – 5):

Large amounts of participation time (Time 1 - 5 sessions [with Time 1, 3, and 5 including a one-hour fMRI scan and a blood draw, and all 5 sessions including 1 wk. of actigraphy recording]) are required of Ps and, thus, reimbursement is needed to compensate Ps adequately for their time and efforts and to ensure their continued participation and cooperation. Note, that we estimate needing to conduct 1.5 times as many Time 1 sessions in Years 1-3 as the number of Ps we wish to enroll in the project per year (e.g., 120 Ps complete Time 1 sessions in Year 1 in order to find the 80 Ps to be enrolled in the main study in Year 1) because some Ps will turn out to be ineligible based on information gathered during the Time 1 session and some will decide they do not wish to participate in the main study and follow-ups.

Below, we detail the different kinds of assessments that are planned during the 5 years of the project and the proposed payment for each type of assessment. We also show the subject payment costs per year

as a function of the number and kinds of assessments to be completed each year. In addition, we have budgeted for bonus payments to Ps who complete all of the components of the protocol. These additional incentive bonuses should increase the likelihood that Ps will complete the sessions. Note that the Ps' completion bonuses are budgeted in the year in which they do their Time 1 session in order to stay under the \$500,000 direct costs salary cap in each year. Finally, in Years 1-3, we have budgeted some funds to give out \$50 prizes in lotteries for Ps who complete the initial screenings of their trait reward sensitivity. These initial screenings are necessary for identifying potentially eligible Ps for the project. Finally, we also budgeted \$20 at Time 1 only to compensate Ps' mothers for completing family history and childhood adversity assessments. If a P completes all components of the study (with the bonus for completion), their total compensation would be \$750 over the course of about three years.

Types of Assessments and Payments:

Initial Screenings – \$50 lottery prizes – 20 each in Years 1 - 3

Time 1 - 5 Sessions - \$40 per P for each 3-4 hour session in Years 1 – 5

fMRI Scans (one each at Times 1, 3, and 5) - \$75 per scan per P

Blood Draws (one each at Times 1, 3, and 5) - \$25 per blood draw per P

1 week of Actigraphy at Times 1 – 5 - \$30 per each actigraphy period per P

Completion Bonus - \$100 per P if P completes all components of the protocol; \$90 if P completes almost all components, etc.

Time 1 Mothers - \$20 per mother

Year 1

Initial Screening – 20 lottery prizes at \$50 each = \$1,000

Time 1 Sessions - \$40/P x 120 Ps = \$4,800

Time 1 Scans - \$75/P x 80 Ps = \$6,000

Time 1 Blood Draws - \$25/P x 80 Ps = \$2,000

Time 1 Actigraphy - \$30/P x 80 Ps = \$2,400

Time 2 Sessions - \$40/P x 80 Ps = \$3,200

Time 2 Actigraphy - \$30/P x 80 Ps = \$2,400

Completion Bonus - \$100/P x 80 Ps = \$8,000

Time 1 Mothers - \$20/Mom x 120 Moms = \$2,400

Total for Year 1 = \$32,200

Year 2

Initial Screening – 20 lottery prizes at \$50 each = \$1,000

Time 1 Sessions - \$40/P x 165 Ps = \$6,600

Time 1 Scans - \$75/P x 110 Ps = \$8,250

Time 1 Blood Draws - \$25/P x 110 Ps = \$2,750

Time 1 Actigraphy - \$30/P x 110 Ps = \$3,300

Time 2 Sessions - \$40/P x 110 Ps = \$4,400

Time 2 Actigraphy - \$30/P x 110 Ps = \$3,300

Completion Bonus - \$100/P x 110 Ps = \$11,000

Time 1 Mothers - \$20/Mom x 110 Moms = \$2,200

Time 3 Sessions - \$40/P x 80 Ps = \$3,200

Time 3 Scans - \$75/P x 80 Ps = \$6,000

Time 3 Blood Draws - \$25/P x 80 Ps = \$2,000

Time 3 Actigraphy - \$30/P x 80 Ps = \$2,400

Time 4 Sessions - \$40/P x 80 Ps = \$3,200

Time 4 Actigraphy - \$30/P x 80 Ps = \$2,400

Total for Year 2 = \$62,000

Year 3

Initial Screening – 20 lottery prizes at \$50 each = \$1,000

Time 1 Sessions - \$40/P x 165 Ps = \$6,600

Time 1 Scans - \$75/P x 110 Ps = \$8,250

Time 1 Blood Draws - \$25/P x 110 Ps = \$2,750

Time 1 Actigraphy - \$30/P x 110 Ps = \$3,300

Time 2 Sessions - \$40/P x 110 Ps = \$4,400

Time 2 Actigraphy - \$30/P x 110 Ps = \$3,300

Completion Bonus - \$100/P x 110 Ps = \$11,000

Time 1 Mothers - \$20/Mom x 110 Moms = \$2,200

Time 3 Sessions - \$40/P x 110 Ps = \$4,400

Time 3 Scans - \$75/P x 110 Ps = \$8,250

Time 3 Blood Draws - \$25/P x 110 Ps = \$2,750

Time 3 Actigraphy - \$30/P x 110 Ps = \$3,300

Time 4 Sessions - \$40/P x 110 Ps = \$4,400

Time 4 Actigraphy - \$30/P x 110 Ps = \$3,300

Time 5 Sessions - \$40/P x 80 Ps = \$3,200

Time 5 Scans - \$75/P x 80 Ps = \$6,000

Time 5 Blood Draws - \$25/P x 80 Ps = \$2,000

Time 5 Actigraphy - \$30/P x 80 Ps = \$2,400

Total for Year 3 = \$82,800

Year 4

Time 3 Sessions - \$40/P x 110 Ps = \$4,400

Time 3 Scans - \$75/P x 110 Ps = \$8,250

Time 3 Blood Draws - \$25/P x 110 Ps = \$2,750

Time 3 Actigraphy - \$30/P x 110 Ps = \$3,300

Time 4 Sessions - \$40/P x 110 Ps = \$4,400

Time 4 Actigraphy - \$30/P x 110 Ps = \$3,300

Time 5 Sessions - \$40/P x 110 Ps = \$4,400

Time 5 Scans - \$75/P x 110 Ps = \$8,250

Time 5 Blood Draws - \$25/P x 110 Ps = \$2,750

Time 5 Actigraphy - \$30/P x 110 Ps = \$3,300

Total for Year 4 = \$45,100

Year 5

Time 5 Sessions - \$40/P x 110 Ps = \$4,400

Time 5 Scans - \$75/P x 110 Ps = \$8,250

Time 5 Blood Draws - \$25/P x 110 Ps = \$2,750

Time 5 Actigraphy - \$30/P x 110 Ps = \$3,300

Total for Year 5 = \$18,700

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals (\$)
Section A, Senior/Key Person	381,890.00
Section B, Other Personnel	978,340.00
Total Number Other Personnel	35
Total Salary, Wages and Fringe Benefits (A+B)	1,360,230.00
Section C, Equipment	
Section D, Travel	15,000.00
1. Domestic	15,000.00
2. Foreign	
Section E, Participant/Trainee Support Costs	
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other	
6. Number of Participants/Trainees	
Section F, Other Direct Costs	1,291,643.00
1. Materials and Supplies	101,100.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	454,691.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Other 1	374,492.00
9. Other 2	12,610.00
10. Other 3	348,750.00
Section G, Direct Costs (A thru F)	2,666,873.00
Section H, Indirect Costs	1,097,356.00
Section I, Total Direct and Indirect Costs (G + H)	3,764,229.00
Section J, Fee	
Section K, Total Costs and Fee (I + J)	3,764,229.00

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS*: 1600794550000

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Northwestern University

Start Date*: 07-01-2020

End Date*: 06-30-2021

Budget Period: 1

A. Senior/Key Person

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . Dr.	ROBIN		NUSSLICK		PD/PI	137,000.00		1.35		20,550.00	5,384.00	25,934.00
2 . Dr.	Gregory	E.	Miller		Co-Investigator	144,225.00		0.71		11,388.00	2,984.00	14,372.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	40,306.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Technician	0			0.00	0.00	0.00
1	Total Number Other Personnel				Total Other Personnel		0.00
					Total Salary, Wages and Fringe Benefits (A+B)		40,306.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

ORGANIZATIONAL DUNS*: 1600794550000

Budget Type*: Project Subaward/Consortium

Organization: Northwestern University

Start Date*: 07-01-2020

End Date*: 06-30-2021

Budget Period: 1

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1**ORGANIZATIONAL DUNS*:** 1600794550000**Budget Type*:** Project Subaward/Consortium**Organization:** Northwestern University**Start Date*:** 07-01-2020**End Date*:** 06-30-2021**Budget Period:** 1

F. Other Direct Costs	Funds Requested (\$)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
	Total Direct Costs (A thru F) 40,306.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	58	40,306.00	23,377.00
				Total Indirect Costs 23,377.00
Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
	Total Direct and Indirect Institutional Costs (G + H) 63,683.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	63,683.00

L. Budget Justification*	File Name: NU Budget Justification_MD.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS*: 1600794550000

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Northwestern University

Start Date*: 07-01-2021

End Date*: 06-30-2022

Budget Period: 2

A. Senior/Key Person

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . Dr.	ROBIN		NUSSLOCK		PD/PI	137,000.00		1.35		20,550.00	5,384.00	25,934.00
2 . Dr.	Gregory	E.	Miller		Co-Investigator	144,225.00		0.6		9,615.00	2,519.00	12,134.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	38,068.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Technician	3.81			17,709.00	4,640.00	22,349.00
1	Total Number Other Personnel					Total Other Personnel	22,349.00
					Total Salary, Wages and Fringe Benefits (A+B)		60,417.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

ORGANIZATIONAL DUNS*: 1600794550000

Budget Type*: Project Subaward/Consortium

Organization: Northwestern University

Start Date*: 07-01-2021

End Date*: 06-30-2022

Budget Period: 2

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2**ORGANIZATIONAL DUNS*:** 1600794550000**Budget Type*:** Project Subaward/Consortium**Organization:** Northwestern University**Start Date*:** 07-01-2021**End Date*:** 06-30-2022**Budget Period:** 2

F. Other Direct Costs	Funds Requested (\$)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	60,417.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1 . MTDC		58	60,417.00	35,042.00
Total Indirect Costs				35,042.00
Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	95,459.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	95,459.00

L. Budget Justification*	File Name: NU Budget Justification_MD.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS*: 1600794550000

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Northwestern University

Start Date*: 07-01-2022

End Date*: 06-30-2023

Budget Period: 3

A. Senior/Key Person

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . Dr.	ROBIN		NUSSLOCK		PD/PI	137,000.00		1.35		20,550.00	5,384.00	25,934.00
2 . Dr.	Gregory	E.	Miller		Co-Investigator	144,225.00		0.6		9,615.00	2,519.00	12,134.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	38,068.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Technician	3.81			17,709.00	4,640.00	22,349.00
1	Total Number Other Personnel					Total Other Personnel	22,349.00
					Total Salary, Wages and Fringe Benefits (A+B)		60,417.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

ORGANIZATIONAL DUNS*: 1600794550000

Budget Type*: Project Subaward/Consortium

Organization: Northwestern University

Start Date*: 07-01-2022

End Date*: 06-30-2023

Budget Period: 3

C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)*

Total funds requested for all equipment listed in the attached file

Total Equipment

Additional Equipment: File Name:

D. Travel

Funds Requested (\$)*

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost

E. Participant/Trainee Support Costs

Funds Requested (\$)*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3**ORGANIZATIONAL DUNS*:** 1600794550000**Budget Type*:** Project Subaward/Consortium**Organization:** Northwestern University**Start Date*:** 07-01-2022**End Date*:** 06-30-2023**Budget Period:** 3

F. Other Direct Costs	Funds Requested (\$)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	60,417.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1 . MTDC		58	60,417.00	35,042.00
Total Indirect Costs				35,042.00
Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	95,459.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	95,459.00

L. Budget Justification*	File Name: NU Budget Justification_MD.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

ORGANIZATIONAL DUNS*: 1600794550000

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Northwestern University

Start Date*: 07-01-2023

End Date*: 06-30-2024

Budget Period: 4

A. Senior/Key Person

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . Dr.	ROBIN		NUSSLICK		PD/PI	137,000.00		1.35		20,550.00	5,384.00	25,934.00
2 . Dr.	Gregory	E.	Miller		Co-Investigator	144,225.00		0.6		9,615.00	2,519.00	12,134.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	38,068.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Technician	3.81			17,709.00	4,640.00	22,349.00
1	Total Number Other Personnel					Total Other Personnel	22,349.00
					Total Salary, Wages and Fringe Benefits (A+B)		60,417.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4**ORGANIZATIONAL DUNS*:** 1600794550000**Budget Type*:** Project Subaward/Consortium**Organization:** Northwestern University**Start Date*:** 07-01-2023**End Date*:** 06-30-2024**Budget Period:** 4**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item**Funds Requested (\$)*****Total funds requested for all equipment listed in the attached file****Total Equipment****Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)***

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost**E. Participant/Trainee Support Costs****Funds Requested (\$)***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees**Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4**ORGANIZATIONAL DUNS*:** 1600794550000**Budget Type*:** Project Subaward/Consortium**Organization:** Northwestern University**Start Date*:** 07-01-2023**End Date*:** 06-30-2024**Budget Period:** 4

F. Other Direct Costs	Funds Requested (\$)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	60,417.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
1 . MTDC		58	60,417.00	35,042.00
Total Indirect Costs				35,042.00
Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	95,459.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	95,459.00

L. Budget Justification*	File Name: NU Budget Justification_MD.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

ORGANIZATIONAL DUNS*: 1600794550000

Budget Type*: Project Subaward/Consortium**Enter name of Organization:** Northwestern University

Start Date*: 07-01-2024

End Date*: 06-30-2025

Budget Period: 5

A. Senior/Key Person

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 . Dr.	ROBIN		NUSSLOCK		PD/PI	137,000.00		1.35		20,550.00	5,384.00	25,934.00
2 . Dr.	Gregory	E.	Miller		Co-Investigator	144,225.00		0.6		9,615.00	2,519.00	12,134.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	38,068.00
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B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Technician	4.8			22,309.00	5,845.00	28,154.00
1	Total Number Other Personnel					Total Other Personnel	28,154.00
					Total Salary, Wages and Fringe Benefits (A+B)		66,222.00

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5**ORGANIZATIONAL DUNS*:** 1600794550000**Budget Type*:** Project Subaward/Consortium**Organization:** Northwestern University**Start Date*:** 07-01-2024**End Date*:** 06-30-2025**Budget Period:** 5**C. Equipment Description**

List items and dollar amount for each item exceeding \$5,000

Equipment Item**Funds Requested (\$)*****Total funds requested for all equipment listed in the attached file****Total Equipment****Additional Equipment:** File Name:**D. Travel****Funds Requested (\$)***

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)

2. Foreign Travel Costs

Total Travel Cost**E. Participant/Trainee Support Costs****Funds Requested (\$)***

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees**Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5**ORGANIZATIONAL DUNS*:** 1600794550000**Budget Type*:** Project Subaward/Consortium**Organization:** Northwestern University

Start Date*: 07-01-2024 End Date*: 06-30-2025 Budget Period: 5

F. Other Direct Costs	Funds Requested (\$)*
Total Other Direct Costs	

G. Direct Costs	Funds Requested (\$)*
Total Direct Costs (A thru F)	66,222.00

H. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	Funds Requested (\$)*
	1 . MTDC	58	66,222.00	38,409.00
Total Indirect Costs				38,409.00
Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number)				

I. Total Direct and Indirect Costs	Funds Requested (\$)*
Total Direct and Indirect Institutional Costs (G + H)	104,631.00

J. Fee	Funds Requested (\$)*

K. Total Costs and Fee	Funds Requested (\$)*
	104,631.00

L. Budget Justification*	File Name: NU Budget Justification_MD.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Budget Narrative – Northwestern University

Senior/ Key Personnel

Multiple Principal Investigator – Robin Nusslock, Ph.D., Associate Professor of Psychology and AT&T Research Chair, NU: Effort is 1.35 AY month per year. Nusslock's research program and expertise is in abnormalities in reward processing and reward-related brain function in unipolar and bipolar mood disorders. His publications have examined abnormalities in reward processing in mood disorders using psychosocial, neurophysiological (EEG), and neural (fMRI/DTI) indices. Dr. Nusslock was trained in clinical affective neuroscience and neuroimaging during his graduate training with Dr. Richard Davidson at the University of Wisconsin-Madison and his postdoctoral fellowship with Dr. Mary Phillips at Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center. He also has a 15-year collaboration and many joint publications with Temple MPI Alloy on reward sensitivity in unipolar and bipolar spectrum disorders. In addition, he is Co-I on one of Dr. Alloy's current NIMH R01 grants (MH077908) on reward-related brain function in the onset and course of bipolar spectrum disorders, for which he is managing all the MRI data. Thus, he has already established the mechanism for transferring MRI data between Temple and Northwestern University and will employ identical procedures in the proposed research. Dr. Nusslock has multiple publications using the proposed fMRI reward paradigm and DTI methods to examine the cortico-striatal reward circuit. He also has considerable experience managing large-scale neuroimaging studies and is currently PI on a multi-site NIMH R01 grant using MRI to examine the relationship between reward-related neural circuitry and mood disorder symptoms (MH100117). As MPI on this proposal, Dr. Nusslock, with the assistance of Temple Co-I Dr. Olino and Temple Consultant Dr. Chein, will assist with the design, implementation, analysis, and interpretation of data from the MRI scans. He will be responsible for preprocessing MRI (fMRI and DTI) data, with the assistance of Co-I Dr. Olino, and he will be involved in analyzing MRI data generated from this project. As MPI at Northwestern University, Dr. Nusslock will be responsible for managing personnel and resources and ensuring overall quality control related to the aforementioned data. In addition, he will assist in the preparation of reports and scientific publications with Dr. Alloy, the other MPI. There is no salary inflation in Y2-Y5.

Co-Investigator – Gregory E. Miller, Ph.D., Louis M. Menk Professor of Psychology, NU: 0.71 AY month in Y1, 0.60 AY month in Y2-Y5. As Co-I, Dr. Miller will be responsible for conducting all immune system assays from blood specimens collected at TU. Dr. Miller is a world leader in the field of behavioral medicine and psychoneuroimmunology. He has particular expertise in the relationship between early life adversity, peripheral inflammation, and risk for mental and physical illness. He has made important contributions to understanding how stress gets under the skin to alter immune functioning in a manner that elevates risk for illness, as well as the effect of intervention programs on inflammatory signaling and stress biology. He runs a laboratory at Northwestern University that is fully equipped to process and analyze systemic and genomic inflammatory signaling, as well as hormonal, and epigenetic data. Moreover, Dr. Miller has published with MPI Nusslock on a neuroimmune network model of the relationship between inflammation and reward/threat-related brain function and risk for mental and physical health. The present proposal reflects an empirical investigation of many of the ideas proposed in this publication. Thus, Dr. Miller has made important contributions to the design of the project and the writing of the grant application. As a Co-I, he will a) provide input on the conceptual and mechanistic linkages between early life adversity, inflammatory signaling, and risk for depression, (b) oversee the immunologic assays of systemic inflammation, and (c) actively participate in the analysis and interpretation of neuroimmune data, and co-author manuscripts that result. Salary is calculated based on the NIH salary cap and is not inflated in out-years.

Other Personnel

Technical Research Assistant – To be named; 31.75% (3.81 calendar months) for Years 2-4 and 40% (4.8 calendar months) for Year 5 calendar year salary support plus fringe benefits are requested. The Technical RA primarily will assist Dr. Nusslock with the preprocessing and analysis of the fMRI data. He/she also may assist Dr. Miller with conducting the CRP and cytokine assays from the blood specimens. Effort for this Technical RA is increased in Year 5, when all of the fMRI and inflammation data will be collected and there is the highest need for data processing and analysis. There is no salary inflation in Y2-Y5.

Graduate Research Assistants - In addition to the salary support for an MRI Technical Research Assistant, the Northwestern MPI will have 2 Ph.D. graduate students funded on university fellowships who will make the

equivalent of a 50% commitment to assist with MRI data processing and analysis for all 5 years of the proposed research. These 2 graduate student appointments are funded by Northwestern University fellowships and thus guaranteed. Both of these Ph.D. students have extensive experience in functional and structural MRI processing and analysis. For example, Casey Young, one of the Ph.D. students who will be working on the project, served as a post-baccalaureate MRI RA for 5 years at UCLA before starting graduate school. She worked closely with Dr. Susan Bookheimer at UCLA, a leader in the field of cognitive neuroscience, and has first authored papers on the application of graph theory to resting state functional data. The second Ph.D. student who will work on this proposal is Ann Carroll, who served as Dr. Joshua Buckholtz's full-time MRI data analyst at Harvard for 2 years before graduate school. Both Casey and Ann already have experience with the MRI data preprocessing and analysis from Dr. Alloy's previous R01 project with Dr. Nusslock (MH077908). Working on this project will provide Casey and Ann with an outstanding training experience and the opportunity to further their career through collaborations and publications. The 31.75% salary support (40% in Year 5) for the MRI Technical RA combined with Casey and Ann's effort makes us confident in our ability to successfully complete the proposed MRI processing and analysis plan.

Fringe Benefits

Employee benefits have been calculated based on the following DHHS-approved rates:

09/01/19 - 08/31/20 and thereafter.... 26.2% (provisional)

Indirect Cost:

F&A has been calculated based on the following DHHS approved rates:

58.0% MTDC 09/01/17 - 08/31/18 and thereafter - Provisional

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals (\$)
Section A, Senior/Key Person	192,578.00
Section B, Other Personnel	95,201.00
Total Number Other Personnel	5
Total Salary, Wages and Fringe Benefits (A+B)	287,779.00
Section C, Equipment	
Section D, Travel	
1. Domestic	
2. Foreign	
Section E, Participant/Trainee Support Costs	
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other	
6. Number of Participants/Trainees	
Section F, Other Direct Costs	
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Other 1	
9. Other 2	
10. Other 3	
Section G, Direct Costs (A thru F)	287,779.00
Section H, Indirect Costs	166,912.00
Section I, Total Direct and Indirect Costs (G + H)	454,691.00
Section J, Fee	
Section K, Total Costs and Fee (I + J)	454,691.00

Total Direct Costs less Consortium F&A

NIH policy (NOT-OD-05-004) allows applicants to exclude consortium/contractual F&A costs when determining if an application falls at or beneath any applicable direct cost limit. When a direct cost limit is specified in an FOA, the following table can be used to determine if your application falls within that limit.

Categories	Budget Period 1	Budget Period 2	Budget Period 3	Budget Period 4	Budget Period 5	TOTALS
Total Direct Costs less Consortium F&A	499,996	499,995	499,995	499,995	499,980	2,499,961

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 03/31/2020

1. Vertebrate Animals Section

Are vertebrate animals euthanized? Yes No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

Yes No

If "No" to AVMA guidelines, describe method and provide scientific justification

.....

2. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

Yes No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period *Anticipated Amount (\$) *Source(s)

PHS 398 Cover Page Supplement

3. Human Embryonic Stem Cells Section

*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://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, 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) (Example: 0004):

4. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: Yes No

If the answer is "Yes" then please answer the following:

*Previously Reported: Yes No

5. Change of Investigator/Change of Institution Section

Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

Change of Grantee Institution

*Name of former institution:

PHS 398 Research Plan

OMB Number: 0925-0001

Expiration Date: 03/31/2020

Introduction

1. Introduction to Application
(for Resubmission and Revision applications)

Research Plan Section

2. Specific Aims
3. Research Strategy*
4. Progress Report Publication List
2. Specific Aims.MD.pdf
3. Research Strategy.MD.pdf

Other Research Plan Section

5. Vertebrate Animals
6. Select Agent Research
7. Multiple PD/PI Leadership Plan
8. Consortium/Contractual Arrangements
9. Letters of Support
10. Resource Sharing Plan(s)
11. Authentication of Key Biological and/or Chemical Resources
7. Multiple PD-PI Plan.pdf
8. Consortium Contractual Arrange.pdf
- Chein letter of support.pdf
10. Resource Sharing.pdf
11. Authentication.pdf

Appendix

12. Appendix

2. SPECIFIC AIMS

Major depressive disorder (MD) is highly prevalent, recurrent, and a major public health problem, and adolescence is an “age of risk” for 1st onset of MD. Depression (Dep) is associated with reduced sensitivity to rewards and low reward-related brain function in cortico-striatal circuitry. However, little work has tested whether low reward responsivity (RR) or attenuated RR development during adolescence predicts 1st onset of MD. A separate literature documents elevated peripheral inflammation in Dep. Yet, research also has yet to examine the development of inflammation across adolescence and whether chronically elevated inflammation or increases in inflammation during adolescence predicts 1st onset of MD. Further, research on inflammation and RR mostly has proceeded in parallel. Recently, however, we and others have proposed neuroimmune network models of Dep. These models draw on research indicating that peripheral inflammatory mediators (e.g., cytokines) access the brain, where they lower RR. This is highly adaptive when regulated. It coordinates sickness behaviors (e.g., inactivity) that facilitate pathogen removal and wound healing by diverting resources to the immune system. When dysregulated, however, inflammation can lead to chronic reductions in RR, which is reflected in anhedonia and dysphoria. This low RR then is proposed to initiate unhealthy, self-medicating behaviors (substance use, poor diet) to manage the dysphoria, as well as sleep disruption and stress generation, which further heighten inflammation. Over time, dysregulation in RR and immune signaling may synergize to form a positive feedback loop, whereby dysregulation in each system exacerbates dysregulation in the other. We propose that reward-immune dysregulation is a two-hit vulnerability for the 1st onset of MD and increases in Dep symptoms (Sxs) in adolescence. Moreover, early adversity and recent stressors influence both RR and inflammation, and may set the foundation for reward-immune dysregulation. This proposal is the first systematic test of these hypotheses. We use a **biobehavioral high-risk approach involving immune and reward measures at multiple units of analysis in a prospective longitudinal design to examine: 1) concurrent and longitudinal bidirectional associations between RR and inflammation; 2) mediators and moderators of their associations, and 3) inflammation and RR as separate and/or joint predictors of risk for 1st onset of MD and increases in Dep Sxs during adolescence.** We predict that chronically low RR or attenuated development of RR will be associated with elevated inflammation. We further predict that chronically high inflammation or increases in inflammation will combine with low RR or attenuated development of RR to predict 1st onset of MD and Dep Sxs. Childhood adversity is expected to moderate and behaviors that increase inflammation (substance use, poor diet, sleep dysregulation, stress-generation) mediate RR-inflammation associations. This proposal is an innovative integration of research on reward and inflammation in understanding 1st onset MD and the pathophysiology of Dep in adolescence.

Three hundred 14-15 year old high school freshmen will complete a prospective, 3-year longitudinal study. Participants (Ps) with no prior history of MD will be selected along the entire dimension of self-reported RR, with oversampling at the low tail of the dimension to increase the likelihood of MD onsets. At Time 1 (T1), T3, and T5, each a year apart, Ps will complete blood draws to quantify inflammation, self-report and behavioral measures of RR, and fMRI scans of reward neural activity and functional connectivity during monetary and social reward tasks. At T1-T5 (with T2 and T4 6 mo. between the yearly sessions), Ps also will complete diagnostic interviews, and measures of Dep Sxs, recent life events coded for reward-relevance and stress generation, and behaviors that increase inflammation. Childhood adversity history will be assessed at T1 only.

Aim 1: Reward responsibility (RR) and inflammation associations

Aim 1.1. We will examine concurrent associations between multiple reward units of analysis (self-report, behavioral, neural) and peripheral inflammation at T1, T3, and T5. We predict that lower RR levels will be associated with higher peripheral inflammation at each time.

Aim 1.2. We will examine bidirectional, longitudinal associations of trajectories of each system with the other over time. Multiple RR units of analysis (i.e., “indices”) and changes in these RR indices from T1 to T3 to T5 will predict changes in inflammation from T1 to T3 to T5 and vice versa, such that attenuated development of RR will be associated with increases in inflammation and vice versa.

Aim 2: Moderators and mediators of reward responsibility (RR) and inflammation associations

Aim 2.1. Childhood adversity will be associated with chronically low RR or attenuated development of RR indices, chronically high inflammation or increases in inflammation over time, and stronger concurrent and longitudinal associations between the two systems.

Aim 2.2. Inflammation-enhancing behaviors (substance use, high-fat diet, sleep disturbance, self-generated reward-deactivation events involving the failure to attain reward or loss of reward) from T1 to T5 will partially mediate RR predictors of changes in inflammation from T1 to T5 and vice versa.

Aim 3: RR and inflammation as predictors of prospective 1st onset of MD and Dep Symptoms

Chronically low or attenuated trajectories of RR indices over time (T1 to T5) and chronically elevated or increasing trajectories of inflammation over time (T1 to T5) will be separate and joint predictors of 1st onset of MD and increases in Dep Sxs between T1 to T5. Reward-deactivation life events (whether self-generated or not) and childhood adversity each will moderate RR indices’ prediction of 1st onset of MD and Dep Sxs and inflammation’s prediction of 1st onset of MD and Dep Sxs over follow-up.

3. RESEARCH STRATEGY

A. SIGNIFICANCE

A.1. Overview. Major depressive disorder (MD) is highly prevalent, recurrent, and a major public health concern accounting for much disability, mortality, and poor quality of life worldwide.¹⁻⁴ Depression (Dep) falls on a continuum of severity and even Dep symptoms (Sxs) in the absence of a diagnosis are associated with significant functional impairment, increased suicide risk, and can progress to MD over time.⁵⁻⁸ Adolescence is an “age of risk” for 1st onset of MD and increases in Dep Sxs.⁹⁻¹⁵ Depressed teens’ significant impairment (e.g., poor academic achievement, substance abuse, etc.) not only wreaks havoc in their lives during adolescence but also limits their opportunities in adulthood.^{8,16-20} Moreover, adolescents do not “out-grow” their Dep; Dep teens often become Dep adults.^{21,22} Despite great public health and scientific significance, the *mechanisms* responsible for adolescent vulnerability to MD are not fully understood. Yet, knowledge of modifiable risk mechanisms is crucial for understanding etiological pathways to MD and translating basic research to powerful interventions that prevent or treat the “epidemic” of Dep during the vulnerable period of adolescence.

Dep is associated with a reduced sensitivity to rewarding stimuli and lower reward-related brain function in cortico-striatal circuitry.²³⁻³⁰ Moreover, low reward responsivity (RR) has been hypothesized to be a vulnerability for MD.^{23,24,27,29} To test the low RR theory of vulnerability for MD, a truly prospective, longitudinal study of 1st onset of MD is required. Although a few (mostly small N) studies have found that low RR at one time predicts increases in Dep Sxs or onset of Dep episodes,³¹⁻⁴⁰ almost no work has tested whether chronically low RR or attenuated development of RR during adolescence predicts 1st onset of MD. In addition, work examining RR development relies on cross-sectional or longitudinal assessments with only two timepoints.⁴¹⁻⁶⁰ However, to examine developmental trajectories of RR as predictors of 1st onset of MD and Dep Sxs, and to test mediators of these predictive associations, at least three timepoints are needed. A separate literature also documents heightened peripheral inflammation in MD.⁶¹⁻⁷¹ However, little research has examined the development of inflammation across adolescence or whether chronically heightened inflammation or increases in inflammation during adolescence predicts 1st onset of MD. To understand the pathophysiology, identify markers of risk, and develop preventive interventions for MD, it is crucial to determine whether low RR and heightened inflammation are preexisting vulnerabilities for 1st onset of MD, as we will do.

Furthermore, research on RR and inflammation in Dep mostly has proceeded in parallel. Recently, however, we and others⁷²⁻⁷⁵ have proposed neuroimmune network models of Dep (**Fig. 1**). These models draw on research indicating that peripheral inflammatory mediators (e.g., cytokines) access the brain, where they lower RR and reward-related brain function.⁷⁶⁻⁸¹ When regulated, this is highly adaptive. It coordinates a set of sickness behaviors (psychomotor slowing, inactivity) that facilitate pathogen removal and wound healing by diverting resources to the immune system. When dysregulated, however, inflammation can lead to chronic reductions in RR, which is reflected in anhedonia and dysphoria. This low RR then is proposed to initiate unhealthy, self-medicating behaviors (substance use, poor diet) to manage the dysphoria, as well as sleep disruption and stress generation, which further heighten inflammation.^{73,82} Over time, dysregulation in RR and inflammation may synergize to form a positive feedback loop, whereby dysregulation in each system exacerbates dysregulation in the other. We propose that this profile of reward-immune dysregulation is a two-hit vulnerability for 1st onset of MD and increases in Dep Sxs in adolescence. Moreover, early life adversity and recent stressors have been found to influence both RR^{27,73,83-93} and inflammation^{71,94-97} (see **Fig. 1**). Thus, the time is ripe to test an integrative reward-inflammation approach to 1st onset of MD in adolescence. In line with the Research Domain Criteria (RDoC), this project will be the first to examine the relationship between individual differences in development of RR and inflammatory vulnerabilities and 1st onset of MD and increases in Dep Sxs in adolescence. **We will use an innovative biobehavioral high-risk approach involving immune and RR measures at multiple units of analysis over three timepoints in a prospective longitudinal design to examine: 1) concurrent and longitudinal bidirectional associations between RR and inflammation; 2) mediators and moderators of their associations, and 3) inflammation and RR as separate and/or joint determinants of risk for 1st onset of MD/increases in Dep Sxs during adolescence.**

A.2. Scientific and public health significance. This proposal integrates research on two organ systems (brain and immune system) to test a novel two-hit vulnerability model for 1st onset of MD. Our high-risk design will allow us to assess whether abnormalities in reward-immune signaling predate onset of 1st MD, reflecting a preexisting vulnerability, or emerge as a consequence of the illness. This is important for understanding etiological pathways to Dep and identifying biobehavioral markers of risk that predate MD onset. Eventually such markers could help identify individuals at elevated risk for Dep, but who have not yet developed Sxs, for early prevention and intervention. Further, identifying reward-immune pathways in the emergence of MD/Dep Sxs could facilitate “a next generation” of behavioral and biological interventions that target brain-to-immune and/or immune-to-brain signaling to treat, and ideally prevent, MD and its lifelong negative consequences.⁷³

A.3. Adolescence is an “age of risk.” Adolescence is a developmental period constituting an “age of risk” for onset and worsening of Dep. Rates of Dep rise markedly from adolescence through early adulthood,⁹⁻¹⁵ with the steepest increase of 1st onset incidence cases occurring between ages 15 – 18.⁹⁻¹² Based primarily on

cross-sectional and two timepoint longitudinal studies, it appears that neural circuitry implicated in reward processing also undergoes rapid development beginning in adolescence. This development generates normative increases in sensitivity to and motivation for rewards,⁴¹⁻⁶⁰ again with a major peak in RR occurring at ages 15-16.^{47,52} In addition, immune system competence increases from childhood to adulthood and then declines in older age,⁹⁸ suggesting that adolescence is a period when the immune system ‘hits its stride.’ However, few longitudinal, multiple timepoint studies have mapped the trajectory of peripheral inflammation during adolescence (but see^{66,69,96,99-103}). Thus, adolescence is an optimal period to investigate individual differences in development of RR and immune function involved in risk for 1st onset of MD.

Reward Model of Major Depression

A.4. Reward hyposensitivity is a risk factor for MD. We and others propose that vulnerability for Dep involves abnormalities in approach motivation and RR.²³⁻³⁰ Reward processing is linked to a cortico-striatal neural circuit involving the ventral striatum (VS) and orbitofrontal cortex (OFC), among other regions.¹⁰⁴⁻¹¹¹ Dopamine is the neurotransmitter most directly involved in reward processing within this circuit.¹⁰⁵ Cortico-striatal activity and functional connectivity are both sensitive to individual differences in RR.^{112,113} Blunted RR (reward **hyposensitivity**) is proposed to increase risk for MD^{23,24} by leading to an excessive decrease in approach motivation when reward system-deactivating (Rew-D) life events involving irreconcilable failures and losses occur, and, in turn, to Dep Sxs/episodes (Fig. 1). Self-report, behavioral, neurophysiological (EEG), neural (fMRI), and life event evidence supports blunted RR in MD.^{23,24} MD Ps and at-risk offspring of Dep parents report lower RR and greater anhedonia¹¹⁴⁻¹¹⁶ and are less responsive to reward stimuli on behavioral and neural indices.¹¹⁷⁻¹²⁶ However, our recent fMRI reward processing meta-analysis indicates that although MD Ps exhibit blunted VS responses to reward, they show enhanced OFC reward responses.¹²⁷ This may be related to functional connectivity findings, which suggest that MD Ps engage the PFC during reward processing in a manner that reduces or blunts the VS, reflecting cortico-attenuation tendencies¹²⁸ that suppress positive emotions (C.1.a.iii.). In prospective studies, blunted RR assessed with behavioral tasks, ERP, or fMRI predicts later Dep Sxs^{34,39,40} and MD.^{31,32,35-38} However, these studies have some limitations: small samples, Ps of only one sex, short follow-ups, assessment of RR at one timepoint only and only in relation to monetary rewards.

Three questions regarding RR and Dep need further investigation. First, research on RR development suggests that there are normative increases in RR during adolescence, with accompanying changes in cortico-striatal neural circuitry.⁴¹⁻⁶⁰ However, studies of RR development in Dep are limited by cross-sectional or longitudinal designs with only 2 timepoints. Thus, it is important to examine whether low RR at one time, stable low RR, and/or attenuated development of RR over time best predicts 1st onset of MD/Dep Sxs in larger samples of both sexes with longer follow-ups. Second, most research on reward neural activity in Dep has focused on monetary rewards. Given the increasing importance of social incentives in adolescence¹²⁹⁻¹³¹ and the major role of social stressors in predicting Dep,¹³²⁻¹³⁵ it is important to also examine neural activity to social rewards as a predictor of 1st onset of MD/Dep Sxs. We¹³⁶ and others^{137,138} have shown that social rewards activate cortico-striatal circuitry and that individuals with and at familial risk for Dep show low VS activation to social rewards.^{136,138} Third, heightened inflammation, exposure to Rew-D events, and inflammation-enhancing behaviors may contribute to changes in RR during adolescent development (see A.7-8, C.1.c., C.1.e.). Our study will examine trajectories of RR indices for both monetary and social rewards across 3 timepoints and the influence of these potential factors that may contribute to change in RR during adolescence.

Inflammation Model of Major Depression

A.5. Inflammation is associated with MD and risk for MD. Low-grade peripheral inflammation has been reported in MD⁶¹⁻⁷¹ and inflammatory models of MD have emerged.^{68,70,71} Meta-analyses^{61-64,67} indicate that some people with MD exhibit elevated peripheral inflammatory biomarkers, including inflammatory cytokines and c-reactive protein (CRP). Further, the “sickness syndrome” (e.g., fatigue, psychomotor slowing, anhedonia, inactivity) triggered by inflammation shares many features with Dep Sxs related to blunted RR, and MD co-occurs with inflammation-related medical disorders.⁷³ Similarly, most patients treated with interferon- α to boost inflammation develop Dep Sxs^{63,139} and some prospective studies by us and others found that heightened inflammation predicts later Dep Sxs and vice versa^{66,69,71,96,99-103,140-142} (C.1.b.). However, not all studies support a role for inflammation in Dep,^{61-64,67} and few prospective studies have tested inflammation as a predictor of Dep Sxs or episodes, with some even supporting the opposite predictive direction.¹⁴³ Moreover, there is a

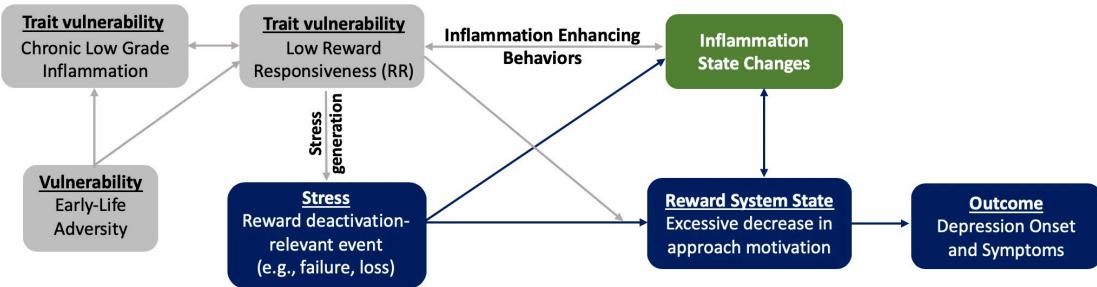


Fig. 1. Integrated Reward-Inflammation Model of Depression

relative dearth of inflammation studies in adolescence and even fewer that track developmental trajectories of inflammation during this period (but see^{66,69,96,99-103}). Our study assesses individual differences in multiple inflammatory biomarkers at 3 timepoints and intervening stressful events. This allows examination of baseline, chronic, and stress-related worsening of inflammation as predictors of 1st onset of MD/Dep Sxs in adolescence, which would provide a novel test of inflammation's role in MD, and clarify inconsistencies in the field.

Integrated Reward - Inflammation Model of Major Depression (Fig.1)

A.6. Immune-to-reward pathway. Growing evidence suggests that peripheral inflammation induces sickness behaviors and Dep Sxs through lowering RR and goal-directed behavior.^{73,74,144,145} Although inflammatory cytokines predominately are released by immune cells in the periphery, recent discoveries show they can access the brain via active transport or leaky regions of the blood-brain-barrier.^{146,147} Studies suggest that RR in the cortico-striatal neural circuit is a primary target of inflammation in the brain.^{74,144} Inflammatory cytokines reduce animals' sensitivity to rewards and increase tolerance to the reinforcing properties of many drugs.^{77,78} In humans, inflammatory products (e.g., endotoxins, interferons) reduce VS activation to monetary rewards.^{72,76,80} Studies suggest that inflammation lowers RR by blunting dopamine transmission in the VS.^{74,76,144} Although highly adaptive when regulated, when dysregulated or chronic, however, it can result in sustained reductions in RR and risk for Dep onset.⁷⁸ In line with this view are studies reporting that low RR and reduced reward-related brain function are associated with elevated peripheral inflammation^{68,73,76-81} (C.1.c.). However, naturalistic, longitudinal studies of bidirectional associations between multiple indices of RR and inflammation, and how changes in one system affect changes in the other, are lacking.

A.7. Reward-to-immune pathway: The role of behaviors that increase inflammation. Recent neuroimmune network models suggest bidirectional associations between the brain and immune system and propose that profiles of RR and reward-related brain function also can influence levels of inflammation.^{73,81} One potential mechanism for this bidirectional association is that Ps with low RR are more likely to engage in behaviors that can increase inflammation, including substance use, consuming a high-fat/high-sugar diet, sleep disturbances, and reward-relevant stress-generation (Fig. 1). Blunted RR may lead to increased substance use and food consumption that promote inflammation over time¹⁴⁸⁻¹⁵¹ (perhaps through obesity, a primary driver of inflammation^{152,153}). According to the reward deficiency model of addiction, persons with low RR self-medicate negative affect and/or induce positive affect through addictive behaviors.^{73,154-160} Consistent with this view, blunted dopamine signaling in the VS is involved in drug and alcohol use, as well as food seeking and obesity,¹⁵⁵⁻¹⁵⁹ and we found that low cortico-striatal activation during reward anticipation predicts substance use frequency, impairment, and time to episode onset.¹⁶⁰ In humans, blunted reward-related brain function may reflect both a pre-existing vulnerability to, as well as a consequence of, addictive behaviors.¹⁶¹

Sleep disruption may be another mechanism linking RR and inflammation. Sleep disruption can increase neural RR and behavioral impulsivity, but decreases accuracy of reward discrimination,¹⁶²⁻¹⁶⁹ most likely through altered dopamine signaling.¹⁶² However, in turn, low RR also has been found to lead to sleep disturbances.¹⁷⁰⁻¹⁷² Blunted RR involving decreased approach and response initiation may lead to neglect of normal routines (e.g., bedtime) and consequent sleep disruption or irregular sleep.^{82,173-175} Subjectively and objectively assessed sleep disturbances, short sleep durations, and experimentally-manipulated sleep deprivation, in turn, are associated with and prospectively predict increases in inflammation¹⁷⁶⁻¹⁸³ (but see¹⁷⁷).

Another proposed inflammation-enhancing behavior is stress-generation (Fig. 1). Ps with low RR are more likely to self-generate goal failures and losses^{174,184,185} (C.1.e.i.). These self-generated Rew-D events may activate stress biology, which increases inflammation⁷³ (C.1.e.i.). Moreover, several inflammation-enhancing behaviors increase during adolescence.¹⁸⁶⁻¹⁸⁸ Taken together, we hypothesize that inflammation-enhancing behaviors (i.e., substance use, poor diet, sleep disruption, stress-generated Rew-D events) will partially mediate the relationship between trajectories of RR and trajectories of inflammation during adolescence.

A.8. Childhood adversity and recent stressors influence both RR and inflammation. Early and recent stress influence both RR and inflammation (Fig. 1). Childhood adversity (e.g., poverty, abuse) affects development of the cortico-striatal reward circuit and is associated with later behavioral and neural reward processing deficits.^{85-87,89,90,92,93} Child adversity also predicts development of an enduring pro-inflammatory phenotype,^{94-97,101,189} as well as MD,¹⁹⁰⁻¹⁹² and enhances the link between inflammation and Dep.^{94,96} Likewise, exposure to recent stressful events instigates inflammatory responses⁷¹ and modulates reward-related brain function.^{83,84,88,91} Recent stress exposure also strengthens the association between RR and inflammation.¹⁹³ Thus, early adversity and recent stressors may set the foundation for heightened cross-talk between the brain and immune system and reward-immune dysregulation in risk for Dep.

A.9. Integrated reward and immune model of MD. The time is ripe to examine bidirectional associations of RR and inflammation with each other and as predictors of 1st onset of MD and Dep Sxs in adolescence. This project will help to identify biomarkers (reward-related neural activation/connectivity and inflammatory signaling) that may separately and interactively predict risk for MD and increase understanding of mediators of reward-immune longitudinal associations that can lead to modifiable targets for intervention. We propose (Fig. 1) that heightened inflammation, when chronic, can lead to sustained reductions in RR and reward-related

brain function, reflected in anhedonia and dysphoria. This low RR then is proposed to initiate unhealthy, self-medication behaviors (substance use, poor diet) to manage the dysphoria, as well as sleep disruption and stress generation, which further heighten inflammation.⁷³ Over time, dysregulation in reward-related brain function and immune signaling may synergize to form a positive feedback loop whereby dysregulation in each system exacerbates dysregulation in the other. We propose that this profile of reward-immune dysregulation is a two-hit vulnerability for MD onset. In particular, we predict that elevated baseline, chronic, or worsening inflammation will combine with low baseline, chronic, or attenuated development of RR to predict 1st onset of MD and Dep Sxs in adolescence. We also predict that these associations will be heightened in teens with early adversity and recent stressors. In C.1.a.–C.1.e. below, we present preliminary data consistent with this model.

B. INNOVATION

This project is highly innovative in the following ways:

B.1. Integrative neuroimmune framework. Our study will be the first to examine bidirectional associations and trajectories of RR and inflammation in the same study and their prospective prediction of 1st onset of MD and increases in Dep Sxs in adolescence. We draw our hypotheses from integrated reward-immune network models that we and others recently have proposed, but that have yet to be tested.

B.2. High-risk design. Selecting Ps at elevated risk for Dep (low self-reported RR), but with no prior history of MD, will allow us to assess whether abnormalities in RR, inflammation, and/or integrated reward-inflammation dysregulation predate onset of Dep, reflecting preexisting vulnerabilities, or emerge as a consequence of MD.

B.3. Multilevel data. Assessing RR at multiple units of analysis will allow us to empirically examine whether these units cohere, or if specific units (self-report, behavioral, neural) more strongly relate to inflammation and MD/Dep Sxs. Functional connectivity analyses will move beyond examining reward neural regions in isolation and assess the relationship between top-down regulatory tendencies and both inflammation and MD/Dep Sxs.

B.4. Multiple timepoints. Using multiple timepoints will allow us to examine how RR and inflammation relate to each other over time, and to assess whether it is abnormalities at one timepoint, stability of these abnormalities, or worsening of reward function and inflammation that best predicts 1st MD onset/Dep Sxs.

B.5. Studying 1st onset MD during adolescence. Adolescence is an optimal time to study reward-immune models of 1st onset of MD given it constitutes an “age of risk” for the onset and worsening of Dep, and is associated with critical developments in both reward neural circuitry and immune system competence.

B.6. Mediators and moderators of reward-inflammation associations. We will examine potential mediators (inflammation-enhancing behaviors) and moderators (early adversity) of bidirectional reward–inflammation associations. This will provide better understanding of potential mechanisms that may contribute to reward – inflammation interactions and prediction of MD/Dep Sxs, and suggest potential targets for novel interventions.

C. APPROACH

C.1. Preliminary Studies

C.1.a. RR – Depression Associations

C.1.a.i. MD is associated with reduced neural responses to reward receipt and negative cortico-striatal functional connectivity. Related to **Aim 3**, higher Dep Sxs were associated with reduced VS activation during reward receipt on a fMRI monetary reward task¹⁹⁴ ($r = -0.33$, $p < .05$). Anhedonia among MD Ps was associated with negative functional connectivity between the VS and OFC during reward processing,¹²⁸ suggesting MD Ps engage the PFC in a way that blunts the VS and rewarding emotions (cortico-striatal attenuation).^{24,195}

C.1.a.ii. RR predicts MD episodes. We found that low RR as assessed by EEG predicted 1st onset of MD³⁶ ($B = -8.40$, $SE = 3.6$, $p = .02$). In our sample of adolescents selected to have different levels of RR (Project TEAM; MH077908), low bilateral VS activation during reward anticipation in the monetary incentive delay (MID) task (the monetary reward task we will use) also predicted onset of MD episodes¹⁹⁶ ($OR = 4.46$, $p = .02$; **Fig. 2**). Further, low behavioral RR (on the CARROT task we will use) interacted with high rates of Rew-D events to predict Dep episode onsets¹⁹⁷ ($Wald = 4.89$, $OR = 1.02$, $p < .03$). These findings all support **Aim 3**.

C.1.b. Inflammation – Depression Associations

In the Project TEAM sample, Dep Sxs were concurrently associated with elevated inflammatory biomarkers (IL-6 and CRP; $r's = .25-.34$, $p's < .035-.015$), controlling for group status, BMI, sex, and medications.

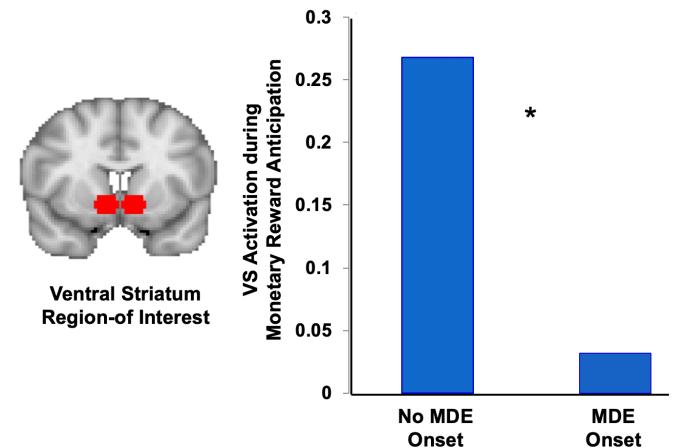


Fig. 2. Prospective onset of major depressive episode (MDE) as a function of ventral striatum (VS) activation during monetary reward anticipation. Mean VS activation during reward anticipation in the Monetary Incentive Delay (MID) task for Ps who did vs did not develop a MDE. * $p = .02$. (Ng et al., in prep).

Further, in our gender, racially and SES diverse adolescent community sample (Project ACE, MH101168), peripheral inflammation at T1 prospectively predicted increases in Dep Sxs ($\beta=.129$, $b=.891$, $SE=.443$, $p<.05$).⁶⁹ In an even stronger test using multilevel modeling, we found that within-P effects of peripheral inflammation predicted prospective Dep Sxs ($\beta=.084$, $t=2.693$, $p<.01$), suggesting a potential causal relationship.¹⁰³ Moreover, increases in IL-6 ($b=.878$, $SE=.324$, $p<.01$) and CRP ($b=.252$, $SE=.110$, $p<.05$) over a yr. following the occurrence of stressful events predicted increases in Dep Sxs over the yr. better than baseline IL-6 and CRP⁶⁶ (Fig. 3). These findings support Aim 3, and highlight the importance of studying changes in inflammation over time as well as baseline levels as a predictor of 1st onset MD/Dep Sxs.

C.1.c. RR – Inflammation Associations

In Project ACE, elevated inflammation was associated with lower bilateral OFC activation ($B= -1.050$, $SE= 0.437$, $p<.05$) during anticipation of social rewards on the Chatroom Interact Task¹⁹⁸ (the social reward task we will use; Fig. 4). In addition, among Ps with a history of MD, elevated inflammation was associated with lower bilateral VS and OFC activation during anticipation (VS: $B= -1.100$, $SE=.494$, $p<.05$; OFC: $B= -1.130$, $SE=.482$, $p<.05$) and receipt (VS: $B= -2.51$, $SE= .867$, $p<.01$; OFC: $B= -1.990$, $SE=.758$, $p<.05$) of monetary rewards.¹⁹⁸ These findings support Aims 1.1. and 1.2.

C.1.d. Childhood Adversity Associations with Both RR and Inflammation

Supporting Aim 2.1, in Project ACE, child adversity on the Children's Life Events Scale¹⁹⁹ (which we will use) was associated with lower VS activation during anticipation and receipt of monetary rewards ($r's= -.37$ to $-.75$, $p's<.05-.01$), and with elevated inflammation ($b's=.065-.141$, $p's=.012-.008$), controlling for BMI. Consistent with child adversity as a potential moderator of associations between inflammation and RR (Aim 2.1), the association between elevated inflammation and lower bilateral VS ($B= -1.05$, $SE=.422$, $p<.05$) and OFC ($B= -.582$, $SE=.311$, $p<.01$) activation to anticipation of monetary rewards was stronger in Ps with child adversity. And, consistent with Aim 3, child adversity moderated the inflammation – MD association, such that higher IL-6 values predicted greater risk for MD episodes 6 mo. later, especially for teens with high adversity.⁹⁶

C.1.e. Behaviors, RR, and Inflammation

C.1.e.i. Reward-deactivation (Rew-D) events predict both neural RR and elevated inflammation. We suggested that self-generation of Rew-D events may partially mediate the association between RR and inflammation (A.7.). Consistent with this hypothesis, in Project TEAM, exposure to more Rew-D events in the yr. prior to an fMRI scan predicted higher OFC ($b=.072$, $p<.008$, $\Delta R^2=.084$) activation to reward anticipation in the MID task.²⁰⁰ Higher rates of Rew-D events in the previous yr. also predicted higher IL-6 levels ($r=.46$, $p<.001$).²⁰⁰ In Project ACE, greater exposure to Rew-D events over 1 yr. predicted increased inflammation over the yr. ($p's<.03-.04$). These findings support Aim 2.2, and suggest that Rew-D events may predict changes in inflammation and RR.

C.1.e.ii. Substance use (SU), neural RR, and inflammation.

We also suggest that inflammation-enhancing behaviors such as SU may partially mediate the association between RR and inflammation. Consistent with this, in Project TEAM, higher SU frequency (see C.4.f.ii.) prospectively predicted decreased reward neural activity on the MID task²⁰¹ ($\beta's= -.25$ to $-.46$, $p's<.05-.001$) and elevated inflammation ($p<.05$), controlling for BMI. Blunted VS and OFC activation during MID reward anticipation also predicted SU frequency ($\beta= -.23$, $t= -2.48$, $p<.05$), impairment ($\beta= -.27$, $t= -2.47$, $p<.05$), and time to SU disorder onset (Wald=7.66, OR=.20, $p<.01$).¹⁶⁰ This supports Aim 2.2, and suggests that substance use may predict changes in inflammation and RR from T1 to T5.

C.1.e.iii. Sleep disruption predicts RR, Inflammation, and Dep Sxs.

In our 20 day EMA study of Project TEAM Ps (MH102310) including measures of sleep, RR, and Dep Sxs, less actigraphic total sleep time tended to predict lower next day

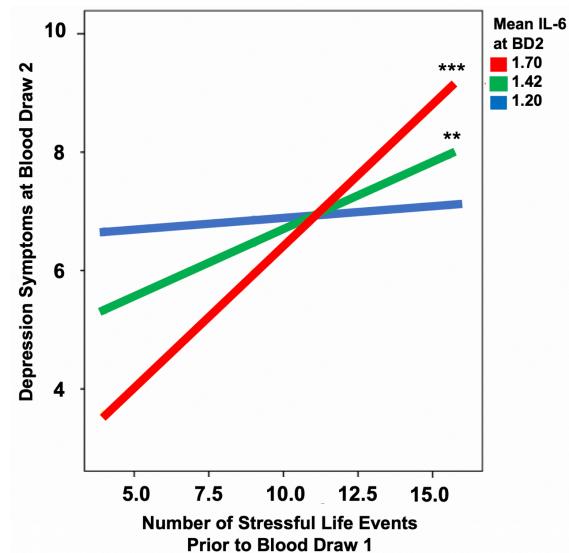


Fig. 3. Prospective depressive symptoms as a function of recent stressful events and increases in inflammation (IL-6) following those stressors. Dep Sxs at blood draw (BD) 2 were greatest for Ps who experienced a higher # of recent stressful events prior to BD1 and who showed the greatest increases in IL-6 between BD1 and BD2 (over a yr.) *** $p<.001$. (Kautz et al., in press).

C.1.e. Orbitofrontal cortex (OFC) activation during social reward anticipation as a function of inflammation

Supporting Aim 2.1, in Project ACE, child adversity on the Children's Life Events Scale¹⁹⁹ (which we will use) was associated with lower VS activation during anticipation and receipt of monetary rewards ($r's= -.37$ to $-.75$, $p's<.05-.01$), and with elevated inflammation ($b's=.065-.141$, $p's=.012-.008$), controlling for BMI. Consistent with child adversity as a potential moderator of associations between inflammation and RR (Aim 2.1), the association between elevated inflammation and lower bilateral VS ($B= -1.05$, $SE=.422$, $p<.05$) and OFC ($B= -.582$, $SE=.311$, $p<.01$) activation to anticipation of monetary rewards was stronger in Ps with child adversity. And, consistent with Aim 3, child adversity moderated the inflammation – MD association, such that higher IL-6 values predicted greater risk for MD episodes 6 mo. later, especially for teens with high adversity.⁹⁶

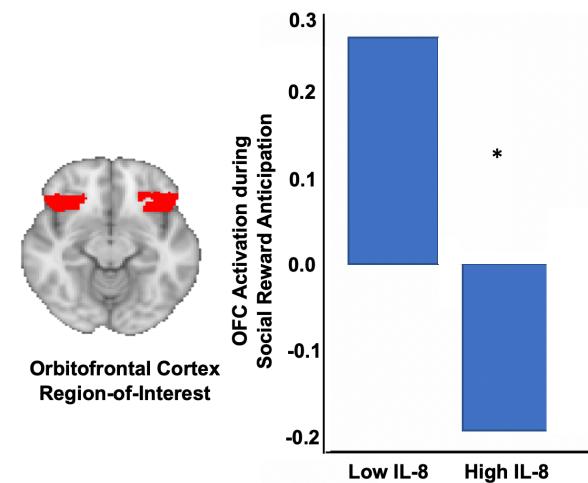


Fig. 4. Orbitofrontal cortex (OFC) activation during social reward anticipation as a function of inflammation. Mean OFC activation during social reward anticipation in the Chatroom Interact Task for Ps with elevated (+1 SD) versus low (-1 SD) levels of peripheral inflammation (IL-8). * $p<.05$. (Alloy et al., in prep).

RR (est=1.875, $p<.06$) and predicted higher next-day Dep Sxs (est= -0.053, $p<.02$).²⁰² Longer actigraphic sleep onset latency and lower sleep efficiency also predicted greater Dep Sxs at 6 mo. follow-up.²⁰² Finally, in our Project ACE sample, self-reported dysregulated sleep behaviors in the past mo. were associated with elevated inflammatory cytokines ($r's = -.14$ to $-.16$, $p's <.05$).

Thus, taken together, our preliminary findings provide a strong basis for the aims of this proposal and suggest that inflammation-enhancing behaviors and sleep disruption can drive changes in both RR and inflammation.

C.2. Project Overview, Rationale, and Investigative Team

C.2.a. Overview and Rationale. We will recruit 300 racially diverse, male and female high school freshmen, ages 14-15, from Phila. and the surrounding area to complete a 3-yr. prospective longitudinal study. Ps with no prior MD will be recruited along the entire RR dimension, from low to high, based on self-reported RR, with oversampling at the low dimensional tail (C.3.). Ps at the low end of the RR dimension are theorized to be at elevated risk for 1st onset of MD/Dep Sxs relative to those along the rest of the dimension. This design will increase the likelihood of MD onsets and facilitate examination of whether individual differences in trajectories of RR and immune function and the interaction between RR and inflammation are vulnerabilities to 1st onset of MD and Dep Sxs. At T1, T3, and T5, each a yr. apart, Ps will complete blood draws to quantify systemic (protein and cytokine biomarkers) inflammation, self-report and behavioral measures of RR, and fMRI scans of activation and functional connectivity within the cortico-striatal reward neural circuit during monetary and social reward tasks. At T1-T5 (with T2 and T4 6 mo. between the yearly sessions), Ps also will complete diagnostic interviews, and measures of Dep Sxs, pubertal maturation, recent life events coded for reward-relevance, and other behaviors that increase inflammation (e.g., substance use, high-fat diet, disrupted sleep), for a total of 3 yrs. of follow-up. Ps' mothers will serve as additional informants at T1 to provide information about the Ps' childhood adversity history and family history of mood disorders. The multiple timepoints will allow us to assess trajectories of RR and inflammation, i.e., whether baseline, chronic, or worsening RR and inflammation abnormalities over time best predict 1st onset of MD/Dep Sxs separately and jointly (and in response to Rew-D events). Assessment of child adversity and Rew-D events and other inflammation-enhancing behaviors allow us to test a potential moderator and mediators, respectively, of RR-immune predictive associations over time.

The decision to recruit 14-15 yr. old high school freshmen was based on several important scientific and feasibility considerations: 1) Epidemiological studies of MD incidence suggest that the steepest rise in rates of 1st onset of MD occurs between ages 15-18⁹⁻¹² (see A.3.); 2) Existing evidence also suggests that RR normatively increases in adolescence, and may start to peak around ages 15-16^{47,52} (A.3.); 3) MPI Alloy's prior experience in Project ACE (MH101168) suggests that Ps are more likely to assent to blood draws starting at age 14; 4) SU (a hypothesized mediator of RR-inflammation associations) begins to increase in mid-adolescence; 5) High school freshmen will still be in the Phila. area for the full 3-yr. follow-up period (e.g., not leaving for college yet); 6) High school freshmen will be relatively homogeneous with respect to life transitions and experiences. Thus, our planned sample gives us the best opportunity for observing trajectories of RR-inflammation associations and prediction of 1st onset of MD (see C.4.a. for expected rates of MD onsets).

C.2.b. Investigative Team. The team has collaborated previously and has expertise in longitudinal studies (Alloy, Nusslock, Ellman, Miller, Olino), reward-related function and neuroimaging (Alloy, Nusslock, Olino, Chein), psychoneuroimmunology (Ellman, Miller), biostatistics (Olino), and Sx, diagnostic, life event, child adversity, and inflammation-enhancing behavior assessments (Alloy, Nusslock, Ellman, Miller, Olino).

C.3. Sample Selection, Characteristics, and Feasibility of Recruitment

C.3.a. Screening and Recruitment. As required, screening and recruitment methods and feasibility data are in 2.5, Human Ss & Clinical Trials Form. Three hundred, 14-15 yr. old, racially diverse male and female high school freshmen from the Phila. area, with no prior MD, will be recruited based on two self-report measures of RR to assess an underlying RR dimension: Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) Scales²⁰³ and Sensitivity to Punishment (SP)/Sensitivity to Reward (SR) Questionnaire (SPSRQ).²⁰⁴ The BAS and SR scales are reliable and valid measures of RR²⁰³⁻²¹² that we used to select Ps with different levels of RR previously.^{205,207} Moreover, we demonstrated that RR as assessed by both measures is a dimensional, not a categorical, vulnerability.²¹³ We will screen up to 5000 Ps on demographics and these two RR measures. Based on their scores on **BOTH** the BAS and SR ($r=.40$) scales, we will recruit Ps as follows: 200 Ps from the low (0-20th%) tail of the RR dimension, and 100 Ps from the rest of the dimension, distributed such that 25 Ps each come from the 21-40th%, the 41-60th%, the 61-80th%, and the 81-100th%. We will recruit equal numbers of males and females within each percentile bin, to allow exploration of sex differences (see C.3.c.). Ps from all races/ethnicities will be eligible. This design, with oversampling at the low tail, insures both that we will have the full dimension of RR represented in the sample and enough Ps at increased risk for MD and Dep Sxs (0-20th%). Final determination of the presence of a prior MD will be based on the full lifetime diagnostic interview given in person at T1 (C.4.a.i.). However, to increase feasibility, Ps with a possible prior MD based on the Dep section of the diagnostic interview given in a phone screening interview prior to T1 will not be invited to the T1 session. This will decrease the # of Ps who have to be excluded at T1 and save much time and money. To account for ineligibility, we will initially recruit 360 Ps to obtain our target sample of N=300.

Based on our prior studies, we estimate a 10% attrition rate across the project, yielding N=270 Ps for data analysis (C.7). MPI Alloy has had great success recruiting Ps in this way previously (MH077908, MH102310).

C.3.b. Exclusion Criteria. As required, our exclusion criteria are in 2.2, Human Ss & Clinical Trials Form.

C.3.c. Sex differences. The well-established female preponderance in rates of Dep first emerges in adolescence,⁹⁻¹³ and females may show reduced self-report and neural RR relative to males.²¹⁴⁻²¹⁶ Preliminary research also suggests that males display increased, and females decreased, reward-related brain function in response to stress.²¹⁷ Females also are more likely than males to be diagnosed with some inflammatory diseases,²¹⁸ and some studies found that inflammatory biomarkers, typically CRP or IL-6, are higher in adult females than males.^{219,220} In our Project ACE (MH101168) adolescent sample, we also found that females had higher levels of CRP and IL-6 than males, both concurrently and prospectively.²²¹ Although sex differences are not a focus of this project, we will explore sex as a moderator of the associations in our aims. We have adequate statistical power to do this for Aims 1, 2, and for predicting Dep Sxs in Aim 3, although we may be underpowered to detect sex differences in prediction of 1st onset of MD in Aim 3 (see C.8.).

C.4. Project Methods (See **Table 1** for a summary of project assessments and their timing).

An important consideration is whether to use assessments designed for youth or adults. Our Ps will be in mid-adolescence at T1, but in late adolescence by T5. Changing assessments in the middle of a longitudinal study (as we did in Project ACE [MH101168]) as Ps age out of the youth versions creates major problems for assessing trajectories, because of lack of comparability of the youth and adult versions. One cannot distinguish whether observed changes in trajectories are due to true changes in the construct or measures that are not comparable. Also, MPI Alloy found that 14-15 yr. old Ps in Project TEAM (MH077908, MH102310) were able to validly complete adult versions of our Sx/diagnostic, RR, and life event assessments, and our fMRI RR tasks are appropriate for adolescents and sensitive to developmental effects.²²²⁻²²⁵ Thus, we have decided to use the same, mostly "adult" versions of our instruments/tasks for the full duration of our project.

C.4.a. Diagnostic/Symptom Assessments (T1-T5; every 6 months).

C.4.a.i. Diagnostic Assessments. At T1, lifetime history of mood and other disorders based on DSM-5 criteria²²⁶ and Research Diagnostic Criteria (RDC)²²⁷ will be assessed with the expanded SADS-L (exp-SADS-L) diagnostic interview²²⁸ by interviewers blind to Ps' RR, inflammation, and childhood adversity scores. Ps who meet criteria for a past MD at T1 will be excluded from the study. Ps will be pre-screened for a past MD with the Dep section of the exp-SADS-L during a phone-screening interview prior to T1. The exp-SADS-L was modified to include DSM criteria,^{205,206,229} has an accompanying Change version, and does not have skip outs in the mood sections, insuring that we obtain all mood Sx ratings even if a P does not meet criteria for a mood disorder. Inter-rater reliability of the exp-SADS-L in MPI Alloy's lab is $\kappa > .90$ for MD.^{205,206,229,230} At T2-T5, interviewer-rated Sxs, functioning, and onsets of DSM-5 or RDC MD and other disorders (e.g., anxiety, eating, SU) since the previous interview will be assessed with an expanded SADS-Change (exp-SADS-C)^{205,206,208,229} interview. Every Dep Sx will be assessed at each timepoint. Similarly, all 9 impairment questions (e.g., psychotherapy/medication use, interference) will be asked at each time. Inter-rater reliability of the exp-SADS-C in MPI Alloy's lab is $\kappa = .90$.^{205,206,208,229} Our prior validity study showed that Sxs on the exp-SADS-C are rated with >70% accuracy compared to daily Sx ratings obtained prospectively.^{206,229} At T1, Ps' mothers also will be given the exp-SADS-L and Family History Interview²³¹ to assess history of mood disorders for themselves and other 1st and 2nd degree relatives, as mothers should be better informants on family history than the teen Ps.

C.4.a.ii. Expected Rates of MD Episodes. In **Aim 3**, we will predict 1st onsets of MD and Dep Sxs prospectively. Epidemiological studies⁹⁻¹² report rates of 1st onset of MD in adolescence ranging from 10 – 25% between ages 15-18, with several studies reporting 15-16% incidence rates. In MPI Alloy's Project ACE (MH101168) community sample of gender, racially, and SES diverse adolescents from Phila., among Ps with no prior MD, we also obtained an overall MD 1st onset rate of 15% over 3 yrs. of follow-up. However, among the Project ACE Ps with low self-reported RR (on the BAS), the MD 1st onset rate was 29.4%. Similarly, in MPI Nusslock's BrainMAPd project (MH100117), with a Chicago sample of adolescents selected to be at high risk

Table 1. Summary and Timing of Assessments

Construct	T1	T2	T3	T4	T5
Reward Responsivity (RR)					
Behav. Inhibition Scale/Behav. Activation Scale (BIS/BAS)	✓	✓			✓
Sensitivity to Punishment/Sensitivity to Reward Ques. (SPSRQ)	✓	✓	✓		✓
Attitudes Toward Self Scale (ATS)	✓	✓	✓		✓
Goal Disengagement/Goal Reengagement Scale (GDGRS)	✓	✓	✓		✓
Responses to Positive Affect Scale (RPAS)	✓	✓	✓		✓
Card Arranging Reward Responsivity Objective Test (CARROT)	✓	✓	✓		✓
Effort Expenditure for Rewards Task (EFFRT)	✓	✓	✓		✓
fMRI Monetary Incentive Delay Task (MID)	✓	✓	✓		✓
fMRI Chatroom Interact Task (CHAT)	✓	✓	✓		✓
Inflammation					
Blood Draw for Peripheral Inflammatory Biomarkers	✓	✓	✓		✓
Childhood Adversity					
Childhood Life Events Scale (CLES) (Ps and Mothers)	✓				
Childhood Trauma Interview (CTI) (Ps and Mothers)	✓				
Life Events					
Life Events Scale (LES)	✓	✓	✓	✓	✓
Life Events Interview (LEI) (Reward & Indep./Depend. coding)	✓	✓	✓	✓	✓
Inflammation-Enhancing Behaviors					
Adolescent Alcohol and Drug Involvement Scale (AADIS)	✓	✓	✓	✓	✓
Food Frequency Questionnaire (FFQ)	✓	✓	✓	✓	✓
Pittsburgh Sleep Quality Index (PSQI)	✓	✓	✓	✓	✓
Actigraphy and Sleep Diary (7 days)	✓	✓	✓	✓	✓
MD/Other Disorders/Dep Symptoms/Pubertal Maturation					
Expanded SADS-L/SADS-Change Diagnostic Interview	✓	✓	✓	✓	✓
Family History Interview (FHI) (Mothers)	✓				
Beck Depression Inventory - II (BDI-II)	✓	✓	✓	✓	✓
PROMIS-Depression Scale (PROMIS)	✓	✓	✓	✓	✓
Temporal Experience of Pleasure Scale (TEPS)	✓	✓	✓	✓	✓
Positive and Negative Affect Scale (PANAS)	✓	✓	✓	✓	✓
Pubertal Development Scale (PDS)	✓	✓	✓	✓	✓

for MD based on low RR (on the BAS), the rate of MD 1st onset was 44% over 3 yrs. of follow-up. Thus, based on these data, we conservatively estimate that 36% (N=72) of the 200 Ps we recruit from the low tail of the RR dimension (0-20th%) based on the BAS and SR, and 15% (N=15) of the 100 Ps recruited from the rest of the RR dimension (21-100th%), will develop a 1st onset of MD during this project, for a total of 87 MD onset cases.

C.4.a.iii. Symptom/Affect Assessments. Dep Sxs and affect also will be assessed at T1-T5 with self-report measures. The Temporal Experience of Pleasure Scale (TEPS),²³² an 18-item self-report assessing anticipatory and consummatory facets of pleasure, will assess anhedonia. General Dep Sxs will be assessed with the Beck Depression Inventory-II (BDI-II)²³³ and PROMIS-Depression Scale.^{234,235} Positive and negative affect will be assessed with the PANAS.²³⁶ These scales comprehensively assess Dep Sxs and affect, have strong reliability and validity,²³²⁻²³⁷ and were used in our prior projects (MH077908, MH102310, MH107495).

C.4.b. Reward Assessments (T1, T3, T5; yearly).

C.4.b.i. Self-report and Behavioral RR Measures. In addition to the BAS and SR measures of self-reported RR, a tendency to overgeneralize from failure will be assessed with the Attitudes Toward Self (ATS) Scale.²³⁸ The ATS is related to Dep Sxs, and interacts with stress to predict Dep prospectively.^{238,239} The Goal Disengagement/Goal Reengagement Scale (GDGRS)^{240,241} measures ability to disengage from goals (e.g., "It's easy for me to reduce my effort toward the goal") and to reengage with new goals (e.g., "I seek other meaningful goals"). It exhibits excellent reliability and validity^{240,241} and predicts inflammation.²⁴¹ Cognitive responses to positive affect will be assessed with the Responses to Positive Affect Scale (RPAS),²⁴² which measures the tendency to accentuate (self- and emotion-focused subscales) or attenuate (dampening subscale) positive affect. Dampening of positive affect should be associated with cortico-striatal attenuation in functional connectivity analyses. Moreover, RPAS dampening is associated with Dep,²⁴²⁻²⁴⁴ and we found that it interacts with RR to predict inflammation and Dep Sxs prospectively.²⁴⁵

We will assess RR further with 2 behavioral tasks. The Card Arranging Reward Responsivity Objective Test^{246,247} (CARROT) is a brief 3-trial task measuring the extent to which Ps increase their card-sorting speed when offered small financial incentives compared to a no-reward condition. It has been validated,²⁴⁸ correlates with self-reported RR,^{205,249} predicts Dep episodes (C.1.a.ii.), and relates to the DRD2 gene.²⁵⁰ In the Effort Expenditure for Rewards (EEfRT) task,²⁵¹ Ps choose between performing a "hard-task" for higher reward or an "easy-task" for smaller reward. Reward magnitude and probability are varied across trials. Anhedonia and MD predict reduced choice of the hard/high reward task.^{251,252} The % of high effort options (the measure we will use) indexes the tendency to expend high effort for reward regardless of its probability. A lower % of high effort trials is associated with lower RR.²⁵³ We have used all these RR measures successfully before, including with 14-15 yr. old Ps (MH077908, MH102310).

C.4.b.ii. Neural RR Measures. Ps will complete 2 fMRI tasks we used previously (MH077908, MH100117, MH107495) to assess neural RR to monetary and social rewards at the same time of the day across yrs. We will use the well-validated Monetary Incentive Delay (MID) task²⁵⁴⁻²⁵⁶ to assess neural activity to monetary rewards for 4 reasons: 1) It has sensitivity to reward neural activity in both healthy Ps¹⁰⁵ and Ps with mood disorders.^{24,195} 2) We found that it predicted MD episodes (C.1.a.ii.). 3) It is appropriate for adolescents²²² and sensitive to developmental effects.²²³ 4) It has good short (ICCs=.52,.63 for left and right VS) and long-term (ICCs=.43, .68 for left and right VS) retest reliability,^{257,258} important to detect within-P changes in neural RR from T1 to T5 not attributable to practice effects. However, MID neural activation exhibits sufficient variation (18.5%-46.2% shared variance)^{257,258} to allow detection of changes in neural RR as a function of changes in inflammation and inflammation-enhancing behaviors. In the MID task, a circle cue signifying the opportunity to win money (Win \$0.00, Win \$0.50, Win \$5.00) or a square cue indicating the possibility of losing money (Lose \$0.00, Lose \$0.50, Lose \$5.00) is presented for 2s. Ps then must press a button when the target appears. On reward trials, Ps win money if they hit the target and do not win if they miss it; on loss trials, Ps avoid losing money if they hit the target and lose money if they miss it. Feedback depicting money won or lost on each trial is then displayed for 2s. The 6 trial types are each presented 15 times in random order, totaling 90 trials.

We will use the Chatroom Interact Task²²⁴ (an updated version of the Chatroom Task²⁵⁹⁻²⁶¹) to assess neural activity to social rewards also for 4 reasons: 1) It reliably activates cortico-striatal neural circuitry.²²⁴ 2) It is sensitive to reward neural activation in Ps with, and at familial risk for, Dep.^{224,225} 3) We have used it successfully in adolescents,²²⁴ and 4) We found that elevated inflammation was associated with lower cortico-striatal activation on this task in Project Ace¹⁹⁸ (MH101168) (C.1.c.). This task was designed to investigate reactions to social acceptance (reward) and rejection (loss) from virtual peers in an online setting. Ps rank virtual same-age, same-sex peers on how much they would like to interact with them based on a photo and their interests, pose for their own photo, and provide their own interests. At the fMRI session, Ps are matched with their two highest rated "virtual peers", and participate in a "chat game" with these peers via remote connection. Photos of the peers and P are projected on the screen two at a time, as each person (the P and the two virtual peers) takes turns selecting who they would rather talk to about common interests (e.g., music, friends). The photo of the selected person is highlighted and an "X" is placed through the photo of the rejected

person. Trials are arranged in blocks with predominant (70%) acceptance or (70%) rejection feedback. A fourth block is used as a motor and perceptual control task to control for viewing faces (self and others) and pressing a button to identify a stimulus appearing on one of the faces. Although implemented in blocks, we will analyze the task based on specific events (acceptance = reward trials; rejection = loss trials). As Ps age, they will complete the same task; however, the profiles and photos will be updated to match Ps' developmental level.

C.4.b.iii. MRI Data Acquisition and Preprocessing. Neuroimaging data will be acquired using a Siemens MAGNETOM Prisma 3.0 Tesla MRI scanner with a 64-channel gradient head coil at TU. Ps will be familiarized with and trained on MRI procedures via a mock scanner to ease concerns and enhance data quality. Scanning protocols will be identical at T1, T3, and T5. Functional runs will use a slice-accelerated multiband EPI sequence (multiband acceleration factor: 2; GRAPPA acceleration factor: 2) covering 64 axial slices (voxel size = 2.0x2.0x2.0mm; TR=2050ms; TE=25ms; FOV=208x208mm; Matrix=104x104; Flip Angle 76°). Structural images will be acquired using an MPRAGE sequence to acquire 208 axial slices (voxel size = 0.8x0.8x0.8mm; TR=2300ms; TE=2.99ms; FOV=256x256; Matrix=320x320; Flip Angle=7°). Data will be processed with SPM software using standard procedures. A nuisance variable for high motion volumes and six variables of no interest for motion will be included in all analyses. High motion volumes (> 2mm) will be censored (we will adjust this censoring threshold for our adolescent Ps if required).

C.4.b.iv. fMRI Analyses. *MID Task*: At the first level (single P), we will use a GLM identifying the 6 trial types (Win or Lose \$0.00, \$1.50, \$5.00) during the anticipation and outcome phases to deconvolve the HRF for the MID task. The anticipation phase will be after Ps see the reward cue and before the target response (2-2.5s). The outcome phase will be after Ps receive feedback on trial outcome (2s). First-level voxel wise t-statistics will be generated for each P in contrasting reward (Win \$1.50, \$5.00) vs non-reward (Win \$0.00) trials to assess reward anticipation and outcome, and loss (Lose \$0.50, \$5.00) vs non-loss (Lose \$0.00) trials to assess loss anticipation and outcome.^{255,256} Primary analyses will focus on reward anticipation and outcome trials given both these phases are associated with Dep.¹²⁷ If analyses support predictions, follow-up analyses will examine loss anticipation and outcome trials to examine specificity of results to reward processing.

Chatroom Interact Task: Although implemented in blocks, we will analyze the task based on specific events (e.g., acceptance, rejection). A first-level fixed-effect model will be constructed for each P and predetermined condition effects at each voxel will be calculated using a t-statistic. Analyses will focus on reward trials (peer acceptance) vs the motor control task given social reward processing deficits are associated with Dep.^{138,224} If analyses support predictions, secondary analyses will examine loss trials (peer rejection) vs the motor control task to examine specificity of results to reward processing.

ROI Parameter Estimates for fMRI Activation Analyses. We will extract fMRI parameter estimates of neural activation during the MID and Chatroom Tasks from a priori regions-of-interest (ROIs) using MarsBar²⁶² (an SPM toolbox), and import them into an external stats package for analyses (C.7.). Primary analyses will use a separate bilateral VS and OFC ROI for both the MID and Chatroom Tasks. These ROIs will be defined according to anatomical atlases to insure independence from functional data.^{263,264} We will conduct supplementary analyses on the left and right VS and OFC ROIs separately and whole brain analyses to assess the specificity of findings to a priori defined ROIs. Family wise error rate at $p<.05$ will be used for all analyses.

Functional Connectivity Parameter Estimates for Analyses. Growing evidence suggests that Dep not only is associated with low VS reactivity, but also a propensity to engage the PFC in a manner that dampens the VS to rewarding stimuli and suppresses positive emotions^{24,128} (C.1.a.iii.). Accordingly, we will use multivariate autoregressive modeling²⁶⁵ to generate parameter estimates of functional connectivity within the cortico-striatal circuit for each P during the MID and Chatroom Tasks. We will focus on a seed-to-seed association between the OFC and VS. In connectivity analyses, a negative (i.e., <0) parameter estimate indicates that "high" activity in one region (e.g., OFC) corresponds with "low" activity in the other region (e.g., VS), reflecting cortico-striatal attenuation tendencies. By contrast, a positive (i.e., >0) parameter estimate indicates that "high" activity in one region (e.g., OFC) corresponds with "high" activity in the other region (e.g., VS). Like our activation analyses, connectivity analyses will focus on reward anticipation and outcome trials during the MID and reward trials (peer acceptance) during the Chatroom Task, with follow-up analyses of loss trials to examine specificity.

C.4.c. Immune Assessments (T1, T3, T5; yearly)

C.4.c.i. Blood Draw Procedures. Blood will be drawn into Serum Separator Tubes (Becton-Dickinson) via antecubital venipuncture by a certified phlebotomist at T1, T3, and T5, between 2-5 PM, to control for diurnal variations and meal intake. This time period is optimal because late afternoon is a stable time of cytokine activity in contrast to other periods of the day when marked diurnal changes occur.^{266,267} Time of blood draw and last meal, and food eaten at last meal will be recorded to include as covariates in analyses if needed. Ps will be asked to fast after 9 am on the day of the blood draw. Ps will be given a meal/snack after the blood draw, before completing other tasks. Blood samples will be centrifuged, and the serum will be harvested, divided into aliquots, then frozen and stored at -80°C, until shipped to Co-I Miller for assays. We followed these procedures successfully in prior studies (MH077908, MH101168).

C.4.c.ii. Potential Immune Confounders. We will statistically control for variables that could confound inflammation analyses,²⁶⁸ including age, race, SES, total adiposity, body temperature, last date of menstruation for females, contraceptive use, medications, and other major illnesses. Total adiposity will be assessed by body mass index (BMI) based on directly measured height and weight. We also will explore whether BMI is an additional mediator of RR-inflammation associations. Body temperature will be taken by ear thermometer and Ps will be rescheduled if they have an acute fever. Other potential confounders will be assessed by interview at the time of the blood draws. Alcohol, nicotine, and drug use will be assessed with the Adolescent Alcohol and Drug Involvement Scale²⁶⁹⁻²⁷¹ (AADIS; C.4.f.ii.) and will be examined as a potential mediator of RR-inflammation associations. See C.4.g. for how we will handle psychotropic medication use.

C.4.c.iii. Inflammatory Assays. We will quantify 5 biomarkers of low-grade inflammation: C-reactive protein (CRP), interleukin (IL)-6, -8, -10, and tumor necrosis factor- α (TNF- α). CRP will be measured by high sensitivity immunoturbidimetric assay on a Roche/Hitachi cobas c502 analyzer (lower limit of detection, 0.2mg/L). Cytokines will be measured in duplicate by electrochemiluminescence (ECL) on a SECTOR Imager 2400A (MesoScale Discovery) with a Human Pro-Inflammatory Ultra-Sensitive assay (MesoScale Discovery), per manufacturer's instructions. Per previous work,²⁷² we will z-score the values of each biomarker and then sum them to form a composite score. A higher score on this composite reflects more low-grade inflammation. Secondary analyses will explore the role of individual biomarkers to assess for specificity. Because CRP values >10 mg/mL are indicative of acute infection, trauma, or chronic illness, we will exclude these observations from analysis.²⁷³ We expect sufficient variation in these 5 biomarkers across T1 to T5, given that 2 yr. retest correlations in our lab were a maximum $r = .56$, accounting for 31.4% of shared variance.

C.4.d. Child Adversity Assessments (T1 only). The Children's Life Events Scale (CLES)¹⁹⁹ is a checklist of 50 moderate to major stressors (e.g., deaths of close family or friends, sexual, physical, and emotional abuse). Given that Ps may have been too young to remember some events, Ps and their mothers separately will respond yes or no to each event that occurred to the P prior to T1 and, if yes, the P's age when it occurred. Total scores (0-50) will serve as one measure of child adversity. The CLES showed predictive validity^{199,274,275} and good internal consistency ($\alpha=.75$) in our previous grant (MH101168). Moreover, it predicted Dep Sxs, neural reward response, and inflammation in interaction with recent stressors (C.1.d.). Ps and their mothers also will separately complete the Childhood Trauma Interview (CTI),²⁷⁶ a semi-structured interview of trauma experiences (separations/losses; physical neglect; emotional, physical, sexual abuse; witnessing violence). It has high inter-rater reliability (ICC=.82-.94), and good validity.^{276,277} Elevated CTI scores were associated with lower RR (on the BAS; $r = -.20$, $p=.004$) and elevated inflammation ($r=.19$; $p=.01$) in a prior grant (MH100117).

C.4.e. Life Events Assessments (T1-T5; every 6 months). At T1-T5, Ps will complete the Life Events Scale (LES),²⁷⁸ with 135 negative events in multiple domains (e.g., school, peers, romantic interests, family, financial, etc.) relevant to adolescents. Events have been coded as Rew-D (events involving goal failures or loss of rewards) or non-Rew-relevant with good inter-rater reliability (α 's=.79-.94).²⁷⁹ Then, Ps complete a Life Events Interview (LEI)^{66,278} about the endorsed events, which also dates their occurrence. Interviewers will be blind to all screening, MD/Dep Sxs, RR, inflammation, and childhood adversity measures. The LEI uses manualized, event-specific definitions to maintain consistency. Events not meeting definitional criteria are disqualified to reduce subjective reporting biases. The LEI also uses the "gold-standard" contextual threat method^{278,280,281} to rate the events' objective impact and independence (e.g., death of a family member) vs. dependence (fight with a friend) on the P's behavior. These procedures have yielded excellent reliability and validity of event dating and ratings ($\kappa=.76$ -.89) in our previous studies and grants.^{278,282}

C.4.f. Inflammation-Enhancing Behavior Assessments (T1-T5; every 6 months).

C.4.f.i. Stress Generation. The # of Rew-D events rated as dependent on Ps' behavior (C.4.e.) will measure stress generation. Self-generated Rew-D events activate stress biology and inflammatory signaling.⁷³

C.4.f.ii. Substance Use and Diet. Ps' frequency of use of nicotine, alcohol, and 10 other drug types over the past mo. will be assessed with the Adolescent Alcohol and Drug Involvement Scale (AADIS).²⁶⁹ The AADIS is reliable and valid²⁶⁹⁻²⁷¹ and associated with neural RR and elevated inflammation (C.1.e.ii.). Ps' frequency of consumption of high fat and high sugar foods will be assessed with the Food Frequency Quest. (FFQ).²⁸³ It allows calculation of nutrient intake, is reliable and valid, and has been used in large-scale survey studies.²⁸³⁻²⁸⁶

C.4.f.iii. Sleep Disruption. We will assess sleep disruption with both subjective and objective measures. The Pittsburgh Sleep Quality Index (PSQI)^{287,288} is the most commonly used, well-validated self-report of sleep quantity and quality. Actigraphy provides an objective, reliable, and valid method for assessing sleep and activity patterns in Ps' natural environment with minimal restriction on normal routines.²⁸⁹⁻²⁹⁴ Actigraphy corresponds highly with sleep diaries and polysomnography, including in adolescents.^{291,292} Ps will wear an Actiwatch (Philips Healthcare, Bend, OR) on their non-dominant wrist continuously for 7 days at each timepoint, only removing it when it might get wet (e.g., bathing) or for the fMRI scans. Data will be sampled in 1-min epochs and stored digitally. Sleep variables will include: sleep onset latency (time between bedtime and sleep onset); wake after sleep onset; sleep duration; sleep efficiency (% time spent asleep); # of awakenings;

and weekday/weekend sleep ratios.²⁹⁵ Also, we will derive hourly activity counts (an objective measure of inactivity during daytime). To assist with interpretation of actigraphy data, Ps also will complete an online sleep diary^{296,297} each morning of the actigraphy wk., which will assess sleep parameters (e.g., bedtime, waketime), naps, medications, caffeine use, exercise for the prior day. Missed assessments will trigger reminders to Ps' smartphones. We have successfully processed actigraphy data and used these sleep measures (MH102310).

C.4.g. Potential Confounding Variables.

C.4.g.i. Pubertal Maturation (T1-T5; every 6 months). Several studies in humans indicate that self-report, behavioral, or neural (functional and structural) RR is associated with pubertal maturation assessed via Tanner stages, the Pubertal Development Scale (PDS)²⁹⁸ or hormone levels, even controlling for chronological age.⁵⁶⁻⁶⁰ Research also suggests a link between pubertal maturation and inflammation.²⁹⁹⁻³⁰¹ However, little direct research has examined pubertal status and levels of inflammatory biomarkers (e.g., cytokines and CRP). In our Project ACE (MH101168) adolescent sample, controlling for chronological age, more advanced pubertal status on the PDS was associated significantly with several inflammatory biomarkers.³⁰¹ Thus, we will assess pubertal maturation with the 5-item self-report PDS at T1-T5 and control for it as needed in our analyses. The PDS asks about growth in height, body hair, skin change, breast (females) or voice (males) change, and facial hair (males) or menstruation (females). Item scores are averaged, yielding a final score of 1-4 (less to more pubertally mature). It has good psychometric properties (average $\alpha=.77$) and convergent validity (r 's of .61-.67 with physician ratings; $r=.84$ with mothers' ratings).^{298,301-304} It also predicts MD episodes and Dep Sxs.³⁰²⁻³⁰⁴

C.4.g.ii. Medication. Given that we will exclude Ps with past MD, we do not expect high rates of medication use at T1 in our sample. However, we will not exclude Ps taking psychotropic medications since this would reduce the representativeness of our sample and limit generalizability of our findings, given that there may be elevated rates of medication use in individuals at risk for MD.^{305,306} We will statistically control for medication status (on vs. off) in analyses. Further, we will re-run analyses after removing Ps taking dopaminergic agonists/antagonists given the role of dopamine in cortico-striatal signaling.¹⁰⁵

C.4.g.iii Other Potential Confounders. We will assess handedness, BMI, contraceptive use, last date of menstruation, major illnesses, history of other psychiatric disorders, and family history of mood disorders (C.4.a.i., C.4.c.ii.) and control for them in analyses as needed.

C.5. Rigor and Reproducibility. Our protocol uses a state-of-the-art approach with high rigor as reflected in: 1) reliance on empirically-informed theory; 2) focus on adolescents at an "age of risk" for MD onset/Dep Sxs; 3) recruitment of Ps along the entire RR dimension as well as over-sampling of high-risk Ps at the low tail of the dimension expected to have higher rates of MD onset; 4) use of multiwave assessments of RR indices, inflammatory biomarkers, life events, behavioral mediators, and MD/Dep Sxs to examine RR and inflammation trajectories as predictors of MD onset and Dep Sxs; 5) use of multilevel and multimethod indices of RR, life events, sleep disruption, and child adversity; 6) use of performance-based tasks, fMRI, and actigraphy to obtain objective assessments; 7) objectively coded, in-depth life events interviews to comprehensively characterize Rew-D events; and 8) assessment of multiple potential confounders.

C.6. Feasibility. This project is highly feasible. 1) MPI Alloy has successfully recruited adolescent Ps differing on RR with our planned methods previously (2.5, Human Ss & Clinical Trials), and has extensive experience successfully conducting prospective longitudinal studies in multiple NIMH R01 grants. 2) Our preliminary studies (C.1.) demonstrate the feasibility and likelihood of promising findings from this project. 3) We have extensive and successful collaborative experience in conducting fMRI scans with the MID and Chatroom Interact tasks, in analyzing and interpreting fMRI data (MH077908, MH107495), in collecting and assaying blood for inflammatory biomarkers (MH077908, MH101168, MH096478), and with all other assessments in prior R01 grants (MH077908, MH101168, MH102310, MH107495). 4) Consultant Chein, Director of TUBRIC, has insured (see letter of support) we will be able to complete the fMRI scans at T1, T3, and T5.

C.7. Data Analysis. Data will be checked for consistency, distributions, and outliers. Assumptions underlying statistical tests will be examined and transformations used as needed. Although we will minimize missing data, we will handle any missing data with full information maximum likelihood estimation.^{307,308} We also will examine the pattern of missing data and run secondary analyses on the Ps with complete data. Preliminary analyses will determine whether potential confounding factors (see C.4.g.) are related to the outcomes and should be covaried in the main analyses. When identified, sensitivity analyses will be conducted to determine whether substantive conclusions hold when control variables are included. For BMI, we also will explore whether it is an additional mediator of RR-inflammation associations, given obesity is a driver of inflammation.^{152,153} When there are multiple indicators of the same construct (e.g., Sxs, child adversity), principal component analyses will be conducted to derive composite indices of constructs. These will be primary variables in analyses and reduce the number of tests conducted. In all sets of analyses, we will examine initial models for each unit of analysis of RR (self-report, behavioral, neural). When multiple units of analysis for RR are associated with outcomes, we will include those units in a more comprehensive model to examine whether each unit provides

unique associations with outcomes. Finally, we will explore sex differences by including sex as a moderator in Aims 1.1, 1.2, 2.2, and RR or inflammation predictions of Dep Sxs in Aim 3.

Aim 1.1. Cross-sectional Reward-Immune Associations: We will use multiple regression analyses to examine the concurrent associations between RR indices and inflammation at T1, T3, and T5.

Aim 1.2. Longitudinal Reward-Immune Associations: We will use parallel process latent growth curve models that include cross-lagged associations between constructs to examine longitudinal, reciprocal associations between RR indices and inflammation from T1 to T5. This will permit modeling between- and within-P associations simultaneously. For this aim, interests focus on within-P, cross-system associations that directly address the study aims concerning directionality of effects with a refined and rigorous analytic method.

Aim 2.1. Childhood Adversity as Moderator: We will examine the linear associations of childhood adversity with RR indices and with inflammation with multiple regression analyses. We will use moderated multiple regression to examine how childhood adversity influences the association between RR indices and inflammation at T1, T3, and T5. Further analyses will be conducted examining childhood adversity as a time-invariant moderator of these associations between intercepts for RR and inflammation and as a moderator of time-varying cross-domain (RR and inflammation) associations within the parallel process growth models.

Aim 2.2. Inflammation-Enhancing Behaviors as Mediators: We will examine indirect effects within parallel process growth models to examine whether inflammation-enhancing behaviors partially mediate RR predictors of changes in inflammation from T1 to T5 and inflammation predictors of changes in RR indices from T1 to T5.

Aim 3. Predictions of MD and Dep Sxs: Using data from the full 3 yrs. of follow-up, we will use parallel process growth models to examine longitudinal associations of T1 intercepts and T1 to T5 slopes of RR indices and inflammation with onset of MD and growth in Dep Sxs from T1-T5. To examine the joint (i.e., interactive) role of T1 RR and inflammation intercepts and growth trajectories influencing MD onset and Dep Sxs, we will specify interactions between the T1 intercepts and latent growth parameters predicting these outcomes. Similarly, child adversity will be included as a time-invariant moderator in a parallel process growth model of RR indices' or inflammation's prediction of MD onset or growth in Dep Sxs from T1-T5. A separate parallel process growth model will examine Rew-D events (whether self-generated or independent) as a time-varying moderator of RR indices' or inflammation's prediction of MD onset or growth in Dep Sxs over follow-up.

C.8. Statistical Power Estimates. Since we anticipate 10% attrition across the entire study (T1-T5; see C.3.a.), we present power estimates for n=270. We conducted simulations to identify power to detect small and small-medium effect sizes (ESs) in Mplus, v.8, using the Monte Carlo Simulation facilities.³⁰⁹

Aim 1. With n=270, we have strong power (>.89) to detect bivariate associations across measures of RR and inflammation for small ESs (i.e., $r=.20$). For our parallel process growth models, we have strong power (>.90) to detect overall associations between slopes of RR and inflammation when associations are small-moderate ($r=.25$). We also have strong power to detect lagged associations across domains when associations are small-moderate ($r=.25$).

Aim 2. For tests of 2-way interactions in Aim 2.1, we conducted simulations to evaluate power to detect significant associations in the relationship between RR indices and inflammation within-person across time. We found that we have adequate power (.75) to detect medium sized ($r=.35$) ESs (i.e., differences in coefficients across high and low levels of moderators – i.e., child adversity or males vs. females). Indirect effects in Aim 2.2 will be examined within a SEM framework. Previous simulations³¹⁰ have demonstrated that there is adequate power (.80) to detect indirect effects for at least small-medium ESs for the predictor to mediator and mediator to dependent variable paths with n=270. In our simulation specifying the same small-medium effects, with n = 270, we have good power to detect these significant indirect effects (.86).

Aim 3. We will predict 1st onsets of MD and Dep Sxs prospectively. As justified in C.4.a.ii., we indicated that we conservatively estimate that 36% (N=72) of the 200 Ps from the low tail of the RR dimension (0-20th% on the BAS and SR), and 15% (N=15) of the 100 Ps recruited from the rest of the RR dimension (21-100th%), will develop a 1st onset of MD by T5, for a total of 87 MD onset cases (29% base rate). Within the parallel process growth modeling framework, we also included small effects ($r=.25$) for all cross-lagged associations between indicators of each construct in the model. We found high power (>.90) to predict the binary MD diagnostic outcome and continuous Dep Sxs. This includes predictions from both the intercepts and slopes of RR and inflammation simultaneously when assuming a small-moderate ($r=.22$) ES. Within these models, we have adequate power (.70) to detect moderation by constructs (e.g., childhood adversity, Rew-D events, sex) when the difference in magnitude of association between RR/inflammation and MD is moderate ($r=.40$) for the binary MD outcome. For these additional moderation analyses, power is >.80 for the Dep Sxs outcome.

C.9. Timeline. As required, our project timeline is in Section 2.7 of the Human Ss & Clinical Trials Form.

C.10. Summary. If funded, this project will provide crucial knowledge about the role of reward-immune dysregulation as a two-hit vulnerability for 1st onset of MD and increases in Dep Sxs in adolescence. As such, it could lead to the development of novel neuroimmune interventions to treat, and ideally prevent, adolescent Dep before it undermines health, educational pursuits, and becomes a lifelong problem in adulthood.

PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

Are Human Subjects Involved	<input checked="" type="radio"/> Yes	<input type="radio"/> No
Is the Project Exempt from Federal regulations?	<input type="radio"/> Yes	<input checked="" type="radio"/> No
Exemption Number	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8	
Other Requested Information		

Human Subject Studies

Study#	Study Title	Clinical Trial?
1	Integrated Reward-Inflammation Model of First Onset of Major Depression in Adolescence	No

Section 1 - Basic Information (Study 1)

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

1.1. Study Title *

Integrated Reward-Inflammation Model of First Onset of Major Depression in Adolescence

1.2. Is this study exempt from Federal Regulations *

Yes No

1.3. Exemption Number

1 2 3 4 5 6 7 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?

Yes No

1.4.b. Are the participants prospectively assigned to an intervention?

Yes No

1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?

Yes No

1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?

Yes No

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

Section 2 - Study Population Characteristics (Study 1)

2.1. Conditions or Focus of Study

- Depression
- Depressive Disorder
- Immunity
- Inflammation
- Reward
- Functional Magnetic Resonance Imaging
- Sleep
- Affect
- Affective Symptoms

2.2. Eligibility Criteria

Inclusion Criteria and Sample Selection. Three hundred, 14-15 year old, racially diverse male and female high school freshmen from Philadelphia and the surrounding community (including Phila., the Phila. suburbs, southern New Jersey [e.g., Camden, Cherry Hill], and northern Delaware [Wilmington and north]) will be recruited based on their scores on two self-report measures of trait reward responsivity (RR) to assess an underlying RR dimension: Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) Scales (203) and Sensitivity to Punishment (SP)/Sensitivity to Reward (SR) Questionnaire (SPSRQ; 204). The BAS and SR scales are reliable and valid measures of RR (203-212) that we have used to select participants (Ps) with different levels of RR previously (205,207; MH077908; MH102310). Moreover, we recently demonstrated that RR as assessed by both measures is a dimensional, and not a categorical, vulnerability (213). Ps will include 14-15 year old high school freshmen for both scientific and feasibility reasons. First, epidemiological studies of incidence of major depressive disorder (MD) suggest that the steepest rise in rates of 1st onset of MD occurs between ages 15-18 (9-12; see A.3.) and evidence also suggests that RR normatively increases in adolescence, and may start to peak around ages 15-16 (47,52; A.3.). Second, MPI Alloy's prior experience in Project ACE (MH101168) suggests that Ps are more likely to assent to blood draws starting at age 14. Third, substance use (a hypothesized mediator of RR-inflammation associations) begins to increase in mid-adolescence. Fourth, high school freshmen will still be in the Philadelphia area for the full 3-year follow-up period (e.g., not leaving for college yet). Finally, high school freshmen will be relatively homogeneous with respect to life transitions and experiences. Thus, our planned sample gives us the best opportunity for observing trajectories of RR-inflammation associations and prediction of 1st onset of MD (see C.4.a.ii. for expected rates of MD onsets). We will endeavor to recruit Ps who are demographically representative of 14-15 year old high school freshmen in Philadelphia and the surrounding area (see 2.5, Recruitment and Retention Plan, Human Ss & Clinical Trials Form). Ps will be recruited primarily via Facebook ads, other social media (e.g., Instagram) ads, Craig's List ads, community newspaper ads, and flyers posted in local coffee shops/restaurants, sports centers, community recreation centers, places of worship, etc. (directed at high school freshmen and/or their parents) throughout Philadelphia area neighborhoods. A second recruitment method will be through contacting Philadelphia area high school principals and requesting permission to screen their freshmen students during homeroom advisory periods. In her previous R01 grants (MH077908, MH102310), MPI Alloy was able to successfully screen 10,000 high school students in this way (205). Please see Section 2.5, Recruitment and Retention Plan, in the Human Ss & Clinical Trials Form, for specific details on our recruitment methods, the feasibility of these methods, and likely sample demographics.

We will screen up to 5,000 14-15 yr. old high-school freshmen on demographics, contact information, and these two RR measures with a screening survey. The screening survey will be administered in several ways depending on method of recruitment. For high school freshmen recruited through social media ads, newspaper ads, or flyers in the community, Ps will be directed to the screening survey on MPI Alloy's HIPAA secured lab website via a link on the Facebook ads, other social media ads, Craig's List ads, newspaper ads, or on the flyers posted in the locations around the community. For Ps recruited during homeroom advisory periods in their high schools, the screening survey will be administered in a paper and pencil format. Either means of completing the screening survey will require P assent and a parent's active or passive consent (see 3.1, Protection of Human Subjects, in the Human Ss & Clinical Trials Form for details). Based on their scores on BOTH the BAS and SR ($r = .40$) scales, we will recruit Ps as follows: 200 Ps from the low (0-20th%) tail of the RR dimension, and 100 Ps from the rest of the dimension, distributed such that 25 Ps come from the 21-40th%, 25 from the 41-60th%, 25 from the 61-80th%, and 25 from the 81-100th%. We will recruit equal numbers of males and females within each percentile bin, to allow exploration of sex differences (see C.3.c.). Ps from all races/ethnicities will be eligible. This design, with oversampling at the low tail, insures both that we will have the full dimension of RR represented in the sample and enough Ps at increased risk for MD and depression symptoms (0-20th%). Final determination of the presence of a prior history of MD will be based on the full lifetime diagnostic interview given in person at Time 1. However, to increase feasibility, Ps with a possible prior MD based on the Depression section of the diagnostic interview administered in a phone screening interview prior to Time 1 will not be

invited to the Time 1 session. This will decrease the number of Ps who have to be excluded at Time 1 and save much time and money. To account for ineligibility, we will initially recruit 360 Ps to obtain our target sample of N=300 Ps. MPI Alloy has had great success recruiting Ps in these ways previously (MH077908, MH102310).

Exclusion Criteria. We will exclude Ps with a history of MD because one of the aims of this project is to predict 1st onset of MD in adolescence. Final determination of the presence or absence of a history of MD will be based on the expanded-Schedule for Affective Disorders and Schizophrenia-Lifetime (exp-SADS-L; 205,206,228,229) diagnostic interview administered to Ps in person at the Time 1 session (see C.4.a.i. in Research Strategy). However, to decrease the number of Ps who need to be excluded at the Time 1 session because of a prior MD diagnosis, we will administer the Depression section of the exp-SADS-L in a phone screening interview prior to inviting Ps for the Time 1 session. Ps who potentially had a prior MD based on the phone screening interview will not be invited to attend Time 1 or enroll in the study.

In addition, we will exclude Ps with a history of cancer, heart disease, surgery, an ongoing autoimmune disease or disorder involving chronic inflammation (e.g., Crohn's Disease, Type 1 Diabetes, Lupus, asthma, severe allergies), and anyone who is HIV positive. We also will exclude anyone taking immunosuppressant medications (e.g., an inhaler, systemic steroids, nonsteroidal anti-inflammatory drugs [NSAIDs]) in the past three months. We believe that this approach strikes the right balance between allowing us to enroll a sample that is generalizable to the broader population, while excluding Ps whose inflammatory profile is likely affected by disease or treatment. These exclusion criteria also will be assessed in the phone screening interview (using the physical health and chronic conditions items from the World Health Organization World Mental Health Composite International Diagnostic Interview [WHO WMH-CIDI] (311) prior to the Ps' Time 1 visit. Ps who meet these exclusion criteria will not be invited to Time 1 or be enrolled in the study. Screening for immune-related diseases and medications with this type of standardized instrument is standard practice in studies of inflammation (312,313). The rate of immune-related diseases in 14-15 year olds is relatively low (314, 315); thus, we should not need to exclude many Ps on this basis. We will re-administer the physical health and chronic conditions items from the WHO WMH-CIDI at the Time 1, Time 3, and Time 5 sessions to assess whether there are any changes in Ps' physical health status as it pertains to autoimmune diseases or disorders involving chronic inflammation. We also will screen for acute infections at the Time 1, Time 3, and Time 5 sessions and will reschedule enrolled Ps if they display a fever (> 99.0 as assessed by an ear thermometer) or self-report symptoms. Because CRP values >10 mg/mL are indicative of acute infection, trauma, or chronic illness, we also will exclude these observations from further analysis (273). Ps also will be excluded according to standard MRI exclusion criteria (e.g., metal in the body, traumatic brain injury, pregnancy, severe claustrophobia; assessed with the TUBRIC standard MRI screening form). Given the nonverbal nature of our fMRI tasks, left-handedness is not considered a justifiable exclusion criterion; instead we will control for handedness if needed. Handedness will be assessed with the Chapman & Chapman Handedness Scale (316). Likewise, we will control for psychotropic medication use (see C.4.g.ii.), but not exclude on the basis of psychotropic medications. Given elevated rates of psychotropic medication use in individuals with, and at risk for, mood symptoms (305,306), excluding such Ps would reduce the representativeness of our sample and limit generalizability of our findings.

Based on the exp-SADS-L diagnostic interview administered in person at Time 1 (see C.4.a.i.), we also will exclude Ps with current psychotic symptoms (hallucinations, delusions) to insure validity of our assessments. To maximize the ecological validity and generalizability of findings from our sample, we will not exclude Ps on the basis of a past history of other psychiatric disorders besides MD. Instead, we will assess for history of other psychiatric disorders (see C.4.a.i. in Research Strategy) and control for other disorders in our analyses as needed (see C.4.g.iii.). Substance and alcohol use will be assessed as inflammation-enhancing behaviors to test Aim 2.2 of the proposal, and thus, we will not exclude Ps based on substance/alcohol use. At Time 1, Ps also will be placed in a mock scanner to insure they can tolerate an MRI scan and can remain still in the scanner. If they cannot, they will be excluded from the study. Prior to placement in the mock scanner, Ps will receive training to reduce movement in the MRI scanner, which should significantly reduce the amount of movement by Ps and ultimately result in better quality images in the real scanner.

2.3. Age Limits	Min Age: 14 Years	Max Age: 15 Years
2.4. Inclusion of Women, Minorities, and Children	2.4. Inclusion.pdf	
2.5. Recruitment and Retention Plan	2.5. Recruitment and Retention.pdf	
2.6. Recruitment Status	Not yet recruiting	
2.7. Study Timeline	2.7. Study Timeline.pdf	
2.8. Enrollment of First Subject	10/01/2020	Anticipated

2.4. Inclusion of Women, Minorities and Children

1. Inclusion of Women and Minorities

Our recruitment procedures provide individuals with an equal opportunity to participate in our study regardless of gender, race, or ethnicity. Our hypotheses are not predicated on gender or ethnic/racial differences, which we have monitored for in prior studies. Indeed, we have not systematically observed differential responses in our prior studies involving reward responsivity (RR) in similar samples. However, given the emergence of sex differences in depression (Dep) in adolescence, and possible sex differences in inflammatory signaling, we will explore sex differences in this study. We plan to recruit a total sample of 300 14-15 year old high school freshmen from Philadelphia and the surrounding community (including Philadelphia, the Philadelphia suburbs, southern New Jersey [e.g., Camden, Cherry Hill], and northern Delaware [Wilmington and north]). We will recruit equal numbers of males (n=150) and females (n=150). In addition, within these equal numbers of males and females, we will recruit an ethnically and racially diverse sample, designed to be demographically representative of 14-15 year olds in the broader Philadelphia area. We anticipate that the sample will have approximately 40% Caucasian and 60% other race individuals, with approximately 12% of these individuals of Hispanic/Latino/a ethnicity. The exact ethnic and racial composition of our proposed sample is delineated in the Planned Enrollment Table in the Inclusion Enrollment Report (IER), Human Subjects and Clinical Trials Information Form (Section 2.8). To ensure that equal numbers of females and males enroll in the study and that ethnic and racial minorities will participate in the study according to the approximate breakdown delineated in the Planned Enrollment Table, we will recruit based on the demographic composition of Philadelphia area 14-15 year olds (see Section 2.5, Recruitment and Retention Plan, Human Subjects and Clinical Trials Information Form).

2. Inclusion of Children

All participants (Ps) in this study will be children, specifically 14-15 year old adolescents. We will recruit 300 14-15 year old high school freshmen from Philadelphia and the surrounding community. The sample will be recruited along the entire RR dimension, from low to high, based on self-reported trait RR, with oversampling at the low tail of the dimension (see C.3.a., Research Strategy for details). We carefully considered the best recruitment age for the sample. We selected the 14-15 age range for our sample based on six important scientific and feasibility considerations: 1) Epidemiological studies of major depressive disorder (MD) incidence suggest that the steepest rise in rates of 1st onset of MD occurs between ages 15-18⁹⁻¹² (see A.3.); 2) Existing evidence also suggests that RR normatively increases in adolescence, and may start to peak around ages 15-16^{47,52} (A.3.); 3) MPI Alloy's prior experience in Project ACE (MH101168) suggests that Ps are more likely to assent to blood draws starting at age 14; 4) Substance use (a hypothesized mediator of RR-inflammation associations) begins to increase in mid-adolescence; 5) High school freshmen will still be in the Philadelphia area for the full 3-year follow-up period (e.g., not leaving for college yet); 6) High school freshmen will be relatively homogeneous with respect to life transitions and experiences. Although we recognize the significance of also studying the role of RR and inflammation in MD in younger children, we would not observe enough 1st onsets of MD during the 3-year follow-up period if we recruited younger children. Moreover, because we will require strict adherence to our study protocol, we believe recruitment from a younger age group would increase noncompliance at this stage of our research. Thus, our planned sample gives us the best opportunity for observing trajectories of RR-inflammation associations and prediction of 1st onset of MD (see C.4.a.ii. for expected rates of MD onsets).

Justifications for Exclusion of Adolescents and Adults >15 Years Old

We carefully considered the best recruitment age for the sample. We selected the 14-15 year old age range because it is an "age of risk" for 1st onset of MD and it is a period of enhanced RR and immune system competence.^{41-60,98} In addition, a much larger proportion of an older sample would already have experienced a 1st onset of MD prior to the start of our study. Moreover, recruitment of Ps older than 15 years might lead to retention issues inasmuch as some older adolescents will leave for college before the end of the prospective follow-up. Thus, we are not recruiting Ps above the age of 15 years old, because this age is beyond the main age of risk for 1st onset of MD, would be developmentally too old to address our research questions, and would present challenges for retention.

2.5 Recruitment and Retention Plan

Recruitment of Study Sample

Initial Screening. We plan to recruit 300, 14-15 year old, racially diverse male and female high school freshmen from Philadelphia and the nearby surrounding community (including Phila., the Phila. suburbs, southern New Jersey [Camden, Cherry Hill], and northern Delaware [Wilmington and north]) to participate in a 3-year prospective study. Note that the nearby Phila. suburbs, southern New Jersey, and northern Delaware are within 30 min. drive time from Temple University. All participant (P) recruitment, data collection, and human subjects research will take place at Temple University (TU). Thus, Institutional Review Board (IRB) approval will be obtained from the TU IRB. The sample will be recruited along the entire reward responsivity (RR) dimension, from low to high, based on self-reported trait RR, with oversampling at the low tail of the dimension. This age range is chosen for 6 scientific and feasibility reasons: 1) the steepest rise in rates of 1st onset of major depressive disorder (MD) occurs between ages 15-18⁹⁻¹² (see A.3.); 2) RR increases normatively in adolescence, and may start to peak around ages 15-16^{47,52} (A.3.); 3) MPI Alloy's prior experience in Project ACE (MH101168) suggests that Ps are more likely to assent to blood draws starting at age 14; 4) substance use (a hypothesized mediator of RR-inflammation associations) begins to increase in mid-adolescence; 5) high school freshmen will still be in the Phila. area for the full 3-year follow-up period (e.g., not leaving for college yet); and 6) high school freshmen will be relatively homogeneous with respect to life transitions and experiences. Thus, our planned sample gives us the best opportunity for observing trajectories of RR-inflammation associations and prediction of 1st onset of MD (see C.4.a.ii. for expected rates of MD onsets).

High school freshmen (ages 14-15) will be recruited in two ways. The primary means of recruitment will be via Facebook ads, other social media (e.g., Instagram) ads, Craig's List ads, community newspaper ads, and flyers posted in local coffee shops/restaurants, sports centers, community recreation centers, places of worship, etc. (directed at high school freshmen and/or their parents) throughout Philadelphia area neighborhoods. These ads and flyers will contain links to an online screening survey on MPI Alloy's HIPAA secured lab website. Specifically, we have budgeted funds to place ads in newfeeds on Facebook and relevant community pages on Facebook (e.g., High School Class of 20xx, vocational school groups, Philly locals, Philly summer events, Philly foodies), other social media, and community newspapers that target 14-15 year olds and/or their parents. To provide incentive for completing the online screening survey, we also have budgeted funds for \$50 random drawing lottery prizes for Ps who complete the online screening survey via the links placed in the Facebook, other social media, and newspaper ads and in the flyers. In addition, we will place ads on the Philadelphia Craig's list for free (also with links to the online screening survey). A second recruitment method will be through contacting Philadelphia area high school principals and requesting permission to screen their freshmen students during one homeroom advisory period. Ps recruited by this method will complete the screening survey on paper (with the freshmen's written assent and passive parental consent). Below, we provide information on the feasibility of these methods.

Ps (ages 14-15 yrs.), with no prior history of MD, will be recruited based on their scores on two self-report measures of trait RR to assess an underlying RR dimension: Carver and White's²⁰³ Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) Scales and Torrubia et al.'s²⁰⁴ Sensitivity to Punishment (SP)/Sensitivity to Reward (SR) Questionnaire (SPSRQ). The BAS and SR scales are reliable and valid measures of RR²⁰³⁻²¹² that we have used to select Ps with different levels of RR previously^{205,207} (MH077908; MH102310). Moreover, we recently demonstrated that RR as assessed by both measures is a dimensional, and not a categorical, vulnerability.²¹³ The screening packet also will contain a Demographics and Contact Sheet in which Ps will provide contact information as well as age, gender, race, ethnicity, English speaking ability, and year in school. The contact information is necessary in order for us to contact potentially eligible Ps to recruit them for the study. The question about year in school (high school freshman is the required answer) is included to increase the chances that the P will be around to complete the study, if enrolled. Finally, the very first part of the online screening packet will include an assent form for the Ps and a consent form for one of their parents. Ps and parents must provide their assent and consent, respectively, on the Screening Consent Form before they can proceed to the rest of the screening survey. The screening survey packet administered in homeroom advisory period for Ps screened in their high schools (with principals' permission) will only contain an assent form for the high school freshmen to sign. Passive parental consent will be obtained in advance for conducting the screening in the homeroom advisory period. The Screening Consent Form will be approved by the TU IRB. The screening packet is the same as we have used previously (MH077908, MH102310), which was previously approved by the TU IRB.

Based on their scores on **BOTH** the BAS and SR ($r=0.40$) scales, we will recruit Ps as follows: 200 Ps from the low (0-20th%) tail of the RR dimension, and 100 Ps from the rest of the dimension, distributed such that 25 Ps come from the 21-40th%, 25 from the 41-60th%, 25 from the 61-80th%, and 25 from the 81-100th%. We will recruit equal numbers of males and females within each percentile bin, to allow exploration of sex differences (see C.3.c.). Ps from all races/ethnicities will be eligible. This design, with oversampling at the low tail, insures both that we will have the full dimension of RR represented in the sample and enough Ps at increased risk for MD and depressive symptoms (0-20th%). We will screen up to 5,000 high school freshmen in Years 1-3 (2020-2022) of the project. To account for ineligibility, we will initially recruit 360 Ps to obtain our target sample of N=300 Ps.

Demographics and Representativeness. As noted above, we will recruit equal numbers of 14-15 year old males and females in each of the RR percentile bins and will endeavor to recruit from racial/ethnic groups to be representative of high school students in Philadelphia and the surrounding areas (see PHS Inclusion Enrollment Report). The racial breakdown of Philadelphia high school age students is 35% White/Caucasian, 43% Black/African-American, 7% Asian or Asian-American, and 15% other race or more than one race, and 12% are Hispanic/Latino(a) ethnicity.³¹⁷ The % of White/Caucasian students in the Phila. suburbs and Delaware is higher. Thus, we will endeavor to recruit 14-15 year old high school freshmen form the Phila. area for this project such that 40% are White/Caucasian, 43% are Black/African-American, 7% are Asian or Asian-American, and 10% are other or more than one race, with 12% of Hispanic/Latino(a) ethnicity.

Recruitment Feasibility. MPI Nusslock (MH100117) and Co-Is Ellman (MH112613) and Olino (MH107495) have used our planned primary methods for recruiting community adolescents in their ongoing R01 grants with much success. For example, MPI Nusslock was able to recruit 53 community adolescents per month in Chicago via Facebook ads. Co-Is Ellman and Olino have been able to recruit about 15 community adolescents per month in Philadelphia via Facebook ads and another 5 per month via posted flyers. Thus, it is reasonable for us to expect to be able to recruit around 20 Ps per month from the community with these methods. In addition, in her previous R01 grants (MH077908, MH102310), MPI Alloy was able to successfully screen and recruit high school students through conducting screenings during homeroom advisory periods with the permission of high school principals.²⁰⁵ She screened approximately 10,000 high school students in this way. Currently, just within the Philadelphia School District (PSD), there are 10,105 high school freshmen attending PSD schools,³¹⁸ with more high school freshmen attending private or parochial schools in Phila. or public, private, and parochial schools in the Phila. suburbs, southern New Jersey, and northern Delaware. Thus, screening up to 5,000 high school freshmen is also feasible.

Moreover, MPI Alloy has screened and recruited Ps based on scores on both the BAS and SR previously (MH077908, MH102310), with >20,000 Ps screened and 750 recruited. Based on the results of one of her previous screening samples of 10,000 high school students, out of 5,000 Ps screened for this new proposed project, 22.5% (n=1,125), 18.3% (n=915), 29.3% (n=1,465), 12.7% (n=635), and 17.2% (n=860) will meet the joint BAS and SR criteria for the 0-20th%, 21-40th%, 41-60th%, 61-80th%, and 81-100th% bins, respectively. Given that we need 200, 25, 25, 25, and 25 Ps, respectively from these 5 percentile bins, and our estimate that 20% of Ps may be ineligible based on the exclusion criteria, we should have more than enough eligible Ps to meet our recruitment goals.

Recruitment of Ps for Time 1 (T1) Session. Ps who meet the BAS and SR inclusion criteria from the initial screening (i.e., who fall into the various percentile bins described above based on both RR measures) will be contacted by phone or email by project staff to set up a phone screening interview to determine whether they have any of the other exclusion criteria that would make them ineligible for the study (for all exclusion criteria and standardized assessment of the exclusion criteria, see Section 2.2 Eligibility Criteria, Human Subjects and Clinical Trial Information Form). If Ps do not meet exclusion criteria and are still eligible for the study after this phone screening interview, the P and his/her mother will be invited to participate in the T1 in-lab session, which will provide baseline assessments (see Table 1 in Research Strategy) and further determine the Ps' eligibility for the study.

At the beginning of the T1 session, Ps and their mothers will sign written informed assent and consent forms, respectively, in the lab before they engage in any of the T1 assessments (see C.4. in Section 3, Research Strategy, Research Plan Form). The research protocol and assent and consent forms specific for the T1 session will be approved by the TU IRB. Based on the lifetime diagnostic interview (exp-SADS-L; see C.4.a.i.) administered in person at Time 1, we will exclude Ps with a past MD because Aim 3 (see Specific Aims) of our project involves prospective prediction of 1st onset of MD. We also will exclude Ps with current

psychotic symptoms (hallucinations, delusions) to insure validity of our assessments. To maximize the ecological validity and generalizability of findings from our sample, we will not exclude Ps on the basis of a past history of other psychiatric disorders. Instead, we will assess for history of other psychiatric disorders (see C.4.a.i.) and control for other disorders in our analyses as needed (see C.4.g.iii.). At T1, Ps also will be placed in a mock scanner to insure they can tolerate an fMRI scan and can remain still in the scanner. If they cannot, they will be excluded from the study. Additional exclusion criteria that are assessed in the phone screening interview prior to T1 are provided in Section 2.2 Eligibility Criteria, Human Subjects and Clinical Trials Information Form.

Recruitment of Ps for the Full 3-Year Prospective Study. If Ps are still eligible for the study after completing the T1 session, they will be invited to participate in the remainder of the T1 assessments (remaining self-reports, behavioral tasks, interviews, MRI scan, and blood draw) and the remaining T2-T5 sessions. All study assessments, procedures, confidentiality provisions, risks and benefits will be described to Ps and their mothers in detail. Those who verbally agree to participate will sign final written informed assent and consent forms, respectively, for the entire 3-year protocol, which will reiterate the purpose of the study, the procedures to be followed, the duration of the study, the risks, and the potential benefits both to themselves and to the acquisition of knowledge for the community at large. The assent and consent forms also will address confidentiality and specify limits to confidentiality (i.e., harm to self or others) and how confidentiality would be broken (e.g., taking the P to the TU Hospital emergency room if the P reports imminent suicidal intent). These final assent and consent forms for the full protocol also will be approved by the TU IRB. All project personnel will undergo training consistent with that required by NIH for grantee organizations and approved by TU. All Ps will understand that they may withdraw from the study at any time without prejudice. Ps who complete written assent procedures (and whose mothers complete written consent procedures) for the study will be scheduled for the T1 MRI scan, and then, for the T2-T5 sessions every 6 months.

Retention of Study Sample

We will use a variety of methods to minimize attrition that were successful in our previous longitudinal projects (MH077908, MH079369, MH101168): 1) promote the study's intrinsic interest for Ps; 2) convey interest in Ps through a stable project staff that Ps come to recognize, flexible scheduling of all sessions, and frequent "check-in" calls; 3) specifically, to minimize interference with Ps' weekday school obligations, all sessions will be scheduled at the Ps' convenience, including on weekends if Ps desire; this will facilitate Ps' willingness to participate; 4) provide breaks and snacks during the sessions, which will show Ps that we appreciate their time and efforts; 5) some of our assessments are fun (CARROT, etc.) and/or engaging (interviews in which the P speaks to an interested listener); previous Ps have enjoyed the assessment sessions; 6) establish excellent rapport with Ps and be available as resources for referrals, etc.; 7) provide appointment reminders; 8) reimburse Ps for travel expenses and pay for parking as needed; 9) send Ps birthday and holiday cards to express our appreciation for their continued participation; 10) let Ps know how important their continued participation is; and 11) compensate them adequately for their valuable time and provide incentive bonuses for completion of the full protocol (see Section L, Budget Justification, Budget Form, for the compensation and bonus incentives provided for Ps' completion of the protocol.)

2.7 Study Timeline

Project staff hiring and training will occur in Months 1-3 of Year 1. Screening of potential participants (Ps) with the Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) Scales,²⁰³ and Sensitivity to Punishment (SP)/Sensitivity to Reward (SR) Questionnaire (SPSRQ)²⁰⁴ will begin in Months 1-3 of Year 1 and continue until the full sample has been successfully recruited. Because much of the screening will be conducted online, MPI Alloy will start the screening process concurrent with project staff training. Notably, scoring of the screening measures will be the first task on which project staff will train. Time 1 sessions will begin in Month 3 of Year 1 and continue through Month 6 of Year 3, as Ps are determined to be eligible and recruited. We plan to start 80 Ps in Year 1 and 110 Ps each in Years 2 and 3 on the Time 1 session, followed by the Time 2 - 5 sessions every 6 months thereafter, for a total of 3 years of follow-up. Sessions will continue through Year 5 for the last Ps who start Time 1 in Year 3. Preprocessing of the MRI data will occur as these data are collected in Years 1-5, and immunological assays will be run in one batch in Year 5 after all blood draws are conducted. Data entry, coding, and analysis will be completed by the end of Year 5.

Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
<u>Study 1, IER 1</u>	Domestic	Temple University, Philadelphia, PA

Inclusion Enrollment Report 1Using an Existing Dataset or Resource*: Yes NoEnrollment Location Type*: Domestic Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): Temple University, Philadelphia, PA

Comments: Our planned enrollment is designed to be representative of high school freshmen in Philadelphia and the surrounding community (including the Philadelphia suburbs, southern New Jersey, and northern Delaware).

Planned

Racial Categories	Ethnic Categories					Total	
	Not Hispanic or Latino		Hispanic or Latino				
	Female	Male	Female	Male			
American Indian/ Alaska Native	0	0	0	0		0	
Asian	10	10	0	0		20	
Native Hawaiian or Other Pacific Islander	1	1	0	0		2	
Black or African American	61	61	4	4		130	
White	46	46	14	14		120	
More than One Race	14	14	0	0		28	
Total	132	132	18	18		300	

Cumulative (Actual)

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

Section 3 - Protection and Monitoring Plans (Study 1)

3.1. Protection of Human Subjects

3.1. Protection of Human Subjects.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

3.1. PROTECTION OF HUMAN SUBJECTS

The goals of this new grant application are to examine: 1) the concurrent and longitudinal bidirectional associations between reward responsivity (RR) and inflammation; 2) mediators and moderators of their associations, and 3) inflammation and RR as separate and/or joint determinants of risk for 1st onset of major depressive disorder (MD) and increases in depression (Dep) symptoms (Sxs) during adolescence. To this end, we will use an innovative biobehavioral high-risk approach involving immune and RR measures at multiple units of analysis over multiple timepoints in a 3-year prospective longitudinal design.

We plan to recruit 300, 14-15 year-old, racially diverse male and female high school freshmen from Philadelphia and the surrounding community (Phila., Phila. suburbs, southern New Jersey, northern Delaware). All subject recruitment, data collection, and human subjects research will take place at Temple University (TU). Thus, Institutional Review Board (IRB) approval will be obtained from the TU IRB.

1. Risks to Human Subjects

1.a. Human Subjects Involvement, Characteristics, and Design

Overview of Study Design. Three hundred 14-15 year-old, racially diverse male and female high school freshmen with no prior history of major depressive disorder (MD) will be recruited. The sample will be recruited along the entire RR dimension, from low to high, based on self-reported trait RR, with oversampling at the low tail of the dimension (see C.3.). This will insure a full range of scores on the RR dimension and adequate numbers of at-risk participants (Ps) at the low tail of the dimension. The 14-15 year-old age range is chosen for several important scientific and feasibility reasons: 1) the steepest rise in rates of 1st onset of MD occurs between ages 15-18⁹⁻¹² (see A.3.); 2) RR increases normatively in adolescence and may start to peak around ages 15-16^{47,52} (A.3.); 3) MPI Alloy's prior experience in Project ACE (MH101168) suggests that Ps are more likely to assent to blood draws starting at age 14; 4) substance use (a hypothesized mediator of RR-inflammation associations) begins to increase in mid-adolescence; 5) high school freshmen will still be in the Phila. area for the full 3-yr. follow-up period (e.g., not yet leaving for college); 6) high school freshmen will be relatively homogeneous with respect to life transitions and experiences. Thus, our planned sample gives us the best opportunity for observing trajectories of RR-inflammation associations and prediction of 1st onset of MD (see C.4.a.ii. for expected rates of MD onsets).

At Time 1 (T1), T3, and T5, each a yr. apart, Ps will complete blood draws to quantify systemic (protein and cytokine biomarkers) inflammation, self-report and behavioral measures of RR, and fMRI scans of neural activation and functional connectivity within the cortico-striatal reward neural circuit during monetary and social reward tasks. At T1-T5 (with T2 and T4 6 mo. between the yearly sessions), Ps also will complete diagnostic interviews, and measures of Dep Sxs, pubertal maturation, recent life events coded for reward-deactivation (Rew-D) relevance, and other behaviors that increase inflammation (e.g., substance use, high-fat diet, disrupted sleep), for a total of 3 yrs. of follow-up (Ps will be ages 17-18 at final follow-up). Ps' mothers will serve as additional informants at T1 to provide information about the teens' childhood adversity history and family history of mood disorders. The multiple timepoints will allow us to assess trajectories of RR abnormalities and inflammation and whether RR and inflammation abnormalities at baseline, that are stable over time, or that worsen over time best predict 1st onset of MD and Dep Sxs separately and jointly in response to Rew-D events. Assessment of childhood adversity and inflammation-enhancing behaviors (substance use, high fat/high sugar diet, sleep disruption, self-generated Rew-D events) allow us to test a potential moderator and mediators, respectively, of reward-immune predictive associations over time.

Human Subjects Involvement and Characteristics.

Sample Selection. Ps will include 14-15 yr. old high school freshmen recruited in two ways. The primary means of recruitment will be via Facebook ads, other social media (e.g., Instagram) ads, Craig's List ads, community newspaper ads, and flyers posted in local coffee shops/restaurants, sports centers, community recreation centers, places of worship, etc. (directed at high school freshmen and/or their parents) throughout Philadelphia area neighborhoods. These ads and flyers will contain links to an online screening survey on MPI Alloy's HIPAA secured lab website. Specifically, we have budgeted funds to place ads in newfeeds on Facebook and relevant community pages on Facebook (e.g., High School Class of 20xx, vocational school groups, Philly locals, Philly summer events, Philly foodies), other social media, and community newspapers that target 14-15 year olds and/or their parents. To provide incentive for completing the online screening

survey, we also have budgeted funds for \$50 random drawing lottery prizes for Ps who complete the online screening survey via the links placed in the Facebook, other social media, and newspaper ads and in the flyers. In addition, we will place ads on the Philadelphia Craig's list for free (also with links to the online screening survey). A second recruitment method will be through contacting Philadelphia area high school principals and requesting permission to screen their freshmen students during one homeroom advisory period. Ps recruited by this method will complete the screening survey on paper (with the freshmen's written assent and passive parental consent). MPI Alloy has successfully recruited high school students with this method previously (MH077908, MH102310).

Ps (ages 14-15 yrs.), with no prior history of MD, will be recruited based on their scores on two self-report measures of trait RR to assess an underlying RR dimension: Carver and White's²⁰³ Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) Scales and Torrubia et al.'s²⁰⁴ Sensitivity to Punishment (SP)/Sensitivity to Reward (SR) Questionnaire (SPSRQ). The BAS and SR scales are reliable and valid measures of RR²⁰³⁻²¹² that we have used to select Ps with different levels of RR previously^{205,207} (MH077908; MH102310). Moreover, we recently demonstrated that RR as assessed by both measures is a dimensional, and not a categorical, vulnerability.²¹³ The screening packet also will contain a Demographics and Contact Sheet in which Ps will provide contact information as well as age, gender, race, ethnicity, English speaking ability, and year in school. The contact information is necessary in order for us to contact potentially eligible Ps to recruit them for the study. The question about year in school (high school freshman is the required answer) is included to increase the chances that the P will be around to complete the study, if enrolled. Finally, the very first part of the online screening packet will include an assent form for the Ps and a consent form for one of their parents. Ps and parents must provide their assent and consent, respectively, on the Screening Consent Form before they can proceed to the rest of the screening survey. The screening survey packet administered in homeroom advisory period for Ps screened in their high schools (with principals' permission) will only contain an assent form for the high school freshmen to sign. Passive parental consent will be obtained in advance for conducting the screening in the homeroom advisory period. The Screening Assent and Consent Forms will be approved by the TU IRB. The screening packet is the same as we have used previously (MH077908, MH102310), which was previously approved by the TU IRB.

Based on their scores on **BOTH** the BAS and SR ($r=0.40$) scales, we will recruit Ps as follows: 200 Ps from the low (0-20th%) tail of the RR dimension, and 100 Ps from the rest of the dimension, distributed such that 25 Ps come from the 21-40th%, 25 from the 41-60th%, 25 from the 61-80th%, and 25 from the 81-100th%. We will recruit equal numbers of males and females within each percentile bin, to allow exploration of sex differences (see C.3.c.). Ps from all races/ethnicities will be eligible. This design, with oversampling at the low tail, insures both that we will have the full dimension of RR represented in the sample and enough Ps at increased risk for MD and depressive symptoms (0-20th%). We will screen up to 5,000 high school freshmen in Years 1-3 (2020-2022) of the project. To account for ineligibility, we will initially recruit 360 Ps to obtain our target sample of N=300 Ps.

MPI Nusslock (MH100117) and Co-Is Ellman (MH112613) and Olino (MH107495) have used our planned primary methods for recruiting community adolescents in their ongoing R01 grants with much success. For example, MPI Nusslock was able to recruit 53 community adolescents per month in Chicago via Facebook ads. Co-Is Ellman and Olino have been able to recruit about 15 community adolescents per month in Philadelphia via Facebook ads and another 5 per month via posted flyers. Thus, it is reasonable for us to expect to be able to recruit around 20 Ps per month from the community with these methods. In addition, in her previous R01 grants (MH077908, MH102310), MPI Alloy was able to successfully screen and recruit high school students through conducting screenings during homeroom advisory periods with the permission of high school principals.²⁰⁵ She screened approximately 10,000 high school students in this way. Currently, just within the Philadelphia School District (PSD), there are 10,105 high school freshmen attending PSD schools,³¹⁸ with more high school freshmen attending private or parochial schools in Phila. or public, private, and parochial schools in the Phila. suburbs, southern New Jersey, and northern Delaware. Thus, screening up to 5,000 high school freshmen is also feasible.

Moreover, MPI Alloy has screened >20,000 Ps and recruited 750 Ps based on scores on both the BAS and SR previously (MH077908, MH102310). Based on the results of one of her previous screening samples of 10,000 high school students, if we screen 5,000 Ps for this new proposed project, 22.5% (n=1,125), 18.3% (n=915), 29.3% (n=1,465), 12.7% (n=635), and 17.2% (n=860) will meet the joint BAS and SR criteria for the 0-20th%, 21-40th%, 41-60th%, 61-80th%, and 81-100th% bins, respectively. Given that we need 200, 25, 25, 25, and 25 Ps, respectively from these 5 percentile bins, and our estimate that 20% of Ps may be ineligible based on the exclusion criteria, we should have more than enough eligible Ps to meet our recruitment goals.

Demographics and Representativeness. As noted above, we will recruit equal numbers of 14-15 year-old males and females in each of the RR percentile bins and will endeavor to recruit from racial/ethnic groups to be representative of high school students in Philadelphia and the surrounding areas (see PHS Inclusion Enrollment Report). The racial breakdown of Philadelphia high school age students is 35% White/Caucasian, 43% Black/African-American, 7% Asian or Asian-American, and 15% other race or more than one race, and 12% are Hispanic/Latino(a) ethnicity.³¹⁷ The % of White/Caucasian students in the Phila. suburbs and Delaware is higher. Thus, we will endeavor to recruit 14-15 year-old high school freshmen from the Phila. area for this project such that 40% are White/Caucasian, 43% are Black/African-American, 7% are Asian or Asian-American, and 10% are other or more than one race, with 12% of Hispanic/Latino(a) ethnicity.

The representativeness of the final sample will be examined by comparing them on age, gender, race, and ethnicity to the screening sample.

Exclusion Criteria. Ps who meet the BAS and SR inclusion criteria from the initial screening (i.e., who fall into the various percentile bins described above based on both RR measures) will be contacted by phone or email by project staff to set up a phone screening interview to determine whether they have any of the other exclusion criteria that would make them ineligible for the study (for all exclusion criteria and standardized assessment of the exclusion criteria, see Section 2.2 Eligibility Criteria, Human Subjects and Clinical Trial Information Form). If Ps do not meet exclusion criteria and are still eligible for the study after this phone screening interview, the P and his/her mother will be invited to participate in the Time 1 (T1) in-lab session, which will provide baseline assessments (see Table 1 in Research Strategy) and further determine the Ps' eligibility for the study.

We will exclude Ps with a history of MD because one of the aims of this project is to predict 1st onset of MD in adolescence. Final determination of the presence or absence of a history of MD will be based on the expanded-Schedule for Affective Disorders and Schizophrenia-Lifetime (exp-SADS-L)^{205,206,228,229} diagnostic interview administered to Ps in person at the T1 session (see C.4.a.i. in Research Strategy). However, to decrease the number of Ps who need to be excluded at the T1 session because of a prior MD diagnosis (and save effort and money), we will administer the Depression section of the exp-SADS-L interview during the phone screening interview after obtaining the Ps' assent and a parent's consent. Ps who potentially had a prior MD based on the Depression section of the exp-SADS-L in the phone screening interview will not be invited to the T1 session or to enroll in the study.

In addition, we will exclude Ps with a history of cancer, heart disease, surgery, an ongoing autoimmune disease or disorder involving chronic inflammation (e.g., Crohn's Disease, Type 1 Diabetes, Lupus, asthma, severe allergies), and anyone who is HIV positive. We also will exclude anyone taking immunosuppressant medications (e.g., an inhaler, systemic steroids, nonsteroidal anti-inflammatory drugs [NSAIDs]) in the past three months. We believe that this approach strikes the right balance between allowing us to enroll a sample that is generalizable to the broader population, while excluding Ps whose inflammatory profile is likely affected by disease or treatment. These exclusion criteria also will be assessed in the phone screening interview (using the physical health and chronic conditions items from the World Health Organization World Mental Health Composite International Diagnostic Interview [WHO WMH-CIDI]³¹¹ prior to the Ps' T1 visit. Screening for immune-related diseases and medications with this type of standardized instrument is standard practice in studies of inflammation.^{312,313} The rate of immune-related diseases in 14-15 year olds is relatively low,^{314,315} thus, we should not need to exclude many Ps on this basis. We will re-administer the physical health and chronic conditions items from the WHO WMH-CIDI at the T1, T3, and T5 sessions to assess whether there are any changes in Ps' physical health status as it pertains to autoimmune diseases or disorders involving chronic inflammation. We also will screen for acute infections at the T1, T3, and T5 sessions and will reschedule enrolled Ps if they display a fever (> 99° as assessed by an ear thermometer) or self-report Sxs. Because CRP values >10 mg/mL are indicative of acute infection, trauma, or chronic illness, we also will exclude these observations from further analysis.²⁷³ Ps also will be excluded according to standard MRI exclusion criteria (e.g., metal in the body, traumatic brain injury, pregnancy, severe claustrophobia; assessed with the TUBRIC standard MRI screening form). Given the nonverbal nature of our fMRI tasks, left-handedness is not considered a justifiable exclusion criterion; instead we will control for handedness if needed. Handedness will be assessed with the Chapman & Chapman Handedness Scale.³¹⁶ Likewise, we will control for psychotropic medication use (see C.4.g.ii.), but not exclude on the basis of psychotropic medications. Given elevated rates of psychotropic medication use in individuals with, and at risk for, mood Sxs,^{305,306} excluding such Ps would reduce the representativeness of our sample and limit generalizability of our findings.

Based on the full exp-SADS-L diagnostic interview administered at T1 (see C.4.a.i.), we also will exclude Ps with current psychotic symptoms (hallucinations, delusions) to insure validity of our assessments. To maximize the ecological validity and generalizability of findings from our sample, we also will not exclude Ps on the basis of a past history of other psychiatric disorders besides MD. Instead, we will assess for history of other psychiatric disorders (see C.4.a.i. in Research Strategy) and control for other disorders in our analyses as needed (see C.4.g.iii.). Substance and alcohol use will be assessed as inflammation-enhancing behaviors to test Aim 2.2 of the proposal, and thus, we will not exclude Ps based on substance/alcohol use. At T1, Ps also will be placed in a mock scanner to insure they can tolerate an MRI scan and can remain still in the scanner. If they cannot, they will be excluded from the study. Ps will receive training to reduce movement in the MRI scanner, which should significantly reduce the amount of movement by Ps and ultimately result in better quality images in the real scanner.

1.b. Study Procedures, Materials, and Potential Risks

Study Procedures and Materials. All data collected from Ps will be collected with their assent and parental consent.

Study Protocol. Once potentially eligible Ps are identified, they will be invited to a T1 session. The T1 session will serve two purposes: 1) it will assess further exclusion criteria for the study; and 2) it will compose the first session of the 3-yr. prospective study. Ps and their parents will complete written informed assent and consent, respectively at the start of T1. **Table 1** (see C.4. in Section 3, Research Strategy, Research Plan Form) shows all measures to be completed during the study and their timing.

An important consideration is whether to use assessment instruments/tasks designed for youth or adults. The challenge is that our Ps will be in mid-adolescence at T1, but in late adolescence by T5. Changing assessment instruments in the middle of a longitudinal study (as we had to do in Project ACE [MH101168]) as Ps age out of the youth versions creates major problems for assessing trajectories, because of lack of comparability of the youth and adult versions. One cannot distinguish whether observed changes in trajectories are due to true changes in the construct being assessed or measures that are not comparable. In addition, MPI Alloy found that 14-15 yr. old Ps in Project TEAM (MH077908, MH102310) were able to validly complete adult versions of our Sx/diagnostic, RR, and life event assessments, and our fMRI RR tasks are appropriate for adolescents and sensitive to developmental effects.²²²⁻²²⁵ Thus, for this reason, we have decided to use the same, mostly “adult” versions of our instruments/tasks for the full duration (T1-T5) of our proposed project.

Diagnostic Assessments (T1-T5; every 6 months). At T1, lifetime history of mood and other disorders based on DSM-5 criteria²²⁶ and Research Diagnostic Criteria (RDC)²²⁷ will be assessed with the expanded SADS-L (exp-SADS-L) diagnostic interview²²⁸ by interviewers blind to Ps’ RR, inflammation, and childhood adversity. Ps who meet criteria for a past MD will be excluded from the study. Ps will be pre-screened for a past MD with the Dep section of the exp-SADS-L during a phone-screening interview prior to T1. The exp-SADS-L was modified to include DSM criteria,^{205,206,229} has an accompanying Change version, and **does not have skip outs** in the mood sections, insuring that we obtain **all** mood Sx ratings even if a P does not meet criteria for a mood disorder. Inter-rater reliability of the exp-SADS-L in MPI Alloy’s lab is $k > .90$ for MD.^{205,206,229,230} At T2-T5, interviewer-rated Sxs, functioning, and onsets of MD and other disorders (e.g., anxiety, eating, SU) since the previous interview will be assessed with an expanded SADS-Change (exp-SADS-C)^{205,206,208,229} interview. MD episodes will be defined according to DSM-5 and RDC criteria. Every Dep Sx will be assessed at every time point. Similarly, **all 9** impairment questions (e.g., psychotherapy/medication use, interference) will be asked at each assessment. Inter-rater reliability of the exp-SADS-C in MPI Alloy’s lab is $k = .90$.^{205,206,208,229} Our prior validity study showed that Sxs on the exp-SADS-C are rated with $> 70\%$ accuracy compared to daily Sx ratings obtained prospectively.^{208,229} We have used the exp-SADS-L and exp-SADS-C successfully before with 14-15 yr. olds (MH077908). At T1, Ps’ mothers also will be given the exp-SADS-L and Family History Interview²³¹ to assess history of mood and other disorders based on DSM-5 and RDC for themselves and other 1st and 2nd degree relatives, as mothers should be better informants on family history than the adolescent Ps.

Symptom/Affect Assessments (T1-T5; every 6 months). Dep Sxs and affect also will be assessed at T1-T5 with self-report measures. We will assess anhedonia with the Temporal Experience of Pleasure Scale (TEPS),²³² an 18-item self-report assessing anticipatory and consummatory facets of pleasure. General Dep Sxs beyond anhedonia will be assessed with the Beck Depression Inventory-II (BDI-II)²³³ and PROMIS-Depression Scale.^{234,235} Positive and negative affect will be assessed with the Positive and Negative Affect Scale (PANAS).²³⁶ These scales comprehensively assess Dep Sxs and affect, have excellent reliability and validity²³²⁻²³⁷ and have been used in our previous projects (MH077908, MH102310, MH107495).

Reward Assessments (T1, T3, T5; yearly). In addition to the BAS and SR measures of self-reported RR, a tendency to overgeneralize from failure will be assessed with the Attitudes Toward Self (ATS) Scale.²³⁸ The ATS is related to Dep Sxs, and interacts with stress to predict Dep prospectively.^{238,239} The Goal Disengagement/Goal Reengagement Scale (GDGRS)^{240,241} measures ability to disengage from goals (e.g., "It's easy for me to reduce my effort toward the goal") and to reengage with new goals (e.g., "I seek other meaningful goals"). It exhibits excellent reliability and validity^{240,241} and predicts inflammation.²⁴¹ Cognitive responses to positive affect will be assessed with the Responses to Positive Affect Scale (RPAS),²⁴² which measures the tendency to accentuate (self- and emotion-focused subscales) or attenuate (dampening subscale) positive affect. Conceptually, dampening of positive affect should be associated with cortico-striatal attenuation in functional connectivity analyses. Moreover, RPAS dampening is associated with Dep²⁴²⁻²⁴⁴ and we found that it interacts with RR to predict inflammation and Dep Sxs prospectively.²⁴⁵

We will assess RR further with 2 behavioral tasks. The Card Arranging Reward Responsivity Objective Test^{246,247} (CARROT) is a brief 3-trial task measuring the extent to which Ps increase their card-sorting speed when offered small financial incentives compared to a no-reward condition. It has been validated,²⁴⁸ correlates with self-reported RR,^{205,249} predicts Dep episodes (C.1.a.ii.), and relates to the DRD2 gene.²⁵⁰ In the Effort Expenditure for Rewards (EEfRT) task,²⁵¹ Ps choose between performing a "hard-task" for higher reward or an "easy-task" for smaller reward. Reward magnitude and probability are varied across trials. Anhedonia and MD predict reduced choice of the hard/high reward task.^{251,252} The % of high effort options (the measure we will use) indexes the tendency to expend high effort for reward regardless of its probability. A lower % of high effort trials is associated with lower RR.²⁵³ We have used all these reward measures successfully before, including with 14-15 yr. olds (MH077908, MH102310).

Ps will complete two fMRI tasks we used previously with adolescents (MH077908, MH100117, MH107495) to assess neural-based RR to monetary and social rewards at the same time of the day across yrs. We will use the well-validated Monetary Incentive Delay (MID) task²⁵⁴⁻²⁵⁶ to assess reward neural activity to monetary rewards for 4 reasons: 1) it has sensitivity to reward neural activity in both healthy Ps¹⁰⁵ and Ps with mood disorders.^{24,195} 2) We previously used the MID and found it predicted MD episodes (C.1.a.ii.). 3) It is appropriate for adolescents²²² and sensitive to developmental effects.²²³ 4) It has good short (ICCs=.52,.63 for left and right VS) and long-term (ICCs=.43, .68 for left and right VS) test-retest reliability,^{257,258} important to detect within-P changes in neural RR from T1 to T5 that are not attributable to practice effects. However, neural activation in the MID task exhibits sufficient variation (18.5%-46.2% shared variance over time)^{257,258} to allow detection of changes in neural RR as a function of changes in inflammation and inflammation-enhancing behaviors.

In the MID task, a circle cue signifying the opportunity to win money (Win \$0.00, Win \$0.50, Win \$5.00) or a square cue indicating the possibility of losing money (Lose \$0.00, Lose \$0.50, Lose \$5.00) is presented for 2s. Ps then must press a button when the solid white square appears. On reward trials, Ps win money if they hit the white square and do not win if the target is missed; on loss trials, Ps avoid losing money if they hit the white square and lose money if the target is missed. Feedback depicting money won or lost on each trial is then displayed for 2s. The 6 trial types are each presented 15 times in random order, totaling 90 trials.

We will use the Chatroom Interact Task²²⁴ (an updated version of the Chatroom Task²⁵⁹⁻²⁶¹) to assess reward neural activity to social rewards also for 4 reasons: 1) it reliably activates cortico-striatal neural circuitry,²²⁴ 2) it has sensitivity to reward neural activation in Ps with, and at familial risk for, Dep,^{224,225} 3) we have used it successfully in adolescent samples,²²⁴ and 4) we found that elevated inflammatory biomarkers were associated with lower cortico-striatal activation on this task in our Project Ace sample¹⁹⁸ (MH101168) (C.1.c.). This task was designed to investigate reactions to social acceptance (reward) and rejection (loss) from virtual peers in an online setting. Ps rank virtual same-age, same-sex peers on how much they would like to interact with them based on a photo and a list of their interests, pose for their own photo, and provide their own interests. At the fMRI session, Ps are matched with their two highest rated "virtual peers", and are told that they will participate in a "chat game" with these peers via remote connection. Photos of the peers and P are projected on the screen two at a time, as each person (the P and the two virtual peers) takes turns selecting who they would rather talk to about a series of common interests (e.g., music, friends). The photo of the selected person is highlighted and an "X" is placed through the photo of the rejected person. Trials are arranged in blocks with predominant (70%) acceptance and predominant (70%) rejection feedback. A fourth block is used as a motor and perceptual control task to control for viewing faces (self and others) and pressing a button to identify a stimulus appearing on one of the faces. Although implemented in blocks, we will analyze the task based on specific events (acceptance = reward trials; rejection = loss trials). As Ps age through the study, they will complete the same task; however, the profiles and pictures provided to the Ps will be updated to match their developmental level.

Neuroimaging data will be acquired using a Siemens MAGNETOM Prisma 3.0 Tesla MRI scanner with a 64-channel gradient head coil at TU. Ps will be familiarized with MRI procedures via a mock scanner to ease concerns and enhance data quality. Scanning protocols will be identical at T1, T3, and T5. Functional runs will use a slice-accelerated multiband EPI sequence (multiband acceleration factor: 2; GRAPPA acceleration factor: 2) covering 64 axial slices (voxel size = 2.0x2.0x2.0mm; TR=2050ms; TE=25ms; FOV=208x208mm; Matrix=104x104; Flip Angle 76°). Structural images will be acquired using an MPRAGE sequence to acquire 208 axial slices (voxel size = 0.8x0.8x0.8mm; TR=2300ms; TE=2.99ms; FOV=256x256; Matrix=320x320; Flip Angle=7°). Data will be processed with SPM software using standard procedures. A nuisance variable for high motion volumes and six variables of no interest for motion will be included in all analyses. High motion volumes (> 2mm) will be censored (we will adjust this censoring threshold for our adolescent Ps if required).

fMRI Analyses. MID Task: At the first level (single P), we will use a GLM identifying the 6 trial types (Win or Lose \$0.00, \$1.50, \$5.00) during the anticipation and outcome phases to deconvolve the HRF for the MID task. The anticipation phase will be after Ps see the reward cue and before the target response (2-2.5s). The outcome phase will be after Ps receive feedback on trial outcome (2s). First-level voxel wise t-statistics will be generated for each P in contrasting reward (Win \$1.50, \$5.00) vs non-reward (Win \$0.00) trials to assess reward anticipation and outcome, and loss (Lose \$0.50, \$5.00) vs non-loss (Lose \$0.00) trials to assess loss anticipation and outcome.^{255,256} Primary analyses will focus on reward anticipation and outcome trials given both these phases are associated with Dep.¹²⁷ If analyses support predictions, follow-up analyses will examine loss anticipation and outcome trials to examine specificity of results to reward processing.

Chatroom Interact Task: Although implemented in blocks, we will analyze the task based on specific events (e.g., acceptance, rejection). A first-level fixed-effect model will be constructed for each P and scan and predetermined condition effects at each voxel will be calculated using a t-statistic. Analyses will focus on reward trials (peer acceptance) vs the motor control task given social reward processing deficits are associated with Dep.^{138,224} If analyses support predictions, secondary analyses will examine loss trials (peer rejection) vs the motor control task to examine specificity of results to reward processing.

ROI Parameter Estimates for fMRI Activation Analyses. We will extract fMRI parameter estimates of neural activation during the MID and Chatroom Tasks from a priori regions-of-interest (ROIs) using MarsBar²⁶² (an SPM toolbox), and import them into an external stats package for analyses (C.7.). Primary analyses will use a separate bilateral VS and OFC ROI for both the MID and the Chatroom Tasks. These ROIs will be defined according to anatomical atlases to insure independence from functional data.^{263,264} We will conduct supplementary analyses on the left and right VS and OFC ROIs separately and whole brain analyses to assess the specificity of findings to a priori defined ROIs. Family wise error rate at $p<0.05$ will be used for all analyses.

Functional Connectivity Parameter Estimates for Analyses. Growing evidence suggests that Dep not only is associated with low VS reactivity, but also a propensity to engage the PFC in a manner that dampens the VS to rewarding stimuli and suppresses positive emotions^{24,128} (C.1.a.iii.). Accordingly, we will use multivariate autoregressive modeling²⁶⁵ to generate parameter estimates of functional connectivity within the cortico-striatal circuit for each P during the MID and Chatroom Tasks. We will focus on a seed-to-seed association between the OFC and VS. In connectivity analyses, a negative (i.e., <0) parameter estimate indicates that "high" activity in one region (e.g., OFC) corresponds with "low" activity in the other region (e.g., VS), reflecting cortico-attenuation tendencies. By contrast, a positive (i.e., >0) parameter estimate indicates that "high" activity in one region (e.g., OFC) corresponds with "high" activity in the other region (e.g., VS). Like our activation analyses, connectivity analyses will focus on reward anticipation and outcome trials during the MID and reward trials (peer acceptance) during the Chatroom Task, with follow-up analyses of loss trials to examine specificity. We predict that cortico-attenuation tendencies during reward processing will be concurrently and longitudinally associated with heightened inflammation, and that these associations will be partially mediated through inflammation enhancing behaviors. We further predict that cortico-attenuation tendencies and heightened inflammation will be joint predictors of 1st onset MD and increases in Dep Sxs.

Immune Assessments (T1, T3, T5; yearly). Blood will be drawn into Serum Separator Tubes (Becton-Dickinson) via antecubital venipuncture by a certified phlebotomist at T1, T3, and T5, between 2-5 PM, to control for diurnal variations and meal intake. This time period is optimal because late afternoon is a stable time of cytokine activity in contrast to other periods of the day when marked diurnal changes occur.^{266,267} Time of blood draw and last meal, and food eaten at last meal will be recorded to include as covariates in analyses if needed. Ps will be asked to fast after 9 am on the day of the blood draw. Ps will be given a meal/snack after the blood draw, before completing other tasks. Sample collection takes about 5 min., and Ps will be observed for 10 min to monitor for potential adverse reactions. Blood samples will be centrifuged, and the serum will be harvested, divided into aliquots, then frozen and stored at -80°C, until shipped to Co-I Miller for assays. We followed these procedures successfully in prior studies (MH077908, MH101168). All blood and assay procedures, handling, and disposal in Alloy's and Miller's labs adhere to Bio-Safety Level 2 standards, with

universal precautions. Note that we have had much experience successfully conducting blood draws with adolescents between 12–20 years of age, with over 1,000 blood draws conducted in MPI Alloy's lab (MH077908, MH101168).

We will statistically control for variables that could confound inflammation analyses,²⁶⁸ including age, race, SES, total adiposity, body temperature, last date of menstruation for females, contraceptive use, medications, and other major illnesses. Total adiposity will be assessed by body mass index (BMI) based on height and weight. We also will explore whether BMI is an additional mediator of reward-inflammation associations. Body temperature will be taken by ear thermometer and Ps will be rescheduled if they have a fever. Other potential confounders will be assessed by interview at the time of the blood draws. Alcohol, nicotine, and drug use will be assessed with the Adolescent Alcohol and Drug Involvement Scale²⁶⁹⁻²⁷¹ (AADIS; C.4.f.ii.) and will be examined as a potential mediator of reward-inflammation associations. See C.4.g. for how we will handle psychotropic medication use.

We will quantify 5 biomarkers of low-grade inflammation: C-reactive protein (CRP), interleukin (IL)-6, -8, -10, and tumor necrosis factor- α (TNF- α). CRP will be measured by high sensitivity immunoturbidimetric assay on a Roche/Hitachi cobas c502 analyzer (lower limit of detection, 0.2mg/L). Cytokines will be measured in duplicate by electrochemiluminescence (ECL) on a SECTOR Imager 2400A (MesoScale Discovery) with a Human Pro-Inflammatory Ultra-Sensitive assay (MesoScale Discovery), per manufacturer's instructions. Per previous work,²⁷² we will z-score the values of each biomarker and then sum them to form a composite score. A higher score on this composite reflects more low-grade inflammation. Secondary analyses will explore the role of individual biomarkers to assess for specificity. Because CRP values >10 mg/mL are indicative of acute infection, trauma, or chronic illness, we will exclude these observations from analysis.²⁷³ We expect sufficient variation in these 5 biomarkers across T1 to T5, given that 2 yr. retest correlations in our lab were a maximum $r = .56$, accounting for 31.4% of shared variance.

Child Adversity Assessments (T1 only). The Children's Life Events Scale (CLES)¹⁹⁹ is a checklist of 50 moderate to major stressors (e.g., family difficulties, deaths of close family or friends, sexual, physical, and emotional abuse). Given that Ps may have been too young at the time of some of the events to remember them, Ps and their mothers separately will respond yes or no to each event that occurred to the P prior to T1 and, if yes, the P's age when it occurred. Total scores (0-50) will serve as one measure of childhood adversity. The CLES showed predictive validity^{199,274,275} and good internal consistency ($\alpha=.75$) in our previous grant (MH101168). Moreover, it predicted inflammation in interaction with recent stressors, Dep Sxs, and neural reward response (C.1.d.). Ps and their mothers also separately will complete the Childhood Trauma Interview (CTI),²⁷⁶ a semi-structured interview of trauma experiences (separations/losses; physical neglect; emotional, physical, sexual abuse; witnessing violence). It has high inter-rater reliability, and good validity.^{276,277} In a prior study, ICC inter-rater reliability for composites from the CTI were .82 to .94. Elevated CTI scores were associated with reduced RR (on the BAS; $r = -.20$, $p=.004$) and elevated inflammation (IL6/IL10 ratio, $r=.19$; $p=.01$) in a previous grant (MH100117).

Life Events Assessments (T1-T5; every 6 months). At T1-T5, Ps will complete the Life Events Scale (LES),²⁷⁸ with 135 negative events in multiple domains (e.g., school, peers, romantic interests, family, financial, etc.) relevant to adolescents. Events have been coded as Rew-D (events involving goal failures or loss of rewards) or non-Rew-relevant with good inter-rater reliability ($\alpha's=.79-.94$).²⁷⁹ Then, Ps complete a Life Events Interview (LEI)^{66,278} about the endorsed events, which also dates their occurrence. Interviewers will be blind to all screening, MD/Dep Sxs, RR, inflammation, and childhood adversity measures. The LEI uses manualized, event-specific definitions to maintain consistency. Events not meeting definitional criteria are disqualified to reduce subjective reporting biases. The LEI also uses the "gold-standard" contextual threat method^{278,280,281} to rate the events' objective impact and independence (e.g., death of a family member) vs. dependence (P had a fight with a friend) on the P's behavior. These procedures have yielded excellent reliability and validity of event dating and ratings ($k=.76$ -.89) in our previous studies and grants.^{278,282}

Inflammation-Enhancing Behavior Assessments (T1-T5; every 6 months). As discussed in A.6 – A.7. in the Research Strategy, we suggest that four types of behavior may at least partially mediate cross-sectional and longitudinal associations between RR and inflammation: stress generation, substance use, dietary consumption, and sleep disturbance. We will assess these inflammation-enhancing behaviors at T1-T5.

Our life events assessment is described above. The number of Rew-D events also rated as dependent on Ps' behavior by interviewers (C.4.e.) will measure stress generation. Self-generated Rew-D events activate stress biology and inflammatory signaling.⁷³

The frequency of Ps' use of nicotine, alcohol, and 10 other drug types over the past mo. will be assessed with the Adolescent Alcohol and Drug Involvement Scale (AADIS).²⁶⁹ The AADIS is reliable and valid²⁶⁹⁻²⁷¹ and

is associated with neural RR and elevated inflammation (C.1.e.ii.). The frequency of consumption of high fat and high sugar foods will be assessed using the Food Frequency Questionnaire (FFQ).²⁸³ It allows calculation of nutrient intake, has established reliability and validity, and has been used in large-scale survey studies.²⁸³⁻²⁸⁶

We will assess sleep disruption with both subjective and objective measures. The Pittsburgh Sleep Quality Index (PSQI)^{287,288} is the most commonly used, well-validated self-report of sleep quantity and quality. Actigraphy provides an objective, reliable, and valid method for assessing sleep and activity patterns in Ps' natural environment with minimal restriction on normal routines.²⁸⁹⁻²⁹⁴ Actigraphy corresponds highly with sleep diaries and polysomnography, including in adolescents.^{291,292} Ps will wear an Actiwatch (Philips Healthcare, Bend, OR) on their non-dominant wrist continuously for 7 days at each timepoint, only removing it when it might get wet (e.g., bathing) or for the fMRI scans. Data will be sampled in 1-min epochs and stored digitally. Sleep variables will include: sleep onset latency (time between bedtime and sleep onset); wake after sleep onset; sleep duration (time between sleep onset and offset); sleep efficiency (% time spent asleep); # of awakenings; and weekday/weekend sleep ratios.²⁹⁵ Also, hourly activity counts will be derived (allowing for an objective measure of inactivity during daytime). To assist with interpretation of actigraphy data, Ps also will complete an online sleep diary^{296,297} each morning of the actigraphy wk. The sleep diary will assess sleep parameters (e.g., bedtime, waketime), naps, medications, caffeine use, exercise, etc. for the day before. Missed assessments will trigger reminder emails/texts to Ps' smartphones. We have previous experience with these sleep assessments and with processing of actigraphy data (MH102310).

Pubertal Maturation (T1-T5; every 6 months). Pubertal maturation may influence both RR⁵⁶⁻⁶⁰ and inflammation.²⁹⁹⁻³⁰¹ Thus, we will assess pubertal maturation with the 5-item self-report Pubertal Development Scale (PDS)²⁹⁸ at T1-T5 and control for it as needed in our analyses. The PDS asks about growth in height, body hair, skin change, breast (females) or voice (males) change, and facial hair (males) or menstruation (females). Item scores are averaged, and the scale yields a final score ranging from 1-4 (less to more pubertally developed). The PDS has acceptable psychometric properties (average $\alpha=.77$) and good convergent validity (r 's of .61-.67 with physician ratings; $r=.84$ with mothers' ratings).^{298,301-304} It also predicts MD episodes and Dep Sxs.³⁰²⁻³⁰⁴

Potential Risks

Our procedures are not invasive and involve standard assessments that have not been found to pose undue risk to Ps. However, in this proposed research, several potential risks exist. First, suicidal ideation and grave disability from severe psychiatric symptoms may be a potential risk. Second, Ps may experience potential psychological discomfort and/or fatigue when completing self-report measures and/or face-to-face interviews. Ps may experience some emotional distress from performing less well on the behavioral tasks (e.g., CARROT) than desired. And, Ps could experience some minor inconvenience associated with the actigraphy assessments. Third, there are also some risks associated with the blood draw procedures. Fourth, there are standard risks associated with the fMRI procedures. Moreover, although our fMRI monetary reward task (MID Task) has no deception, there is minor deception involved in the fMRI social reward task (Chatroom Interact Task). Finally, as in all clinical studies, there is a risk for potential breaches of confidentiality as well as the potential risk for coercion. We briefly review each of these potential risks here and then the means by which these potential risks will be addressed are described below in the "Protections Against Risks" section.

1) Risks Associated with Interview, Questionnaire, and Behavioral Task Assessments

Suicidal or Grave Disability Risk. Given that some Ps in this project will be at risk for developing MD, there is a potential for the emergence of imminent suicidal risk or the development of grave disability related to severe Dep Sxs and impairment. Suicidal ideation and Dep Sxs are assessed at the T1-T5 sessions (every 6 months). If a P endorses suicidal ideation on our self-report Dep Sxs measures or our diagnostic interviews at any of these sessions, the interviewer will conduct a Risk Assessment Interview (regularly used in MPI Alloy's lab) to determine the severity and imminence of the risk. The interviewer then immediately will notify MPI Alloy and/or one of the lab's other crisis supervisors to discuss the degree of risk involved and appropriate actions are taken based on the level of risk assessed (see "Protection Against Risks" section below). Similarly, if a P has an onset of MD or another disorder and is experiencing impairment as determined by the exp-SADS-L or exp-SADS-C diagnostic interview, appropriate referrals are made (see "Protections Against Risk" section below). If the P is determined to be experiencing grave disability related to any kind of psychiatric Sxs, the interviewer immediately will notify MPI Alloy and/or one of the lab's other crisis supervisors and appropriate referrals are made (see "Protections Against Risks"

section below). Clear criteria and procedures for addressing suicidality and grave disability have been established and are regularly used in the MPI Alloy's lab, and are delineated in the "Protections Against Risks" section below.

Suicide Risk Assessment. The Risk Assessment Interview used in MPI Alloy's lab is derived from a suicide risk interview from the Beck Institute for Cognitive Behavior Therapy and the Beck Scale for Suicide Ideation (BSS).³²⁰ The interview includes the following 12 questions, with appropriate follow-ups depending on the P's response to each question: 1) "How have you been feeling over the month, including today? Have you been thinking a lot about death or dying, or wishing you were dead, yourself?" (If No, move to question 7; If yes, ask question 2); 2) "Can you tell me a bit about some of the things that have been upsetting you?"; 3) "Have you thought about killing yourself?"; 4) "Have you made a plan or thought about how you would kill yourself?" (If No, move to question 5; if Yes, ask 4a) 4a) "What was it?"; 5) "Do you think you will try to kill yourself in the future?" (If No, move to question 7; If yes, ask question 6); 6) "What do you think would happen if sometime in the next few days you started to feel like you wanted to die?" (IF NO RESPONSE, ASK: Do you think you would try to kill yourself?); 7) "Have you ever thought about or actually tried to kill yourself in the past?" (If No, the interview is over; If Yes, reassess current mood, then ask remaining questions); 8) "What did you do? What happened?"; 9) "Has anyone you've known died recently? Who was it? Can you tell me what happened?"; 10) Has anyone you've known ever killed themselves or tried to kill themselves? Can you tell me about this?; 11) "Have you talked with anyone about these feelings (about feeling like you want to die)? Who have you talked to? Was it helpful? When did you talk with this person?"; 12) "If you start to feel hopeless again and you feel like you want to die, is there anyone you could talk to?"

Participant Distress, Fatigue, and Minor Inconvenience During Assessments. Ps may experience some psychological discomfort when filling out self-report measures and/or completing face-to-face diagnostic and life events interviews. These discomforts may include: (1) emotional distress from discussing potentially sensitive topics; (2) the invasion of psychological privacy inherent in psychological assessment; and (3) fatigue and/or boredom. In addition, Ps may experience some emotional distress from performing less well on the behavioral tasks than expected or desired. Although the above sources of discomfort are possible, it is not anticipated that the procedures will cause undue risk. Our experience with adolescent Ps in MPI Alloy's previous NIMH-funded longitudinal projects with assessments similar to those proposed here (e.g., MH077908, MH079369, MH101168, MH102310), confirms that no unusual or harmful reactions have occurred. In fact, many of our Ps look forward to meeting with their interviewer and participating in the regular assessments. In addition, the behavioral tasks are presented to Ps as "games" and most Ps find participating in these tasks to be fun and enjoyable.

It also is possible that there may be slight inconvenience or discomfort associated with wearing the Actiwatch to objectively assess sleep and activity patterns throughout the day for 7-day periods at T1-T5. However, the Actiwatch is nearly identical to a normal wristwatch that is simply worn on the non-dominant wrist all day (and only removed during showering, bathing, or at other times when it could get wet or for the fMRI scans). Thus, the Actiwatch is no more inconvenient or uncomfortable than a normal wristwatch. There are no good alternatives to actigraphy for objectively monitoring daily physical activity and sleep outside the laboratory. Studies using actigraphy²⁸⁹⁻²⁹⁵ have not found any undue discomfort or inconvenience from wearing these instruments. Moreover, in MPI Alloy's previous grant in which Ps wore Actiwatches for 20 days (MH102310), our Ps did not experience undue discomfort or inconvenience from wearing these instruments. Our procedures for addressing psychological discomfort, fatigue, boredom, and inconvenience from the assessment procedures are provided in the "Protections Against Risks" section below.

2) Potential Breaches of Confidentiality and Risk for Coercion

Potential breaches of confidentiality may occur with regard to research data (paper copy, computerized, immune assays, fMRI brain images, actigraphy) and in interactions with project personnel. We will protect against these potential breaches by having only appropriately trained project staff having access to project data and interacting with Ps, marking all Ps' research data with a non-personally identifiable ID number only, and with appropriate storage of all research data and data linking Ps' ID numbers with their identities and contact information. As is true in any research study, there is the risk of coercion. Details of our

procedures to protect confidentiality and privacy and minimize coercion are provided in the “Protections Against Risks” section below.

3) Risks Associated with Blood Specimen Collection Procedures

Discomfort or Apprehension. The expected risks of the collection of blood samples are minimal. There is the risk of discomfort or apprehension from the needle stick; however, the needles used to collect blood are very small (23g) and the procedure is done within seconds by a certified phlebotomist with minimal pain expected.

Bruising, Tenderness, or Slight Bleeding at Site of Needle Stick. Although these complications are very rare, there is a risk of skin bruising, tenderness, or bleeding from the needle stick.

Vasovagal Response. There is a small risk of vasovagal response, which may result in a brief fainting spell that lasts seconds.

Infection Risk. Any time the skin is broken, there is a slight risk for infection (redness of the skin, burning sensation, chills and fever).

Psychological Risk. The major psychological risk involved in the collection of blood specimens and assay results from the P is breach of confidentiality.

4) Risks Associated with fMRI Procedures

fMRI Risks. Magnetic resonance imaging is non-invasive, widely used, and safe. The potential risks such as static magnetic field, radio-frequency field, magnetic field gradients, and acoustic noise are rarely dangerous or life threatening. According to current knowledge, the risks of fMRI when exclusion criteria are observed are extremely small and the benefits of these investigations to clinical and neuroscience research are large. Ps will receive a brief prescreening interview to eliminate those with contraindications. Prior to participation in the fMRI scan, Ps will receive a complete screening by a certified technician at the Temple University Brain Research & Imaging Center (TUBRIC), where the fMRI scans will be conducted. Ps will be studied only if they pass the Society of Magnetic Resonance Imaging standardized MRI screening protocol (exclusions for ferrous metal in any part of body, such as pacemakers, cochlear implants, surgical clips or metal fragments, serious medical conditions, claustrophobia). Ps also will be asked about possible pregnancy, and screened for any history of head trauma involving unconsciousness, and neurological illness All Ps who are suitable will have the procedures to be performed explained in full and any questions they have will be answered. Potential risks and benefits from the fMRI scan will be reviewed.

Potential risks to Ps without contraindications include mild anxiety, claustrophobic reaction, and movement of ferromagnetic objects. Certain MRI scanning procedures can produce loud (>100 dB) noises; thus, ear protection will be provided by the use of sound-reduction earplugs plus a form-fitting pillow. Ps also will be placed in a mock scanner at the T1 session to insure they can tolerate an fMRI scan and can remain still in the scanner. If they cannot comply, they will be excluded from the study. However, Ps also will receive training in the mock scanner. This should not only reduce movement in the MRI scanner and ultimately result in better quality images, but it also will reduce Ps' apprehension about the scan. During each fMRI scan, the Ps will be constantly monitored for any side effects and will be provided with treatment if necessary. The fMRI scan may be aborted if the P has any discomfort. The safety of the Ps will be continually monitored. Beyond these risks, there are no known side effects of fMRI to Ps without contraindications. There are no alternative procedures to those described in this proposal.

Mild Deception Involved in the fMRI Social Reward Task. For our fMRI social reward paradigm (Chatroom Interact task), Ps will be led to believe that other adolescents are participating in the study in other locations across the country at the same time, which is not true. Further, all of the sequence of feedback is randomized for each P. Thus, Ps may experience mild distress from when they are not chosen by the “virtual peer.” The TU IRB has previously approved this fMRI task for our prior grants (MH107495; PA CURE grant).

2. Adequacy of Protection Against Risks

2.a. Informed Consent and Assent

Recruitment and Assent/Consent of Ps for Initial Screening. For Ps recruited through Facebook, other social media, Craig's List, or newspaper ads or flyers, those ads or flyers will contain links to an online screening survey on MPI Alloy's HIPAA secured lab website. The very first part of the initial online screening packet will be Assent and Consent Forms. Ps and one of their parents must provide their assent and consent, respectively, on the online Assent and Consent Forms before they can proceed to the rest of the screening survey. These forms will be approved by the TU IRB. For Ps recruited through their high schools, the screening survey will be completed on paper in their homeroom advisory periods, and the first page will be an Assent Form that Ps must sign. Parents of freshmen in the high school will be mailed a letter describing the study and the planned screening survey in advance and will be asked for passive consent. Parents will be given instructions in the letter about how to indicate if they do not wish their son or daughter to participate in the screening. The online and paper screening packets are the same as we have used previously (MH077908, MH102310) and were previously approved by the TU IRB.

Recruitment and Consent of Ps for Time 1 Session. Ps who meet the BAS and SR inclusion criteria from the initial screening (i.e., who fall into the various percentile bins described above based on both RR measures) will be contacted by phone or email to set up a phone interview with the P (when his/her parent is also available) to determine whether they have any of the other exclusion criteria for the study (see "Human Subjects Involvement and Characteristics" above for these exclusion criteria). These exclusion criteria are designed to ensure that there are no contraindications or confounding factors for the fMRI scans or immune assays that are part of the protocol, and to screen out Ps who appear to have had a prior MD. At the beginning of the phone call, Ps and a parent will be told that the purpose of the phone screening interview is to determine potential eligibility for the study, and will be asked to provide verbal assent and consent, respectively, before proceeding with the phone interview. The verbal assent and consent process will be recorded to document that it occurred, and Ps will be informed of the recording. The verbal assent and consent process (and script) will be approved by the TU IRB. If Ps do not meet exclusion criteria and are still eligible for the study after this phone interview, they will be invited to participate in the T1 in-lab session with their mothers (or primary female caregivers; hereafter referred to as "mothers" because 93% were the biological mothers in MPI Alloy's Project ACE [MH07369, MH101168]), which will further determine their eligibility for the study.

At the beginning of the T1 session, mothers will be asked to read and sign active, written consent forms for their own and their adolescent child's participation and the adolescent will be asked to provide written assent before they engage in any of the T1 assessments (described in "Study Procedures and Materials" above). The research protocol and consent and assent forms for the T1 session will be approved by the TU IRB. The consent and assent forms will indicate that at any time during the T1 session, the mother and/or adolescent can opt out of any aspect of the T1 session without penalty. In addition, the consent and assent forms indicate that the only exceptions to confidentiality are: 1) if physical or sexual maltreatment of the adolescent is revealed (note that we are not explicitly assessing current physical and sexual abuse), in which case we must inform the proper authorities; or 2) if the adolescent or mother indicates or exhibits suicidality or clinically significant psychiatric Sxs. (In this case, we will need to break confidentiality to ensure that the adolescent or mother gets help; see "Protections Against Risks" section below.)

Based on the lifetime diagnostic interview (exp-SADS-L) administered at T1, we will exclude adolescent Ps with a past history of MD or with current psychotic Sxs (hallucinations, delusions). If Ps are not excluded because of a prior MD or current psychotic Sxs based on the exp-SADS-L interview, then they will complete the remaining T1 assessments. They also will be placed in a mock scanner at T1 to insure they can tolerate an fMRI scan and can remain still in the scanner. If they cannot, they will be excluded from the study. Prior to placement in the mock scanner, Ps will receive training to reduce movement in the MRI scanner and to feel more comfortable in the scanner. This should significantly reduce the amount of movement by Ps and result in better quality images in the real scanner, as well as reduce any apprehension about the scans.

Recruitment and Consent of Ps for the Full Protocol. If Ps are still eligible for the study after completing the lifetime diagnostic interview during the T1 session and the mock scan, they will be invited to participate in the full 3-year study protocol. All study assessments, procedures, confidentiality provisions, risks and benefits will

be described to Ps and their mothers in detail. Those who verbally agree to participate in the study will sign another written informed assent form and their mothers will sign another written informed consent form, which will reiterate the purpose of the study, the procedures to be followed, the duration of the study, the risks, and the potential benefits both to themselves and to the acquisition of knowledge for the community at large. The assent and consent forms also will address confidentiality and specify limits to confidentiality (i.e., child abuse, harm to self or others) and how confidentiality would be broken (e.g., taking the P to the Temple U. Hospital emergency room if the P reports imminent suicidal intent). All project personnel will undergo training consistent with that required by NIH for grantee organizations and approved by our institution. All Ps will understand that they may withdraw from the study at any time without prejudice. The research protocol and assent and consent forms for the full protocol will be approved by the TU IRB. Ps and their mothers who complete written assent and consent procedures, respectively, for the study will complete the remainder of the T1 study assessments (i.e., blood draw and fMRI scan) and be scheduled at the appropriate times for the T2 – T5 sessions.

2.b. Protections Against Risk

As discussed in “Study Procedures, Materials, and Potential Risks” above, potential risks include: 1) suicidal ideation and grave disability from severe psychiatric symptoms, 2) potential psychological discomfort and/or fatigue from completing self-report questionnaires and/or face-to-face diagnostic and life events interviews, emotional distress from performing less well on the behavioral tasks than desired, or minor inconvenience from wearing the actiwatches, 3) potential breaches of confidentiality or risk for coercion, and 4) potential risks associated with the blood specimen collection and fMRI procedures. Each of these is addressed in turn here. However, in general it should be noted that our procedures involve standard assessments or procedures that have not been found to pose undue risk to Ps. Indeed, we have conducted all of these assessments with adolescents previously in prior grant projects (MH077908, MH101168, MH102310, MH107495). We will employ several procedures for protecting against and minimizing any potential risks to Ps. At the outset of the assenting and consenting process, the Ps are provided with MPI Alloy’s phone number and email address, as well as the lab phone number, to contact in case any questions or concerns arise. MPI Alloy is an experienced clinical psychologist. In addition, all project personnel will undergo training consistent with that required by NIH for grantee organizations and approved by our institution. The research protocols and consent and assent forms will be approved by the IRB of Temple University.

1) Risks Associated with Interview, Questionnaire, Behavioral Task, and Actigraphy Assessments

Protections against Suicidal or Grave Disability Risk. In a study of risk for depression, it is critical to have a plan to ensure that a referral for a P with active suicidality or serious psychopathology (e.g., depression with impairment) is made. MPI Alloy’s lab has a comprehensive crisis protocol that outlines clearly in step-by-step fashion what project interviewers should do if a P expresses suicidal (or homicidal) ideation during the T1-T5 sessions. This protocol is consistent with legal requirements and has been approved by the TU IRB. If a P indicates evidence of suicidal ideation at any of the project assessments on our self-report depressive symptom measures or our diagnostic interviews, project interviewers are trained to conduct a Risk Assessment Interview (described under Suicide Risk Assessment above) to determine if the ideation is currently present (within the last 30 days) or in the past, how imminent the threat is, whether the P has an active plan and means to carry it out, etc. After this information is gathered, interviewers are trained to contact either MPI Alloy or one of the other designated lab crisis supervisors (e.g., the lab’s postdoctoral fellow, the lab’s Director of Clinical Training, Co-I Dr. Ellman, Co-I Dr. Olino, or Dr. Robert Fauber, the Director of Temple University’s Psychological Services Center, our in-house psychology clinic, etc.) immediately for consultation and assistance. Together, the lab crisis supervisor and interviewer formulate a plan of action depending on the information that is gathered as part of the Risk Assessment Interview. If the P reports past suicidal ideation (more than 30 days prior), no immediate action is required, and the interviewer provides the P with referral information, including 24-hour crisis intervention services. If the P reports current suicidal ideation and that ideation is frequent, severe, or involves a suicide plan, the crisis supervisor and interviewer inform the P’s mother, or if the suicidal individual is the mother (relevant at T1 only), work with the mother to involve a responsible person in the mother’s life (e.g., a family member, therapist, close friend). The crisis supervisor and interviewer also will discuss plans for safety with the P, work with the P to commit to seeking treatment, and provide the P with referral information. As part of the assenting and consenting process (and written in the

assent and consent forms), Ps are informed that if they experience suicidal ideation, confidentiality may need to be broken in order to protect their safety and get them help.

If any P expresses serious, imminent suicidal intent in any of the interviews or self-report instruments, the following plan and back-up plan is followed to ensure the safety of the P. First, the MPI, other lab crisis supervisor, and/or interviewer discuss the suicidal ideation with the P. A determination of whether or not the P currently is under the care of a psychiatrist, psychologist, or other mental health professional is made (presumably, this information already would have been gathered in the interview). The following steps are followed in the case of a P who is currently in treatment. If the P is in treatment but not at immediate risk for self-harm although in distress, we will encourage him/her to make contact with his/her mental health professional. To ensure that we know if the P makes contact with his/her mental health professional, we will ask the P for consent to call his/her therapist to make sure he/she, in fact, made the contact (i.e., make a contract with P giving us permission to call the therapist to make sure P arrived at the scheduled time). If the therapist informs us that P completed the contact when we call, then we know that the referral has been completed. Alternatively, if the therapist says P did not make contact with him/her at the appointed time, then we will institute a back-up plan consisting of the following. First, we will call the P to see why the contact was not made. If the P is no longer suicidal, then it will not be necessary to proceed further. Alternatively, if the P is still suicidal but refuses to go for treatment, we will call the P's mother (if the suicidal P is an adolescent) and the appropriate police department to transport the P to an appropriate facility (either to the P's therapeutic facility or to the appropriate emergency room). Alternatively, if the P currently is in treatment and is at immediate risk for self-harm, we will contact the call system responsible and inform them about the situation. We will make it clear that the P is a research participant and not in a treatment relationship with us. We will give the relevant details regarding the P's potential for self-harm. If that system is slow to respond, we will proceed with calling the appropriate police department as described above.

The following plan and back-up plan will be followed for Ps who currently are not in treatment. If the P is not at immediate risk for self-harm, we will encourage the P or the P's mother to contact an appropriate clinic or counseling center (e.g., TU Psychological Services Center or hospital outpatient services) to make an appointment for services. If the P agrees, then the same plan for obtaining the P's consent for us to call the clinic or counseling center to determine if the P made the contact will be followed, and, if a contact is not made, the back-up plan described above will be followed. Alternatively, if the P is not currently in treatment with anyone and is assessed to be at significant risk for self-harm, the appropriate police department will be called to transport the P to the appropriate emergency room. If the P has insurance that requires use of a particular hospital, or expresses a marked preference for a particular hospital, we will contact that hospital first. We will ask to speak with the psychiatrist on call, and identify the situation as an emergency with a possible need to hospitalize. If the P does not express a preference, we will call the Temple University Hospital emergency room if the P is in Philadelphia or the appropriate hospital emergency room if the P is not in Philadelphia. Of course, in all four cases above, we will document all telephone conversations and procedures taken.

In addition, grave disability may result from a full-blown syndrome of major depression, and a plan needs to be in place for determining when a referral is required (and completed) for this potential outcome. In this case, we will review the circumstances of the episode with Dr. Robert Fauber, the Director of TU's Psychological Services Center. With the aid of this consultation, we will make a judgment regarding the seriousness of the episode and the need for referral. The critical determination to be made is whether or not the P shows a high likelihood of grave disability. If any (or more) of the following four factors is present, we define the P as suffering grave disability and make a referral: 1) Suicidal; 2) Physically reckless behavior; 3) Judgment impaired; and/or 4) Serious functional impairment that seriously compromises the P's life or the lives of those close to the P (e.g., not going to school for a lengthy period of time). In the cases of grave disability involving potential harm to self, the procedures described in the preceding paragraph will be followed to ensure the referral is completed, and, if not completed, the back-up plan described above will be followed. In cases involving potential harm to others, the police will be called to transport P to the appropriate facility. In other cases involving impairment, a referral for services will be made. MPI Alloy's lab has an extensive list of referral sites, a number of which are low-cost, including the TU Psychological Services Center.

Finally, any P who requests psychological/psychiatric help throughout the course of the study (or whose parent requests help for their adolescent child) also will be given referral information.

In the case of homicidal ideation, we have a duty to warn if a P identifies the potential victim. Interviewers will do this in consultation with the MPI or other lab crisis supervisor. In situations involving potential duty to warn, the Temple University legal service may be consulted by MPI Alloy.

Moreover, it is possible that we will learn that an adolescent is being maltreated in the course of one of our assessments. In this case we are required to inform proper authorities. If a parent is not the perpetrator of the maltreatment, we also will inform the P's parent. As part of the consenting and assenting process (and written in the consent and assent forms), the Ps are informed that if they experience abuse, confidentiality may need to be broken in order to inform the proper authorities as required by law and to assist them in getting help.

We have used these safeguards with success in our previous NIMH-funded projects (MH077908, MH079369, MH101168, MH102310).

Protections against Participant Distress or Fatigue During Assessments. Experienced project interviewers (clinical psychology PhD students and MA level psychologists, post-BA extensively trained project interviewers) trained to maintain confidentiality and address any distress that arises will conduct the questionnaire, interview, and behavioral task assessments under the direct supervision of MPI Alloy. Subsequent to each research assessment, the interviewers will spend time with each P discussing any questions or doubts the P may have about the project or the particular assessment. In the event that any P experiences psychological discomfort from any aspect of project participation, our project interviewers, who are trained to deal with any upset resulting from participation in the study, will talk with the P until his/her discomfort has subsided. In addition, MPI Alloy is a PhD clinical psychologist who will talk with Ps if necessary. Every effort will be made to make the environment comfortable, snacks and beverages are offered (after any blood draw and except during the fMRI scans), frequent breaks are taken, and the assessment is stopped if the P wishes or if their stress levels increase significantly. Ps will be reminded that they can refuse to answer any question that they find too personal or distressing. In addition, the assessments are scheduled at Ps' convenience in MPI Alloy's lab on the main campus of TU, which is easily accessible to community residents. Our experience with adolescent Ps in previous NIMH-funded similar projects (e.g., MH07798, MH101168) confirms that no unusual or harmful reactions have occurred and most Ps find engaging in the assessments and tasks to be enjoyable.

Protections against Participant Distress or Inconvenience During Actigraphy. It is possible that there may be slight inconvenience or discomfort associated with wearing the Actiwatch to objectively assess sleep and physical activity during 7-day periods at T1-T5. However, the Actiwatch is no more inconvenient or uncomfortable than a normal wristwatch. If the P experiences too much discomfort from wearing the Actiwatch, he/she can simply remove the instrument and discontinue their participation in the actigraphy. In our previously completed 20-day EMA study (MH102310) that used the same actiwatches as proposed here, there were no instances of major discomfort among our Ps.

2) Potential Breaches of Confidentiality and Risk for Coercion

Confidentiality will be carefully maintained and protected. The only exceptions to confidentiality are if the P develops suicidality and/or significant psychiatric symptoms or episodes (in which case we must break confidentiality to ensure the P's safety and that the P gets help). Potential risks due to loss of confidentiality will be minimized by having all information collected and handled by research staff trained to deal appropriately with sensitive issues and who have completed the Temple University IRB training and HIPAA training. All information will be treated as confidential material and will be available only to the research team. Information is not sent to other professionals except when the P or his/her parent specifically consents or requests this in writing. Research data from Ps are marked with an I.D. number only and kept in password-protected databases or in locked file cabinets inside the PI's HIPAA secure, electronically alarmed lab. No data will have P names on them, except for consent/assent forms, which will be stored separately from all other data in a locked file cabinet in the PI's electronically alarmed lab. There are two different kinds of computer databases of information: 1) a clinical database including identification numbers, names, contact details and other protected personal and health information, and 2) research databases that include only identification numbers to identify Ps and the various research data used for analysis. Access to the clinical database is limited to the MPIS and project directors/coordinators and access to the research databases is limited to project staff who require these for their work. Databases are accessible only through password-protected interfaces and are maintained on a HIPAA secure network. No P will be identified in any report resulting from this project; only aggregate data will be reported. Brain images and immune assay data likewise will be de-identified using only the P ID number. De-identified MRI data will be transferred from TUBRIC to the Northwestern MPI Nusslock's laboratory using the Extensible Neuroimaging Archive Toolkit (XNAT). XNAT is designed to transfer MRI with maximal security

for maintaining data confidentiality and integrity. In addition, at the end of the project, de-identified MRI data also will be shared in the NIMH Data Archive (NDA), a public database. Likewise, de-identified blood specimens will be shipped to the Northwestern Co-I Miller's laboratory for immune assays.

Additionally, confidentiality is carefully maintained and protected between adolescent Ps and their mothers. To maintain the adolescent's confidentiality, mothers are not allowed to see their child's responses to study assessments. This procedural safeguard is explained to mothers and adolescents in advance at the beginning of the study. The only exception to this protection of the adolescent's confidentiality is if the youth exhibits suicidality/homicidality, and/or significant psychiatric symptoms or diagnoses during the ongoing study. In such cases, the mother is informed of her child's condition. The only other exception to this safeguard of the adolescent's confidentiality is if the adolescent reports maltreatment. In such cases, the mother is informed of the maltreatment as long as she is not the perpetrator. In addition, the proper authorities are notified in order to keep the adolescent safe. Likewise, information that the mother provides about the adolescent or about herself in self-report questionnaires or interviews is not shared with the adolescent.

The risk of coercion will be minimized by following standard procedures for obtaining informed assent and consent. We will fully explain the study procedures, risks, benefits, and alternatives to all Ps. Ps will be free to withdraw at any time, and will receive compensation for time devoted to the project.

3) Risks Associated with Blood Specimen Collection Procedures

Protections Against Risks Associated with Discomfort or Apprehension. The expected risks of the collection of blood samples are minimal. There is the risk of discomfort or apprehension from the needle stick; however, the needles used to collect blood are very small (23g) and the procedure is done within seconds by a nationally certified phlebotomist, with minimal pain expected. Ps will be given the option of having EMLA cream (a topical anesthetic) applied to their inner arm, which would eliminate even minimal pain. Ps will be able to end their participation in the blood draw at any time. Over 1000 blood draws of adolescents have been conducted in MPI Alloy's lab (MH101168, MH077908) with no adverse outcomes.

Protections Against Bruising, Tenderness, or Bleeding at Site of Needle Stick. Although these complications are very rare, there is a risk of skin bruising, tenderness, or bleeding from the needle stick. As mentioned above, the needles used to collect blood are very small (23g) and the procedure is done within seconds by a certified phlebotomist, thus minimizing the risk of bruising, tenderness, or bleeding at the site of the needle stick.

Protections Against Vasovagal Response. There is a small risk of vasovagal response, which may result in a brief fainting spell that lasts seconds. For this reason, all blood draws will take place while the P is seated and each P will be observed for 10 minutes following the needle stick, should such an event occur. There will be a comfortable area designated for Ps to wait until they are released. Drinking water and orange juice and eating crackers will be available for Ps.

Protections Against Infection Risk. Any time the skin is broken there is a slight risk for infection (redness of the skin, burning sensation, chills and fever). All of the blood procedures as well as the area of blood collection will adhere to the Bio-Safety Level 2 (BSL-2) standards, using universal precautions, and will be adapted to handle and process blood borne pathogenic agents. Sterilized, single use equipment will be used to draw blood and will be properly disposed of following a blood draw procedure. Blood will be handled in contained vials. Blood drawing equipment will never be in contact with blood from another individual. Moreover, all blood draw procedures will involve injection site preparation using alcohol pads, and the phlebotomist will wear disposable sterile gloves. In case adverse symptoms occur, or if there are questions after the procedure, Ps will be given contact information to get in touch with phlebotomy and research personnel. Also, within two days after the blood draw, we will make a well-check call to Ps. All blood procedures, handling, and disposal in MPI Alloy's lab meet all Environmental Health and Radiation (EHRS) standards. In disposing of blood collection materials, any contaminated waste (gauze, gloves, etc.) is placed in a biohazard bag opened with a foot pedal. A sharps container is used for unused blood collection tubes, capped needles, and their plastic covers. The waste is dropped off in the designated area for department hazardous waste to be collected, and is picked up by EHRS.

Protections Against Psychological Risk. The major psychological risk involved in the collection of blood specimens and assay results from the Ps is breach of confidentiality. We will take extra measures to protect the confidentiality of Ps' blood specimens and assay results and will explain these extra precautions to Ps (see Protections Against Potential Breaches of Confidentiality and Risk for Coercion, below).

4) Risks Associated with fMRI Procedures

Protections Against fMRI Procedure Risks. At T1, T3, and T5 at the same time of day, Ps will participate in fMRI monetary and social reward tasks (Monetary Incentive Delay [MID] task and Chatroom Interact task, respectively). Magnetic resonance imaging is non-invasive, widely used, and safe. The potential risks such as static magnetic field, radio-frequency field, magnetic field gradients, and acoustic noise are rarely dangerous or life threatening. According to current knowledge, the risks of fMRI when exclusion criteria are observed are extremely small and the benefits of these investigations to clinical and neuroscience research are large.

To minimize risks, potential Ps will receive a prescreening phone interview to exclude those with contraindications. Prior to participation in each fMRI scan at T1, T3, and T5, Ps will receive a complete screening by a certified technician at the Temple University Brain Research & Imaging Center (TUBRIC), where the fMRI scans will be conducted. Ps will be studied only if they pass the Society of Magnetic Resonance Imaging standardized MRI screening protocol (exclusions for ferrous metal in any part of the body, such as pacemakers, cochlear implants, surgical clips or metal fragments, serious medical conditions, claustrophobia). Ps also will be asked about possible pregnancy, and screened for any history of head trauma involving unconsciousness, and neurological illness. Ps who are suitable will have the procedures to be performed explained in full and any questions they have will be answered. Potential risks and benefits from this research will be reviewed. All Ps will understand that they may withdraw from the fMRI scan at any time without prejudice. The research protocol and consent form will be approved by the TU IRB. Furthermore, all researchers involved in the collection of fMRI data will be required to complete an fMRI safety course given by the TUBRIC and they will be supervised by the project's Consultant, Dr. Jason Chein, Director of the TUBRIC.

Potential risks to Ps without contraindications include mild anxiety, claustrophobic reaction, and movement of ferromagnetic objects. Anxiety and claustrophobic reactions will be minimized in two ways: by thoroughly explaining the procedures and the nature of the magnetic resonance scanner to Ps prior to the fMRI scan, and by placing Ps in the mock scanner and providing them with training during the T1 session so that they can accommodate to the scanner prior to undergoing an actual fMRI scan. During the scanning procedures, the Ps are continually monitored visually and auditorily for any potential problems, and Ps are assured that they can and will be removed from the scanner at any time if problems should arise or they indicate that they are experiencing discomfort. As noted above, Ps will be screened twice prior to study, once at the time of the screening phone interview, and a second time when they arrive at the TUBRIC. Certain MRI scanning procedures can produce loud (>100 dB) noises; thus, ear protection will be provided by the use of sound-reduction earplugs plus a form-fitting pillow. Ps will be informed that they cannot have any metal on their person when they enter the fMRI imaging room. The Ps will be constantly monitored for any side effects and will be treated appropriately if needed. The fMRI study may be aborted if the P has any discomfort. The safety of the Ps will be continually monitored. Beyond these risks, there are no known side effects of fMRI to Ps without contraindications. There are no alternative procedures to those described in this proposal. Note that the investigators have extensive prior experience conducting fMRI scans involving these tasks with adolescents in our prior grant projects (MH077908, MH101168, MH100117, MH107495).

All of the fMRI data collected will be kept strictly confidential and coded and stored only with the P's ID number. Under no circumstances will individually identifiable data be released to anyone without the written assent of the P and consent of his/her parent. Ps will be informed that the brain scans are for research purposes only and results will not routinely be shared with Ps. However, results will be shared with the Ps at their written request or if there is an incidental finding, as described below. MRI data will be transferred from TUBRIC to MPI Nusslock's Northwestern lab using the Extensible Neuroimaging Archive Toolkit (XNAT). XNAT provides the ability to export data into a number of convenient formats with maximal security for maintaining data confidentiality and integrity. The XNAT system is already functional at Temple University and will allow the investigative team to effortlessly transfer data back and forth between Temple University and Northwestern University in a completely secure and confidential manner. Drs. Nusslock, Alloy, and Chein have successfully used this system for data transfer between Temple and Northwestern for the past six years as part of another NIH R01 grant (MH077908).

Protections Against Deception During the fMRI Social Reward Task. In our social reward paradigm (Chatroom Interact task), there is deception concerning the outcomes of trials and Ps may temporarily feel sad or embarrassed when they are not chosen by one of their virtual peers in the game. No participants have expressed significant distress during or following these situations in our prior studies using this task (MH101168, MH107495, PA CURE grant). In using the Chatroom task in one of our previous studies in which debriefing occurred 9-months after the assessment, a number of Ps did not recall how they felt following the task, or while participating in the task. As this task will be completed at T1, T3, and T5, debriefing Ps concerning this deception will not occur until after the T5 assessment. We will do this to maintain the integrity of the task, which would be invalid if deception was not employed.

Incidental finding: Structural and functional images of the brain will be collected during the fMRI scanning session, raising the possibility of detecting a brain abnormality not otherwise known to the P. Ps are explicitly told that the scans are not designed to find abnormalities. If a worrisome finding is seen on a scan, a radiologist or other physician will be asked to review the relevant images. Based on his/her recommendation (if any), MPI Alloy or the consulting physician will contact the P's mother, inform the P's mother of the finding, and recommend that the P's mother seek medical advice for the P as a precautionary measure.

3. Potential Benefits of the Proposed Research to Research Participants and Others

The benefits of the research are both general and personal. The potential benefits to society are multiple in terms of the knowledge to be gained from this project (see "Importance of the Knowledge to be Gained" below). On a personal level, Ps may derive some benefit from being able to verbalize topics of concern and from having someone listen to their life experiences. Although the diagnostic and life events interviews essentially are research-oriented, the interviewers' sympathetic listening and understanding may have positive effects. Similarly, the prospective follow-ups may reflect an awareness of and concern with Ps' personal lives and psychological adjustment that may prove beneficial to individual Ps. Also, the T1-T5 sessions enable us to identify and provide help for Ps who develop serious depression or who may be suicidal before they can act. Ps also will benefit indirectly by knowing that they are contributing to research that can be applied to improving understanding of immune and reward systems function as well as potential advances in treatments of depression. Thus, the risks to Ps are reasonable in relation to the anticipated benefits to them and others.

4. Importance of the Knowledge to be Gained

This project has great scientific and public health significance. Major depression is among the most prevalent forms of psychopathology, typically begins in adolescence, is highly recurrent, and is frequently associated with severe personal, social, and economic costs.^{14,9-15} Even depression symptoms in the absence of a diagnosis are associated with significant functional impairment, increased suicide risk, and can progress to diagnosed major depression.⁵⁻⁸ Given that major depression is relatively prevalent, can be severe and extremely impairing, and is associated with serious personal, economic, and societal consequences, it is critical to identify vulnerabilities and possible mechanisms, as we will do, that can be targeted in preventive interventions. Second, this project provides the first major investigation of reward system and peripheral inflammation interactions underlying vulnerability to first onset of major depression in adolescence. Although prior studies have examined the role of reward responsivity (RR) or inflammation separately in major depression, our study will be the first to investigate whether joint RR-inflammation dysregulation predicts first onset of major depression. Third, this project is the first to examine bidirectional RR – inflammation associations at multiple units of analysis for the reward system. Although some studies have examined RR predictors of inflammation and inflammatory predictors of RR, ours will be the first to examine bidirectional associations of the systems at baseline and over time in the same study and their joint prospective prediction of first onset of major depression. Moreover, by assessing reward responsivity with self-report, behavioral, and neural (fMRI activation and functional connectivity) measures, we will attain a more in-depth understanding of the two systems' interrelationships and joint prediction of major depression and increases in depression symptoms. Further, assessing reward responsivity at multiple units of analysis will allow us to empirically examine whether these units cohere, or if specific units (self-report, behavioral, or neural) more strongly relate to inflammation and major depression/depression symptoms. Moreover, the multiple timepoints for assessing reward responsivity and inflammation will allow us to assess whether single timepoint, stable, or worsening RR abnormalities and inflammation over time best predict major depression and depression symptoms separately and jointly in response to reward-deactivation relevant events. Understanding mechanisms of vulnerability is crucial for translating knowledge about the risk factors and causes of depression to theoretically coherent

interventions designed to prevent or treat this impairing condition. For example, identifying reward-immune pathways in the etiology of major depression could facilitate the generation of novel neuroimmunological interventions that target brain-to-immune and/or immune-to brain signaling to treat, and ideally prevent, depression.⁷³ Fourth, the project will contribute to the development of assessments that may identify adolescents with endophenotypes who are likely to develop major depressive disorder before such dysfunction occurs and, thus, who can most benefit from early preventive interventions. Fifth, the project is unique in examining moderators (childhood adversity) and mediators (the inflammation-enhancing behaviors of stress generation, substance use, poor diet, and sleep disruption) of RR – inflammation bidirectional associations.

In summary, this project will 1) inform our understanding of potential etiological pathways and biobehavioral mechanisms involved in initial onset of major depression and increases in depression symptoms in adolescence; 2) help identify intermediate phenotypes for these pathways; 3) provide tools for the early identification of individuals at risk for major depression in need of preventive intervention; and 4) facilitate development of treatments targeted at ameliorating systemic immune and reward processing abnormalities. This knowledge is crucial for translating basic research to powerful interventions that may short-circuit the impairing consequences of depression.

In view of these factors, the short and long-term benefits to society and to the individual participant outweigh the relatively small potential risks.

Section 4 - Protocol Synopsis (Study 1)

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

Delayed Onset Studies

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

Research Plan Form

7. Multiple PD/PI Leadership Plan

This grant application utilizes a multiple PD/PI leadership approach between one investigator at Temple University in the Department of Psychology (Dr. Alloy) and one investigator at Northwestern University in the Department of Psychology (Dr. Nusslock), who have collaborated on a grant since 2013 and on multiple publications over the past 17 years. This application—which proposes to examine bidirectional relationships between reward responsivity and inflammation in risk for developing a first onset of major depressive disorder and increases in depressive symptoms during adolescence—capitalizes on both of the PD/PI's strengths and substantial research expertise. Furthermore, it builds upon their active and productive collaborative effort: they collaborated on a R01 from NIMH (PI, Dr. Alloy; MH077908) examining reward sensitivity (including reward-related brain function) in first onset of adolescent bipolar spectrum disorder (some data from this R01 forms the basis of part of the current R01 proposal), and they have published numerous articles from this current grant.

Dr. Alloy has a documented, long-standing record of expertise and experience in studying reward responsivity and processing, inflammation, social and circadian rhythm disruption, cognitive vulnerabilities, life stress, emotion regulation, and developmental precursors (including childhood adversity) in mood disorders, including both unipolar depression and bipolar spectrum disorders, for over 40 years. Specifically relevant to this application, she has published extensively on the role of reward system responsivity and processing in unipolar depression and bipolar spectrum disorders, and she has several recent published and in press articles and multiple additional manuscripts under review or in preparation on the role of inflammation in unipolar depression and bipolar spectrum disorders. She has been the PI of multiple NIMH R01 grants, including most recently one that examines reward responsivity (including reward-related brain function) in first onset of adolescent bipolar spectrum pathology (with Dr. Nusslock as Co-I), one that examines cognitive, executive functioning, emotion regulation, and psychosocial stress risk factors in combination with inflammation as vulnerabilities to adolescent depression, and one that examines the interaction of the reward and the circadian rhythm systems in onset and course of bipolar spectrum disorders. Furthermore, also relevant to the current proposal, Dr. Alloy's grant from the PA Department of Health examines reward responsivity – inflammation associations as a function of family history (maternal depression) and environmental (childhood adversity) risk factors for depression in adolescence. In addition to these grants, she also has an extensive record of continuous external funding since 1974. Dr. Alloy is in the top 1% of most cited authors in psychology, with over 350 publications. She is the recipient of multiple lifetime/career scientific achievement awards from multiple professional organizations for her work on the etiology and course of mood disorders. Dr. Alloy has successfully laid the groundwork for the proposed study as PI of her two NIMH R01 grants (MH077908 and MH101168) examining: 1) inflammation in combination with cognitive, emotion regulation, child adversity, and psychosocial stress as risk factors for adolescent depression, and 2) self-report, behavioral, and neural reward processing as risk factors for bipolar spectrum disorder mood symptoms and episodes, together with Dr. Nusslock who served as Co-I of this latter grant. Therefore, she is well-qualified to serve as MPI with Dr. Nusslock on the proposed study.

Dr. Nusslock's research program and expertise is in abnormalities in reward processing and reward-related brain function in unipolar and bipolar mood disorders. His publications have examined abnormalities in reward processing in mood disorders using psychosocial, neurophysiological (EEG), and neural (fMRI/DTI) indices. He and Co-I Dr. Miller are the original authors of the Neuroimmune Network model,⁷³ which highlights bidirectional signaling between the brain and body in mental and physical illness. This model informs the conceptual foundation for this proposal. He also has a 17-year collaboration and many joint publications with MPI Alloy on reward responsivity in unipolar and bipolar spectrum disorders. In addition, he was Co-I on one of Dr. Alloy's NIMH R01 grants (MH077908) on reward-related brain function in the onset and course of bipolar spectrum disorders, for which he is managing all the MRI data. Thus, he already has established the mechanism for transferring MRI data between Temple and Northwestern University and will employ identical procedures in the proposed research. Dr. Nusslock has multiple publications using the proposed fMRI monetary reward paradigm to examine the cortico-striatal reward circuit. Thus, he already has well-established preprocessing and analytic pipelines for managing the MRI data in the proposed research. He also has considerable experience managing large-scale neuroimaging studies and is currently PI on a multi-site NIMH R01 grant using MRI to examine the relationship between reward-related neural circuitry and mood disorder symptoms (MH100117). Therefore, he is well-qualified to serve as MPI with Dr. Alloy on the proposed study.

Both Dr. Alloy and Dr. Nusslock will have overall responsibility for the scientific conduct of the work, intellectually and logically, and will oversee data analysis, submission of all required reports and presentation of results. They will work collaboratively to address any issues that may arise across different facets of the study. Dr. Alloy and Dr. Nusslock will lead weekly grant study meetings to discuss the status of the project, including regulatory issues, recruitment, assessments, and data. Dr. Nusslock will participate in grant study meetings at Temple University by phone and by GotoMeeting or another online meeting/web conferencing software platform. Dr. Alloy's effort will focus on recruitment, screening, and monitoring participation and adherence of participants to the 3-year protocol (involving Time 1 - 5 assessment sessions, 3 blood draws, 3 MRI scans, and 5 7-day periods of actigraphy), and she will closely supervise study staff and the coordination of the study at Temple University. Dr. Alloy will serve as contact PI and will be responsible for submitting all necessary documents to NIH, including IRB approvals, and annual progress reports, after receiving Dr. Nusslock's input. Dr. Nusslock's effort will focus on the design, implementation, analysis, and interpretation of data from the MRI scans. He will be responsible for preprocessing MRI (fMRI activation and functional connectivity) data, with the assistance of Co-I Dr. Olino and Consultant Dr. Chein, and he will be involved in analyzing MRI data generated from this project. As MPI at Northwestern University, Dr. Nusslock will be responsible for managing personnel and resources and ensuring overall quality control related to the aforementioned data. MRI data will be collected at Temple University and securely transferred to Dr. Nusslock's laboratory at Northwestern University using the Extensible Neuroimaging Archive Toolkit (XNAT). In addition, he will assist in the preparation of reports and scientific publications with Dr. Alloy, the other MPI. Both PIs will work directly with the study staff (e.g., RAs) and with Co-Is Dr. Miller and Dr. Ellman as needed, regarding the design, conduct, and interpretation of the inflammation assays. In addition, both PIs will work closely with Co-I Dr. Olino to oversee preliminary and primary statistical analyses and interpretation of the main study findings. Both PIs will jointly write publications and future grant proposals resulting from this grant.

In addition to the weekly study meetings as stated above, the PIs will communicate as frequently as is necessary either by phone or e-mail to discuss experimental design, data analysis, and all administrative responsibilities. The PIs will work together to discuss any changes in the scientific direction of the research project and the re-allocation of funds or resources, if necessary. A publication policy will be established based on the relative scientific contributions of the PIs and key personnel.

Intellectual Property

The PIs will be joint authors on any publications or conference presentations resulting from this research project. The Technology Transfer Office at each of the PI's institutions (Temple University and Northwestern University) will be responsible for preparing and negotiating an agreement for the conduct of the research, including any intellectual property. An Intellectual Property Committee composed of representatives from each of the PI's institutions will be formed to work together to ensure the intellectual property developed by the PIs is protected according to the policies established in the agreement.

Conflict Resolution

The PIs have an excellent, long-standing, highly collegial, professional relationship. However, if a potential conflict develops, the PIs will meet and attempt to resolve the dispute. If they fail to resolve the dispute, the disagreement will be referred to an arbitration committee consisting of two impartial senior officials from each of the PI's institutions (Temple University and Northwestern University), mutually agreed upon by both PIs. No member of the arbitration committee will be directly involved in the research grant or in the disagreement.

Change in PI Location

If one PI moves to a new institution, the NIH will be notified, and attempts will be made to transfer the relevant portion of the grant to the new institution. In the event that one of the PIs cannot carry out her or his duties, a new PI will be recruited as a replacement, subject to the approval of that PI's institution.

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8. Consortium/Contractual Arrangements

In this application, Temple University as the submitting institution is subcontracting with Northwestern University.

Temple University is the submitting institution and grantee because all participant recruitment and data collection will take place at Temple University. MPI, Dr. Lauren Alloy, will focus on recruitment, screening, and monitoring participation and adherence of participants to the 3-year protocol (involving Time 1-5 assessment sessions, 3 blood draws, 3 MRI scans, and 5 7-day actigraphy periods), and she will closely supervise study staff and the coordination of the study at Temple University. Dr. Alloy will serve as contact PI and will be responsible for submitting all necessary documents to NIH, including IRB approvals, and annual progress reports, after receiving MPI Dr. Robin Nusslock's input.

Dr. Alloy has a documented, long-standing record of expertise and experience in studying reward responsiveness and processing, inflammation, social and circadian rhythm disruption, cognitive vulnerabilities, life stress, emotion regulation, and developmental precursors (including childhood adversity) in mood disorders, including both unipolar depression and bipolar spectrum disorders, for over 40 years. Specifically relevant to this application, she has published extensively on the role of reward system responsiveness and processing in unipolar depression and bipolar spectrum disorders, and she has several recent published and in press articles and multiple additional manuscripts under review or in preparation on the role of inflammation in unipolar depression and bipolar spectrum disorders. She has been the PI of multiple NIMH R01 grants, including most recently one that examines reward responsiveness (including reward-related brain function) in first onset of adolescent bipolar spectrum pathology (with Dr. Nusslock as Co-I), one that examines cognitive, executive functioning, emotion regulation, and psychosocial stress risk factors in combination with inflammation as vulnerabilities to adolescent depression, and one that examines the interaction of the reward and the circadian rhythm systems in onset and course of bipolar spectrum disorders. Furthermore, also relevant to the current proposal, Dr. Alloy's grant from the PA Department of Health examines reward responsiveness – inflammation associations as a function of family history (maternal depression) and environmental (childhood adversity) risk factors for depression in adolescence. In addition to these grants, she also has an extensive record of continuous external funding since 1974. Dr. Alloy is in the top 1% of most cited authors in psychology, with over 350 publications. She is the recipient of multiple lifetime/career scientific achievement awards from multiple professional organizations for her work on the etiology and course of mood disorders. Dr. Alloy has successfully laid the groundwork for the proposed study as PI of her two NIMH R01 grants (MH077908 and MH101168) examining: 1) inflammation in combination with cognitive, emotion regulation, child adversity, and psychosocial stress as risk factors for adolescent depression, and 2) self-report, behavioral, and neural reward processing as risk factors for bipolar spectrum disorder mood symptoms and episodes, together with Dr. Nusslock who served as Co-I of this latter grant. Therefore, she is well-qualified to serve as MPI with Dr. Nusslock on the proposed study.

Northwestern University. The subcontract with Northwestern University is to provide support for 15% of the academic year salary of MPI, Dr. Robin Nusslock, for five years, 8% of the academic year salary of Co-I, Dr. Gregory Miller, for Year 1 and 7% for Years 2-5, and one Technical RA at 31.75% effort for Years 2-4 and 40% effort for Year 5.

As MPI on this proposal, Dr. Nusslock will focus on the design, implementation, analysis, and interpretation of data from the MRI scans. He will be responsible for preprocessing MRI data, with the assistance of Co-I Dr. Olino and Consultant Dr. Chein, and he will be involved in analyzing MRI data generated from this project. As MPI at Northwestern University, Dr. Nusslock also will be responsible for managing personnel and resources and ensuring overall quality control related to the aforementioned data. MRI data will be collected at Temple University and securely transferred to Dr. Nusslock's laboratory at Northwestern University using the Extensible Neuroimaging Archive Toolkit (XNAT). In addition, he will assist in the preparation of reports and scientific publications with Dr. Alloy, the other MPI. Both PIs will work directly with the study staff (e.g., RAs) and with Co-Is Dr. Miller and Dr. Ellman as needed, regarding the design, conduct, and interpretation of the inflammation assays. In addition, both PIs will work closely with Co-I Dr. Olino to oversee preliminary and primary statistical analyses and interpretation of the main study findings. Both PIs will jointly write publications and future grant proposals resulting from this grant.

Dr. Nusslock's research program and expertise is in abnormalities in reward processing and reward-related brain function in unipolar and bipolar mood disorders. His publications have examined abnormalities in reward processing in mood disorders using psychosocial, neurophysiological (EEG), and neural (fMRI/DTI) indices. He and Co-I Dr. Miller are the original authors of the Neuroimmune Network model⁷³ which highlights bidirectional signaling between the brain and body in mental and physical illness. This model informs the conceptual foundation for this proposal. He also has a 17-year collaboration and many joint publications with MPI Alloy on reward responsivity in unipolar and bipolar spectrum disorders. In addition, he was Co-I on one of Dr. Alloy's NIMH R01 grants (MH077908) on reward-related brain function in the onset and course of bipolar spectrum disorders, for which he is managing all the MRI data. Thus, he has already established the mechanism for transferring MRI data between Temple and Northwestern University and will employ identical procedures in the proposed research. Dr. Nusslock has multiple publications using the proposed fMRI monetary reward paradigm to examine the cortico-striatal reward circuit. Thus, he already has well-established preprocessing and analytic pipelines for managing the MRI data in the proposed research. He also has considerable experience managing large-scale neuroimaging studies and is currently PI on a multi-site NIMH R01 grant using MRI to examine the relationship between reward-related neural circuitry and mood disorder symptoms (MH100117). Therefore, he is well-qualified to serve as MPI with Dr. Alloy on the proposed study.

As Co-I at Northwestern University, Dr. Miller will be responsible for conducting all immune system assays from blood specimens collected at Temple University. Dr. Miller is a world leader in the field of behavioral medicine and psychoneuroimmunology. He has particular expertise in the relationship between early life adversity, peripheral inflammation, and risk for mental and physical illness. He has made important contributions to understanding how stress gets under the skin to alter immune functioning in a manner that elevates risk for illness, as well as the effect of intervention programs on inflammatory signaling and stress biology. He runs a laboratory at Northwestern University that is fully equipped to process and analyze systemic and genomic inflammatory signaling, as well as hormonal, and epigenetic data. Moreover, Dr. Miller has published with MPI Nusslock on a neuroimmune network model of the relationship between inflammation and reward/threat-related brain function and risk for mental and physical health. The present proposal reflects an empirical investigation of many of the ideas proposed in this publication. In addition, Dr. Miller is co-author with MPI Alloy on two articles under review on reward-inflammation associations. Thus, Dr. Miller has made important contributions to the design of the project and the writing of the grant application. As a Co-I, he will a) provide input on the conceptual and mechanistic linkages between early life adversity, inflammatory signaling, and risk for major depression, (b) oversee the immunologic assays of systemic inflammation, and (c) actively participate in the analysis and interpretation of neuroimmune data, and co-author manuscripts that result.

Technical Research Assistant – To be named; 31.75% (3.8 person-months) for Years 2-4 and 40% (4.8 person-months) for Year 5 calendar year salary support plus fringe benefits are requested. The Technical RA primarily will assist Dr. Nusslock with the preprocessing and analysis of the fMRI data. He/she also may assist Dr. Miller with conducting the CRP and cytokine assays from the blood specimens. Effort for this Technical RA is increased in Year 5, when all of the fMRI and inflammation data will be collected and there is the highest need for data processing and analysis.

In addition to the 31.75% salary support for an MRI Technical Research Assistant for Years 2-4 and 40% salary support for Year 5 of the proposed research, the Northwestern MPI will have 2 Ph.D. graduate students funded on university fellowships who will make the equivalent of a 50% commitment to assist with MRI data processing and analysis for all 5 years of the proposed research. These 2 graduate student appointments are funded by Northwestern University fellowships and thus guaranteed. Both of these Ph.D. students have extensive experience in functional and structural MRI processing and analysis. For example, Casey Young, one of the Ph.D. students who will be working on the project, served as a post-baccalaureate MRI RA for 5 years at UCLA before starting graduate school. She worked closely with Dr. Susan Bookheimer at UCLA, a leader in the field of cognitive neuroscience, and has first authored papers on the application of graph theory to resting state functional data. The second Ph.D. student who will work on this proposal is Ann Carroll, who served as Dr. Joshua Buckholtz's full-time MRI data analyst at Harvard for 2 years before graduate school. Working on this project will provide Casey and Ann with an outstanding training experience and the opportunity to further their career through collaborations and publications. The 31.75% salary support (40% in Year 5) for the MRI Technical RA combined with Casey and Ann's effort makes us confident in our ability to successfully complete the proposed MRI processing and analysis plan.

The signature of the Authorized Organization Representative on the SF424 (R&R) cover component signifies that the applicant and Drs. Nusslock and Miller understand and agree to the following statement:

The appropriate programmatic and administrative personnel of each organization involved in this grant application are aware of the agency's consortium agreement policy and are prepared to establish the necessary inter-organizational agreement(s) consistent with that policy.



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September 19, 2019

Dr. Lauren B. Alloy
Laura H. Carnell Professor of Psychology
Department of Psychology
Temple University
Philadelphia, PA 19122

Dear Lauren:

It is my pleasure to serve as an unpaid consultant for your and Dr. Robin Nusslock's NIMH R01 grant entitled, "Integrated Reward-Inflammation Model of First Onset of Major Depression in Adolescence." I have enjoyed working with you and Robin on your previous NIMH R01 grant investigating reward-related brain function over the past 6 years.

Your new proposal to investigate bidirectional associations between immune and multilevel reward function and their joint prediction of risk for first onset of major depression and increases in depressive symptoms in adolescence is a highly innovative and important study. It will increase our understanding of the etiological pathways contributing to the onset of major depression, and as such, may facilitate the development of novel interventions for depression that target neuroimmune pathways.

My extensive expertise and experience conducting neuroimaging research, including on the neural circuits underlying reward processing in adolescents, will allow me to make regular contributions to the design, planning, and execution of the neuroimaging components of this project. I will work closely with Dr. Nusslock and his research team on implementing preprocessing and analysis pipelines for both structural and functional MRI data. In addition, as Director of the Temple University Brain Research & Imaging Center (TUBRIC), in which the neuroimaging components of your study will be conducted, I will assist in the facilitation of the logistical aspects of your project. Specifically, I will insure that participants in this project can be scanned at the cost of \$425 per hour (peak times) or \$350 per hour (off peak times) at Times 1, 3, and 5 (each a year apart) at the same time of day.

In summary, I am delighted to provide my support for your grant application, and I look forward to working with you and Robin on the execution of this project. I will devote 3% of unpaid effort to this project.

Best Regards,

A handwritten signature in black ink that reads "Jason Chein".

Jason Chein, Ph.D.
Associate Professor of Psychology
Director of Temple University Brain Research & Imaging Center
Temple University

10. Resource Sharing

Data Sharing Plan

We are committed to resource and data sharing of the neuroimaging (fMRI) data collected in this project and to having our data become a part of the National Institute of Mental Health (NIMH) Data Archive (NDA), as per guidelines outlined on its website (<https://data-archive.nimh.nih.gov/>). To this end, we have used the Cost Estimation calculator on this NDA website to estimate the data preparation and data sharing costs (estimated at \$10,000 direct costs), and have included these costs in our budget and budget justification. If our proposal is funded, we understand that we would sign a data sharing agreement. We also would insure that our consent forms include appropriate language about the sharing of de-identified data in a public database.

11. Authentication of Key Biological and/or Chemical Resources

Assay Facilities

The Northwestern University Foundations of Health Research Center is directed by Co-I Dr. Gregory Miller. The Center provides sample processing, cell separation, tissue culture, tissue homogenization, nucleic acid extraction, plus immunoassay, qPCR, and flow cytometry services.

In our project, five biomarkers will be measured in circulation to index low-grade inflammation: C-reactive protein (CRP), interleukins (IL-), 6, 8, 10, and tumor necrosis factor- α (TNF- α). Blood will be drawn into Serum Separator Tubes (Becton-Dickinson) and centrifuged at 1000 x g for 15 minutes, after which serum will be harvested, divided into aliquots, and frozen at -80°C. At study completion, biomarkers will be measured in a single batch. For CRP, thawed samples will be centrifuged to remove all solid material. CRP will be measured by high sensitivity immunoturbidimetric assay on a Roche/Hitachi cobas c502 analyzer (lower limit of detection, 0.2mg/L). Cytokines will be measured in duplicate by electrochemiluminescence (ECL) on a SECTOR Imager 2400A (MesoScale Discovery) with a Human Pro-Inflammatory Ultra-Sensitive assay (MesoScale Discovery), per manufacturer's instructions. In our prior work, this kit's detection thresholds have been .10 pg/ml, and the intra-assay and inter-assay coefficients of variation have been \leq 4.3% and \leq 7.5%, respectively.³¹⁹

To authenticate findings, Dr. Miller will perform confirmation assays on 10 percent of the sample using a second platform, where inflammatory biomarkers are measured with standard high-sensitivity ELISA kits from R&D Systems. Based on our previous research, we anticipate that rank-order correlations between platforms will exceed .80, which will authenticate the primary method. If not, we will conduct further measurements on a third (arbiter) platform to determine which of the original two methods is superior.