GRANT NO. VMR2022-02

GRANT BETWEEN
THE STATE OF MICHIGAN
DEPARTMENT OF LICENSING AND REGULATORY AFFAIRS
AND
WAYNE STATE UNIVERSITY

GRANTEE/ADDRESS:

Patty Yuhas Kieleszewski, Associate Director
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GRANT ADMINISTRATOR/ADDRESS:

David Harns
Cannabis Regulatory Agency
Department of Licensing and Regulatory Affairs
2407 N. Grand River
Lansing, MI 48906
(517) 284-8599

GRANT PERIOD: September 1, 2022 to August 31, 2027

TOTAL AUTHORIZED BUDGET: $3,536,524

SIGMA Vendor I.D.: CV0048715
SIGMA Payment Address Code: 144

GRANT

This is Grant #VMR2022-02 between the Department of Licensing and Regulatory Affairs (Grantor), and Wayne State University (Grantee), subject to terms and conditions of this grant agreement (Agreement).

1.0 Statement of Purpose

The recipients of this grant will coordinate and manage research into the efficacy of marijuana in treating the medical conditions of United States armed services veterans and preventing veteran suicide. The clinical trials performed during this research must be approved by the United States Food and Drug Administration (FDA). This FDA approval must be presented to the Grantor before the clinical trials may begin.

1.1 Statement of Work

The Grantee agrees to undertake, perform, and complete the following project:

Evaluate, coordinate and manage researchers whose clinical trials are approved by the United States Food and Drug Administration. The researchers will efficiently research the efficacy of marijuana in treating the medical conditions of United States armed services veterans and preventing veteran suicide, and are capable of performing the project within the established guidelines. The clinical trials performed during this research must be approved by the United States Food and Drug Administration (FDA). This FDA approval must be presented to the Grantor before the clinical trials may begin.

These services are more specifically described in the Grantee's Proposal, Attachment A.

1.2 Detailed Budget

A. This Agreement does not commit the State of Michigan (State) or the Department of Licensing and Regulatory Affairs (LARA) to approve requests for additional funds at any time.

B. If applicable, travel expenses will not be reimbursed at rates greater than the State Travel Rates, Attachment C, without the prior written consent of the Grant Administrator.

C. Attachment B is the Budget. The Grantee agrees that all funds shown in the Budget are to be spent as detailed in the Budget.

Changes in the Budget of less than 5% of the total line item amount do not require prior written approval, but Grantee must provide notice to the Grant Administrator.

Changes in the Budget equal to or greater than 5% of the total line item amount will be allowed only upon prior review and written approval by the Grant Administrator. A formal grant amendment must be signed by both the Grantor and Grantee.

1.3 Payment Schedule

The maximum amount of grant assistance offered is $3,536,524.

An initial advance of 50% of the total grant award will be made to the selected applicant(s) after a Grant Agreement is fully executed.

Two subsequent advances of 20% of the total grant award will be provided upon submission of a Financial Status Report/Payment Request accompanied by documentation showing that at least 50% of the prior advance has been expended.

Ten (10) percent of the total grant award will be held back pending verification and approval of monthly financial status reports as well as an Interim Project Status Report.

Public Act 279 of 1984 states that the state shall take all steps necessary to assure that payment for goods or services, is mailed within 45 days after receipt of the goods or services, a complete invoice for goods or services, or a complete contract for goods or services, whichever is later.

1.4 Monitoring and Reporting Program Performance

A. Monitoring. The Grantee shall monitor performance to assure that time schedules are being met and projected work by time period is being accomplished.

B. Quarterly Reports. The Grantee shall submit to the Grant Administrator **quarterly** performance reports that briefly present the following information:

1. Percent of completion of the project objectives. This should include a brief outline of the work accomplished during the reporting period and the work to be completed during the subsequent reporting period.

2. Brief description of problems or delays, real or anticipated, which should be brought to the attention of the Grant Administrator.

3. Statement concerning any significant deviation from previously agreed-upon Statement of Work.

C. A Final Report is required. The Grantee will do the following:

1. Submit one draft copy of the final report for review by the Grant Administrator.

2. The final report will include the following information:

a. A summary of the project implementation plan and any deviations from the original project as proposed.

b. Accomplishments and problems experienced while carrying out the project activities.

c. Coordinated efforts with other organizations to complete the project.

d. Impacts, anticipated and unanticipated, experienced as a result of the project implementation.

e. Financial expenditures of grant money and other contributions to the project, in-kind and/or direct funding.

f. Any experience in applying the project products and anticipated "next steps".

g. Actual Budget expenditures compared to the Budget in this Agreement. Include the basis or reason for any discrepancies.

PART II - GENERAL PROVISIONS

2.1 Project Changes

Grantee must obtain prior written approval for project changes from the Grant Administrator. **See Section 1.2, Detailed Budget.**

2.2 Delegation

Grantee may not delegate any of its obligations under the Grant without the prior written approval of the State. Grantee must notify the State at least 90 calendar days before the proposed delegation, and provide the State any information it requests to determine whether the delegation is in its best interest. If approved, Grantee must: (a) be the sole point of contact regarding all contractual project matters, including payment and charges for all Grant Activities; (b) make all payments to the subgrantee; and (c) incorporate the terms and conditions contained in this Grant in any subgrant with a subgrantee. Grantee remains responsible for the completion of the Grant Activities, compliance with the terms of this Grant, and the acts and omissions of the subgrantee. The State, in its sole discretion, may require the replacement of any subgrantee.

2.3 Project Income

To the extent that it can be determined that interest was earned on advances of funds, such interest shall be remitted to the Grantor. All other program income shall either be added to the project budget and used to further eligible program objectives or deducted from the total

program budget for the purpose of determining the amount of reimbursable costs. The final determination shall be made by the Grant Administrator.

2.4 Share-in-savings

The Grantor expects to share in any cost savings realized by the Grantee. Therefore, final Grantee reimbursement will be based on actual expenditures. Exceptions to this requirement must be approved in writing by the Grant Administrator.

2.5 Order of Spending

Unless otherwise required, Grantee shall expend funds in the following order: (1) private or local funds, (2) federal funds, and (3) state funds. Grantee is responsible for securing any required matching funds from sources other than the State.

2.6 Purchase of Equipment

The purchase of equipment not specifically listed in the Budget, Attachment B, must have prior written approval of the Grant Administrator. Equipment is defined as non-expendable personal property having a useful life of more than one year. Such equipment shall be retained by the Grantee unless otherwise specified at the time of approval.

2.7 Accounting

The Grantee shall adhere to the Generally Accepted Accounting Principles and shall maintain records which will allow, at a minimum, for the comparison of actual outlays with budgeted amounts. The Grantee's overall financial management system must ensure effective control over and accountability for all funds received. Accounting records must be supported by source documentation including, but not limited to, balance sheets, general ledgers, time sheets and invoices. The expenditure of state funds shall be reported by line item and compared to the Budget.

2.8 Records Maintenance, Inspection, Examination, and Audit

The State or its designee may audit Grantee to verify compliance with this Grant. Grantee must retain, and provide to the State or its designee upon request, all financial and accounting records related to the Grant through the term of the Grant and for 7 years after the latter of termination, expiration, or final payment under this Grant or any extension ("Audit Period"). If an audit, litigation, or other action involving the records is initiated before the end of the Audit Period, Grantee must retain the records until all issues are resolved.

Within 10 calendar days of providing notice, the State and its authorized representatives or designees have the right to enter and inspect Grantee's premises or any other places where Grant Activities are being performed, and examine, copy, and audit all records related to this Grant. Grantee must cooperate and provide reasonable assistance. If any financial errors are revealed, the amount in error must be reflected as a credit or debit on subsequent invoices until the amount

is paid or refunded. Any remaining balance at the end of the Grant must be paid or refunded within 45 calendar days.

This Section applies to Grantee, any parent, affiliate, or subsidiary organization of Grantee, and any subgrantee that performs Grant Activities in connection with this Grant.

If the Grantee is a governmental or non-profit organization and expends the minimum level specified in OMB Uniform Guidance ($750,000 as of December 26, 2013) or more in total federal funds in its fiscal year, then Grantee is required to submit an Audit Report to the Federal Audit Clearinghouse (FAC) as required in 200.36.

2.9 Competitive Bidding

The Grantee agrees that all procurement transactions involving the use of state funds shall be conducted in a manner that provides maximum open and free competition. When competitive selection is not feasible or practical, the Grantee agrees to obtain the written approval of the Grant Administrator before making a sole source selection. Sole source contracts should be negotiated to the extent that such negotiation is possible.

3.0 Liability

The State is not liable for any costs incurred by the Grantee before the start date or after the end date of this Agreement. Liability of the State is limited to the terms and conditions of this Agreement and the grant amount.

3.1 Intellectual Property

Unless otherwise required by law, all intellectual property developed using funds from this Agreement, including copyright, patent, trademark and trade secret, shall belong to the Grantee.

The Grantee will agree to grant to the State a nonexclusive, irrevocable license to reproduce, translate, publish, use, and dispose of all copyrightable material developed as a result of the project.

3.2 Safety

The Grantee, and all subgrantees are responsible for insuring that all precautions are exercised at all times for the protection of persons and property. Safety provisions of all Applicable Laws and building and construction codes shall be observed. The Grantee, and every subgrantee are responsible for compliance with all federal, state and local laws and regulations in any manner affecting the work or performance of this Agreement and shall at all times carefully observe and comply with all rules, ordinances, and regulations. The Grantee, and all subgrantees shall secure all necessary certificates and permits from municipal or other public authorities as may be required in connection with the performance of this Agreement.

3.3 General Indemnification

Inasmuch as each party to this grant is a governmental entity of the State of Michigan, each party to this grant must seek its own legal representation and bear its own costs; including judgments, in any litigation which may arise from the performance of this grant. It is specifically understood and greed that neither party will indemnify the other party in such litigation.

3.4 Termination

A. Termination for Cause

The State may terminate this Grant for cause, in whole or in part, if Grantee, as determined by the State: (a) endangers the value, integrity, or security of any location, data, or personnel; (b) becomes insolvent, petitions for bankruptcy court proceedings, or has an involuntary bankruptcy proceeding filed against it by any creditor; (c) engages in any conduct that may expose the State to liability; (d) breaches any of its material duties or obligations; or (e) fails to cure a breach within the time stated in a notice of breach. Any reference to specific breaches being material breaches within this Grant will not be construed to mean that other breaches are not material.

If the State terminates this Grant under this Section, the State will issue a termination notice specifying whether Grantee must: (a) cease performance immediately, or (b) continue to perform for a specified period. If it is later determined that Grantee was not in breach of the Grant, the termination will be deemed to have been a Termination for Convenience, effective as of the same date, and the rights and obligations of the parties will be limited to those provided in Subsection B, Termination for Convenience.

The State will only pay for amounts due to Grantee for Grant Activities accepted by the State on or before the date of termination, subject to the State's right to set off any amounts owed by the Grantee for the State's reasonable costs in terminating this Grant. The Grantee must pay all reasonable costs incurred by the State in terminating this Grant for cause, including administrative costs, attorneys' fees, court costs, transition costs, and any costs the State incurs to procure the Grant Activities from other sources.

B. Termination for Convenience

The State may immediately terminate this Grant in whole or in part without penalty and for any reason, including but not limited to, appropriation or budget shortfalls. If the State terminates this Grant for convenience, the State will pay all reasonable costs, as determined by the State, for State approved Grant Responsibilities.

3.5 Conflicts and Ethics

Grantee will uphold high ethical standards and is prohibited from: (a) holding or acquiring an interest that would conflict with this Grant; (b) doing anything that creates an appearance of impropriety with respect to the award or performance of the Grant; (c) attempting to influence or appearing to influence any State employee by the direct or indirect offer of anything of value; or (d) paying or agreeing to pay any person, other than employees and consultants working for Grantee, any consideration contingent upon the award of the Grant. Grantee must immediately notify the State of any violation or potential violation of these standards. This Section applies to Grantee, any parent, affiliate, or subsidiary organization of Grantee, and any subgrantee that performs Grant Activities in connection with this Grant.

3.6 Non-Discrimination

Under the Elliott-Larsen Civil Rights Act, 1976 PA 453, MCL 37.2101, et seq., and the Persons with Disabilities Civil Rights Act, 1976 PA 220, MCL 37.1101, et seq., Grantee and its subgrantees agree not to discriminate against an employee or applicant for employment with respect to hire, tenure, terms, conditions, or privileges of employment, or a matter directly or indirectly related to employment, because of race, color, religion, national origin, age, sex, height, weight, marital status, partisan considerations, or a disability or genetic information that is unrelated to the person's ability to perform the duties of a particular job or position. Breach of this covenant is a material breach of this Grant.

3.7 Unfair Labor Practices

Under MCL 423.324, the State may void any Grant with a Grantee or subgrantee who appears on the Unfair Labor Practice register compiled under MCL 423.322.

3.8 Force Majeure

Neither party will be in breach of this Grant because of any failure arising from any disaster or acts of god that are beyond their control and without their fault or negligence. Each party will use commercially reasonable efforts to resume performance. Grantee will not be relieved of a breach or delay caused by its subgrantees. If immediate performance is necessary to ensure public health and safety, the State may immediately Grant with a third party.

3.9 Media Releases

News releases pertaining to the Grant or project to which it relates must not be made without prior written State approval, and then only in accordance with the explicit written instructions of the State.

4.0 Website Incorporation

The State is not bound by any content on Grantee's website unless expressly incorporated directly into this Grant.

4.1 Certification Regarding Debarment

The Grantee certifies, by signature to this Agreement, that neither it nor its principals are presently debarred, suspended, proposed for debarment, declared ineligible, or voluntarily excluded from participation in this Agreement by any federal or State department or agency. If the Grantee is unable to certify to any portion of this statement, the Grantee shall attach an explanation to this Agreement.

4.2 Illegal Influence

The Grantee certifies, to the best of his or her knowledge and belief that:

A. No federal appropriated funds have been paid nor will be paid, by or on behalf of the Grantee, to any person for influencing or attempting to influence an officer or employee of any agency, a member of Congress, an officer or employee of Congress, or an employee of a member of Congress in connection with the awarding of any federal contract, the making of any federal grant, the making of any federal loan, the entering into of any cooperative agreement, and the extension, continuation, renewal, amendment, or modification of any federal contract, grant, loan or cooperative agreement.

B. If any funds other than federal appropriated funds have been paid or will be paid to any person for influencing or attempting to influence an officer or employee of any agency, a member of Congress, an officer or employee of Congress, or an employee of a member of Congress in connection with this grant, the Grantee shall complete and submit Standard Form-LLL, "Disclosure Form to Report Lobbying," in accordance with its instructions.

C. The Grantee shall require that the language of this certification be included in the award documents for all grants or subcontracts and that all subrecipients shall certify and disclose accordingly.

The State has relied upon this certification as a material representation. Submission of this certification is a prerequisite for entering into this Agreement imposed by 31 USC § 1352. Any person who fails to file the required certification shall be subject to a civil penalty of not less than $10,000 and not more than $100,000 for each such failure.

The Grantee certifies, to the best of his or her knowledge and belief that no state funds have been paid nor will be paid, by or on behalf of the Grantee, to any person for influencing or attempting to influence an officer or employee of any State agency, a member of the Legislature, or an employee of a member of the Legislature in connection with the awarding of any state contract, the making of any state grant, the making of any state loan, the entering into of any cooperative agreement, and the extension, continuation, renewal, amendment, or modification of any state contract, grant, loan or cooperative agreement.

4.3 Governing Law

This Grant is governed, construed, and enforced in accordance with Michigan law, excluding choice-of-law principles, and all claims relating to or arising out of this Grant are governed by Michigan law, excluding choice-of-law principles. Any dispute arising from this Grant must be resolved in Michigan Court of Claims. Grantee consents to venue in Ingham County, and waives any objections, such as lack of personal jurisdiction or forum non conveniens. Grantee must appoint agents in Michigan to receive service of process.

4.4 Compliance with Laws

Grantee must comply with all federal, state and local laws, rules and regulations.

4.5 Disclosure of Litigation, or Other Proceeding

Grantee must notify the State within 14 calendar days of receiving notice of any litigation, investigation, arbitration, or other proceeding (collectively, "Proceeding") involving Grantee, a subgrantee, or an officer or director of Grantee or subgrantee, that arises during the term of the Grant, including: (a) a criminal Proceeding; (b) a parole or probation Proceeding; (c) a Proceeding under the Sarbanes-Oxley Act; (d) a civil Proceeding involving: (1) a claim that might reasonably be expected to adversely affect Grantee's viability or financial stability; or (2) a governmental or public entity's claim or written allegation of fraud; or (e) a Proceeding involving any license that Grantee is required to possess in order to perform under this Grant.

4.6 Assignment

Grantee may not assign this Grant to any other party without the prior approval of the State. Upon notice to Grantee, the State, in its sole discretion, may assign in whole or in part, its rights or responsibilities under this Grant to any other party. If the State determines that a novation of the Grant to a third party is necessary, Grantee will agree to the novation, provide all necessary documentation and signatures, and continue to perform, with the third party, its obligations under the Grant.

4.7 Entire Grant and Modification

This Grant is the entire agreement and replaces all previous agreements between the parties for the Grant Activities. This Grant may not be amended except by signed agreement between the parties.

4.8 Grantee Relationship

Grantee assumes all rights, obligations and liabilities set forth in this Grant. Grantee, its employees, and agents will not be considered employees of the State. No partnership or joint venture relationship is created by virtue of this Grant. Grantee, and not the State, is responsible for the payment of wages, benefits and taxes of Grantee's employees and any subgrantees. Prior performance does not modify Grantee's status as an independent Grantee.

4.9 Dispute Resolution

The parties will endeavor to resolve any Grant dispute in accordance with this provision. The dispute will be referred to the parties' respective Grant Administrators or Program Managers. Such referral must include a description of the issues and all supporting documentation. The parties must submit the dispute to a senior executive if unable to resolve the dispute within 15 business days. The parties will continue performing while a dispute is being resolved, unless the dispute precludes performance. A dispute involving payment does not preclude performance.

Litigation to resolve the dispute will not be instituted until after the dispute has been elevated to the parties' senior executive and either concludes that resolution is unlikely, or fails to respond within 15 business days. The parties are not prohibited from instituting formal proceedings: (a) to avoid the expiration of statute of limitations period; (b) to preserve a superior position with respect to creditors; or (c) where a party makes a determination that a temporary restraining order or other injunctive relief is the only adequate remedy. This Section does not limit the State's right to terminate the Grant.

5.0 Severability

If any part of this Grant is held invalid or unenforceable, by any court of competent jurisdiction, that part will be deemed deleted from this Grant and the severed part will be replaced by agreed upon language that achieves the same or similar objectives. The remaining Grant will continue in full force and effect.

5.1 Waiver

Failure to enforce any provision of this Grant will not constitute a waiver.

5.2 Signatories

The signatories warrant that they are empowered to enter into this Agreement and agree to be bound by it.

E-SIGNED by Andrew Brisbo
on 2022-08-30 08:40:21 EDT

2022-08-30 08:40:21 UTC

Andrew Brisbo, Executive Director
Cannabis Regulatory Agency
Department of Licensing and Regulatory Affairs
State of Michigan

Date

E-SIGNED by Anshu Varma
on 2022-08-29 14:45:34 EDT

2022-08-29 14:45:34 UTC

Anshu Varma, Division Director
Procurement & Administration Division
Bureau of Finance and Administrative Services
Department of Licensing and Regulatory Affairs
State of Michigan

Date

E-SIGNED by Patty Yuhas Kieleszewski
on 2022-08-29 14:31:58 EDT

2022-08-29 14:31:58 UTC

Patty Yuhas Kieleszewski
Associate Director, Contract Administration
Sponsored Program Administration
Wayne State University

Date

GRANT NO. VMR2022-02

State of Michigan
Department of Licensing and Regulatory Affairs
Marijuana Regulatory Agency

VETERAN MARIJUANA RESEARCH (VMR) GRANT PROGRAM

2022

REQUEST FOR PROPOSALS

VETERAN MARIJUANA RESEARCH (VMR) GRANT

RESPONSE DOCUMENT

ESTIMATED TIMELINE	
Issue Date	April 1, 2022
Inquiries Due	April 15, 2022
Inquiries Response Posted	May 1, 2022
Proposals Due	June 1, 2022
Anticipated Start Date	July 30, 2022

PART V: INFORMATION REQUIRED FROM APPLICANT(S)

Applicant(s) must submit one proposal. Electronically submitted proposals must have a scanned signature or e-signature and cannot exceed 15 MB.

Applicant(s) must provide responses to each section below. Be as descriptive as possible and answer each question in its entirety; some questions have multiple components. In your responses, provide a straight-forward, concise description of the applicant(s)'s ability to meet the requirements of the RFP. Questions that do not apply should be answered "N/A."

V-A Identification of Organization

State the full name and address of the organization, the organization's federal identification number, the organization's telephone and fax numbers, and what percentage of the organization is located in Michigan.

BEGIN APPLICANT RESPONSE

Wayne State University

Sponsored Program Administration

5057 Woodward Avenue

13th floor, Suite# 13202

Detroit, MI 48202-4050

Federal ID # 38-6028429

Tele: (313) 577-2653

Fax: (313) 577-5055

100% located in Michigan

END APPLICANT RESPONSE

V-B Authorized Negotiator

State the name of one (1) contact person and his/her telephone number, fax number, and electronic mail address. The contact person must be authorized to be the negotiator for the proposed Grant Agreement with the State.

BEGIN APPLICANT RESPONSE

Patty Yuhas Kieleszewski

Associate Director, Contract Administration

Sponsored Program Administration

5057 Woodward Avenue

13th floor, Suite 13203

Detroit, MI 48202-4050

Tele: (313) 577-9227

Fax: (313) 577-5055

Email: aa6841@wayne.edu

END APPLICANT RESPONSE

V-C Method for Addressing the Problem

State in succinct terms the applicant(s)'s proposed method for addressing the problem presented in Section III-B, Problem Statement. Describe any significant obstacles the applicant(s) has had coordinating and managing clinical trial research.

BEGIN APPLICANT RESPONSE

This proposal is for a Supplement to our currently funded 2021 Veteran Marijuana Research (VMR) Grant, entitled "Wayne State Warriors Marijuana Clinical Research Program: Investigating the Impact of Cannabinoids on Veterans' Behavioral Health" (PIs: Lundahl and Ledgerwood), which will be referred to as the 'Parent Study' going forward.

The proposed application is a Supplement Study to the Parent Study and is entitled "Investigating the Therapeutic Impact of Cannabinoids on Neuroinflammation and Neurobiological Underpinnings of Suicide Ideation in Veterans with PTSD" (PIs: Marusak and Woodcock).

A Supplement Study is an add-on to a current, ongoing study that would significantly expand the scope and impact of the Parent Study, while dramatically reducing costs associated with running the Supplement on its own, as a separate study. Execution of this Supplement Study will leverage the clinical research infrastructure, personnel and scientific expertise, recruitment channels, and community outreach efforts supported in the Parent Study. Here, we propose an exceptionally efficient neuroimaging study which aims to undercover the brain mechanisms related to the therapeutic effects of cannabinoids for alleviating psychiatric burden and reducing suicide risk among US armed forces veterans living in the state of Michigan.

I. EXECUTIVE SUMMARY

Posttraumatic stress disorder (PTSD) affects 13-31% of US armed forces veterans, which is nearly double the prevalence of PTSD in the general population (6-10%). Importantly, *a PTSD diagnosis is one of the strongest risk factors for suicide*, and PTSD symptoms frequently co-occur with anxiety, depression, and other mental health problems. While evidence-based treatments for PTSD work well for some patients, many patients fail to adequately respond to treatment, and relapse rates remain unacceptably high. Thus, *there is a critical need to identify more effective treatments for PTSD and suicidal ideation*.

Emerging research highlights the key role of neuroinflammation in anxiety, depression, PTSD, and suicide. Indeed, excessive neuroinflammation is thought to disrupt brain circuits that control impulse and emotion regulation — which are implicated in suicidal thoughts and behaviors. *Therefore, neuroinflammation may contribute to the high rates of suicidal ideation, depression, and PTSD among veterans*. Treatments that aim to reduce neuroinflammation may be effective for attenuating these

psychiatric symptoms. One such promising treatment is cannabis/cannabinoids. Recent studies in animal models suggest that both Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) may effectively suppress neuroinflammation[1], which suggests THC and CBD may exhibit potential therapeutic effects on PTSD and suicidal ideation. However, no studies have evaluated these relationships among individuals with PTSD, or in any population.

The proposed study will leverage the extensive resources and expertise at Wayne State University (WSU) in neuroimaging and the neurobiology of psychiatric illness to delineate, for the first time, the impact of cannabis treatment on neuroinflammation and neurobiological mechanisms known to underpin PTSD, depression, and suicidal ideation. This project was designed to fill critical gaps in the scientific literature, and will be the first to (1) fully characterize the role of neuroinflammation in psychiatric symptoms in veterans, (2) evaluate the efficacy of cannabis/cannabinoids for suppressing neuroinflammation and for modulating inhibitory control or emotion regulation, and to characterize/identify the underlying neural network function that subserve these processes; and, (3) examine whether neuroinflammation is a viable treatment target for reducing depression, PTSD, and suicide risk among veterans with PTSD. This study will be a supplement (add-on) to our ongoing 2021 Veteran Marijuana Research (VMR) project, the 'Parent Study'. We will apply state-of-the-art neuroimaging approaches to significantly expand the scope and impact of our ongoing work, with an eye toward improving outcomes for veterans living in Michigan. The proposed supplement will leverage the infrastructure, expertise, and clinical trial methods that have already been established for the Parent Study and provides an opportunity to deliver a novel study that is both high in impact and innovation, while minimizing significant start-up time and study costs.

II. VISION STATEMENT

Our team at WSU is uniquely suited to conduct this timely and significant study. Indeed, we are one of the only groups in the Midwest with the requisite FDA, DEA, and NIH licenses and certificates to conduct human cannabis research and have been conducting such studies for over 20 years. Our team also brings over 60 combined years of specialized experience and expertise in advanced neuroimaging approaches to study the neurobiology of psychiatric illness. The proposed project will significantly expand the scope and impact of the Parent Study, while dramatically reducing costs associated with running the supplement as its own, separate study. In particular, this proposal capitalizes on the extensive neuroimaging facilities and resources at WSU, including the PET Center and MR Research Facility, while building on the work already established or underway in our ongoing VMR study, including: acquiring and receiving the necessary federal approvals to conduct a cannabis treatment trial, establishing working relationships with veterans' associations, recruitment channels, and clinical protocols. The proposed study will take place at the WSU Warrior Care Center, which is new space on the first floor of the Tolan Park Medical Building designated to conduct our current, ongoing LARA/CRA-funded cannabis trial.

WSU is well positioned to lead the Midwest in excellence in both cannabis research and education. WSU has over 26,000 undergraduate, graduate, and graduate professional students, and is designated a Research I university. WSU is ranked in the top 100 universities by the NSF in total research expenditures, in the top 50 public universities in R & D expenditures, and holds a "Very High Research" designation by the Carnegie Foundation. In fact, WSU is one of only seven public universities in the U.S. to receive the highest Carnegie Foundation ratings for both research intensiveness and community engagement. The WSU School of Medicine is the largest single-campus medical school in the nation and was ranked 68th in research by the U.S. News and World Report. Michigan's only urban research university, WSU fulfills a unique niche in providing access to a world-class education and research training. WSU's urban mission is to give instruction of the highest quality, to excel in research/creative activity, and to provide service to the professions and disciplines, to the private sectors, and especially to the urban community. The university is comprised of centers, institutes, departments and laboratories. Each offers unique facilities that together form a strong network of research, education and collaborative opportunities. For example, the School of Medicine is

integrated with numerous closely located sister institutions especially the Detroit Medical Center (several hospitals) and the Detroit VA Hospital. An ability to successfully manage large-scale initiatives is evidenced by faculty leadership in the $150M+ Perinatology Research Branch of the NIH, NC-Designated Comprehensive Cancer Center, Center for Urban Responses to Environmental Stressors (CURES), and more. All finances and related account audits are expertly managed by Sponsored Programs Administration as this division manages the University's entire research portfolio. All human and animal model research, including safety regulations, is overseen by the university's Institutional Review Board (IRB), which would also apply its oversight to this research. Additionally, the neuroimaging procedures proposed here will be reviewed by the WSU PET Center and its Radiation Safety Board, and the MR Research Facility.

Together, this program of research has potential to benefit veterans living in the state of Michigan, while filling significant gaps in the scientific literature and in public knowledge of how cannabis affects the brain and psychiatric outcomes. This foundational study will shed new light on the brain mechanisms underlying the therapeutic effects of cannabis, while laying the groundwork to identify veterans who might benefit most from cannabinoid therapeutics.

III. OBSTACLES

There are significant obstacles to conducting research on therapeutic potential of cannabis. We have identified six primary obstacles to this line of research which can be effectively addressed through the Veteran Marijuana Research program. These obstacles include:

(1) Federal regulations are currently largely prohibitive to conducting human cannabis research, and these are particularly difficult for new researchers to navigate. Fortunately, much of that foundational work has already been established by the Parent Study. ***In particular, Drs. Lundahl and Greenwald have the requisite FDA, DEA, and NIH licenses and certificates to conduct human cannabis research and have been doing such studies for over 20 years. Specifically, Drs. Lundahl and Greenwald have a DEA Schedule I-V license which allows us to study the therapeutic efficacy of smoked cannabinoids in our laboratory at Wayne State University. Moreover, the FDA IND to study the therapeutic efficacy of smoked cannabinoids in community-based clinical trials is currently in progress and will be in place before this Supplement Study begins.***

(2) Neuroimaging studies are prohibitively expensive and sources of extra- and intramural funds to support large scale, neuroimaging studies of cannabis and its potential therapeutic benefits is lacking. ***Funding received from the Veteran Marijuana Research Program supports the Parent Study, which will be the first, large-scale, randomized, controlled clinical trial examining the efficacy of cannabinoids to treat PTSD and suicidality in US armed forces veterans. The proposed Supplemental Imaging Study would capitalize on this existing infrastructure and the available expertise and resources at Wayne State University in cutting-edge neuroimaging approaches, while keeping costs at a minimum. In particular, we are seeking additional funding to support the Parent Study to apply these novel methods to the study of neuroinflammation in veterans with PTSD. This would be the first study to examine the effects of cannabis/cannabinoid treatment on neuroinflammation and neural network dysfunction in patients with PTSD, depression, or suicidality. This project would significantly expand the scope and impact of the Parent Study, and has potential to benefit veterans with PTSD, depression, or at risk of suicide in the state of Michigan.***

(3) Recruitment, enrollment, and retention of Veterans in clinical research studies can have its unique set of barriers, both institutional (i.e., VA regulations and policy) and logistical (i.e., Veterans' access to healthcare and research opportunities). ***As part of the funded Parent Study, we have established recruitment channels and working partnerships with veterans' organizations. We have also developed a novel, mobile system of assessment, drug delivery, and study maintenance aimed at overcoming the recruitment barriers. As a part of this Supplement Study, we will identify which individuals are best suited for cannabis-based***

treatment, and the neurobiological mechanisms through which cannabinoids may act suppress neuroinflammation and reduce PTSD symptoms, depression, and suicidal thinking among US armed forces veterans.

(4) Veteran reports of cannabinoid use to treat their symptoms are widespread, however, at present the Department of Veterans Affairs is not supportive of cannabinoid therapeutic trials. ***The Parent Study will establish a large-scale, community-based study of cannabinoid use and its potential to decrease PTSD and anxiety symptoms, improve mood, and lessen veteran suicidality. This would provide an attractive alternative research and clinical arena for treatment-seeking veterans. The proposed Supplement will significantly expand the scope and impact of this work by identifying neural mechanisms that contribute to suicide risk and other psychiatric symptoms, as well as characterize therapeutic pathways to optimize treatment effectiveness.***

(5) Despite the widespread use of cannabis, including among US armed forces veterans, it is unknown how cannabis interacts with the brain, which would better capture the therapeutic potential of cannabis for treating PTSD and suicidality. ***This Supplement proposes the first-ever neuroimaging study of cannabis treatment in US armed forces veterans with PTSD, or in any population. Our approach is high in impact and innovation, as it uses state-of-the-art brain imaging methods that are targeted at mechanisms known to underpin PTSD and suicidality.***

(6) There are known safety issues to studying the brain mechanisms among US armed forces veterans. In particular, common neuroimaging approaches, including magnetic resonance imaging (MRI), works by producing a strong magnetic field that allows for the non-invasive measure of brain structure and function in awake, living human beings. The radiowaves and magnetic fields associated with the MRI scan, at the strengths used, are thought to be without harm. However, the MR scanner uses a very strong magnet that will attract some metals and affect some electrical devices. Veterans may have metal implants (e.g., pins, joints, plates) or may be exposed to metal shrapnel during active duty and thus, would be unsafe for MR scanning. Therefore, it is critical that any MRI study in veteran populations thoroughly screen for potential MRI contraindications. ***The proposed study will utilize a comprehensive four-tiered screening procedure to ensure that participants are safe for neuroimaging scanning. Our MRI safety screening procedure will go beyond 'typical' studies by employing a ferromagnetic wand and walk-through detectors, as objective measures of safety, and will be among the most comprehensive MRI safety screening protocols in the United States.***

END APPLICANT RESPONSE

V-D Management Summary

(1) Describe management procedures that will be used by the organization to complete the proposed project.

(2) Describe the organization's quality control measures, including measures for ensuring compliance as well as eligibility determination. In your description, include information regarding separation of duties.

(3) Selected applicant(s) must provide fiscal control and financial accounting procedures that will assure that grant funds will be accounted for and properly dispersed in a way that will allow the Issuing Office to clearly review and verify all grant related expenditures. Describe the organization's internal control policy:

- Identify the type of accounting system/software the organization will use to account for grant funds,

- Identify how duties will be separated,
- Describe how the organization will account for grant funds, i.e., will grant funds be placed in a separate bank account, will the grant funds be assigned a unique code(s) within the organization's overall accounting system. Ensure funds are maintained in a non-interest-bearing account.
- Indicate whether internal and external audits of the organization's operations are performed on an annual basis. Selected applicant(s) must provide a copy of the organization's most recent audited financial statement as well as a copy of the organization's most recent single audit as required by OMB Circular 200.36

(4) Describe your agency's data security plan.

BEGIN APPLICANT RESPONSE

This proposal is for a Supplement to our currently funded 2021 Veteran Marijuana Research (VMR) Grant, entitled "Wayne State Warriors Marijuana Clinical Research Program: Investigating the Impact of Cannabinoids on Veterans' Behavioral Health" (PIs: Lundahl and Ledgerwood), which is referred to as the 'Parent Study' throughout.

The proposed application is a Supplement to the Parent Study and is entitled "Investigating the Therapeutic Impact of Cannabinoids on Neuroinflammation and Neurobiological Underpinnings of Suicide Ideation in Veterans with PTSD " (PIs: Marusak and Woodcock). Execution of this Supplement Study will leverage the clinical research infrastructure, personnel and scientific expertise, and community outreach efforts supported in the Parent Study and thus, is an exceptionally efficient neuroimaging study which aims to undercover the brain mechanisms related to the therapeutic effects of cannabinoids for PTSD and depression/suicidal thinking among veterans.

The following information overlaps with the Parent Study but is also applicable to the Supplement application described herein:

(1-3) Management Procedures, Quality Control Measures, and Financial Accounting Procedures

All grant applications and awards must be approved by the Wayne State University (WSU) Sponsored Program Administrative (SPA) department. Once the grant is awarded, the research team is notified by our SPA office and an index or account number is set up for that specific grant or fund award. The SPA office prepares the financial reports for the agency at each reporting period. They also send notifications and reminders if progress reports are due. The SPA office will load the budget based on what was submitted to the agency in our BANNER Accounting system.

At the department level, once a grant index number is established, our administrative team meets to review the contract. Cordell Crutchfield is our grant & contract administrator within the Department of Psychiatry and Behavioral Neurosciences. Sonya Blair is our HR program specialist, Michelle Caton and Valerie Felder are purchasing agents, and Jennifer Ballard-Traynor is the administrative director. The administrative team meets to review the contract with the PI. The purpose of the initial meeting is to understand the project, review the budget, and read through the contract so that all of the requirements are understood and will be abided by.

Sonya will add effort to the grant based on the budget and the PI's sign off on. This is done through an Electronic Personnel Action Form (EPAF), which is an online system for making personnel changes. Once Sonya processes this effort addition, this is reviewed by Jennifer, then by individuals in HR and the School of Medicine's Business Affairs office. All approvers will review the budget loaded in our

Banner Accounting system, to ensure there are funds in the “personnel” expense account before approving.

The research team, including Co-Principal Investigators (Co-PIs), Co-Investigators (Co-Is), or the research coordinator will place orders via a Procurement Card ($2,000/transaction, with a $20,000/month spending limit) or for larger expenses, via email to either Michelle or Valerie. The orders are then placed in our WayneBuy Procurement System. At WSU, all purchasing orders must be pre-approved before making the purchase. Upon receiving the order form from the research team, Michelle and/or Valerie will enter that order in WayneBuy. Once submitted, there are several approvers that must review the order before a Purchase Order (PO) is submitted to the vendor. Jennifer reviews all orders that are placed within the department. She reviews the grant budget to determine if the good/service was initially budgeted for. If it was, she approves it, if it was not, she will reach out to the PI for justification of the purchase. All charges on the grant must be 100% for that specific study. Once approved, the request goes to Business Affairs to review against the budget posted in Banner. Then it goes to the SPA office to review to ensure compliance with that specific grant. Lastly, a representative from the Purchasing office will review to ensure the requisition is compliant with the University. There are several approvers in this process to create a separation of duties and to ensure compliance for both the granting agency and the University.

Once the PO is approved, it is sent to the vendor to fulfill the order. The vendor will then submit an invoice to WSU for payment. Invoices under $1,000 do not require departmental review. Any invoice over $1,000 needs to be reviewed by the department to ensure the good or service was received. Then a receipt is entered in the WayneBuy system which prompts Disbursements to make the payment. All payments are made by the Disbursement office and do not go through the Department. Departments at WSU do not have the ability to issue payments to vendors.

All travel has to be preapproved in our Concur TravelWayne system. In this system, the user needs to estimate the expenses, enter the conference or research related travel information, indicate the index number to charge, and upload the conference brochure or research purpose. The request needs to be approved by Jennifer for grant compliance and budget review and to the Chair, Dr. David Rosenberg. Once approved, the traveler can submit receipts to an expense report in the system. These are reviewed first by Jennifer and then by the Business Affairs office. Once fully approved, the expense is posted to the grant index in Banner.

WSU uses the Clincard System to pay out research subject incentives. These are debit cards that are loaded with funds once a research participant completes a milestone. Jennifer sets up the studies in the Clincard system based on the approved IRB protocol for the study. She will enter the study name, grant index number, and the payment milestones. The physical cards are ordered through the Procurement office. The cards do not have funds on them until they are loaded through the Clincard system. We do not keep cash or preloaded debit/gift cards for the purpose of paying subjects. Users are given access to the Clincard system to load the cards once a participant is seen. A separate user will be added as a card approver once funds are loaded. The approver does not have access to the Clincards as to separate duties. The system also requires social security numbers for each subject being paid, and the university runs reports on a regular basis to ensure no SSN matches a WSU employee's SSN. The university front loads funds to the Clincard system and each month charges are posted to Banner based on the index number for each study. For the proposed Supplement, participants will be paid for completing the additional neuroimaging sessions on the Clincard they received for payment on the Parent Study.

WSU uses the Banner ERP system to manage student and employee information and financial data for all funding received. Access to Banner relies on strict security measures and is only given to eligible employees. To separate duties, administrative employees in the Department of Psychiatry only have read-only access to Banner. The grant budget is loaded by SPA, the personnel expenses are added by the above EPAF system, expenses are added as WayneBuy and TravelWayne expenses are approved and paid, and research subject payments are posted monthly as they are paid out.

Our SPA office will invoice the granting agency on a monthly basis (unless otherwise stated in the contract) for all expenses that have posted to the grant in Banner. Invoices are normally to be paid 30 days upon receipt of the invoice. Once the invoice is paid, it is recorded under the grant so that we are able to track the revenue in that same index number.

An audit or review is performed each year in compliance with regulatory requirements or Board of Governor mandates. In certain instances, to achieve efficiencies, these audits may be performed biannually. Below is a link to our internal auditor web page with information on what systems are audited, the timeliness of audits, best practices, safeguarding assets, etc. https://internalaudit.wayne.edu/

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(3) All clinical research and participant encounters performed as part of this project will be subject to at least four levels of oversight from the Departmental to the Federal level. First, the Department of Psychiatry and Behavioral Neurosciences in the Wayne State School of Medicine has a Departmental Review Board (DRB) that reviews and approves research conducted by faculty in the Department. This is a prerequisite step to submission to Wayne State University's Institutional Review Board (IRB), the principal research oversight committee located at the University. In addition to IRB review, the neuroimaging protocols (PET and MRI) are reviewed separately by the PET Center and the MR Research Facility for safety and design. Additionally, Dr. Lundahl, the lead Principal Investigator on the Parent Study, is required to submit progress reports regularly as part of her approved and funded program of studies using cannabinoids to both the US Food and Drug Administration (FDA) and the US Drug Enforcement Administration (DEA).

(4) Data Security

Access to the Database

All data collected for this project will be stripped of all identifiable information and each participant will be assigned an individual code. These codes will be kept in a master file, separated from the identifiable information, by using a different passcode and kept in a different folder in a password protected server. All of the data for this project will be collected specifically for research purposes. Hard copy files will be kept in locked file cabinets within locked offices. Electronic data (e.g., MRI or PET scans, behavioral responses) will be housed on a secure password protected server, with access restricted to staff for this specific research study. The server is located between two firewalls (one university, one department level), with nightly remote (i.e., off-site) backups to prevent data loss. Participant numbers without personal identifiers assigned to each participant will be the only means by which collected information is labeled. The master code is the only list that will link the names of the participants with their participant numbers will be kept in a secure, password- protected computer account on a separate drive from research coded data and will be accessible only to IRB-approved members of the research team.

Back-up of Database

The server is automatically backed up on a daily basis to a secure remote (i.e., off-site) location to prevent data loss. WSU will permit study monitors and oversight boards with access to data files and scanned case report forms stored on a HIPAA-compliant account (e.g., OneDrive, Dropbox Business). The study monitor will download a copy of the data files and scanned case report for data collection and quality assurance purposes. Our statistician will create static analytic files for interim and final analyses and will report the date the data is finalized, and number of subjects included in that database.

END APPLICANT RESPONSE

V-E Work Plan

Provide clear and concise work plans for meeting the following components, with detailed explanation:

1) Provide for the coordination and overseeing of clinical trial(s) to determine the efficacy of marijuana in treating the medical conditions of U.S. armed services veterans and preventing veteran suicide.
2) Recruit and evaluate researchers to accomplish the goals of this grant.
3) Demonstrate the ability to work with researchers who can garner the United States Food and Drug Administration approval for the clinical trials.
4) Ensure the maximum amount of grant dollars are used to coordinate and oversee clinical trials with a minimal amount of grant dollars used for administrative costs.
5) Work with organizations closely tied to veterans and veterans' programs.
6) Provide the Grant Administrator with a grant budget to which monitoring and reporting will be tied. Please see attachment A for the budget template to be used.
7) Establish research goals, approve projects, exercise financial and management oversight, and document and review results.
8) Publish the results of the clinical trials.

BEGIN APPLICANT RESPONSE

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Work Plan Items 1-8 are addressed briefly below and in greater detail in the **Work Plan**, below. Additionally, many elements are met by the experience and qualifications of the assembled clinical neuroimaging research team (described below).

(1) The funded Parent Study brings together an expert clinical research team with decades of experience conducting clinical trials and managing recruitment of hundreds of research participants for complex and nuanced psychopharmacological and behavioral treatment trials, including among individuals with PTSD, depression, and those using cannabis to self-medicate. The Parent Study involves an FDA-regulated randomized controlled trial of cannabis for the treatment of depression and PTSD in US armed forces veterans and preventing veteran suicide. Our team has all of the regulatory and legal approvals (i.e., Schedule I-V DEA license and clinical trial FDA IND) to conduct a clinical trial evaluating the efficacy of smoked cannabis/cannabinoids in people. There are few, if any, other sites in the Midwest who have the licenses and regulatory approvals in place to conduct such research. And, our clinical research team has been conducting such studies for nearly 20 years at WSU. The proposed Supplement application seeks to build on that robust clinical research infrastructure and investigate the brain mechanisms that underlie vulnerability to psychiatric symptoms in veterans to PTSD, including suicidal thoughts. This study will also identify neurobiological systems that may predict therapeutic response to cannabinoid administration. Our neuroimaging team, including Drs. Marusak, Woodcock, Muzik, and Rabinak, have more than 60 years of clinical neuroimaging research experience combined and each direct highly productive neuroimaging research labs at WSU that apply functional neuroimaging and neurochemical/molecular imaging methodologies to investigate the neurobiological underpinnings of psychiatric disorders.

(2) The proposed Supplement Study leverages the extensive expertise and resources available at WSU in neuroimaging and the role of neuroinflammation and neurobiological underpinnings in psychiatric illness. Drs. Marusak and Woodcock each direct productive NIH-funded neuroimaging laboratories which necessitate coordination across a team of trained neuroimaging technicians, data managers, and research assistants and coordination with the MRI and PET scanning core facilities at WSU. At present, Drs. Marusak and Woodcock are conducting 5 ongoing neuroimaging research studies and direct a highly productive, combined team of 46 individuals, including professional research assistants, postdoctoral research fellows, MRI and PET technicians,

and students at all levels (undergraduate, masters, MD, PhD). More details, including roles in the proposed Supplement, are described below.

(3) The funded Parent Study already has all of the necessary legal and regulatory licenses approved or underway, including DEA Schedule I-V license and FDA IND for the cannabis clinical trial. The Supplement will adhere to all the legal and regulatory requirements defined in the Parent Study. Because the Supplement Study is an 'add-on' to the Parent Study, there will be no, or minimal, delays in launching the Supplement Study which maximizes our efficiency, both research and fiscal, but more importantly, provides veterans in Michigan immediate access to a controlled therapeutic trial using cannabis/cannabinoids.

(4) The research team has decades of experience in conducting human subjects research related to cannabis and cannabinoid administration, trauma exposure, anxiety, PTSD, and substance use disorders. The team is well-versed in the management of multi-million dollar federally- and privately-funded research projects. Logistics, institutional research support infrastructure, and fiduciary responsibility exists within WSU. All finances and related account audits are expertly managed by Sponsored Programs Administration, which manages WSU's entire research portfolio. With regard to fiscal responsibility and minimalization of administrative costs, the proposed Supplement is exceptionally efficient: only **2.5% of the total budget** will be spent on administrative salaries/fringe benefits. As the proposed Supplement leverages the considerable infrastructure of funded Parent Study, administrative and non-research-related expenditures will be nominal.

(5) This Supplement will capitalize on the work of the Parent Study in establishing working relationships with veterans associations. We established contact with 15 Veterans groups including the Veterans of America, Michigan Veterans Affairs Agency, Veterans of Foreign Wars (VFWs) and several others to create a recruitment network capable of reaching Veterans either for whom cannabis is an existing treatment strategy or might be an attractive intervention for them to alleviate their symptoms of PTSD, depression, and suicidality. Recruitment documents including study flyers and informational brochures have been created, approved by our IRB and printed for advertising and distribution to these and other organizations. Social media and other advertising platforms to supplement recruitment have also been identified. We created a website (Warriorcare.net) which is dedicated to the research program where veterans and their families can get information about the studies, complete initial screening for eligibility, access other resources, and contact us. The website is near completion and should be up and running by May 31, 2022.

This work will be continued and further augmented in the proposed add-on project. Improving outcomes for veterans will continue to be the primary focus of the clinical research team assembled for the proposed project.

(6) Just as with the Parent Study, the Supplement Study grant budget will be provided to our departmental pre- and post-award administrators, Jennifer Ballard-Traynor and Cordell Crutchfield. Jennifer will monitor all grant expenses on a quarterly and as-needed basis, and send accounting reports to the PI(s) on this project. Expenses are monitored for compliance and to stay within the original budgeted categories. Jennifer will work with the SPA office on the financial reporting requirements of this grant.

(7) Our research goals include enrolling 100 of the 200 veterans from the Parent Study in the proposed Supplement Study. We propose the first study to evaluate the effects of cannabis/cannabinoids on neuroinflammation and neurobiological mechanisms shown to underpin PTSD, depression, and suicidal ideation. These goals are outlined in detail, below. This Supplement will be an 'add-on' to the Parent Study, which is an FDA-regulated trial of different THC:CBD combinations for alleviating depression, PTSD, and suicidal ideation in veterans. Financial, management, and human subjects aspects of this study will be overseen by multiple bodies at WSU, including the Institutional Review Board (IRB), Sponsored Programs Administration, the Department of Psychiatry and Behavioral Neuroscience's Departmental Review Board, the PET Center and its Radiation Safety Board, and the MR Research Facility. All results will be documented and reviewed by all members of the research team, including the biostatistics core.

(8) We anticipate publishing at least 3 manuscripts/year during Years 3-5 of the proposed project. Manuscripts will be submitted to high-quality peer-reviewed journals related to cannabis and cannabinoids, trauma and PTSD, or psychiatric outcomes. We will also plan to disseminate preliminary results in annual professional conferences (e.g., International Cannabinoid Research Society, Society of Biological Psychiatry, American

College of Neuropsychopharmacology, NeuroReceptor Mapping, BrainPET, College on Problems of Drug Dependence, Human Brain Mapping), and in public communications and community engagement. For example, we plan to disseminate findings to our partnered veterans groups and associations, local cannabis dispensaries and cultivars, on social media, and to the State of Michigan CRA. Data from the proposed project would also provide compelling support for NIH applications proposing any of several potential avenues of research that would continue the important work of evaluating the therapeutic efficacy of cannabis/cannabinoids in alleviating psychiatric symptoms and suicidality among veterans in Michigan.

Work Plan

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Investigating the Therapeutic Impact of Cannabinoids on Neuroinflammation and Neurobiological Underpinnings of Suicide Ideation in Veterans with PTSD

A Supplement to: Wayne State Warriors Marijuana Clinical Research Program: Investigating the Impact of Cannabinoids on Veterans' Behavioral Health

Specific Aims

Posttraumatic stress disorder (PTSD) affects 13-31% of US military veterans, which is nearly double the prevalence of PTSD in the general population (6-10%). Importantly, PTSD is one of the strongest risk factors for suicide, and PTSD symptoms frequently co-occur with anxiety, depression, and other mental health problems. While there are evidence-based treatments for PTSD that work for some, research shows that up to 50% of individuals with PTSD who engage in treatment fail to adequately respond and only 36% experience clinically significant improvement.[2,3] Outcomes are even worse among low resource and racial/ethnic minority populations, such as Detroit, Michigan, highlighting the need to develop more effective, accessible treatments. The staggeringly high rates of suicide, PTSD symptoms, and depression among veteran populations, in particular, underscores the critical need to identify effective treatments that are tailored to the specific neurobiology of this population.

Emerging studies on the neurobiological underpinnings of depression[4-10], PTSD[11-15], and especially, suicide[16-23] point to the key role of neuroinflammation in these conditions. Indeed, it is thought that excessive neuroinflammation can be neurotoxic and disrupt functioning of brain circuits that are critical for cognitive, motivation, and reward processing, which may contribute to suicidal thoughts and behaviors[16,18,19,21]. Therefore, treatments that reduce neuroinflammation may be effective for reducing suicidal ideation symptoms[16,18,19,21]. One potential treatment to reduce neuroinflammation is cannabis/cannabinoids[24-31]. Research in animal models suggests that Δ9-tetrahydrocannabinol (THC) or cannabidiol (CBD) alone or in combination have anti-inflammatory properties[32-37], and may therefore be a promising therapeutic approach for veterans with PTSD or suicidal ideation. Despite compelling preclinical data, the role of neuroinflammation, and whether neuroinflammation may be targeted by cannabinoids in humans with PTSD or suicidal ideation, is unknown.

Here, we propose the first study of neuroinflammation as a potential treatment target for alleviating PTSD, depression, and suicidal ideation in US armed forces veterans. An overall summary of our scientific model is provided in Figure 1. The proposed neuroimaging study is a supplement (add-on) to our currently funded Veteran Marijuana Research (VMR) randomized controlled clinical trial (i.e., Study 1 of the Parent study) investigating the potential therapeutic effects of controlled dosing of cannabis/cannabinoids in veterans. In particular, we propose to add state-of-the-art neuroimaging approaches that enable us to test, using a pre-post design, whether cannabis treatment of varied THC/CBD concentrations differentially impacts neuroinflammation and neurobiological mechanisms *implicated in suicide ideation, depressed mood, and PTSD symptomatology.* We will also be well positioned to address several critical gaps in our understanding of therapeutic potential of cannabis/cannabinoids that would not typically be available. Indeed, neuroimaging studies in the

context of large clinical trials are typically prohibitively expensive and require extensive resources, personnel, and unique expertise. By leveraging our ongoing clinical trial and the extensive neuroimaging resources and expertise available at WSU, we will significantly expand the scope and impact of the ongoing Parent Study while keeping costs to a minimum (administrative costs = 2.5% of total budget).

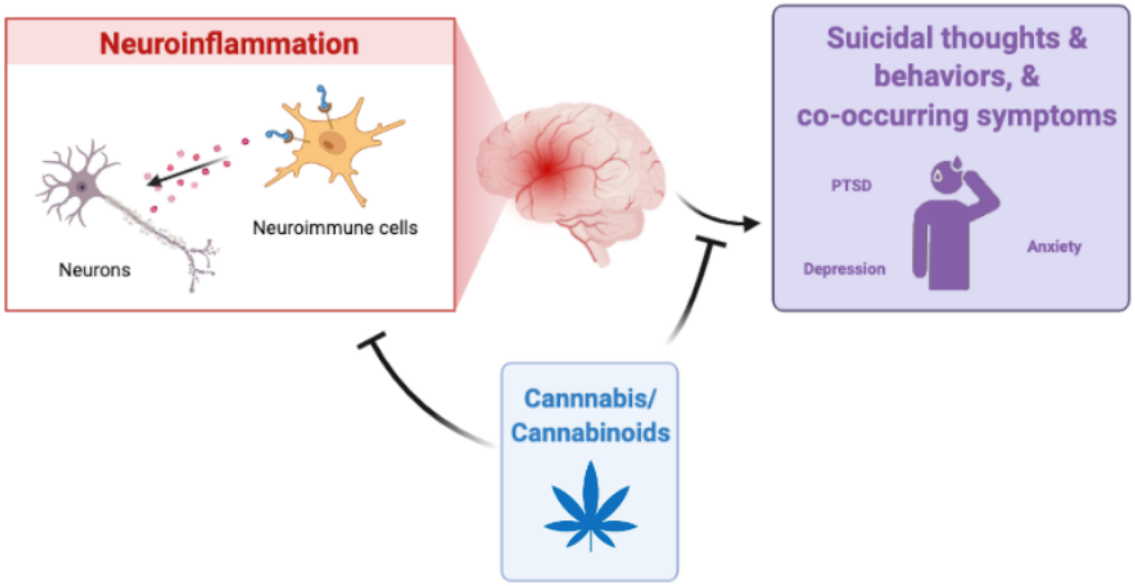


Figure 1: Overall conceptual model of the proposed Supplement Study. Emerging research suggests that excessive and persistent inflammation in the brain (i.e., "neuroinflammation") plays a key role in altering brain functioning in ways that increase risk of suicidal thoughts and behaviors and co-occurring symptoms. Cannabis and cannabinoids, which are anti-inflammatory agents, may alleviate suicidality by attenuating neuroinflammation in veterans. This study will be the first to characterize the role of neuroinflammation in risk of suicidal thoughts and behaviors, and co-occurring symptoms in veterans or in any population. It will also be the first to evaluate neuroinflammation and brain functioning as a potential mechanisms for the therapeutic effects of cannabis and cannabinoids.

Design Overview for the Supplement Study and Integration with the funded Parent Study

The Parent FDA-regulated Study involves randomizing 200 Michigan veterans with PTSD into one of four different THC (Δ9-tetrahydrocannabinol) : CBD (cannabidiol) dose conditions (High THC:High CBD; HighTHC:Low CBD; Low THC:High CBD, and Low THC:Low CBD) for a 12-week treatment phase. For the proposed Supplement, half of the 200 participants from the Parent Study (N=100; 25 of the 50 participants in each dose condition) will additionally complete two brain imaging assessments: one before (i.e., baseline scan) and one after the 12-week treatment period (i.e., post scan). Primary outcomes include: A) neuroinflammatory state as measured via positron emission tomography (PET) imaging with the radiotracer, α-[^{11}C]methyl-L-tryptophan (AMT); B) resting or 'basal' neural network communication as measured via functional magnetic resonance imaging (fMRI); and C) brain activation during well-validated inhibitory control (Go/No-Go) and emotion regulation (Emotional Stroop) tasks as measured via fMRI. We will focus on brain regions that are consistently linked to both PTSD symptom severity and suicidal ideation, and that are densely populated with cannabinoid receptors (which are modulated by acute cannabis/cannabinoid administration). Further, the collection of whole-brain, multi-modal neuroimaging data (structural MRI, functional MRI, and PET imaging data) during the same session will allow us to explore the impact of cannabis/cannabinoid administration on the relationship between neuroinflammatory state and neural network activation and interactions throughout the brain, and link these brain metrics to clinical outcomes (e.g., reduction in suicidal ideation or

PTSD/depression symptoms over time). This highly innovative approach will provide unprecedented insight into the neurobiological underpinnings of PTSD and suicidal ideation and the potential therapeutic effects of cannabis (and associated brain mechanisms) on these and other critical outcomes (e.g., quality of life, depressive symptoms). Findings from this Supplement Study may also identify veterans who will benefit most from cannabinoid therapeutics and specific THC:CBD dose combinations therein. This project will also inform a personalized medicine approach for veterans with PTSD in the future.

The specific aims of this Supplement Study are:

Aim 1: To determine whether 12-weeks of controlled dosing of cannabis/cannabinoids reduces levels of neuroinflammation. Based on published findings among rodents (no human studies exist; ours would be the first), we hypothesize that 12-weeks of controlled dosing of cannabis/cannabinoids will significantly reduce a marker of neuroinflammation. Specifically, we propose to apply PET [^{11}C]AMT imaging to quantify tryptophan-kynurenine metabolic rate, a marker that is sensitive and responsive to neuroinflammatory state, in brain regions of interest before and after 12-weeks of controlled dosing of 4 THC:CBD dose groups. Relative to baseline, we hypothesize that all 4 dose groups will exhibit significant reductions in tryptophan-kynurenine metabolic rate at post-scan, i.e., reduced neuroinflammation. Based on prior studies suggesting that high levels of CBD (alone or in combination with high THC) reduce neuroinflammation more effectively than high THC alone, we hypothesize that the High:High THC:CBD and Low:High THC:CBD dose groups will be associated with greater reductions in tryptophan-kynurenine metabolic rate than the Low:Low THC:CBD and the High:Low THC:CBD dose groups. Further, we hypothesize that patients who exhibit the greatest reduction in neuroinflammation will also experience the greater reduction in suicidality and PTSD symptomatology after 12-weeks of controlled dosing of cannabis/cannabinoids.

Aim 2: To determine whether 12-weeks of controlled dosing of cannabis/cannabinoids improves neural network communication and brain functioning. Based on published findings among rodents and acute cannabis dose challenges in humans (no chronic treatment studies exist; ours would be the first), we hypothesize that 12-weeks of controlled dosing of cannabis/cannabinoids will significantly modulate brain activation in regions involved in impulse control and emotion regulation. Specifically, we will apply fMRI to quantify neural response during two validated tasks that are widely used in the literature to study the neural correlates of PTSD and suicidality. We will quantify neural response in brain regions of interest before and after 12-weeks of controlled dosing of 4 THC:CBD dose groups. Relative to baseline, we hypothesize that all 4 dose groups will exhibit significant reductions in neural activation in regions associated with the generation of suicidal thoughts (e.g., insula) and significant increases in neural activation in regions associated with impulse control or emotion regulation (e.g., dorsolateral prefrontal cortex) at post-scan. Further, we hypothesize that the High:High THC:CBD and Low:High THC:CBD dose groups will be associated with greater reductions in neural activation than the Low:Low THC:CBD and the High:Low THC:CBD dose groups, suggesting that high levels of CBD (alone or in combination with high THC) will improve neural network communication and brain functioning more effectively than high THC alone. Further, we hypothesize that patients who exhibit the greatest improvement in neural activity (e.g., decreased activation in insula, increased activation in dorsolateral prefrontal cortex) will also experience the greater reduction in suicidality and PTSD symptomatology after 12-weeks of controlled dosing of cannabis/cannabinoids.

Aim 3: To determine whether higher levels of neuroinflammation at baseline are associated with a higher likelihood and severity of suicidal thoughts and behaviors in veterans with PTSD. In this study, we propose the first large-scale investigation of the neuroinflammation in PTSD patients with and without suicidal thoughts. Specifically, we will apply PET [^{11}C]AMT imaging to quantify tryptophan-kynurenine metabolic rate in brain regions of interest before onset of the Parent Study, i.e., baseline scan (prior to receipt of controlled cannabis/cannabinoid dosing). We hypothesize that PTSD patients who report suicidal thoughts and behaviors will exhibit significantly higher neuroinflammation across brain regions of interest compared to PTSD patients who do not report suicidal thoughts. Further,

we hypothesize that patients who exhibit the highest levels of neuroinflammation will also report the most severe suicidal symptoms (and as stated above, will experience the greatest therapeutic benefit from controlled cannabis/cannabinoid dosing).

Aim 4: To determine whether PTSD patients with co-occurring suicidality exhibit disrupted neural network communication and altered patterns of brain activation compared to PTSD patients without suicidality. The proposed study will be one of few large-scale studies to characterize the neural correlates of PTSD and suicidality *specifically in US armed forces veterans*. In particular, we will apply fMRI to quantify neural response in brain regions of interest before onset of the Parent Study, i.e., baseline scan (prior to receipt of controlled cannabis/cannabinoid dosing). We hypothesize that PTSD patients who report suicidal thoughts and behaviors will exhibit significantly higher activation in brain regions associated with the generation of negative or suicidal thought, and lower activation in brain regions associated with impulse and emotion regulation, compared to PTSD patients who do not report suicidal thoughts. We also expect that patients who exhibit the greatest neural network dysfunction will experience the greatest therapeutic benefit from controlled cannabis/cannabinoid dosing (i.e., greatest reductions in PTSD symptom severity and suicidal thoughts over time).

Exploratory Aim: To determine whether reductions in neuroinflammation correlate with improvements in neural network functioning over the course of the 12-week trial. This study will be the first to measure neuroinflammation (using PET [^{11}C]AMT imaging) and neural activity (using fMRI) concurrently in individuals with PTSD. The available preclinical literature suggest that cannabis/cannabinoid treatment may reduce neuroinflammation, which may, in turn modulate neural network activity and subsequent generation of suicidal thoughts, and transition from thoughts to behaviors. Based on this overall conceptual model, we will explore whether reductions in neuroinflammation correlate with improvements in neural network functioning over the course of the trial. We will begin with region-of-interest analyses, focused on *a priori* brain regions before exploring voxel-level or data-driven analyses (e.g., independent components analysis)

In sum, the proposed Supplement will augment the scope of our current project and provide the first-ever insights into how cannabis/cannabinoids may impact neurobiological mechanisms directly linked to PTSD, depression, and suicidality. This study leverages our ongoing Parent Study and the extensive resources and expertise in cannabis/cannabinoid research and novel neuroimaging approaches to the study of psychiatric illness at WSU, while minimizing costs (administrative costs are only 2.5% of our budget). Indeed, to our knowledge, we are one of the *only groups in the Midwest* able to measure neuroinflammation with the PET [^{11}C]AMT tracer and apply advanced multi-echo functional MRI techniques to the study of psychiatric illness. We are also *one of the only groups in the Midwest* with necessary FDA, DEA, and NIH licenses and certificates to conduct human cannabis research, including administration studies, and have been doing so for over 20 years. Furthermore, this study will recruit veterans from our Parent Study at WSU in Detroit, and will therefore ***directly benefit veterans in the state of Michigan.***

Background and Significance

Posttraumatic stress disorder (PTSD) is one of the "signature wounds of war"[38], affecting 13-31% of US military veterans[39-42]. The prevalence rate of PTSD among military veterans is nearly double that of the general population (6-10%)[43]. PTSD is a major public health concern, contributing to substantial impairment and economic burden on individuals and society. Indeed, a recent study showed that annual total costs of PTSD are staggering, at upwards of $232.2 billion in 2018[44]. Although the military population is only a small proportion of the overall US population, annual average costs related to PTSD are much higher ($25,684 per individual) than in civilian populations ($18,640 per individual), which may reflect unique disability[44]. PTSD is associated with an increased risk of morbidity and mortality, including comorbid psychiatric (e.g., depression, anxiety) and substance use disorders, sleep disturbances, interpersonal problems, and cardiovascular events (e.g., myocardial infarction, stroke)[45,46].

Importantly, PTSD is one of the strongest risk factors for suicide[47]. A recent study of over 1.5 million veterans in the US Veterans Health Administration system showed that those with PTSD symptoms had a 58% increased risk of suicide mortality compared to those without[38]. There is some evidence that *suicide rates have increased in recent years*, despite increased funding and public attention to this problem[48]. In their latest annual report, the VA found that an average of 17.2 veterans per day died by suicide in 2019. The alarmingly high suicide rates in veterans are likely due to untreated or undertreated PTSD and comorbid disorders. The staggeringly high rates of suicide, PTSD symptoms, and depression among veteran populations, in particular, underscores the critical need to identify effective treatments that are tailored to the specific neurobiology of this population.

While there are evidence-based treatments for PTSD that work for some, up to 50% of individuals with PTSD who engage in treatment fail to adequately respond and only 36% experience clinically significant improvement[2,3]. Further, many gold-standard treatments, such as exposure-based cognitive behavioral therapy, involve rehearsing their trauma and are thus emotionally taxing as well as time consuming. Prior studies have found high rates of intolerability and dropout, including in veteran populations[49]. Outcomes are even worse among low resource and racial/ethnic minority populations, such as Detroit, Michigan, highlighting the need to develop more effective, accessible treatments.

The pathophysiology underlying the development of suicidal thoughts and behaviors is not fully understood. However, there is accumulating evidence for the involvement of the neuroimmune system, especially among individuals with co-occurring stress- and trauma-related disorders, i.e., PTSD[7,16,18,19,50-53]. Initial findings implicating neuroinflammation in suicidality came from two postmortem studies published in 2008 which showed elevated markers of microglia levels and cytokine expression among suicide victims[22,54]. Since those initial findings, evidence consistent with neuroinflammation in suicidality has been shown numerous times via plasma biomarkers and postmortem findings[7,17,21,50-53]. However, to date, no published studies have investigated neuroinflammatory state of PTSD patients with and without suicidal thinking. *Thus, it remains unclear if suicidality is associated with in vivo neuroinflammation in individuals with PTSD: a question we will address in the proposed study.* In particular, *we propose the first in vivo imaging study of neuroinflammatory state among individuals with PTSD using PET [^{11}C]AMT imaging and the first study to link suicidal thoughts and behaviors to neuroinflammation in individuals with PTSD.*

Neuroinflammation is known to impair cognitive function[55-57] (including work we published[58]), and if untreated, can lead to neurotoxicity[59-65] and long-standing impairments to reward sensitivity, affect, and motivation[66-75]. Impairments in the brain circuits that underlie these processes are implicated in suicidal thoughts and behaviors, and co-occurring symptoms. For example, prior research by Dr. Rabinak (Co-I) has shown brain activity in the prefrontal cortex during emotion regulation in veterans with PTSD (vs. combat-exposed controls, Figure 2)[76]. Altered functioning of brain circuits that govern impulse and emotion regulation are most consistently associated with suicidal thoughts and behaviors, as well as PTSD and related psychopathology (e.g., anxiety, depression)[77]. In this application, we propose to investigate whether severity of suicidal thoughts and behaviors relate to impaired brain function and disrupted neural network communication while at rest and during performance of cognitive tasks: a classical inhibitory control task (Go/No-Go) and an emotion regulation task (Emotional Stroop task). Further, we will integrate data collected from our two neuroimaging modalities (PET, fMRI) and investigate whether a neuroinflammatory state is associated with disrupted neural network activation and communication.

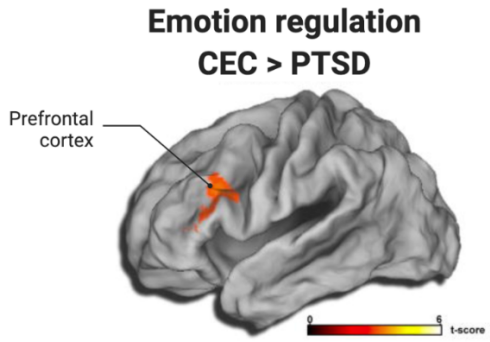


Figure 2: Disrupted brain functioning in veterans with PTSD vs. combat-exposed controls (CEC) without PTSD. Relative to CEC, individuals with PTSD demonstrated lower brain activity in the dorsolateral prefrontal cortex during an emotion regulation task. The prefrontal cortex is involved in impulse and emotion regulation, suggesting a neural correlate of impaired ability to suppress negative and/or suicidal thoughts in PTSD. Brain activity was measured using fMRI. Image adapted from Rabinak et al., 2014[76].

One promising treatment that may target excessive neuroinflammation is cannabis/cannabinoids[26,27,78,79]. Research in animal models suggests that THC and CBD alone or in combination have anti-inflammatory properties[32-36,80], and may therefore have therapeutic potential in veterans experiencing high levels of PTSD. However, it is unknown if treatment with cannabis/cannabinoids exhibit anti-inflammatory effects in the human brain or how THC:CBD dose combinations impact brain function and neural network communication. With regard to neuroinflammation, cannabinoid type 1 (CB1) receptors are expressed constitutively on microglia cells[26,30,78], which are a key part of the brain's immune system, whereas cannabinoid type 2 (CB2) receptors are only expressed on activated microglia (not 'resting', i.e., quiescent, microglia)[26,28,30,78]. Both THC and CBD have been shown to exert anti-inflammatory effects. THC, which interacts directly with both CB1 and CB2 receptors, can reduce antigen presentation, inhibit T-cell response, and attenuate pro-inflammatory cytokine secretion[24,27,79]. Similarly, CBD, which likely acts via indirect pathways or modulation of the endocannabinoid (eCB) system, has been shown to decrease pro-inflammatory Th1 cytokine secretion and may be neuroprotective against excitotoxicity[32,33,35,78,81]. Thus, THC:CBD dose combinations may offer differential therapeutic effects at reducing neuroinflammation which may be specific to each patient. However, the above findings were shown in preclinical or cellular studies. The extent to which THC and CBD attenuate neuroinflammation in people remains unknown. In the proposed study, we will investigate whether 12-weeks of controlled THC:CBD dosing differentially influences neuroinflammatory state of veterans with PTSD.

Research in animal models demonstrates that low-dose THC can have anxiety- and depression-relieving effects via CB1 receptors in the brain[82,83]. In addition, emerging studies in both humans and animal models suggest that CBD may reduce anxiety, but that these effects are independent of the CB1 receptor. Cannabis may also exert antidepressant and anxiolytic effects by influencing the eCB system, which is emerging as a key regulator of stress, emotion regulation, and mood. Growing research links PTSD, depression, and suicidality to disruptions in eCB signaling, particularly in brain areas that are rich in CB1 receptors and critical for stress responding, impulse control, and emotion regulation[84-86]. Given that emotion dysregulation and impulsive behavior are important risk factors for PTSD and suicide[87], dysfunction of brain regions that subserve these processes are thought to contribute to PTSD symptoms and suicidal thoughts and behaviors. These same brain regions are susceptible to excessive neuroinflammation, and may therefore be a therapeutic target alleviating risk of suicidal thoughts and behaviors. *However, the effects of cannabis treatment on neural network activation have not been evaluated in individuals with PTSD or in the context of a clinical treatment trial: research gaps we will address in the proposed study.*

Many US veterans report using cannabis to self-treat for PTSD and depression-related disturbances, including stress, anxiety, hyperarousal, negative mood, executive function (cognitive) deficits, pain and poor sleep quality.[88] Rates of cannabis use have increased over the past decade in the US general population, as well as among US military veterans. Despite this widespread use, few studies have examined cannabis as a potential treatment for PTSD. One study of 404 medical cannabis-users who self-identified as having PTSD found immediate reductions in PTSD symptom severity after acute cannabis inhalation, but did not observe any significant longer-term change in symptoms over time[89]. A prospective study of 150 individuals with PTSD found that cannabis users were 2.57 times more likely to no longer meet DSM-5 criteria for PTSD after one year as compared to non-users[90]. In the first preliminary randomized controlled trial, Bonn-Miller and colleagues randomly assigned 80 veterans with PTSD to receive one of three active concentrations of smoked cannabis (High THC: Low CBD, Low THC: High CBD, or High THC: High CBD) or an active placebo (Low THC: Low CBD) over three weeks. The others found that all three active dose combinations improved symptoms initially after only three weeks of dosing. Interestingly, only participants in the THC+CBD group (~7.9% THC and ~8.1% CBD) exhibited improvement after week 3, which suggests that different dose combinations may have different effects[91]. However, more studies are needed to identify who is likely to benefit from cannabis treatments, and at which dose combinations — which is something that neuroimaging can assist with. Nonetheless, this brief, preliminary trial demonstrated that smoked cannabis was generally well tolerated and did not lead to deleterious effects in patients. Larger scale randomized placebo-controlled clinical trials are needed to investigate the efficacy of cannabinoids for PTSD symptoms, suicidality, and co-occurring conditions. Our currently funded Veteran Marijuana Research (VMR) study ("Parent study", Study 1) is one of the first FDA-regulated, randomized, controlled clinical trials of cannabis for treating suicidal ideation and PTSD in veterans. In the Parent Study, 200 Michigan veterans are randomized into one of four different THC: CBD dose conditions (High THC:High CBD; HighTHC:Low CBD; Low THC:High CBD, and Low THC:Low CBD; 50 patients/group) for a 12-week treatment trial.

Here, we propose a Supplement (add-on) to our ongoing VMR study, which would be the first-ever neuroimaging study of cannabis treatment in US armed forces veterans with PTSD, or in any population. We propose to image up to 100 participants before and after the 12-week treatment trial (Parent Study) to investigate neurobiological changes that may be associated with the therapeutic benefits of controlled cannabis/cannabinoid dosing. This approach is high in impact and innovation, as we propose to use state-of-the-art brain imaging approaches that are targeted at neurobiological mechanisms known to underpin PTSD and suicidality. The overarching model, shown in Figure 3, is that the development of PTSD (with or without suicidal ideation, plan, or intent) is associated with a heightened inflammatory state in the brain and that cannabis treatment may alleviate symptoms by reducing inflammation.

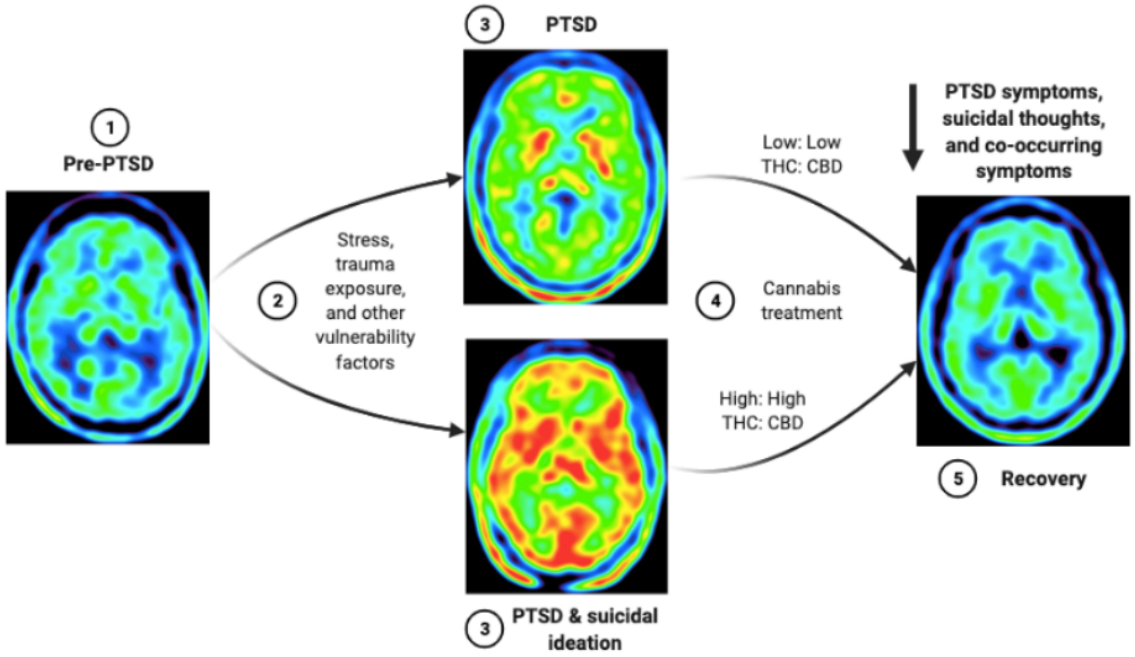


Figure 3: Proposed pathway by which cannabis treatment may alleviate suicidal thoughts and PTSD symptoms, by reducing neuroinflammation. 1) Inflammation is low in individuals without PTSD. 2) Exposure to stress or trauma during active military duty may lead to the development of PTSD and suicidal ideation in susceptible individuals. 3) PTSD and suicidal ideation may be characterized by a state of heightened neuroinflammation. 4) Controlled cannabinoid dosing may be used to reduce neuroinflammation. 5) Lower levels of neuroinflammation may have therapeutic benefit, including lower PTSD symptoms, suicidal thoughts, and co-occurring symptoms. Image modified from Muzik et al., 2017[92].

The supplement will significantly expand the scope and impact of the Parent Study, while minimizing costs. This project will also take advantage of the breadth of expertise of neuroimaging experts at WSU, including in novel approaches to the study of neuropsychiatric disease and neuroinflammation. In particular, Dr. Eric Woodcock (Co-PI) was recently recruited to WSU from Yale University's robust neuroimaging program. He received advanced training in PET imaging methods to study the neuroimmune system in patients with and without psychiatric or substance use disorders. Relevant to this proposal, Dr. Woodcock is PI on an NIH-funded research study using PET imaging to investigate neuroinflammation in addiction and was PI on a recently completed NIH-funded clinical trial investigating the acute effects of opioid administration on neuroinflammation using PET imaging[58,93-95]. Dr. Otto Muzik (Co-I) is a senior PET imaging scientist and a world-renowned expert in PET [^{11}C]AMT imaging, e.g.,[92,96-100]. Together, Drs. Woodcock and Muzik have more than 40 years of PET imaging experience and are well-prepared to execute the PET [^{11}C]AMT imaging studies described herein. Dr. Woodcock will lead the PET imaging methods proposed here (Aims 1 and 3) with support from Dr. Muzik. Drs. Hilary Marusak (Co-PI) and Christine Rabinak (Co-I) provide extensive experience and expertise in functional MRI (fMRI) approaches in healthy, trauma-exposed individuals, and individuals with psychiatric disorders, including PTSD. Relevant to this proposal, Dr. Marusak is the PI of an NIH-funded neuroimaging study on the impact of cannabinoids on emotion regulation in adolescents, and Dr. Rabinak is the PI of an NIH-funded trial on the impact of cannabinoids (synthetic THC) on emotion regulation and treatment outcomes in adults with PTSD. Together, Drs. Marusak and Rabinak have more than 20 years of specialized functional neuroimaging training and experience, and have led 4 NIH-funded neuroimaging studies using similar methods as proposed here. Dr. Marusak will oversee the MRI methods proposed here (Aims 2 and 4) with support from Dr. Rabinak. The highly-novel integration of the PET and fMRI data for the Exploratory Aim will be a collaborative team effort involving Drs. Woodcock, Muzik, Marusak, and Rabinak.

Of note, WSU is located in the heart of Detroit, Michigan, a predominantly low resource, majority urban environment with an at-risk population for psychiatric disorders[101]. Indeed, prior research demonstrates that lower income, minority residents are disproportionately burdened by mental health problems, including depression and PTSD[102]. Therefore, this project is uniquely poised to address health disparities by focusing our recruitment efforts in a largely low resource, minority community (Detroit, Michigan), where rates of mental disorders are higher than national averages and treatment outcomes are distressingly poor — including in veteran populations[103].

Innovation

Innovations of this Supplement application are clear, namely:

1. This study would be the first to incorporate neuroimaging to study the therapeutic potential of cannabis/cannabinoids for treating PTSD and suicidal ideation in veterans. Adding neuroimaging to our current trial will complement and extend the ongoing parent trial by providing the first-ever test of whether cannabis treatment impacts neurobiological mechanisms directly linked to PTSD, depression, and suicidality. This will also be the first randomized controlled trial of chronic cannabis treatment to incorporate brain imaging. Incorporating measures of brain function and neurobiological mechanisms are critical as (1) changes in the brain often precede or predict later changes in symptomatology, and (2) it is unclear whether controlled cannabis dosing is anti-inflammatory in the brain. Further, use of brain imaging will (3) identify targets to tailor treatment approaches to be the *most effective*, thereby optimizing outcomes for veterans with PTSD and comorbid disorders. In particular, the biomarkers and brain circuits measured for this study can be used at baseline to predict who will respond best to different THC:CBD combinations, thus guiding how treatments are delivering and minimizing costs (time and money) associated with trying different treatments that may ultimately be ineffective. Therefore, this supplement has direct, real-world implications for veterans experiencing PTSD or suicidality (high public health significance). This project will also advance our current scientific understanding of how cannabis affects the brain, and the role of neuroinflammation and impulse and emotion regulation-related brain activity in the development and expression of PTSD, suicidality, and comorbid conditions.

2. Application of state-of-the-art functional neuroimaging approaches. This Supplement Study will apply neuroimaging tools that have been recently developed and linked to PTSD, depression, and suicidality. We will apply a methodologically rigorous approach, using well-validated methods that our WSU neuroimaging team is uniquely suited to implement. In particular, we will measure impulse- and emotion-related activation using blood-oxygen-level-dependent (BOLD) fMRI, which is the most commonly used measure of brain activity in MR imaging. BOLD fMRI measures changes in blood flow at rest or in response to an experimental task, and is a surrogate measure of neuronal activity. We will apply the most cutting-edge fMRI approach that incorporates multi-echo (ME) and multi-band fMRI derived from the Human Connectome Project, a large NIH-funded initiative to map the complete structural and functional neural connections in the human brain. One of this innovations of this sequence is that we collect multiple "echoes" — or readouts — of brain functioning at the same time, which contrast with most conventional fMRI sequences that collect only a single readout. This has several advantages over conventional (i.e., single-echo) fMRI, including: (1) greater quality control and removal of imaging artifact from the data (e.g., head motion, physiological noise), (2) improved fMRI effect sizes and elevated statistical power, (3) enhanced regional specificity, and (4) better coverage of brain regions prone to signal dropout, such as the prefrontal cortex, amygdala, and hippocampus — which are highly relevant for PTSD, depression, and suicidality[104-107]. Despite the demonstrable advantage of ME fMRI data acquisition and processing approaches, there is a paucity of studies using ME fMRI to the study of PTSD and suicidality, or how cannabis/cannabinoids use may ameliorate psychiatric symptoms. Our team has more than 34 years of combined experience implementing and analyzing fMRI data in psychiatric populations, and over 10 combined years with ME fMRI, specifically.

3. Application of a quantitative molecular imaging approach to measure in vivo neuroinflammatory state. PET [^{11}C]AMT imaging is a robust and precise molecular imaging method that yields a quantitative measure of tryptophan-kynurenine metabolic rate, a marker of neuroinflammation[92,97-100,108-112]. Kynurenine metabolic rate is low in the healthy human brain consistent with a 'quiescent' or 'resting' microglia state in which neuroimmune signaling is minimal[5,99,113,114]. By contrast, kynurenine metabolic rate is robustly upregulated by pro-inflammatory neuroimmune signaling, especially interferon-γ (IFN-γ) and toll-like receptor-4 (TLR-4) stimulation[4,5,51,99,109,112-119].. Thus, PET [^{11}C]AMT imaging yields a sensitive *in vivo* imaging marker of pro-inflammatory neuroimmune state of patients. Further, the outcome measure is a rate constant, kynurenine metabolic rate yields a quantitative metric that may reflect the extent of 'M1'-dominated (i.e., 'classically activated' or neuroinflammatory) vs. 'M2' ('alternatively activated' or neuroprotective) microglial state in our patients' brains[8,110,112,115,116,120]. We assert that PET [^{11}C]AMT imaging is preferable to alternative PET imaging markers, e.g., translocator protein (TSPO). PET TSPO imaging is fraught with logistical, analytic, and scientific challenges and has yielded inconsistent and controversial findings[121-126]. By contrast, PET [^{11}C]AMT imaging is less burdensome on patients (arterial line not required)[94], doesn't require genetic testing for study eligibility[125], and yields a sensitive and specific measure of kynurenine metabolic rate which reflects neuroinflammatory state.

4. Multi-modal neuroimaging yields synergistic advantages to understanding the therapeutic potential of cannabis/cannabinoids for treating PTSD and suicidal ideation. Exciting recent studies suggest a role of excessive neuroinflammation and aberrant neural activity in PTSD and suicidality, using PET and MRI methods, respectively. However, these methods have never before been combined in a study of PTSD, suicide, depression, or cannabis/cannabinoids. Thus, this study *is poised to break new ground* in our understanding of whether cannabis can be used to combat neurobiological mechanisms directly implicated in the development of PTSD and suicidal ideation. In particular, this will be the first study to measure neuroinflammation in combination with fMRI, and will allow us, for the first time, to evaluate whether cannabis-related therapeutic effects are *mediated (i.e., explained by)* its effects on neuroinflammatory processes and modulation of specific brain circuits. Whereas prior studies have speculated about these relationships, *we will be the first study to test and evaluate them in people.*

Methods for the Proposed Supplement Study

Research Settings

Wayne State University (WSU). WSU is ranked in the top 50 American public universities for research expenditures receiving the highest rating for research activities provided by the Carnegie Foundation. Further, WSU is one of only 7 universities in the USA to receive the highest Carnegie Foundation rating for *research intensiveness* and for *community engagement*. WSU School of Medicine has the unique distinction of being the *largest single campus medical school* in the USA and is the *only medical school* in the city of Detroit. The Metro Detroit area is estimated to be the 12th largest metro area in the United States, consisting of three populous counties: Wayne, Oakland, and Macomb. The Department of Psychiatry and Behavioral Neurosciences, the Detroit Medical Center (DMC), and the Detroit John D. Dingell Veterans' Affairs Medical Center are the main mental health service providers for the city of Detroit and its surrounding suburban population. Our team is integrated within this research and healthcare network.

Tolan Park Medical Building (WSU medical campus). In this proposed supplement, the two study visits (one before and one after the parent clinical trial) will begin and end at the Tolan Park Medical Building, centrally located adjacent to the Detroit Medical Center and the John D. Dingell VA Medical Center. Visits will occur within the WSU Warrior Care Center, new space designated to conduct our current, ongoing LARA/CRA-funded cannabis trial. The Warrior Care Center is housed on the first floor of the Tolan Park Medical Building, and consists of a reception area, small kitchen, conference room, and two private interview rooms for testing. This is same location in which the screening and baseline sessions will occur for the Parent Study and therefore participants will already be

familiar. Further, the research team has additional space as a part of the Human Pharmacological Lab (HPL) on the second floor (two elevators in the building). There is free gated parking out front of the Tolan Park Medical Building that is monitored by a security guard during normal business hours (8AM-5PM; Mon-Fri) during which this study will take place.

MR Research Facility (WSU medical campus). The first brain scan will occur at the MR Research Facility, which is located in Harper Hospital (Detroit Medical Center) — a 5-minute walk from the Tolan Park Medical building. The MR Research Facility has complete and well-supported facilities to conduct MRI research. The facility's research-dedicated 70 cm open bore Siemens VERIO 3T scanner (Siemens Medical Solutions, Erlangen, Germany) is fully equipped for state-of-the-art functional and structural neuroimaging, with 12- and 32-channel head-coils and a comprehensive library of pulse sequences for acquiring T_1- and T_2-weighted images including high resolution anatomical imaging, as well as diffusion-, susceptibility- and perfusion- imaging. The MRRF is fully equipped for stimuli presentation and collection of behavioral and physiological data (heart rate, blood oxygenation, respiratory rate). The proposed MRI scans will utilize advanced multi-echo/multi-band functional magnetic resonance imaging (ME/MB fMRI) and multi-echo MP-RAGE (ME-MPRAGE) scanning sequences, which will measure brain function and structure while minimizing potential confounds, such as head motion.

PET Imaging Center (WSU medical campus). The WSU PET Center is located in Children's Hospital of Michigan (a 5-minute walk from the MRRF and Tolan Park Medical Building). The PET center is an 8800 square feet facility housing scanning rooms, cyclotron laboratory, patient prep rooms and computing facilities. The laboratory includes 2 PET scanners and one common control room. The facility houses a GE Discovery STE PET/CT scanner (GE Medical Systems, Milwaukee, WI) which combines a Light-Speed 16-slice CT with an advanced BGO PET system yielding 47 image planes with a 16cm axial FOV. In addition, a high-resolution Siemens ECAT EXACT HR (Siemens PET systems, Knoxville, TN) is installed capable of acquiring data both in 2D (septa extended) and 3D (septa retracted) modes. Adjacent to the scanner are 6 patient prep rooms for behavioral testing and placement of venous lines. All PET systems and all data analysis workstations are connected to a central Computer Network for off-line data processing and archiving. The PET Center cyclotron and chemistry laboratories are housed immediately adjacent to the PET scanning room. A Siemens-CTI 11 MeV negative ion cyclotron and radiopharmaceutical synthesis system is fully operational. This instrument is capable of irradiating four targets (two simultaneously) with 11 MeV protons. The cyclotron laboratory is equipped with computer-controlled fully automated radiopharmaceutical production systems for producing routine positron-emitting compounds and gaseous radioactive effluent monitoring systems. In addition, a new GE PET Trace 18 MeV negative ion cyclotron, together with a 500 square feet production and quality control lab has been installed adjacent to the PET Center in 2012. The GE PET Trace cyclotron is capable of simultaneously irradiating 6 targets (two F^{18}, two C^{11}, one O^{15} and N^{13} target) with either protons or deuterons. The production lab is fully GCMP compliant and contains 4 hot cells and 2 new F^{18} modules (GE Fastlab) for the routine production of FDG. The PET Center chemistry laboratories are equipped with the necessary equipment needed to produce and develop PET radiopharmaceuticals for clinical use. Included are radio-HPLC systems with appropriate mass (ultraviolet, refractive index) and radioactivity (NaI scintillation) detectors coupled to a data acquisition and management system. A radio-TLC scanner (Berthold) is used for radiochemical analysis. Appropriate radiation monitoring equipment, including area survey monitors and hand and foot counter, are in place, including a 50 square-feet class-100 clean room equipped with a laminar-flow hood for the preparation of sterile components. Access to analytical instrumentation for the characterization of cold radiopharmaceutical precursors (IR, NMR, Mass Spectrometers) are provided by the Chemistry Department at WSU. The radiochemistry laboratory is equipped with all the necessary standard laboratory equipment, including balances, pH meters, glassware, etc. The WSU PET center is uniquely well-equipped to synthesize [^{11}C]AMT, conduct [^{11}C]AMT scans, and analyze [^{11}C]AMT data for this study.

Participant Recruitment and Selection

The methods for the proposed supplement will be approved by the WSU IRB before any study procedures begin. In addition, the neuroimaging protocols (PET and MRI) are reviewed separately by

the PET Center and the MR Research Facility for safety and design. All participants enrolled in the Parent Study (Study 1) will be screened for eligibility for the supplemental brain imaging scans. Therefore, all inclusion and exclusion criteria for the Parent Study apply to this supplement. Additionally, the following eligibility criteria will apply for the imaging scans: Exclusion criteria. Participants will be excluded if they (1) have any MRI contraindications, such as braces, claustrophobia, implanted metal (self-report and ferromagnetic detectors), or are pregnant (urine HCG) or (2) would exceed annual radiation limits set by the Food and Drug Administration (FDA) by completing this study (5 rem in any 12-month period). Eligibility will be determined at the screening visit for the Parent Study to minimize subject burden. Subject safety to complete the MRI and PET imaging will be confirmed a second time on scan day (i.e., pregnancy test and ferromagnetic screening will be repeated), in accordance with MR Research Facility and PET Center policies. Up to 100 participants who meet eligibility criteria at the screening visit will be invited to participate in the supplemental neuroimaging study. Enrollment in this Supplemental study will continue until we meet our recruitment targets (N=100 baseline scans; n=25 in each of the four pharmacological dosing groups) and will not impact recruitment for, or participation in, the Parent Study. Participants will complete a separate informed consent procedure for the Supplemental study. All imaging study procedures and risks will be described in detail in the imaging study consent form, and will be reviewed with participants. After answering participant questions and verifying complete understanding of study procedures and potential risks, study staff will obtain informed consent and subjects will be scheduled for their first (baseline) imaging session. This session will be scheduled prior to the start of the trial, between the screening and baseline visits of the Parent Study, as detailed below (Figure 4). After the end of the 12-week Parent Study, subjects will be scheduled for their second and final imaging session. Upon completion of that imaging session, subjects will have completed this supplemental imaging study. We anticipate modest (20%) attrition during the 12-week treatment trial and anticipate 80 subjects will complete the post-scan.

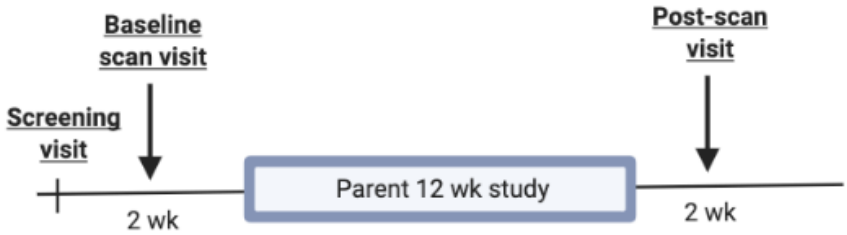


Figure 4: Proposed study timeline

Supplemental Screening Measures

Participants will be screened thoroughly as a part of the Parent Study. In addition to the screening measures employed in the Parent Study, subjects will also complete the following measures to determine eligibility for the supplemental imaging study. The ***WSU MR Research Facility Screening Form*** will be administered at the screening visit to determine initial self-reported eligibility for brain imaging, and re-administered prior to the final scan session to ensure safety. The WSU MR Research Facility Screening Form is used to screen participants for MRI contraindications and will be reviewed separately by both the study staff and the MRI Technologist (MR Research Facility) for safety. Participants with implants (e.g., ports) will be asked to contact their surgeon/treating physician for the device manufacture and number to be screened for conditional safety at 3T MRI. Available data indicate that exposure to MRI magnetic fields and radiofrequency signals, at the level and in the manner used for the research described in this proposal, do not present a potential health risk to participants. However, since the magnetism of the MRI device attracts certain metals, individuals with these metals in them (specifically pacemakers, braces, infusion pumps, aneurysm clips, metal prostheses, metal joints, rods, plates or other metal objects) will not be eligible to participate in the brain scan. The amalgam in dental fillings is less susceptible to this effect and is therefore allowed. A ***ferromagnetic wand*** will be

purchased for this study and used at in the lab at the screening visit to detect potential MRI contraindications. Further, subjects will undergo a second, more sensitive screening via a ***walk-through ferromagnetic detector*****,** which will be purchased and installed for this study. This detector will be mounted at the MR Research Facility and, will be used to screen participants for ferromagnetic material immediately prior to MR scanning. Thus, we propose a 4-tier MRI screening protocol for verifying veterans will be safe for MR scanning: 1) assess any implants (device manufacturer and number) for conditional safety at 3T MRI , 2) self-report MR Research Facility Screening form, 3) ferromagnetic wand, and 4) walk-through ferromagnetic detector. This 4-tier screening protocol is especially critical for subject safety in this study as veterans may be exposed to metal shrapnel during active duty and thus, would be unsafe for MR scanning.

Menstrual Cycle. Menstrual cycle phase will be tracked, but not controlled, in this study. Hormone contraception will not be exclusionary.

Experimental Methods

Overview of Supplemental Study Design. The proposed study will supplement our current randomized, double-blind placebo-controlled 12-week trial to examine effects of THC and CBD on PTSD symptom severity and suicidal ideation among 200 US armed forces veterans in an outpatient setting (Study 1 from the Parent Study). In the Parent Study, a total of 200 veterans will be randomized into one of four treatment groups (50 in each: High THC:Low CBD, High THC:High CBD, Low THC:High CBD, and Low THC:Low CBD, which will serve as a functional placebo). For the proposed Supplement, 100 of the 200 patients from the Parent Study (25 from each pharmacological group; High:Low THC:CBD) will undergo a neuroimaging assessment within 2-weeks prior to the start of the Parent Study, i.e., 'baseline'. Patients who complete the Parent Study will undergo a second neuroimaging assessment (identical to baseline) within 2-weeks after completion of the THC:CBD 12-week treatment trial, i.e., 'post scan'. We anticipate modest (20%) attrition during the 12-week treatment trial and anticipate 80 subjects will complete the post-scan. See Supplement Study timeline provided in Figure 4. During each neuroimaging assessment, patients will complete one 60-minute PET AMT scan and one 60-minute MRI scan, which consists of structural and functional measurements (see details below).

Rationale for Supplemental Study Design. The rationale for imaging subjects once before and once after the funded 12-week Parent Study is three-fold: 1) We aim to capture the within-subject changes that may occur in response to controlled THC:CBD dose combinations; 2) We aim to capture the differential effects of suicidal thinking on neuroimaging outcomes at onset of the clinical trial; and 3) We aim to minimize disruptions to subject recruitment/enrollment in the funded Parent Study and thus, we do not propose any imaging during, i.e., in the middle of, the 12-week trial.

Overview of Imaging Session Methods. Imaging sessions will last about 6.5 hours, and begin at 8:30 AM and end around 3:00 PM. See Figure 5 for a timeline of events and assessments. Imaging sessions will follow a standard protocol in which assessments occur at the same time across participants to control for diurnal rhythm effects. In addition, participants will be instructed to eat breakfast and intake caffeine prior to the 8:30 AM arrival time, as they must be fasted for at least 5 hours prior to the PET scan (which starts at 1:30 PM) to ensure stable levels of tryptophan prior to scanning. All instruments will be administered by trained research assistants or postdoctoral research fellows supervised by Drs. Woodcock and Marusak. Drs. Woodcock and Marusak are highly experienced neuroimaging experts, who have a combined 22 years of experience performing similar neuroimaging assessments in traumatized populations or individuals with psychiatric and/or substance use disorders. Drs. Woodcock and Marusak will also be supported by Drs. Muzik and Rabinak, leading experts in the application of PET [^{11}C]AMT imaging to study psychiatric and neurological disorders, and the application of functional neuroimaging approaches to develop new cannabinoid therapeutics to treat PTSD in veteran and civilian populations, respectively.

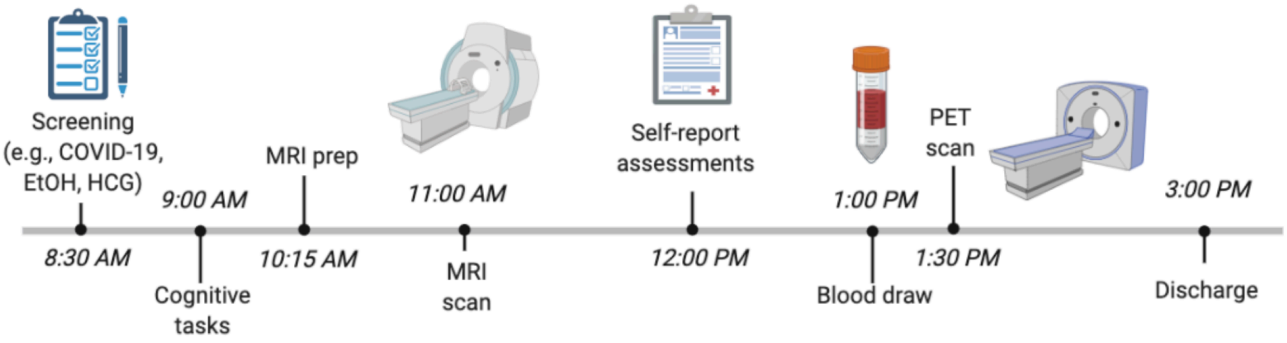


Figure 5: Experimental timeline

Screening Assessments. Upon arrival to our laboratory at 8:30 AM for the imaging study session, participants will be greeted by our study staff and will undergo a brief COVID-19 screening. Subjects will have their temperature taken via infrared forehead thermometer, sanitize their hands, and will complete the WSU Daily Covid Screener. Subjects will be provided a face mask if they do not have one. After verification of no COVID-19 symptoms, subjects will be verified sober (expired breath alcohol < 0.02%) and expired carbon monoxide measured (biomarker of recent tobacco smoking). Subjects will complete a comprehensive 16-panel urine drug screen (CLIAwaived Inc.®) and urine pregnancy test (HCG; females only). Participants will also complete brief screening questionnaires to capture any elevation in suicidal thoughts, behaviors, or depressive symptoms on the day of the scan visit (Suicide Behavior Questionnaire-Revised [SBQ][127], Columbia–Suicide Severity Rating Scale [C-SSRS][128], and Beck Depression Inventory-II [BDI-II][129]). If suicidal or homicidal ideation is present, one or both of the PIs on the Parent Study who are licensed psychologists (Drs. Lundhal and/or Ledgerwood) will be immediately contacted and the participant will be assessed by a clinician, as detailed below. After verification that subjects are sober, and for females, not pregnant, and not at imminent suicidal or homicidal risk, we will move forward with the remainder of the imaging study protocol. From 9:00-10:00 AM, subjects will complete a thorough computerized cognitive battery in a private study room. Research assistants will orient subjects to each task (described in detail below) and assist subjects in completion of the task. For most tasks, there is a 'practice' version that will orient subjects to the task and what is being asked of them.

Cognitive Tasks. At 9:00 AM, participants will complete a battery of standardized behavioral assessments to estimate memory, psychomotor functioning, and impulsivity. These assessments will be performed on a computer, using Presentation or Millisecond software, and be used for sub-group correlation and regression analyses. These assessments include:

1. *Monetary Incentive Delay (30-minutes).* The Monetary Incentive Delay task is a relatively simple, widely used task to assess reward processing along the hedonic spectrum of positive (wins) to negative (losses) valence measure. Prior studies show that that reward-related processing is relevant risk of depression, PTSD, and substance use disorders, and is widely used in the cannabis/cannabinoid literature to study effects on reward-related processing. This is a simple task that facilitates investigation of reward processing along the hedonic spectrum of positive (wins) to negative (losses) valence and is widely used in both the PTSD and cannabis/cannabinoid literature. As money earned on this task is paid as a 'bonus' study payment (up to $20), subjects are incentivized to perform this task optimally.
2. *Object-Location Associative Learning (10-minutes).* In the Object-Location Associative Learning task, subjects are instructed to learn associations between objects and their location on a 3x3 grid. This task is a widely used measure of hippocampal-dependent associative learning, which has been proposed as an endophenotypic therapeutic target in PTSD. Indeed, prior

research indicates that PTSD subjects exhibit impaired associative learning which have been associated with functional and volumetric hippocampal deficits.

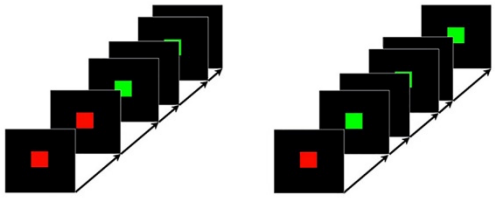
3. *Balloon Analogue Risk Task (7-minutes).* In the Balloon Analogue Risk Task (BART) is a widely used measure of risk-taking behavior, and prior research suggests higher risk seeking in individuals with PTSD (vs. without). During the task, participants are instructed to earn money by pumping up balloons ($0.02 earned for each 'pump') and 'banking' the money earned before the balloon 'pops'. There are 30 balloons that are programmed to 'pop' after a random number of 'pumps'. If the balloon 'pops' before the money is banked, the subject earns nothing for that balloon. The primary outcome is mean number of pumps for unexploded balloons which is a behavioral metric that reflects risk seeking. Participants will receive up to $30 in additional compensation to incentivize their performance on the task.
4. *Cannabis Stroop Task (6-minutes).* In the Cannabis Stroop task, neutral words (e.g., book) and cannabis-related words (e.g, THC, joint) will be presented on screen in one of 4 different colored fonts (blue, green, red, and yellow). Subjects are instructed to ignore the content/meaning of the word and to verbalize the color of the font as quickly as possible. This task utilizes the classical Stroop interference effect by contrasting response latency and accuracy for cannabis-related words vs. neutral words to assess attentional bias toward cannabis-related words.
5. *Hypothetical Monetary Delay Discounting (2-minutes).* In this 5-trial delay discounting task, subjects will be asked to choose between a smaller amount of money now (e.g., $5) or a larger amount (e.g., $10) at 5 variable adjusting delays (e.g, 3-days, 1-week, etc.). Subjects will complete this task twice: first as a 'practice' and then as a 'real' trial to assess delay discounting rate, *k*. Discounting rate is calculated based on subject's preference for smaller, immediate monetary rewards vs. larger, delayed monetary rewards. Higher *k* values indicate greater discounting of future rewards in preference for smaller immediate rewards, indicative of temporal myopia, which is associated with both PTSD and cannabis use.

MRI Preparation and Screening Methods. From 10:00-10:15 AM, participants will have a brief break to stretch their legs and use the restroom. At 10:15 AM, subjects will be oriented to the MRI scan protocol. Research staff will orient subjects to the MRI environment and prepare him/her for the MRI scan. In addition, subjects will complete brief, practice runs of each cognitive task (Emotional Stroop and Go/No-Go tasks) before the MRI scan. At 10:30 AM, research staff will escort the participants to the MRI center. The MRI Technologist will prepare the subject to be scanned, e.g., emptying pockets, removing jewelry, and removing shoes. Next, the MRI Technologist will review the MRI screening form with the subject before asking participants to walk through the ferromagnetic detector to confirm safety for the MRI scan. Participants who have any potential MRI contraindication will not be allowed to complete the scan or subsequent scans. Ineligible participants will be escorted back to Tolan Park and compensated $50 for the time. These participants will continue participation in the parent clinical trial, but will not participate in the supplemental imaging study. Given the nature of the proposed study population (i.e., veterans), we anticipate a small subset of participants (fewer than 10%) will have MRI contraindications that were not detected by the hand-held ferromagnetic detector wand during screening visit. We have budgeted additional funds to compensate for these potential screen fails.

MR Imaging Methods. The MRI scan session will last less than 1-hour in total (11am-Noon), which has been shown to be well-tolerated by individuals with PTSD, including veterans and civilians. During the 1-hour scan, we will collect five different imaging datasets. First, we will collect a high-resolution T_1-weighted structural scan using a multi-echo MPRAGE sequence (ME-MPRAGE; ~7-minutes; TR = 2530ms, TEs=1.79, 3.65, 5.51, 7.37ms, FOV=256mm x 256mm, 1 x 1mm-thick slices, voxel size=1mm^3 isotropic). This anatomical scan will be used for anatomical coregistration for the PET and MRI data as well as for exploratory volumetric or cortical thickness analysis. Second, we will collect a T2-weighted anatomical scan (~2.5 minutes; TR = 7080ms, TE=77ms, FOV=220mm x 165mm, 80 x 2mm-thick slices, voxel size=0.9 x 0.4 x 2.0mm), which will be used to screen for the presence of pathological conditions that may affect brain activity (e.g., hemorrhage, axonal damage). Third, we will

collect whole-brain ME blood oxygen-level dependent (BOLD) fMRI data while subjects are 'resting' in the scanner (eyes-closed) across one resting state run separated by a brief break (ME-fMRI; 10-minutes; TR = 1500ms, TEs=13.6, 30.87, 48.14ms, FOV=209mm x 209mm, 51 x 2.9mm-thick slices, voxel size=2.9mm^3 isotropic). Resting-state fMRI data will be used to evaluate group differences and temporal changes in large scale functional neural networks that are implicated in PTSD, depression, and suicide (i.e., default mode network, salience network). Fourth, we will collect whole-brain ME BOLD fMRI data while subjects perform two tasks that directly assess neurobiological mechanisms underlying PTSD, depression, and suicidal ideation: (1) a response inhibition task (Go/No-Go task; ~12-minutes; TR = 1500ms, TEs=13.6, 30.87, 48.14ms, FOV=209mm x 209mm, 51 x 2.9mm-thick slices, voxel size=2.9mm^3 isotropic) and (2) an emotion regulation task (Emotion Stroop task; ~13-minutes; TR = 1500ms, TEs=13.6, 30.87, 48.14ms, FOV=209mm x 209mm, 51 x 2.9mm-thick slices, voxel size=2.9mm^3 isotropic). These tasks are described in detail below. Tasks will be viewed by participants using a mirror affixed to the head coil, and behavioral responses (e.g., response latency, accuracy) will be collected using an MR-compatible response device.

1. *Inhibitory Control (Go/No-Go) Task.* We will use a Go/No-Go task to measure brain activity related to response inhibition, a type of inhibitory control. In this Go/No-Go task (Figure 6), red and green colored squares will appear centered on screen for 250ms at pseudo-random delays (mean = 1.25s; range 1.0-1.5s). Subjects will be instructed to button press as quickly as possible after presentation of either Green squares only ('Go/No-Go' blocks) or both Green and Red squares ('All-Go' blocks). This task consists of four 48s blocks of 'Go/No-Go' and four 48s blocks of 'All-Go' presented in a pseudo-random order; each block is separated by 38s of static fixation cross rest. By virtue of presenting the 'No-Go' stimuli infrequently (Red squares; 20% of stimuli) during the 'Go/No-Go', responses to the 'Go' stimuli become 'prepotent' (Green squares; 80% of stimuli; 4:1 ratio), and thus, necessitate engagement of inhibitory control neurocircuitry to withhold a response. The total length of this task is 698s (~12-minutes). Response latency and accuracy will be measured. Thus, this task evokes neural activation during a simple motor control task ('All-Go') and during an inhibitory control task ('Go/No-Go'). As the 'All-Go' and 'Go/No-Go' are yoked to identical task parameters and stimuli, we can isolate the neural substrates of response inhibition and investigate differential recruitment of neural resources as a function of trauma history, recent depression symptoms, and other psychiatric variables. By including a 'true' rest condition (static fixation cross), we can separately evaluate neural network profiles during motor control vs. inhibitory control. Further, we will investigate Time effects and Time by Dose interactions by quantifying the within-subject changes in neural network activation before/after completion of the Parent Study. Finally, response latency (delay between stimulus onset and button press response), omission errors (failure to respond after 'Go' stimuli), and commission errors (failure to inhibit after 'No-Go' stimuli) will be calculated for each subject and time point. These behavioral metrics facilitate isolation of inhibitory control proficiency (commission errors) during the 'Go/No-Go' task, separate from sustained attention issues (omission errors) and speed-accuracy trade-offs (response latency).



Name:	'All-Go'	'Go/No-Go'
Process:	Motor Control	Inhibitory Control
Ratio:	50:50 Green:Red	80:20 Green:Red
Respond:	Green & Red	Green

Figure 6: Inhibitory control task. The ability to inhibit pre-potent responses (or impulses) is a core feature of suicidal thoughts, and the transition from suicidal thoughts to behaviors. Impulse control is measured isolated by contrasting brain and behavioral responses measured during Go/No-Go trials with All-Go trials.

2. *Emotion Regulation (Emotional Stroop) Task:* We will use an Emotional Stroop task to measure emotion regulation-related brain activity. This task was selected because it has been widely using in individuals with trauma exposure, PTSD, depression, anxiety, and other psychiatric disorders, predicts treatment response, and measures automatic or non-conscious forms of emotion regulation[130-134]. During the task (see Figure 7), participants view either fearful or happy faces with the word "FEAR" or "HAPPY" superimposed on each faces. Subjects will be instructed to button press as quickly as possible to indicate whether the expression of the face is fearful (left buttonpress) or happy (right buttonpress), while trying to ignore the task-irrelevant word stimuli. In some trials, the emotional expression of the face and the word are congruent (i.e., "FEAR" superimposed on a fearful face); in other cases, the expression of the face and the word are *incongruent* (i.e., "FEAR" superimposed on a happy face). The latter trial is associated with a slowing in behavioral responses and reduced accuracy — creating conflict. That is, the emotional content of the face is in direct competition with the meaning of the word. Interestingly, prior studies have demonstrated that two incongruent trials in a row are associated with a performance *increase*, such that participants perform better after repeated conflict trials (i.e., incongruent followed by incongruent trial [iI]), as compared to non-repeated conflict trials (i.e., congruent followed by incongruent trial [cI]). This phenomenon is thought to represent an automatic or non-conscious form of emotion regulation, because participants are unaware of these effects. Prior studies using neuroimaging demonstrate that a core set of brain regions involved in emotion regulation is activated by emotional conflict regulation, including the amygdala and ventral anterior cingulate cortex (vACC). These brain responses are isolated by contrasting the iI > cI trials. This event-related task consists of 163 presentations of happy or fearful faces. Faces are presented for 1.0s in a pseudorandom order, counterbalance across trial types for expression, word, response button, and face gender. The interstimulus interval ranges from 2.0-4.0s. Total length of this task is 766s (12.77 minutes). Response latency and accuracy will be measured. This task evokes neural activation to emotional conflict (incongruent > congruent trials) as well as emotional conflict regulation (iI > cI trials). Further, we will investigate Time effects and Time by Dose interactions by quantifying the within-subject changes in neural network activation before/after completion of the parent clinical trial and 12-weeks of high:low THC:CBD administration. Finally, response latency (delay between stimulus onset and button press response) and accuracy (correctly identifying the facial expression) will be calculated for each subject and time point. These behavioral metrics facilitate isolation of emotion regulation during the Emotional Stroop task, separate from speed-accuracy trade-offs (response latency).

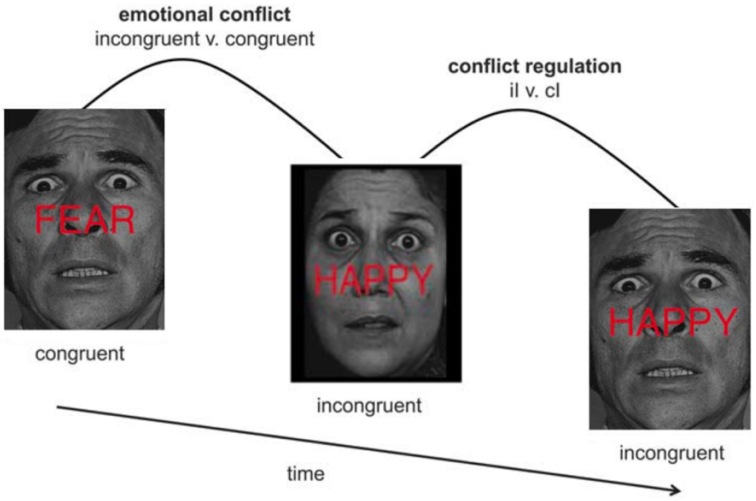


Figure 7: Emotion regulation task. Emotion conflict regulation is considered an automatic form of emotion regulation, which is linked to suicidal thoughts and behaviors, and PTSD. Emotion conflict regulation is isolated by contrasting brain and behavioral responses measured during incongruent trials preceded by another incongruent trial (iI) with incongruent trials preceded by a congruent trial (cI).

Self-Report Assessments. After completion of the MRI scan (12:00 PM), participants will be escorted to the PET center (~3min walk). After checking in at the PET center for the 1:30 PM scan, participants will be escorted to a private waiting room. While waiting for the PET scan, subjects will complete measures of: 1) affect[135]; 2) mood state[136]; 3) perceived stress[137,138]; 4) stress mindset[139]; 5) distress tolerance[140]; 6) anhedonia symptoms[141]; and 7) impulsivity[142,143]. Subjects who smoke cigarettes will also complete a 7-day cigarette smoking timeline follow-back and the Fagerstrom Test for Nicotine Dependence (FTND)[144] (5min).

Blood Labs and Plasma Biomarkers. After completion of the self-report assessments (~12:45 PM), a nurse will prep subjects for the PET scan including placement of two venous lines: one for [^{11}C]AMT radiotracer injection and the other for timed blood sample collection (for estimation of the input function during PET scanning; see below). Prior to administration of the radiotracer, a PET nurse will collect 8ml of whole blood for various peripheral biomarker assays (2x 4ml EDTA vacutainer tubes). These samples will be used for genomic analyses, standard blood panels (e.g., lipids, CBCs), as well as measurement of peripheral levels of tryptophan and other large neutral amino acids (LNAAs), kynurenine, and kynurenine pathway metabolites (e.g., kynurenic acid, quinolinic acid); immune system markers (C-reactive protein and cytokines/chemokines, e.g., IL-1β, IL-6, TNFα, and IFNγ); stress system markers (cortisol and noradrenaline); and sex hormone levels (e.g., estradiol, testosterone, and progesterone). Blood samples will be immediately transported back to the lab space for processing and storage.

PET Imaging Methods. As described above, a PET nurse will place two venous catheters. One venous line will be established for injection of [^{11}C]AMT (0.2 mCi/kg; 30s bolus) and a second venous line for collection of timed blood samples for plasma [^{11}C]AMT radioactivity (0.5 ml/sample; 0, 10, 20, 30, 40 and 60 minutes after AMT injection). Subjects will be placed in the PET camera at 1:15pm in anticipation of radiotracer injection at 1:30pm. Subjects will undergo a 60-minute PET [^{11}C]AMT scan on a GE Discovery STE PET/CT scanner. During the first 20-minutes, a dynamic PET scan of the heart will be performed (12x10s, 3x60s, and 3x300s) in 2D-mode to measure the left ventricular (LV) input function. After 20 minutes, the brain will be imaged in high-sensitivity 3D-mode (12 x 3min) and the input function will be measured via venous blood samples[113,145]. Attenuation correction will be performed based on a low-level CT scan (100kV, 60mA).

Debrief and Discharge. Following completion of the PET scan, participants will be treated to their choice of lunch at the DMC food court, then escorted back to the Tolan Park Medical Building (<10min walk). Subjects will be debriefed and paid for his/her participation. Subjects will be able to eat their lunch in a private room while awaiting their transportation (personal vehicle or Uber/taxi) or discharged immediately upon receipt of study payment (subject preference).

Primary Outcome Measures

fMRI Data Analyses. fMRI data will be analyzed using Statistical Parametric Mapping (SPM). As stated above, ME fMRI data will be acquired in this study, leveraging sophisticated Echo Planar Imaging sequences used in the Human Connectome Project. The acquisition of 3 echoes facilitates sophisticated pre-processing analyses to remove sources of noise in the data (e.g., head motion). Preprocessing, denoising, and quality assurance steps will be applied to fMRI data collected during the two tasks using a custom preprocessing pipeline, based on AFNI's afni_proc.py. The preprocessing pipeline includes, in brief: (1) removal of the first 4.5 s of data (prior to first stimulus onset) to allow for signal equilibration, using AFNI's 3dTcat, (2) time shifting of the echo timeseries to account for differences in slice acquisition timing, using AFNI's 3dTshift, (3) co-registration of the second echo times for motion correction and for anatomical-functional coregistration, with the saved transformation matrix applied to the first and third echoes, using AFNI's 3dvolreg and 3dAllineate, (4) within-brain mask creation based on the first echo, to restrict ICA to within-brain areas, using AFNI's 3dAutomask, (5) ICA and optimal combination of the BOLD timeseries using tedana software, including global signal control,105 (6) skull-stripping and warping of the anatomical image to the Montreal Neurological Institute (MNI) template, using AFNI's @auto_tlrc, and (7) 12-paramter affine anatomical-functional co-registration, using AFNI's align_epi_anat.py. No temporal filtering or spatial smoothing will be applied, see Kundu et al. for discussion. Preprocessed and fully denoised BOLD timeseries will then be submitted to analysis using conventional methods (GLM, event-related design, random effects) in SPM12 software, following prior work. Trial onset times for experimental conditions will be modeled and convolved with the hemodynamic response function. First-level models will be created with the task conditions and BOLD response will be isolated to the contrast Go/No-Go > Rest for the inhibitory control task, and iI > cI for the emotion regulation task.

PET Imaging Data Analyses. All PET [^{11}C]AMT images will be corrected for attenuation, tracer decay, and scatter, and reconstructed using OSEM iterative reconstruction. Summed dynamic PET images will be co-registered to structural MRI scans in MNI template space for identification of regions of interest. Using the Anatomical Automatic Labeling (AAL) template, *a priori* regions of interest (depicted in Figure 8 below) will be co-registered to PET data in MNI space for quantification of kynurenine metabolic rate. To quantify kynurenine metabolic rate, Patlak graphical analysis[146] will be performed using the LV arterial input function and the dynamic emission sequences as described previously[145]. This method yields the unidirectional uptake rate constant (K-complex) in each region of interest which represents [^{11}C]AMT metabolic rate and the physical trapping of [^{11}C]AMT metabolites in tissue. As described above, [^{11}C]AMT metabolic rate is highly sensitive to neuroinflammatory state and has been shown to be robustly upregulated in numerous inflammatory conditions, especially IFNγ and TLR4 stimulation[118,119,147,148], and thus, higher kynurenine metabolic rate reflects more neuroinflammation.

Clinical Plan for Addressing Elevated Suicidality

All participants will be monitored for increases in suicidal ideation throughout their participation in the Parent Study. The same clinical plan for addressing elevated suicidality in the Parent Study will also apply to the proposed neuroimaging sessions. Exacerbations in suicide risk may be detected in a variety of ways: 1) a participant may report increased suicidality or suicidal behaviors to a research assistant; 2) participants may note increased suicidality on the C-SSRS, SBQ or BDI-II; or 3) we may become aware of increased suicidality through a clinical or collateral sources such as a therapist or family member.

In the event that a participant reports suicidal ideation, either at the initial study intake or during the study, the research assistant will immediately contact Drs. Lundahl and/or Ledgerwood who are licensed clinical psychologists in the State of Michigan. Both Drs. Lundahl and Ledgerwood have experience working with individuals who have depression and express suicidal ideation. Additionally, Drs. Mischel and King are board certified psychiatrists on the Parent Study and will be available throughout the study for consultation and clinical evaluation. Dr. Lundahl or Ledgerwood will meet with the participant and conduct a risk assessment. Important components of a suicide risk assessment include assessment of the presence of suicidal ideation, past attempts, plan for an attempt, lethality of the suicide plan and past attempts, and accessibility to means for a suicide attempt. Dr. Lundahl or Ledgerwood will assess each of these specific domains. In cases where the participant is not at immediate risk (i.e., the participant is experiencing mild thoughts about death, has no intention or plan to commit suicide, reports many things to live for, has a strong social support network and has a forward-looking perspective), Dr. Lundahl or Ledgerwood will continue to monitor the individual, make frequent assessments of his/her suicidality at subsequent visits and assessment time-points, and they will refer the individual to outpatient mental health treatment. Assessments of suicidality are routinely conducted every two weeks in the study, but Dr. Lundahl and/or Ledgerwood will conduct more frequent follow-up in cases where the participants' risk of suicide is significantly elevated from prior assessment time-points. In cases where the suicide risk is high (i.e., wish to die, suicide plan, access to methods, etc.), or unknown, Dr. Lundahl and/or Ledgerwood will conduct further assessment, and may hospitalize the participant if s/he believes that the participant may attempt suicide upon leaving the facility. We have adopted a similar policy in our ongoing studies.

Compensation

All participants will be paid up to $500 for each scanning session, which includes the bonus payments that can be earned during completion of the Balloon Analogue Risk Task and Monetary Incentive Delay Task (total of 2 sessions = up to $1,000). This is in addition to the amount compensated for the Parent Study, as this requires two additional study visits (≈6.5 hrs for each session = ≈13 total hours). This amount is comparable to other imaging studies that involve both an MRI and PET scan within the same study visit. Participants who arrive for the session but are deemed ineligible (e.g., walk-through ferromagnetic detector) or opt out of the scanning (anticipated to be <10% of subjects) will be compensated $50 for that session.

Study Timeline

The proposed study will leverage our ongoing Parent Study, which is expected to begin enrollment for Study 1 during Fall 2022, which will correspond with the start of data collection for the proposed supplement. The proposed supplement project will take about 5 years to complete. During the first three months of the award period, we will submit to the IRB to amend our current protocol to include the imaging sessions, setup and test the MRI and PET sequences and tasks, establish quality assurance and processing pipelines, and hire additional research, and train all staff (new and existing) on methodology. We will begin data collection as soon as Study 1 begins, during Year 1. We will recruit veterans for this Supplement Study until we achieve 25 in each dosing group (N=100 total). Participants who are eligible for scanning (e.g., no MRI or PET contraindications) based on the initial screening visit, will be invited to complete this supplement. In addition, we expect that up to 20% may be lost to attrition over the course of the trial. Therefore, we plan to enroll up to 100 veterans into the Supplement Study to account for up to 20% attrition such that 80 veterans complete both imaging assessments ('baseline' and 'post' scans). Data collection will be at a pace of ≈4 sessions/month (1 session/week) over ≈4.25 years which will accommodate 6-9 months for data analyses and manuscript preparation/submission.

Data Analyses

Data analyses will follow standard procedures for fMRI and PET data, and in collaboration with Dr. Ghosh at the WSU Biostatistics Core. This study will leverage neuroimaging data collected across two timepoints (baseline, post) using a repeated-measures, within-between design. All variables will be examined for outliers (z-scores ≥ 3.3) and normality of distribution (skewness, kurtosis). Appropriate transformations will be used (e.g., Box-Cox, Power etc.) when distributional assumptions are not

fulfilled before the final analysis. Sphericity will be verified (Mauchly's Test) prior to repeated-measures analysis of variance and Huynh-Feldt correction for repeated measures will be applied. Variables for which baseline differences exist will be used as covariates.

Aims 1 and 3: *Aim 1:* For the PET AMT imaging data, we will first extract K-complex values will be extracted from *a priori* regions of interest. Then, to assess the therapeutic effects of cannabis on PET AMT data, a 4 (cannabis dosing condition) x 2 time (baseline, post) repeated measure (RM)-ANCOVA will be used to test for changes in K-complex values over time and between groups, controlling for demographic variables, e.g., age. Significant interactions will be analyzed using simple effects tests. Analyses will be performed using two complementary approaches: (1) a hypothesis-driven region of interest-based analysis; and (2) exploratory whole-brain voxel-wise analysis. Our *a priori* brain regions of interest are shown in Figure 8, defined by anatomical atlases and meta-analyses. These regions were selected because they have been most frequently reported in neuroimaging studies of suicidal thoughts and behaviors and PTSD. Follow-up analyses will investigate relationships between the change in clinical variables over time, e.g., severity of suicide and PTSD symptoms, and the change in K-complex values from 'baseline' to 'post' scan in brain regions of interest using partial correlations, controlling for demographic variables. *Aim 3:* K-complex values will be extracted from *a priori* regions of interest and submitted to multiple regression to evaluate whether the severity of suicidal thoughts and behaviors among veterans with PTSD is associated with upregulated tryptophan-kynurenine metabolic rate at the 'baseline' scan, controlling for demographic variables, e.g., age. Follow-up analyses will investigate relationships between clinical variables, e.g., severity of suicide and PTSD symptoms, and K-complex values in brain regions of interest using partial correlations controlling for demographic variables.

Aims 2 and 4: *Aim 2:* FMRI analyses will be performed in SPM12 software. To assess the potential therapeutic effects of cannabis on fMRI data, a 4 (cannabis dosing condition) x 2 time (baseline, post) RM-ACOVA will be used to test for changes in brain activation over time and between groups, controlling for potential imbalance between groups in demographic (e.g., age) or baseline symptom severity. Significant interactions will be analyzed using simple effects tests. Analyses will be performed using two complementary approaches: (1) a hypothesis-driven region of interest-based analysis; and (2) exploratory whole-brain voxel-wise analysis. Regions of interest are shown in Figure 8. Region of interest results will be considered significant using the gold-standard small-volume family-wise error correction, $pFWE < 0.05$. For the second approach, we will employ ANCOVA across the entire brain to generate hypotheses for future study (whole brain voxel-wise and cluster-level correction, $pFWE < 0.05$). Secondary network analyses will apply a Generalized Psychophysiological Interaction (gPPI) analysis to evaluate task-dependent functional coupling between brain regions of interest. GPPI models the response of target brain regions in terms of the interaction between the physiological response of the seed (i.e., midline dACC and amygdala) and the contrast of interest (e.g., Go/No-Go > Rest and iI > cI). Within the seed, the time-series will be derived from the effects of interest contrast to identify significant activation. The resultant PPI maps will be submitted to second-level random effects analyses with two factors modeled, cannabis condition (4 groups) and time (baseline, post), to assess main and interaction effects (whole-brain corrected). We will also use regression analyses to explore (1) associations among change in neural activity over time and change in PTSD symptom severity, suicidal ideation, psychiatric symptoms, health, pain, quality of life, and other trial outcome variables, and (2) whether brain activity at baseline predicts treatment response, within and across cannabis conditions. *Aim 4:* Brain activation will be extracted from *a priori* regions of interest and submitted to multiple regression to evaluate whether the severity of suicidal thoughts and behaviors among veterans with PTSD is associated with more disrupted brain functioning at the 'baseline' scan, controlling for demographic variables, e.g., age. Follow-up analyses will investigate relationships between clinical variables, e.g., severity of suicide and PTSD symptoms, and K-complex values in regions of interest using partial correlations controlling for demographic variables.

Exploratory Aim: Analytic strategies to integrate PET and fMRI data will consist of region-of-interest based analyses interest. First, we will compute change in neuroinflammation (K-complex) values from baseline to post trial (i.e., ΔNeuroinflammation) in our brain regions of interest, using the PET data.

ΔNeuroinflammation will then be entered as a regressor of interest in second-level fMRI analyses to predict change in brain activation from baseline to post trial (ΔBOLD signal) during the impulse control and emotion regulation tasks, controlling for demographic variables (e.g., age). FMRI will be masked within brain regions of interest, using small-volume family-wise error correction, $pFWE < 0.05$. In addition to our *a priori* region of interest approach, we will also explore independent components analysis (ICA) and other data-driven approaches for fMRI to guide integration with the PET data.

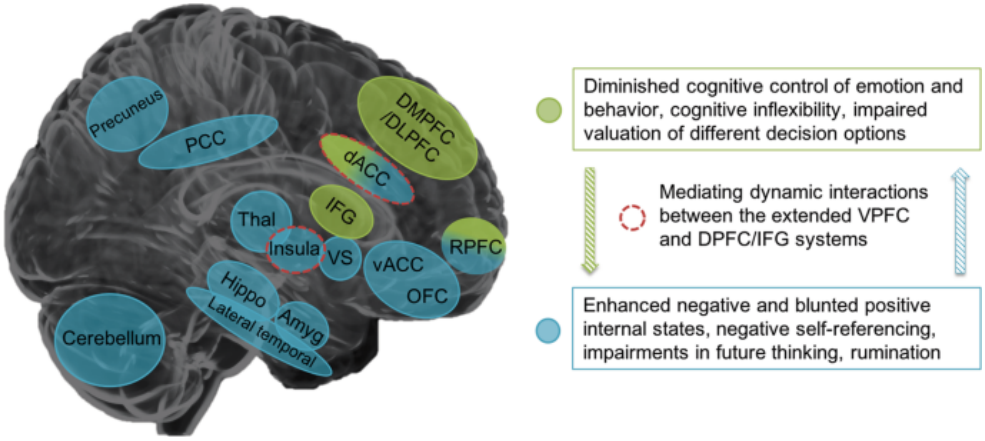


Figure 8: Brain regions of interest that subserve emotion and impulse regulation. Alterations in these brain regions are implicated in suicidal thoughts and behaviors, as well as anxiety, PTSD, and depression. Image from Schmaal et al., 2019, Molecular Psychiatry[77]. Brain regions in blue are implicated in the generation of suicidal ideation by causing excessive negative internal states and self-referential thoughts, blunted positive internal states, and rumination. Brain regions in green exacerbate suicidal thoughts and facilitate suicidal behaviors by diminishing control over impulse regulation and emotion regulation. Activity and communications between these different brain regions may contribute to the transition from suicidal thoughts to behaviors. Abbreviations: DMPFC dorsomedial prefrontal cortex, dACC dorsal anterior cingulate cortex, RPFC rostral prefrontal cortex, OFC orbitofrontal cortex, vACC ventral anterior cingulate cortex, PCC posterior cingulate cortex, Thal thalamus, VS ventral striatum, Hippo hippocampus, Amyg amygdala, DLPFC dorsolateral prefrontal cortex, IFG inferior frontal gyrus, Put putamen, Caud caudate

Future Directions

Results from this supplement could benefit U.S. veterans immediately in terms of demonstrating changes in the *brain*, which often precede or predict subsequent changes in symptomology. This project minimizes startup costs and time by leveraging our currently funded study, and takes advantage of our team's extensive experience and expertise in neuroimaging and conducting human cannabis research to benefit veterans living in the state of Michigan. The proposed supplement will augment the scope of our current project, as it would provide new understanding of *neurobiological mechanisms*, which can be used to develop and deliver more effective, targeted treatments that have greatest potential to improve outcomes for veterans. In addition to having real-world implications for guiding treatments, this project will have substantial impact on the field of cannabis/cannabinoid research, as we will have new understanding of not just *whether*, but *how* cannabis impacts PTSD symptom severity and suicidality. This study is high in impact and innovation, and would be the first study to incorporate *brain imaging* measures into studies of cannabis as a potential therapeutic for PTSD and suicidality. Results have the possibility to transform our understanding of the impact of cannabis on mechanistic targets that are known to undergird PTSD and suicide. In addition to guiding treatment, this study would also serve the dual purpose of providing new understanding of the role of neuroinflammation and aberrant neural activity in the PTSD, depression, and suicidality, and whether these processes can be targeted by

cannabis/cannabinoid treatment. Another focus would be personalized medicine, and the ability to predict, based on neuroimaging markers, who might or might not respond well to specific THC/CBD ratios and doses. Data from the proposed project would provide compelling support for NIH applications proposing any of these future avenues of research.

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END APPLICANT RESPONSE

V-F Current and Prior Experience and Funding Disclosure

Current and prior experience in administering clinical trials is important to the selection process. Each applicant(s) must provide a copy of the organization's most recent audited financial statement and single audit (if applicable). The audited financial statement and single audit must be sent under separate cover.

Proposals submitted by applicant(s) should include:

(1) A description of the organization's experience in conducting the type of work proposed. Include current activities and activities for the previous ten years. Include project results.

(2) If applicant(s) received a similar grant award from the State of Michigan in prior years for the type of project proposed, provide a summary of project accomplishments. Include a plan for addressing and resolving past problems.

(3) Current funding source(s) and the level of funding for the current year and the previous ten years.

BEGIN APPLICANT RESPONSE

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Wayne State University (WSU) has complete and well supported facilities and infrastructure to conduct high-quality large-scale neuroimaging research on potential therapeutic effects on cannabis. WSU is Detroit's public, urban research university. Founded in 1868, WSU offers a range of academic programs through 13 schools and colleges, and has over 26,000 undergraduate, graduate, and graduate professional students. The campus in Midtown Detroit comprises 100 buildings over 200 acres, including the School of Medicine, the Eugene Applebaum College of Pharmacy and Health Sciences, the College of Nursing, and more. The university is home to the >$150M Perinatology Research Branch of the National Institutes of Health, the Karmanos Cancer Center, a National Cancer Institute-designated comprehensive cancer center, a National Institute of Environmental Health Sciences Core Center - Center for Urban Responses to Environmental Stressors (CURES), and a National Institute on Minority Health and Health Disparities Center for Multiple Chronic Diseases Associated with Health Disparities: Prevention, Treatment, and Management. WSU received the highest Carnegie Foundation classification for research activity, and was awarded $320M in research awards, grants, and contracts in 2021. WSU is a member of the University Research Corridor, an alliance of Michigan's three largest

research institutions that includes the University of Michigan and Michigan State University. The goal of the Research Corridor is to stimulate Michigan's economy by leveraging intellectual capital available and draw new businesses that can educate the future work force and develop future, new industries. The WSU School of Medicine is the largest single-campus medical school in the nation and was ranked 68th in research by the U.S. News and World Report. The School of Medicine is located within the Detroit Medical Center (DMC), facilitating patient care and cross-collaboration between physicians and researchers. Moreover, WSU recently launched WayneHealth, a non-profit multi-specialty academic group practice with nearly 400 dedicated physicians offering clinical care in 50 medical specialties. As Michigan's only urban research university, WSU fulfills a unique niche in providing access to a world-class education and research training. WSU's urban mission is to give instruction of the highest quality, to excel in research/creative activity, and to provide service to the professions and disciplines, to the private sectors, and especially to the urban community. WSSU is also Michigan's most diverse campus, with nearly 1,100 students coming from 70 countries outside of the U.S. The Mike Ilitch School of Business was recognized as a top business school for veterans by Military Times. Further, the 2015 $93M WSU Integrative Biosciences (iBio) Center, situated near TechTown, WSU's business incubator, is dedicated to cutting-edge research that aims to eliminate health disparities in the Detroit area. **As detailed below, WSU has a track-record of successfully implementing and executing projects of this size (large-scale federal and state grants) and scope.**

Our research team at WSU is also uniquely positioned to execute advanced neuroimaging studies into the efficacy of cannabis and cannabinoids for the treatment of PTSD and suicidal ideation in US armed forces veterans. Indeed, our research and clinical team included in the Supplement as well as the Parent study have decades of specialized experiencing in clinical research related to cannabis/cannabinoids, PTSD, and neuroimaging of psychiatric illness. Our team also has established working relationships with local veterans associations through our work on the Parent Study, and **a track record of state and federal grant awards, including our ongoing LARA/CRA VMR grant and leading over 24 NIH-funded studies, as outlined below.** In addition, we are one of the only groups in the Midwest with the necessary DEA, FDA, and NIH licenses required to administer cannabis and one of the only groups with specialized neuroimaging training on the application of advanced neuroimaging to study psychiatric illness, including multi-echo fMRI and PET [^{11}C]AMT imaging. We are well prepared to apply these cutting-edge imaging techniques to the study of therapeutic potential of cannabis/cannabinoids in the treatment of PTSD and suicidality in veterans.

In addition to implementing this highly impactful project, WSU is poised to lead the Midwest in cannabis education and research. Our vision, as described above, is to advance our understanding of the therapeutic potential and risks of cannabis/cannabinoids, and deliver safe and effective treatments for veterans and other at-risk groups. We envision leading the region in graduate and undergraduate education (e.g., School of Medicine, College of Pharmacy and Health Sciences, College of Nursing, College of Liberal Arts and Sciences), as well as public education, advocacy, and community engagement. Our team already gives regular lectures on cannabis and cannabinoids to medical students, residents, and fellows, and is well positioned to communicate findings from this project. Our goal is to start with preparing the next generation of medical professionals counsel patients on cannabis and cannabis-based medicine. Our research team also includes trainees at several levels, including clinical psychology practicum students, medical students, undergraduate students, and neuroscience PhD students; therefore, this project provides ample opportunity to advance research on therapeutic potential cannabis and cannabinoids for the treatment of PTSD, suicidality, depression, and other mental disorders.

The research and clinical team for the Supplement and Parent study are housed at the Tolan Park Medical Building, which is located in close proximity to the Detroit Medical Center, and is a 5–10-minute walk from the John D. Dingell Department of Veterans Affairs Medical Center and the WSU MR and PET scanning facilities. The Tolan Park Medical Building houses the Department of Psychiatry and Behavioral Neuroscience's Substance Abuse Research Division, the Brain Imaging Research Division, and the Detroit Trauma Project. The proposed research team is embedded within these units. The Brain Imaging Research Division conducts multi-modal neuroimaging investigations to study the

pathophysiology and treatment of psychiatric and substance use disorders. The Detroit Trauma Project, directed by Professor and the David and Patricia Barron Chair for PTSD Neurobiology at WSU, Dr. Jovanovic (Co-I on the Parent Study), is a group focused on the interaction of traumatic experiences, neurophysiology, neuroendocrinology, and genetics in anxiety, PTSD, and other stress-related disorders in adults and children. The Substance Abuse Research Division conducts several studies related to pharmacological, environmental, and individual difference determinants of drug seeking/use, behavioral economic approaches to substance abuse and policy, novel medication and behavioral therapy trials in substance-using populations (e.g. HIV+, nicotine and opioid dependence, pregnant women, co-occurring psychiatric problems), screening and brief intervention using technological advances, epidemiologic studies in special populations, and health services research. Several experimental chambers are equipped with a specialized ventilation system to allow for smoked cannabis administration. The proposed study will take place in the **WSU Human Pharmacology Laboratory (HPL) and the Warrior Care Center**. The HPL currently occupies half of the 2nd floor at Tolan Park, covering about 4,500 sq. ft. Dr. Greenwald, who is Director of the Division and Laboratory and Co-I on the Parent Study, was directly involved in designing this modern space with the architects, ensuring appropriate security (WSU Police and DEA), and working with WSU Information Technology personnel to ensure computer capabilities, Ethernet connectivity, password-protected server access, etc. The HPL has 2 screening rooms, 5 private testing rooms (equipped with specialized HVAC negative-pressure system to allow smoking on-site), and a central monitoring room with computers and audio/visual (with digital-recording) equipment. Research assistants monitor participants throughout sessions. Test rooms are equipped with Macintosh computers coupled to the monitoring room. Other equipment includes physiological monitors, automated external defibrillator and a crash cart. There is a physical examination room with ECG, exam table, weighing scale, phlebotomy, and centrifuge. There is ample office and storage space for research support staff (e.g., receptionist, research/clinical assistants). Students occupy workstations in this space. There is also a confidential file locked storage room, locked supplies storage room, copier/mail room, common day (break) room with vending machine, and toilets. A locked DEA-compliant room located in the laboratory is used for drug storage (locked safe, freezer/refrigerator, -20°C freezer for storing biological samples) and handling/preparation. The Warrior Care Center is a new space designated to conduct the Parent Study, which is housed first floor of the Tolan Park Medical Building, providing an easily accessible, comfortable space for participant testing and to accommodate family members who accompany veterans to sessions. The Warrior Care Center has a welcoming and private reception area with comfortable seating, access to snacks and beverages, and WiFi access. There is also a small kitchen, conference room, and two private interview rooms for testing.

(1) Current and past State of Michigan funding for INVESTIGATORS on the Current Supplement Proposal

Leslie H. Lundahl, PhD

Active State of Michigan Support:

Veteran Marijuana Research Grant Program, Cannabis Regulatory Agency, State of Michigan Leslie Lundahl (Lead PI)
Title: Wayne State Warriors Marijuana Clinical Research Program: Investigating the Impact of Cannabinoids on Veterans' Behavioral Health
Purpose: To investigate the effects of varying doses of THC and CBD on depression, anxiety, and PTSD with the goal of reducing suicide rates and improving behavioral health in US Military Veterans.
Role in Project: Lead PI
09/01/20 – 8/31/22

Total direct costs = $6,259,037

We received funding from the VMR/CRA in August, 2021 for our project, entitled "Wayne State Warriors Marijuana Clinical Research Program: Investigating the Impact of Cannabinoids on Veterans' Behavioral Health". In this randomized, controlled clinical trial we are recruiting veterans with PTSD who report using cannabis. **We are conducting two studies that are complementary and linked via their aims and methodology**. In **Study 1**, 200 veterans are randomized into one of four different THC:CBD dose conditions (High THC:High CBD; High THC: Low CBD; Low THC:High CBD, and Low THC:Low CBD) for a 12-week treatment phase. In **Study 2**, 150 veterans are assigned into *either* a naturalistic group (n=75) and are followed as they continue to use cannabis as they normally do (observation only), *or* into a "THC reduction group" (n=75) in which veterans are asked to switch from their typical cannabis product to using a lower THC/higher CBD product; adherence to this switch is incentivized using contingency management. **Both studies** involve assessments bi-weekly throughout a 12-week treatment phase, and at 3- (post-treatment), 6-, 9, and 12-months post-baseline. Study 1 also includes additional weekly assessments. **Primary outcomes** include clinical assessments of PTSD symptom severity, mood and anxiety symptoms, and suicidality. **Secondary measures** include (1) neurocognitive function; (2) overall health, sleep quality, pain, healthcare utilization, and quality of life; (3) individual differences in fear learning and extinction associated with PTSD symptom severity; (4) saliva for DNA analysis to examine genetic and epigenetic markers associated with the endocannabinoid system; and, (5) urine, blood, and saliva samples to quantify levels of endocannabinoids and their metabolites (e.g., anandamide [AEA] and 2-AG), as well as THC and CBD and their metabolites, to examine whether these levels vary as a function of THC:CBD dose mixtures and differentially affect outcomes. Data will be analyzed to determine which THC and CBD levels might be associated with the outcome measures. These data will be used to (1) develop a predictive algorithm that will help determine personalized profiles of patients who may be at increased risk for suicide; and, (2) develop a profile of who might most benefit from cannabinoid therapeutics.

Summary of Accomplishments/Progress

Since receiving this award we have been building the infrastructure needed to support the logistical operation of study related elements including participant recruitment and study visit mechanics. A significant amount of effort was dedicated to anticipating potential obstacles and identifying solutions to these obstacles. For example, cannabis products are not approved for use within the Department of Veterans Affairs (VA) at present which requires the study team to recruit Veteran participants from Detroit-area community-based organizations. We established contact with 15 Veterans groups including the Veterans of America, Michigan Veterans Affairs Agency, Veterans of Foreign Wars (VFWs) and several others to create a recruitment network capable of reaching Veterans either for whom cannabis is an existing treatment strategy or might be an attractive intervention for them to alleviate their symptoms of PTSD, depression, and suicidality. Recruitment documents including study flyers and informational brochures have been created, approved by our IRB and printed for advertising and distribution to these and other organizations. Social media and other advertising platforms to supplement recruitment have also been identified. We created a website (Warriorcare.net) which is dedicated to the research program where veterans and their families can get information about the studies, complete initial screening for eligibility, access other resources, and contact us. The website is near completion and should be up and running by May 31, 2022.

We obtained Departmental Review Board and University Institutional Review Board (IRB) approval for both studies. The clinical staff has completed training on how to administer all of the study-related measures and conduct the diagnostic interviews. We have created online versions (Qualtrics) of all questionnaires and measures so veterans can complete them online, and we have set up a clinical trial tracking system for both studies.

Our safety plan is finalized and our Data Safety Monitoring Board (DSMB) has been established.

We have identified a cannabis administration device that will address concerns about potential diversion or use of more than the daily allotted amount (Study 1).

Protocol details relating to secondary outcomes have been finalized and include a system for endocannabinoid collection, processing, storage, and analysis, and coordination of the genotyping analyses at the WSU Genome Sciences Core (for genotype-phenotype associations).

We started recruitment for Study 2 in mid-May. We have scheduled several "meet and greets" with veterans organizations to occur in June and July, where we will present study information and display and distribute brochures to recruit participants. We plan to start recruitment for Study 1 at the end of June, 2022.

Summary of Obstacles/Mitigation Plans
NIDA Drug Supply Program, which has supplied cannabis flower for Dr. Lundahl's cannabis studies over the past 20 years, is not able to supply the THC:CBD concentrations in the quantities we need for the trial. Thus, we reached out to the other three federally-registered DEA Schedule I growers and found that we will likely not be able to obtain all four THC:CBD concentrations in the quantities needed from one grower and will have to work with more than one, which requires the submission of additional FDA IND applications. However, we are highly experienced with both FDA and DEA regulatory processes and do not anticipate any difficulties obtaining these additional INDs or filing the protocols with the DEA. We also are in discussions with a Michigan grower who is able to supply exactly what we need, and is interested in pursuing the certifications needed to become a federally-compliant research supplier. We have set up a "pre-IND" meeting with the grower's chemists and regulatory staff at the FDA, which is scheduled in June. While we recognize this is likely a lengthy process with no guarantee of success, we anticipate this clinical trial will take several years to complete and we may be able to use this MI grower toward the later part of the study.

THE CURRENT PROPOSAL IS FOR A SUPPLEMENT TO OUR 2021 VMR GRANT

David Ledgerwood, PhD

Active State of Michigan Support:

Veteran Marijuana Research Grant Program, Cannabis Regulatory Agency, State of Michigan Leslie Lundahl (Lead PI)
Title: Wayne State Warriors Marijuana Clinical Research Program: Investigating the Impact of Cannabinoids on Veterans' Behavioral Health

Purpose: To investigate the effects of varying doses of THC and CBD on depression, anxiety, and PTSD with the goal of reducing suicide rates and improving behavioral health in US Military Veterans.
Role in Project: Co-PI
09/01/20 – 8/31/22
Total direct costs = $6,259,037

THE CURRENT PROPOSAL IS FOR A SUPPLEMENT TO OUR 2021 VMR GRANT

Completed State of Michigan Support:

Dani Meier (PI), Mid-State Health Network 10/2018 – 9/2019
Title: Michigan Gambling Disorder Prevention Project – FY19 Proposal Mid-State Health Network
Study Goals: To examine the prevalence of gambling disorder among youth and among substance abuse patients in Michigan.
Amount: Direct: $33,704

State of Michigan Department of Health, Bureau of Substance Abuse and Addiction Services David Ledgerwood (PI) 10/2012 – 9/2013
Title: Evaluation of the Clinical Need for Residential Treatment Services for Problem Gambling in Michigan
Study Goals: To evaluate the clinical need for residential treatment services for problem gambling in the State of Michigan
Role in project: PI

COMPLETED PROJECTS WERE UNRELATED TO THE CURRENT PROPOSAL.

Hilary A. Marusak, PhD

Active State of Michigan Support:

Veteran Marijuana Research Grant Program, Cannabis Regulatory Agency, State of Michigan Leslie Lundahl (Lead PI)
Title: Wayne State Warriors Marijuana Clinical Research Program: Investigating the Impact of Cannabinoids on Veterans' Behavioral Health
Purpose: To investigate the effects of varying doses of THC and CBD on depression, anxiety, and PTSD with the goal of reducing suicide rates and improving behavioral health in US Military Veterans.
Role in Project: Co-I
09/01/20 – 8/31/22
Total direct costs = $6,259,037

THE CURRENT PROPOSAL IS FOR A SUPPLEMENT TO OUR 2021 VMR GRANT

(2) Current and past funding for INVESTIGATORS on the Current Proposal

Hilary A. Marusak, PhD

Active Research Support:

K01 NIH MH119241 Marusak (PI) 07/01/2019-06/30/2024
Title: Endocannabinoids and the development of extinction recall neural circuitry in adolescents
This study characterizes age-related changes in extinction recall, frontolimbic activity, and endocannabinoid signaling across adolescence (ages 10-17).
Amount: $871,180 (total costs)
Role in project: Principal Investigator

R01 NIH MH111682 Jovanovic (PI) 09/23/2016-6/30/2022 NCE
Title: Impact of Trauma Exposure on Critical Periods in Brain Development and Fear Processing in Children
This longitudinal study will examine the timing and duration of trauma exposure in children ages 9-11.
Role in project: Co-Investigator
Amount: $389,424 (R01 MH111682-01); $110,599 (Supplement: R01 MH111682_03S1)

R01 NIH DE031117 Seligman and Geers (Co-PIs) 07/01/2021-06/30/2024
Title: Mechanisms of latent inhibition as a proactive interference for preventing dental anxiety.
The purpose of this project is to identify the mechanism(s) underlying the latent inhibition of dental fear, allowing for more precise engagement of these target(s).
Role in project: Site Lead and Study Co-Investigator
Amount: $76,242 (WSU Subcontract)

The Children's Foundation, Pediatric Research Grant
R1-2022-72
Marusak and Luat (MPI)
Effects of cannabidiol on anxiety and behavioral problems among children with epilepsy (year 2)
01/01/2022-12/31/2022
This prospective observational study will track seizure frequency, anxiety symptoms, and behavioral problems among pediatric epilepsy patients who are newly started on CBD (Epidiolex).
Role: Co-Principal Investigator
Amount: $65,000 (total costs)
WSU Office of the Provost Social & Behavioral Determinants of Health Research Stimulus Program Marusak and Barcelona (Co-PIs) 07/01/2021-06/30/2022
Title: Behind the "runner's high": Endocannabinoid levels as a potential mediator of the beneficial effects of exercise on cognitive performance and mental health in youth
This pilot study tests the impact of acute exercise on circulating endocannabinoid concentrations, anxiety, mood, and cognitive performance in children and adolescents.
Role in project: Co-Principal Investigator
Amount: $20,000

WSU P30ES020957 Center for Urban Responses to Environmental Stressors (CURES), Pilot Grant
Marusak (PI) 10/01/2021-03/31/2023
Title: Effects of urban air pollution on neurodevelopmental markers of anxiety risk during adolescence

This study examines the impact of particulate matter air pollution on fear extinction, frontolimbic brain circuitry, and anxiety symptoms in adolescents
Role: Principal Investigator
Amount: $65,000 (total costs)

Richard Barber Interdisciplinary Research Grant
Marusak and Barcelona (MPI) 05/01/2022-08/01/2022
Title: Mindfulness meditation: A brain booster in youth
This pilot study evaluates the impact of a brief meditation session on endocannabinoid concentrations, anxiety, mood, and cognitive performance in children and adolescents.
Amount: $20,000 (total costs)

Wayne State University P50 Center MD017351 ACHIEVE GreatER Pilot Grant
Hicks (PI) 3/1/2022-2/28/2024
Screening for social risks and health: The role of stress reduction
This pilot study will evaluate whether a community resource navigator (vs. resource pamphlet) can reduce social determinants of health and perceived stress in African Americans at high risk of cardiovascular disease.
Role: Co-Investigator
Amount: $40,000 (total costs)

Completed Research Support:

The Children's Foundation Pediatric Research Grant R1-2021-31 Marusak (PI)
02/08/2021-12/31/2021
Title: Effects of cannabidiol on anxiety and behavioral problems among children with epilepsy
This prospective observational study will track seizure frequency, anxiety symptoms, and behavioral problems among pediatric epilepsy patients who are newly started on CBD (Epidiolex).
Role in project: Co-Principal Investigator
Amount: $57,575 (total costs)

American Public Health Association NVDRS New Investigator Award Marusak (PI)
4/23/2021-4/30/2022
Title: Youth firearm-related deaths in the United States
Role in project: Principal Investigator
Amount: $6,500

WSU Dept. of Psychiatry and Behavioral Neurosciences New Investigator Grant
Marusak (PI) 10/1/2020-8/31/2021
Title: Impact of adolescent cannabis use on endocannabinoid signaling and emotion regulation neural circuitry
Role in project: Principal Investigator
Amount: $25,000

Kids Kicking Cancer Marusak (Local PI) 11/01/2019-10/31/2020
Title: The Heroes Circle – Children Healing Children
This project examines the impact of a novel martial arts-based school curriculum (vs. a standard control socioemotional development curriculum) on stress, anxiety, and behavioral problems in elementary school children (Year 2).
Role in project: Local Principal Investigator

Amount: $68,819 (WSU subcontract)

State of Michigan Opioid Management Project Award to Kids Kicking Cancer Goldberg (PI), Greenwald (local PI) 08/01/2018-07/31/2019
Title: The Heroes Circle Opioid Project 2018
This project evaluates a novel martial arts-based virtual reality intervention for individuals with opioid use disorder who are on methadone maintenance treatment.
Role in project: Co-Investigator
Amount: $90,836 (WSU subcontract)

Kids Kicking Cancer Marusak (local PI) 07/01/2018-12/31/2019
Title: The Heroes Circle – Children Healing Children
This project examines the impact of a novel martial arts-based school curriculum (vs. a standard control socioemotional development curriculum) on stress, anxiety, and behavioral problems in elementary school children (Year 1).
Role in project: Local Principal Investigator
Amount: $33,325 (WSU subcontract)

American Cancer Society Postdoctoral Fellowship PF-16-057-01-PCSM Marusak (PI) 07/01/2016-06/30/2019
Title: Neurobehavioral correlates of learning and memory in child cancer survivors
This project compares brain and behavioral responses during implicit and explicit learning and memory paradigms in child cancer survivors vs. controls.
Role in project: Principal Investigator
Amount: $163,500

St. Baldrick's Foundation Supportive Care Research Grant 523497 Marusak (PI) 07/01/2017-02/28/2019
Title: Martial arts therapy and brain mechanisms for cancer-related pain
This study examines the impact of a novel martial arts-based intervention on pain, quality of life, and neural activity in the pain neuromatrix in children with cancer.
Role in project: Principal Investigator
Amount: $45,015.93

Barbara Ann Karmanos Cancer Institute, Pilot Project Grant from the American Cancer Society 14-238-04-IRG Rabinak (PI) 09/01/2016-08/31/2017
Title: Understanding emotional brain network organization in survivors of childhood cancer
This project examines emotion processing neural circuitry in pediatric cancer survivors, and correlates with anxiety and posttraumatic stress symptoms.
Role in project: Co-Investigator
Amount: $30,000

Eric Woodcock, PhD

Active Research Support:

R00 DA048125 Woodcock (PI) 05/01/2021-04/30/2024
Title: Multimodal Investigation of the Neuroimmune System in Opioid Use Disorder
This study is evaluating whether patients with opioid use disorder exhibit elevated levels of neuroimmune system markers using MRS *myo*-inositol and PET [^{11}C]AMT imaging

Amount: $746,994 (total costs)
Role in project: Principal Investigator

R00 DA048125-04S1 Woodcock (PI) 05/01/2022-04/30/2023
Title: Supplement to: Multimodal Investigation of the Neuroimmune System in Opioid Use Disorder
Administrative supplement to provide additional research support for the execution of R00 DA048125
Amount: $76,310 (total costs)
Role in project: Principal Investigator

R21 DA047621 Cosgrove/Malison (MPIs) 02/01/2019-01/31/2023 (NCE)
Title: Neuroimmune disruption in opioid use disorder
This study is evaluating whether patients with opioid use disorder exhibit elevated levels of neuroimmune system markers using PET [^{11}C]PBR28 imaging
Amount: $460,625 (total costs)
Role in project: Collaborating Investigator

Completed Research Support:

K99 DA048125 Woodcock (PI) 05/15/2019-04/30/2021
Title: Multimodal Investigation of the Neuroimmune System in Opioid Use Disorder
This study evaluated whether a single dose of morphine evaluated neuroimmune system markers in healthy adult volunteers
Amount: $291,025 (total costs)
Role in project: Principal Investigator

K99 DA048125-02S1 Woodcock (PI) 05/01/2020-04/30/2021
Title: Supplement to: Multimodal Investigation of the Neuroimmune System in Opioid Use Disorder
Administrative supplement to provide additional research support for the execution of K99 DA048125
Amount: $42,519 (total costs)
Role in project: Principal Investigator

T32 DA022975 Sinha/Mason (MPIs) 07/01/2017-05/15/2019
Title: Neuroimaging Sciences Training Program
This training grant facilitates exemplary postdoctoral training in advanced neuroimaging applications to study substance use disorders
Amount: $257,718 (total costs)
Role in project: Postdoctoral Fellow

F31 DA040369 Woodcock (PI) 04/11/2016-07/30/2017
Title: Neuropharmacological investigation of frontostriatal network function and nicotine-seeking behavior in current smokers
This study investigated the neurochemical and neural network mechanisms that might mediate acute stress-induced nicotine-seeking behavior in out-of-treatment cigarette smokers
Amount: $60,600 (total costs)
Role in project: Principal Investigator

Young Investigator Award Woodcock (PI) 08/01/2015-09/30/2016

Title: Neuropharmacological investigation of frontostriatal network function and nicotine-seeking behavior in current smokers
This study investigated the neurochemical and neural network mechanisms that might mediate acute stress-induced nicotine-seeking behavior in out-of-treatment cigarette smokers
Amount: $25,000 (total costs)
Role in project: Principal Investigator

Leslie H. Lundahl, PhD

Active Research Support:

R21 DA047662
Role: Principal Investigator
Title: Human Laboratory Model to Screen Drugs with Opioid Analgesic-Sparing Effects: Cannabidiol/Morphine Combinations.
Purpose: The objective of this study is to develop a rigorous human laboratory paradigm to evaluate potential opioid-sparing compounds that could lead to medications that reduce reliance on chronic use of high dose opioid medications for safer and more effective pain relief.
Source: NIH/NIDA
03/01/19– 02/28/23
Total Direct Costs: $275,000

R21 DA040150
Role: Principal Investigator
Title: Effects of Stress- and Drug Cue-Exposure on Craving and Marijuana Seeking Behavior in Regular Cannabis Users.
Purpose: To understand cue- and stress-induced cannabis abuse to effectively target these risk factors for intervention, we propose to investigate subjective, physiologic, and endocrine responses to a pharmacologic stressor combined with drug-related cues in chronic cannabis users, and examine additive effects on marijuana craving and seeking.
Source: NIH/NIDA
5/01/17 – 05/31/22 (NCE)
Total Direct Costs: $275,000

R01 DA044946-02
Role: Co-Investigator (PI: Mark Greenwald, PhD)
Title: Opioid/Benzodiazepine Polydrug Abuse: Integrating Research on Mechanisms, Treatment and Policies.
Purpose: (1) Determine from behavioral health treatment records prevalence of patients' presenting BZD/opioid PSU vs. BZD or opioid use alone, and relationships between drug use and psychiatric/physical comorbidities, medications, demographics, and treatment outcomes; (2) Among patients, characterize substance use and deficits in affective, neurocognitive, behavioral, and health function; (3) Determine whether simultaneous vs. concurrent BZD/opioid users differ in affective phenotypes, neurocognitive and behavioral measures.
Source: NIH/NIDA
Proposed funding period: 09/01/18 –08/31/23
Total direct costs = $1,684,808

Completed Research Support:

R01 DA015462-09A1
Role: Co-Investigator (PI: Mark Greenwald, PhD)
Title: Biobehavioral Studies of Opioid Seeking: Effects of Buprenorphine/Naloxone Dose on Experimental Stress Reactivity and Opioid Abstinence.
Purpose: In this 3rd funding cycle, determine in volunteers with opioid use disorder whether: (1) short-term maintenance on buprenorphine/naloxone dose-dependently attenuates biobehavioral responding to an experimental pharmacological stressor (yohimbine/hydrocortisone), and (2) stressor reactivity predicts opioid abstinence during and up to 3 months after outpatient buprenorphine/naloxone dose tapering.
Source: NIH/NIDA
9/30/16 – 7/31/20 (NCE)
Total Direct Costs: $1,500,491

R21 DA040770
Role: Principal Investigator
Title: Marijuana Cue-Reactivity and Seeking Behavior in Regular Cannabis Users: Pilot Test of Glutamatergic Modulation.
Purpose: Determine whether: (1) marijuana cues increase marijuana puff-seeking behavior, and whether craving moderates this effect, (2) N-acetylcysteine, relative to placebo, attenuates marijuana cue-reactivity or drug seeking.
Source: NIH/NIDA
08/15/16 – 07/31/19 (NCE)
Total Direct Costs: $247,000

R01 DA034537
Role: Co-investigator (PI: David Ledgerwood, PhD)
Title: Behavioral Treatments for Smoking Cessation in HIV.
Purpose: This clinical trial will test the efficacy of prize-based contingency management for promoting smoking reduction and cessation, using urinary cotinine and expired carbon monoxide as behavioral targets.
Source: NIH/NIDA
9/1/13-8/31/17 (NCE)
Total Direct Costs: $1,268,634

R01 DA032678
Role: Co-investigator (PI: Mark Greenwald, PhD)
Title: Behavioral Economic Analysis of Medical Marijuana Use in HIV+ Patients.
Purpose: Remediate knowledge and policy gaps related to medical marijuana use by studying subgroups of marijuana-using HIV/AIDS patients (certified medical users, non-certified therapeutic users and recreational users) in Michigan's largest HIV primary care clinic with a prospective mixed-method approach that uses behavioral-economic simulations of marijuana demand, longitudinal health monitoring, and probability survey procedures.
Source: NIH/NIDA
9/15/11– 6/30/16
Total Direct Costs: $1,019,851

2 R01 DA015462
Role: Co-investigator (PI: Mark Greenwald, PhD)
Title: Biobehavioral Studies of Opioid Drug-Seeking Behavior.

Purpose: Determine the neurochemical mechanisms of stress-potentiated opioid-seeking and biobehavioral responses.
Source: NIH/NIDA
09/30/11– 11/30/15
Total Direct Costs: $751,403

R01 DA026761
Role: Principal Investigator
Title: Smoked Marijuana Discrimination and Marijuana Choice in Humans: A Laboratory Model. Purpose: To develop and test a laboratory model of smoked marijuana discrimination and choice to self-administer marijuana for testing medications for treatment of cannabis use disorders.
Source: NIH/NIDA
7/2009 – 6/30/12
Total Direct Costs: $500,000

1P30 NR010676-01
Role: Co-investigator (PI: Shirley Moore, PhD (School of Nursing, Case Western Reserve University)
Title: Center of Excellence to Build the Science of Self-Management: A System Approach
Project: Parenting of Young Children By Women in Substance Abuse Treatment (Project PI: Linda Lewin, Wayne State University School of Nursing)
Source: NIH/National Institute of Nursing Research
1/01/10– 9/30/12
Total Direct Costs: $450,648 (for 2012)

R01 DA026861
Role: Co-investigator (PI: Mark Greenwald, PhD)
Title: Human Laboratory Model of Cocaine Treatment: Behavioral Economic Analysis.
Purpose: Determine the extent to which the magnitude and probability of non-drug positive reinforcement attenuates cocaine demand elasticity.
Source: NIH/NIDA
8/01/09 – 10/31/12
Total Direct Costs: $890,000

David Ledgerwood, PhD

Active Research Support:

R61HL155793-01 NIH/NHLBI P Cunningham (MUSC, MPI), Sylvie Naar (FSU, MPI) 4/30/2021-4/30/2023
Title: Clinical Trial of the Fit Families Multicomponent Obesity Intervention for African American American Adolescents and Their Caregivers: Next Step from the ORBIT Initiative (Co-Investigator)
Study Goals: To develop and test a behavioral intervention designed to increase physical activity,
diet monitoring and weight loss among teens and their primary caregivers.
Role in project: Co-PI
Amount: Direct $535,121 – all sites

R01CA243910 NIH/NCI E.J. Edelman (MPI), S. Bernstein (Yale; MPI) 9/18/2019-8/30/2024

Title: A SMART Approach to Treating Tobacco Use Disorder in Persons Living with HIV
Study Goals: To use a tailored smart design study to examine the efficacy of combined medication (NRT, varenicline) and behavioral treatment (contingency management) for smoking cessation among people living with HIV.
Role in project: Consultant

R01MD011322 NIH/National Institute on Drug Abuse P.I.(Co): D. Ledgerwood (Co-PI) P. Cunningham (Co-PI) 8/2016 – 9/2021
Title: Behavioral Incentives to Increase Caregiver Engagement in Juvenile Drug Court
Study Goals: To assess the efficacy of adolescent and caregiver contingency management
treatments for enhancing adherence to Juvenile Drug Court and substance
Role in project: Co-PI
Amount: Direct: $149,022 – Wayne State University amount

Completed Research Support:

MGRP-LG-15-13 Manitoba Gambling Research D. Ledgerwood (MPI), L. Najavits (Boston U; MPI)
12/2015 – 9/2021
Title: Online Coping Skills Counseling for Problem Gambling and Trauma
Role in project: MPI
Amount: Direct: $449,999 CDN

R21 CA222939-01A1 C. Kopetz (PI)
Title: Intermittent and Daily Smoking: A Comparison Between Mechanisms
Study Goals: To investigate the role of social sues compared to smoking cues on smoking-relevant outcomes in intermittent and daily smokers.
Role in project: Co-PI
Amount: Direct: $275,000

R01DA034537-01A1 NIH/National Institute on Drug Abuse David Ledgerwood (PI)
8/2013 –
7/2019
Title: Behavioral Treatments for Smoking Cessation in HIV
Study Goals: To assess the efficacy of contingency management treatments for smoking cessation in individuals receiving treatment for HIV. We also propose evaluating a stepped care model to provide appropriate levels of care based on initial treatment response.
Role in project: PI
Amount: Direct: $1,109,615

Dani Meier (PI), Mid-State Health Network 10/2018 – 9/2019
Title: Michigan Gambling Disorder Prevention Project – FY19 Proposal Mid-State Health Network
Study Goals: To examine the prevalence of gambling disorder among youth and among substance abuse patients in Michigan.
Amount: Direct: $33,704

Level IV (Approved) Ontario Problem Gambling Research Centre David Ledgerwood (PI)

10/2011 – 9/2016
Title: Effectiveness of Cognitive-Motivational Behaviour Therapy in Community Treatment
Study Goals: To examine the effectiveness of a combined CBT/MI treatment approach for
pathological gambling administered by community-based therapists.
Role in project: PI
Amount: Total Direct: $508,109

U01HL097889 NIH/NHLBI Sylvie Naar-King (PI) 9/2009 – 6/2014
Title: Intervention Procedures for Adherence to Weight Loss Recommendations in Black
Adolescents
Study Goals: To develop interventions to address obesity in adolescents, and to examine the
efficacy of these interventions.
Role in project: Co-PI (20% in Year 1; 5% subsequent years; Project Lead for Pilot study of
Contingency Management for weight loss in obese adolescents)

State of Michigan Department of Health, Bureau of Substance Abuse and Addiction Services
David Ledgerwood (PI) 10/2012 – 9/2013
Title: Evaluation of the Clinical Need for Residential Treatment Services for Problem Gambling in Michigan
Study Goals: To evaluate the clinical need for residential treatment services for problem gambling in the State of Michigan
Role in project: PI
Amount: Total Direct: $43,318

R01 DA026861 NIH/NIDA Mark Greenwald (PI) 7/2009 – 6/2012
Title: Human Laboratory Model of Cocaine Treatment: Behavioral Economic Analysis
Study Goals: Determine the extent to which non-drug alternatives (positive reinforcement and
punishment), combined with novel medications, attenuate cocaine demand elasticity.
Role in project: Co-PI (10%)

R01 DA026761-01 NIH/NIDA Leslie Lundahl (PI) 7/2009 – 6/2012
Title: Smoked Marijuana Discrimination and Marijuana Choice in Humans: A Laboratory Model
Study Goals: To develop and test a laboratory model of smoked marijuana discrimination and
choice to self-administer marijuana for testing medications for treatment of cannabis use disorders.
Role in project: Co- PI (10%)

Christine A. Rabinak, PhD

Active Research Support:

K23 MH125315

Role: Co-Mentor (PI: Reilly Kayser, MD)
Title: *"**Multimodal Assessment of Cannabinoid Target Engagement in Adults with Obsessive-Compulsive Disorder**."* Purpose: The purpose of this research study is to test how a medication called nabilone (Cesamet) affects neurocognitive processes involved in obsessive-compulsive disorder (OCD), including threat response, processing of fear signals, and habitual behavior.
Source: NIH/NIMH
07/01/21– 06/30/26
Total Direct Costs: $795,170

Role: Co-Investigator (PI: Hilary Marusak, PhD)
Title: *"**Effects of Urban Air Pollution on Neurodevelopmental Markers of Anxiety and Risk during Adolescence**."* Purpose: To test the hypothesis that adolescents with higher (vs. lower) recent PM2.5 exposure exhibit poor fear regulation and lower frontolimbic activation, which will in turn, be associated with higher anxiety.
Source: WSU CURES Pilot Project Program
10/01/21– 03/31/23
Total Direct Costs: $65,000

F30 DA052118
Role: Co-Mentor (PI: Tabitha Moses; Primary Mentor: Mark Greenwald, PhD)
Title: *"**Neuromodulation of Stress-Induced Dysfunction and Drug-Seeking in Opioid Use Disorder: Comparison of Fronto-Cortical Targets**."* Purpose: This project will explore whether repetitive transcranial magnetic stimulation (rTMS) might improve treatment outcomes for people with opioid use disorder entering methadone treatment.
Source: NIH/NIDA
05/01/21– 04/30/25
Total Direct Costs: $250,395

R01 DE031117
Role: Co-Investigator (MPI: Laura Seligman, PhD & Andrew Geers, PhD)
Title: *"**Identifying the Mechanism of Latent Inhibition to Prevent Dental Fear.**"*
Purpose: Identify the mechanism(s) underlying the latent inhibition of dental fear, allowing for more precise engagement of these target(s), and to examine whether individual differences related to ethnicity that could help account for the disparities observed in oral health and dental fear, are related to the engagement of these targets.
Source: NIH/NIDCR
07/01/21– 06/30/24
Total Direct Costs: $1,165,137

R01 MH122867
Role: Co-Investigator (PI: Ann Rasmusson, MD)
Title: *"**Facilitation of Extinction Retention and Reconsolidation Blockade by IV Allopregnanolone PTSD**."* Purpose: This study tests whether a single intravenous (IV) dose of allopregnanolone (Allo) compared to placebo (which is non-active): promotes consolidation of extinction learning (sub-study 1) or blocks reconsolidation physiological responses triggered by aversive memories (sub-study 2). The study also tests whether Allo compared to placebo affects retention of non-aversive memories.
Source: NIH/NIMH
04/01/20– 03/31/25
Total Direct Costs: $882,879

F31 MH124279
Role: Primary Mentor (PI: Nicole Zabik)
Title: *"**Neural and Behavioral Mechanisms of Avoidance Behavior and its Impact on Fear Extinction in Adults with PTSD**."* Purpose: This study will test how avoidance impacts extinction of fear and its underlying brain mechanisms in an adult population.
Source: NIH/NIMH
09/01/20– 08/31/23
Total Direct Costs: $155,709

K01 MH11924
Role: Primary Mentor (PI: Hilary Marusak, PhD)
Title: *"**Endocannabinoid Signaling and the Development of Fear Extinction Recall during Adolescence**."* Purpose: The goal of this project is to evaluate in adolescents the novel hypotheses that: (1) fear extinction recall ability increases across adolescence, (2) age-related increases in extinction recall correspond with increased activation of hippocampus (HPC)-ventromedial prefrontal cortex (vmPFC) circuitry, and (3) higher blood levels of the eCB anandamide (AEA) correspond with better extinction recall and/or higher activation within HPC-vmPFC circuitry among adolescents.
Source: NIH/NIMH
04/01/19– 03/31/24
Total Direct Costs: $806,651

1IKRX002686
Role: Co-Mentor (PI: Veronica Chui, PhD; Primary Mentor: Alana Conti, PhD)
Title: *"**Comorbidity of PTSD and Alcohol Dependence: Endocannabinoid Regulation**."* Purpose: 1) Evaluate the effects of traumatic stress and ethanol dependence on ethanol consumption and anxiety behavior as a function of ethanol withdrawal duration. 2) Examine changes in CB signaling associated with ethanol-induced withdrawal behaviors as a factor of withdrawal duration. 3) Evaluate the efficacy of a selective CB1 agonist, methanandamide, to block stress-induced ethanol dependence and withdrawal outcomes.
Source: Veteran Affairs Career Development Program
06/01/18– 05/31/23
Total Direct Costs: $721,346

R61/33 MH11193
Role: Primary Investigator
Title: *"**Effects of THC on Retention of Memory for Fear Extinction Learning in PTSD**."*Purpose: The goal of the current proposal is to investigate the cannabinoid system as a potential pharmacological target for improving the learning that goes on in therapy and perhaps increasing efficacy and durability of exposure therapy in treating PTSD (e.g. shortening treatment while strengthening and prolonging gains).
Source: NIH/NIMH
02/24/17– 02/23/23
Total Direct Costs: $2,629,881

Completed Research Support:

New Investigator Grant Program
Role: Co-Investigator (PI: Hilary Marusak, PhD)
Title: *"**Impact of Adolescent Cannabis Use on Endocannabinoid Signaling and Emotion Regulation Neural Circuitry**."* Purpose: The pilot project tested the novel hypotheses that

adolescent cannabis use is associated with increased risk of anxiety and SUDs via reduced activation and/or coupling within emotion regulation neural circuitry and low signaling of the eCB AEA.
Source: WSU Department of Psychiatry & Behavioral Neurosciences
10/01/20– 08/31/21
Total Direct Costs: $25,000

NARSAD Young Investigator Grant
Role: Principal Investigator
Title: *"**Effects of FAAH Genotype on Fear-Related Brain Activation during Fear Extinction**."* Purpose: The primary objective is to determine whether FAAH genotype differences are evident at behavioral and neural levels during recall of extinction learning.
Source: Brain & Behavior Research Foundation
01/15/17– 07/14/19 [NCE]
Total Direct Costs: $70,000

PF-16-057-01-PCSM
Role: Primary Mentor (PI: Hilary Marusak, PhD)
Title: *"**Neurobehavioral Correlates of Learning and Memory in Child Cancer Survivors**."* Purpose: The fellowship project was designed to identify neurobehavioral correlates of learning and memory in young (~ages 6-9) cancer survivors.
Source: American Cancer Society
07/01/16– 06/30/19
Total Direct Costs: $163,500

Women in Health and Medical Research
Grant Role: Consultant (PI: Izelle Labuschagne, PhD)
Title: *"**Epigenetic and hormonal influences on brain mechanisms underlying sex differences in human social behavior: a pilot study**."* Purpose: To examine sex-specific and environmental modulation of the amygdala (and related subregions and neural networks) and associations with epigenetic variations in the oxytocin receptor and variations in basal levels of oxytocin.
Source: Australian Catholic University
01/02/17– 01/02/19
Total Direct Costs: $52,000

#523497
Role: Co-Investigator (PI: Hilary Marusak, PhD)
Title: *"**Martial Arts Therapy and Brain Mechanisms for Cancer-Related Pain**."*Purpose: The project tested the hypothesis that Kids Kicking Cancer, a martial arts therapy program, can reduce pain and target its underlying neural mechanisms in young cancer patients and survivors.
Source: St. Baldrick's Foundation
07/01/17– 12/31/18 [NCE]
Total Direct Costs: $50,000

K01 MH101123
Role: Principal Investigator (Primary Mentor: Mark Greenwald, PhD)
Title: *"**Cannabinoid Control of Fear Extinction Neural Circuits in Post-Traumatic Stress Disorder**."* Purpose: The objective of the proposed project is to test the hypotheses that administration of THC will enhance recall of fear extinction in patients with PTSD

and that these effects will be mediated via increased activation and functional connectivity of the vmPFC and HPC.
Source: NIH/NIMH
04/01/14– 12/31/18 [NCE]
Total Direct Costs: $604,569

14-238-04-IRG
Role: Principal Investigator
Title: *"**Understanding Emotional Brain Network Organization in Survivors of Childhood Cancer**."* Purpose: The goal of the project was to identify neurobiological mechanisms associated with early cancer experience.
Source: Barbara Ann Karmanos Cancer Institute
09/01/16– 08/31/17
Total Direct Costs: $30,000

MICHR T2 Translational Science Award
Role: Principal Investigator
Title: *"**Neural Mechanisms Underlying Attentional Training in Social Anxiety Disorder**."* Purpose: The aims of the proposed study are to investigate: 1) Threat processing between social anxiety disorder (SAD) and healthy controls (HC); 2) Compare threat processing from pre- to post-attential bias modification training in SAD; and 3) Effects of attential bias modification training directionality (toward vs. away from threat) in SAD.
Source: Michigan Institute for Clinical & Health Related Research
02/01/14– 01/31/25
Total Direct Costs: $50,000

MICHR Postdoctoral Translational Scholars Program Award
Role: Principal Investigator (Primary Mentor: K. Luan Phan, MD)
Title: *"**Behavioral and Brain Mechanisms Underlying Recall of Fear Extinction Memory in Anxiety Disorders**."* Purpose: This translational research project specifically aims to assess the behavioral and brain mechanisms of fear extinction memory recall in healthy humans volunteers and determine whether extinction of fear responses is impaired in social anxiety disorder and whether such impairment is related to dysfunctional activation of brain regions known to be involved in recall of fear extinction memory (e.g. vmPFC, HPC).
Source: Michigan Institute for Clinical & Health Related Research
07/01/11– 06/30/13
Total Direct Costs: $100,000

Otto Muzik, PhD

Active Research Support

Quergen 19-1088 Muzik (PI) 05/01/2019 - 10/30/2022
Title: A PET/CT study of QQ-Proteins bio-distribution and pharmacokinetics in cancer-bearing animals.
This study is investigating the efficacy of protein re-programming in various cancer tissue types.
Amount: $ 50,000 (total cost)
Role in Project: Principal Investigator

Jack Dorsay Foundation Muzik/Diwadkar (MPI) 01/01/2019 - 12/31/2022
Title: Investigation of the Wim Hof Method for Psychiatric Intervention
This study is evaluating the efficacy of the Wim Hof Method in alleviating symptoms in patients with bipolar disorder.
Amount: $ 168,000 (total cost)
Role in Project: Co-Principal Investigator

KCI-0012 Muzik/Shields (MPI) 06/01/2021 - 12/31/2022
Title: Radiosynthesis and Toxicity Studies for the PET Tracer 1-(2-[18F]fluoroethyl)-L-tryptophan
The objective of this study is to develop a new F18-labeled PET tracer that allows the investigation of tryptophan metabolism in humans.
Total Award: $ 50,000 (total cost)
Role in Project: Co-Principal Investigator

R00 DA048125 Woodcock (PI) 05/01/2021-04/30/2024
Title: Multimodal investigation of the neuroimmune system in opioid use disorder
This study is evaluating whether patients with opioid use disorder exhibit elevated levels of neuroimmune system markers using MRS myo-inositol and PET [11C]AMT imaging
Amount: $746,994 (total costs)
Role in project: Collaborating Investigator

Completed Research Support

R01 CA123451-06 Juhasz (PI) 02/01/14 - 12/31/18
Title: Tryptophan metabolism in human brain tumors
“Tryptophan metabolism in human brain tumors”
The goal of this study was to determine the clinical utility of alpha[C-11]-methyl-L-tryptophan PET in brain tumors.
Total Award: $1,035,000 (total costs)
Role in project: Co-Investigator

R01DK102455-01 Muzik (PI) 07/01/2014 - 12/30/2017
Title: Sympathetic innervation of cold-activated brown and white fat in lean young adult.
The major goal of this project was to quantify sympathetic innervation in brown fat at rest and following cold exposure in adults and to determine whether activation of brown fat contributes significantly to overall energy metabolism.
Total Award: $ 800,000 (total costs)
Role in project: Principal Investigator

OVPR DOTS Muzik (PI) 12/01/2014 – 11/30/2017
Title: BA in WAT: Mechanisms and quantitative significance in lean and obese subjects.
The goal of this study was to determine whether cold exposure leads to expression of brown adipocytes (BA) in white adipose tissue (WAT).
Total Award: $ 80,000 (total costs)
Role in project: Principal Investigator

BRAIN Initiative Muzik (PI) 01/01/2015 – 12/30/2017
Title: Clinical quantification of molecular imaging data based on integrative PET and MRI analysis.

The goal of this study was to develop an integrative software environment that allows absolute quantification of PET data in the clinical routine.
Total Award: $ 120,000 (total costs)
Role in project: Principal Investigator

R21 AG047953-01 Peng (PI) 09/01/2014 – 08/30/2016
Title: Altered Copper Metabolism as Theranostic Biomarker in Alzheimer's Disease.
The objective of this study was to assess the efficacy of Cu64 PET/CT imaging in diagnosing early Alzheimer's Disease.
Total Award: $ 275,000 (total costs)
Role in project: Co-Investigator

R21-DK090598 Muzik (PI) 9/20/2010 - 9/19/2013
Title: Quantitative assessment of oxidative metabolism in brown fat.
The focus of this study was to quantify the metabolic rate of oxygen in cold-activated Brown Adipose Tissue (BAT).
Total Award: $ 275,000 (total costs)
Role in project: Principal Investigator

END APPLICANT RESPONSE

a. Personnel

Selected applicant(s) must be able to staff a project team that clearly possesses skill and experience in coordinating clinical trials. In the narrative, identify the authorized contact person and key personnel to be involved with this project by name and title and provide a brief summary of their experience, qualifications, and the work to be performed.

If other organizations will be playing a role in the proposed project, provide sufficient background information that will give the Issuing Office a reasonable understanding of each organization’s qualifications.

Include a detailed organizational chart including names, titles, and geographic location of all individuals that will contribute to the project.

Attach a copy of your confidentiality agreement and provide a list of personnel and the date that the confidentiality agreement was signed.

BEGIN APPLICANT RESPONSE

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Hilary A. Marusak, PhD. Dr. Marusak is a tenure-track Assistant Professor in the Department of Psychiatry and Behavioral Neurosciences at WSU, and directs the Trauma History Investigation of Neurodevelopment in Kids (THINK lab). Dr. Marusak has >11 years of experience conducting neuroimaging research in patients with trauma exposure and psychiatric disorders, especially anxiety and posttraumatic stress disorder (PTSD). Her lab uses a variety of structural and functional magnetic resonance imaging (MRI) techniques to study neurobiological mechanisms leading to the development of anxiety and PTSD in youth. Recently, her lab has focused on the role of the endocannabinoid system in modulating frontolimbic brain development and risk of trauma-related disorders, and has developed a novel line of research to examine behavioral (e.g., exercise, meditation) or pharmacological interventions (e.g., CBD) that target the endocannabinoid system for the

treatment and/or prevention of anxiety and PTSD in youth. Dr. Marusak's lab also studies the impact of cannabinoids during development (e.g., prenatal cannabis exposure, adolescent cannabis use) on neurodevelopmental and mental health outcomes. Dr. Marusak is a Co-I on the Parent Study, and her role is to characterize the effects of cannabis and THC/CBD dose concentrations on endocannabinoid signaling. Dr. Marusak is the PI of a currently funded NIH/NIMH project (MH119241) that aims to characterize age-related changes in endocannabinoid signaling across adolescence, and associations with fear extinction, fear extinction neural circuitry, and anxiety and PTSD symptomology. Dr. Marusak is the PI of two other related projects: she is the Co-PI on a study funded by the Children's Foundation to examine the impact of CBD on anxiety and endocannabinoid levels in pediatric epilepsy patients, and is the Co-PI of a recently funded university award (WSU Office of the Provost) to examine the impact of acute exercise and meditation on endocannabinoid levels and anxiety in youth. Dr. Marusak also works closely with the other study personnel on research on cannabis, cannabinoids, and the endocannabinoid system. For example, Dr. Marusak works with Drs. Lundahl and Ledgerwood on the Parent Study; Dr. Lundahl is a Co-I on Dr. Marusak's ongoing Children's Foundation study on CBD; and Dr. Rabinak is a Mentor on Dr. Marusak's ongoing NIH/NIMH project. Dr. Marusak has also served as an NIH Grant Reviewer as a part of the Early Career Reviewer program, and serves on the editorial board for the *Journal of Neuroscience Research*. Thus, she has the necessary scientific, administrative, and neuroimaging experience needed lead this exciting study, together with Co-PI Woodcock and the Co-Is.

Eric Woodcock, PhD. Dr. Woodcock is a tenure-track Assistant Professor in the Department of Psychiatry and Behavioral Neurosciences at WSU, and directs the Woodcock Lab. Dr. Woodcock has >10 years of experience conducting psychiatric research and >10 years of experience conducting neuroimaging research in patients with psychiatric disorders. His research has focused on the investigation of neurobiological mechanisms underlying psychiatric disorders, especially substance use disorders (SUDs), using multimodal *in vivo* neuroimaging techniques. Recently, his lab has focused on studying the role of neuroimmune signaling in SUDs using positron emission tomography (PET) imaging and proton magnetic resonance spectroscopy (^{1}H MRS). Relevant to the current proposal, Dr. Woodcock has conducted seminal research using PET imaging as a marker of neuroimmune signaling after neuroinflammatory challenges, including morphine and lipopolysaccharide, and among patients with psychiatric disorders. His PET imaging expertise includes study design, signal processing, quantification of radiotracer uptake/binding, and statistical analysis. Dr. Woodcock has the scientific expertise necessary to acquire and quantify PET [^{11}C]AMT imaging data collected in this proposal. Therefore, Dr. Woodcock has the necessary scientific, administrative, and neuroimaging experience needed lead this exciting study alongside Co-PI Marusak and the rest of the team.

Leslie H. Lundahl, PhD. Dr. Lundahl is an Associate Professor in the Department of Psychiatry and Behavioral Neurosciences at Wayne State University who has been conducting clinical human behavioral pharmacology studies for over two decades. Her expertise is in developing and refining efficient and rigorous human laboratory models to study factors involved in drug seeking and drug taking, such as drug abuse liability, drug-drug interactions, effects of stress and environmental cues on choice to use drugs, and subjective and physiological responses to drugs administered in the laboratory. She has been the Principal Investigator on six federal (NIH/NIDA) cannabis-related grants and several university grants, and served as Co-Investigator on many other federal, state, and private grants examining alcohol, nicotine, cannabis, cocaine, opiates, methamphetamine, and MDMA. Dr. Lundahl holds an IND that allows cannabis and cannabinoid administration to humans. Her current projects include evaluating the potential therapeutic efficacy of cannabidiol (CBD), alone and in combination with low doses of morphine, for treating pain, investigating the effects of stress and marijuana cue exposure on marijuana craving and self-administration, and establishing the pharmacokinetic profile of CBD. Dr. Lundahl's research is funded by the National Institute on Drug Abuse (NIDA), where she serves on several grant review committees. More recently Dr. Lundahl has become interested in potential therapeutic effects of cannabinoids. She was recently awarded a grant from the Veteran Marijuana Research Grant Program, overseen by the Cannabis Regulatory Agency in the State of Michigan, to investigate the effects of varying doses of THC and CBD on PTSD symptom severity, depression, and anxiety, with the goal of reducing suicide rates and improving behavioral health in US Military Veterans. She is also a clinical psychologist with over 25 years of experience in the assessment

and treatment of psychiatric and substance use disorders, and she has served as diagnostician and clinician on multiple randomized clinical trials of psychiatric and substance use disorders. In her clinical practice she specializes in depression, anxiety, and substance use issues. Thus, she has the necessary scientific, administrative, and clinical experience to support Co-PIs Marusak and Woodcock on the proposed work, along with the rest of the team on the Parent Study.

David Ledgerwood, PhD. Dr. Ledgerwood is a clinical psychologist and Professor studying various aspects of substance use, including cannabis, tobacco, opioids, and others. He is currently Director of the Nicotine and Tobacco Research Division in the Department of Psychiatry and Behavioral Neurosciences. He has expertise in conducting clinical trials for treatment efficacy and effectiveness. Dr. Ledgerwood has conducted research in several areas that complement the proposed work, including examining trauma, PTSD and suicidality among individuals with gambling disorder, and individuals receiving treatment for opioid use disorder. He is Co-Principal Investigator of a recently completed tele-health trial examining the efficacy of Seeking Safety for co-occurring trauma and gambling problems (Najavits, Ledgerwood, & Afifi, 2022, Currently Under Review). He is currently co-Principal Investigator on the LARA-funded Veteran Marijuana Research Grant, which is exploring the use of cannabinoids (THC and CBD) for treating PTSD, suicidality and other mental health symptoms. Additionally, Dr. Ledgerwood worked on the Vietnam Era Study, a NIH-funded longitudinal cohort study at Washington University that examines PTSD, suicidality, and other co-occurring conditions among Vietnam era veterans originally recruited in 1971. Dr. Ledgerwood's research has been funded by NIH and foundation grants. He serves on a number of editorial and grant review boards. His funded research involves primarily conducting clinical trials for behavioral interventions for individuals with nicotine use disorder, substance use disorder, and gambling disorder. Currently, Dr. Ledgerwood is conducting clinical trials and other clinical research with colleagues at several universities across North America including Medical University of South Carolina, Baylor University, University of Massachusetts Medical School, University of Windsor, and Yale University.

Christine A. Rabinak, PhD. Dr. Rabinak is the Director of Translational Neuropsychopharmacology Lab within the Department of Pharmacy Practice at WSU. Dr. Rabinak completed her postdoctoral training in the Mental Health Service, specifically the PTSD Clinic, at the Ann Arbor Veteran Affairs Healthcare System and the Department of Psychiatry at the University of Michigan. During her training, she was involved in a clinical trial of sertraline in veterans with PTSD returning from Operation Iraqi Freedom and Operation New Dawn and has several peer-reviewed publications from this work. Since then, Dr. Rabinak has established an internationally-recognized, productive, comprehensive and continuously funded research program in translational psychiatric neuroscience. Dr. Rabinak's expertise is in PTSD, cannabinoids, fMRI, and fear learning. Most relevant to this proposal, Dr. Rabinak is the past PI of a NIMH K01 Career Development Award and current NIMH R61/R33 Exploratory Clinical Trials of Novel Interventions for Mental Disorders to test whether pharmacological enhancement of eCB signaling (via synthetic THC) improves neurobehavioral mechanisms underlying extinction recall in adults with PTSD. These studies require that she maintains a DEA Schedule II-V Controlled Substance Research license and submits Investigative New Drug applications to the FDA. She is also the PI of a recently completed NARSAD grant to study genetic variation in the endocannabinoid system and neurobehavioral mechanisms of extinction recall in healthy adults To-date, her research performance has afforded her national and emerging international recognition. Notably, Dr. Nora Volkow, the Director of the National Institutes of Drug Abuse, invited Dr. Rabinak to speak at a research summit convened by the NIH (March 22-23, 2016), which focused on the neurological and psychiatric effects of marijuana, other cannabinoids, and the endocannabinoid system. The goal of the meeting was to ensure evidence-based information is available to inform practice and policy, particularly important at this time given the rapidly shifting political landscape regarding the recreational and medicinal use of marijuana. Dr. Rabinak and Dr. Marusak have a fruitful and long-standing collaborative relationship. Together, they have published over 24 articles and have been awarded several federally-funded and foundation grants. Dr. Rabinak is excited to further support and augment this collaborative team for this innovative and timely proposal.

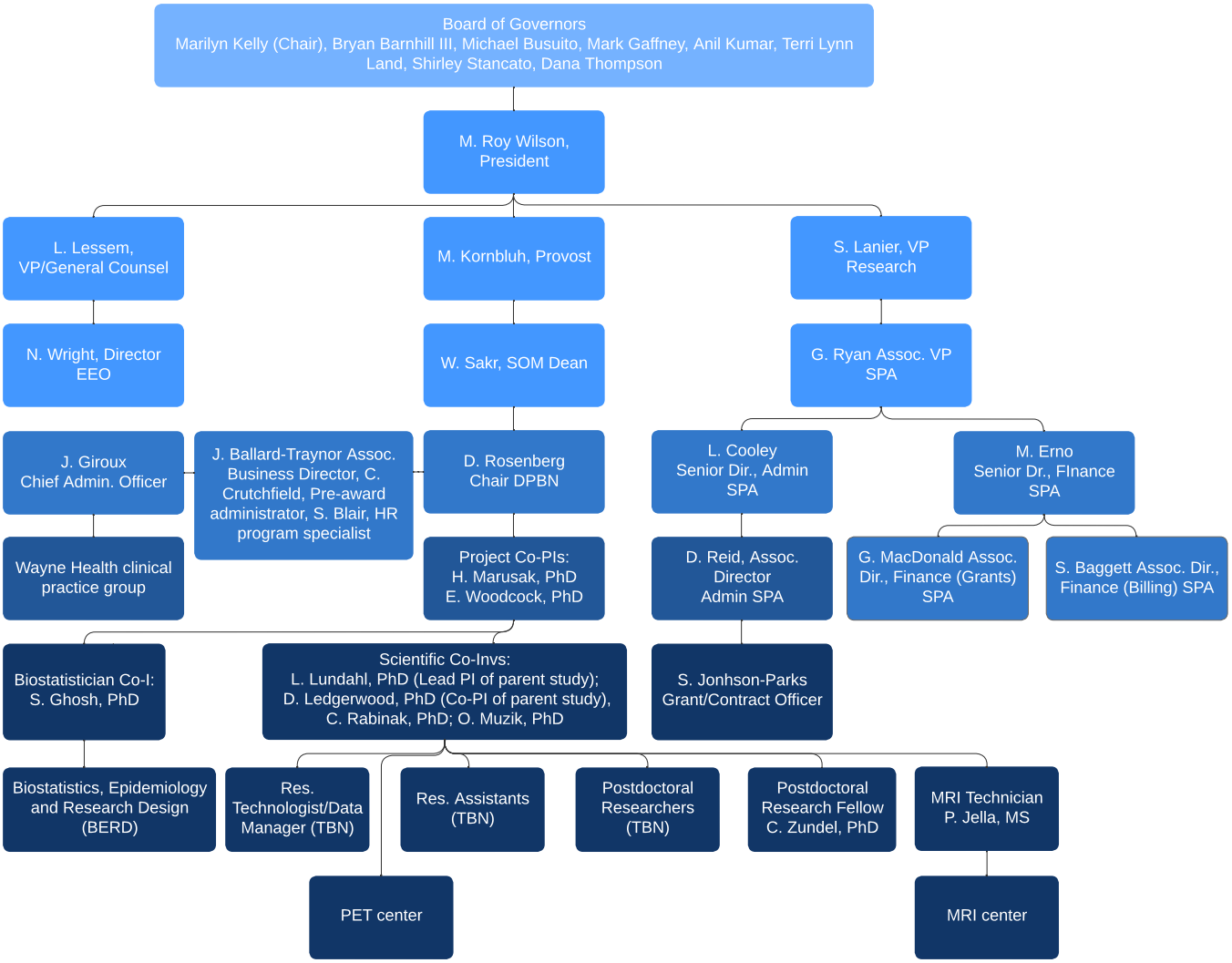
Otto Muzik, PhD. Dr. Muzik is a Professor in the Departments of Radiology and Pediatrics at Wayne State University with a degree in Medical Physics. Dr. Muzik is an expert in Positron Emission Tomography (PET) imaging and pharmacokinetic data analysis techniques with 25+ years of experience. Pertinent to this project, Dr. Muzik is a world-renowned expert in the application of PET [^{11}C]AMT imaging to study psychiatric and neurological disorders with more than 20 years and 1000 patient scans of experience using PET [^{11}C]AMT imaging. Dr. Muzik will provide guidance for the acquisition and analysis of PET [^{11}C]AMT data throughout the Supplement Study.

Samiran Ghosh, PhD. Dr. Ghosh is a Biostatistician and tenured Professor with significant experience in designing and running randomized intervention trials. He has experience writing and supporting trials similar to the proposed project and has also actively developed novel statistical methods for adaptive and Bayesian RCT. As a core leader of Biostatistics, Epidemiology and Research Design (BERD a core facility) at WSU, Dr. Ghosh work with the Co-PIs and their team for successful completion of the project. For this project, he will oversee implementation of statistical analyses and interpretation of findings. He is currently working with Drs. Marusak, Lundahl, and Ledgerwood on the Parent VMR Study, and on several other NIH-funded awards with our team.

Organizational Chart

Investigating the Therapeutic Impact of Cannabinoids on Neuroinflammation and Neurobiological Underpinnings of Suicide Ideation in Veterans with PTSD

May 18, 2022



Confidentiality Agreement

Please see the attachment for a copy of our signed confidentiality agreement. The date that the affirmation memo for confidential/non-disclosure agreements was signed by key personnel is listed below.

Hilary Marusak, PhD	May 26, 2022
Eric Woodcock, PhD	May 26, 2022
Leslie Lundahl, PhD	May 26, 2022
David Ledgerwood, PhD	May 26, 2022
Christine Rabinak, PhD	May 26, 2022
Otto Muzik, PhD	May 26, 2022
Samiran Ghosh, PhD	May 26, 2022

END APPLICANT RESPONSE

b. Budget

To enable the Issuing Office to evaluate all project costs, **applicant(s) will submit a proposed budget and corresponding budget narrative.** Please see attachment A for the required budget format. The budget and narrative must include only VMR grant funds in the budget; do not include matching, leveraged, cost share or any other type of supplemental funds. The budget narrative must identify the budget line item and number, provide a detailed description for each line, and include individual unit prices.

Selected applicant(s) will be required to provide supporting documentation for all grant expenditures incurred during the term of the grant. Accounting records must be supported by source documentation including, but not limited to, general ledgers, time sheets, payroll registers, invoices, check copies and bank statements, or cancelled checks. Expenses will be verified based on actual expenditures incurred within the grant period that are supported by source documentation, not budgeted amounts.

i. **Budget Changes** – Any changes to the budget must be pre-approved by the Grant Administrator. Changes in the budget of less than 5% of the total line item amount do not require a formal amendment; however, a revised budget should be submitted to the Grant Administrator for approval. The allowable transfer should be calculated as less than 5% of the total line item that the funds are being transferred from.

   Cumulative changes in the budget equal to or greater than 5% of the total line item amount may be permitted only upon prior review and written approval by the Grant Administrator. A formal grant amendment must be signed by both the grantor and grantee.

ii. **Disallowed Costs** – Disallowed costs include but are not limited to the following: sick pay, vacation pay, holiday pay, bonuses, overtime, tuition reimbursement/remission, vehicle allowance, seminars, conferences, meetings, subscriptions, dues, and memberships.

iii. **Administrative Costs** – Administrative costs cover expenses related to general administrative functions and coordination of functions and oversight related to VMR administrative functions. Administrative costs should include costs of goods and services required for administrative functions of the program; travel costs incurred for official business in carrying out administrative activities or the overall management of the VMR; costs of information systems related to administrative functions; and contractual services related to sub-recipients or vendors that are solely for the

performance of administrative functions. **Total administrative and indirect costs must be identified, labeled clearly, and may not exceed 10% of the overall grant.**

iv. **Budget Requirements** – the proposed budget will display three (3) headings identified as the: Line Item, Budget Category, and Total. The budget line items that need to be included, at a minimum, are listed below. The budget should reflect the best estimate of actual costs using whole numbers. Please refrain from using decimals or formulas. Refer to the budget example provided in Attachment D.

1. **Personnel** – In the budget, include the name, job title, and salary for each staff position to be paid for by the grant. Time sheets and payroll registers must be submitted for each staff position, and hours worked must be grant related. Fringe benefits may not exceed 35% of each employee's salary. Fringe benefits will be reimbursed based on actual expenditures per employee up to 35%, not on budgeted amounts. Allowable benefits include: health, dental, and optical insurance, employer-paid Social Security and Medicare tax, Michigan and Federal unemployment tax, and other miscellaneous fringe benefits (life insurance, long- and short-term disability insurance, worker's compensation, and retirement program contributions up to 4%). Applicant(s) must provide details on the organization's method of calculating fringe benefit expenses that will be charged to the grant including whether fringe benefits are calculated on an annualized basis or based on the length of the grant term.

The budget narrative must include the number of weeks the individual will work on the grant; number of hours per week a full time employee of the organization is expected to work; a description of the work to be performed by each individual; the estimated hours to be worked; actual pay rate; the fringe benefit percentage being charged to the grant for each employee; the percentage of the employee's time allocated to the grant; whether each employee is salaried-exempt, salaried-non-exempt or hourly; and any other applicable information related to the individual's duties and responsibilities in connection with this grant.

Individuals that are not on selected applicant(s)'s payroll, e.g., independent contractors, individuals receiving a Form 1099, temporary workers, etc., must be placed under the Contractual Services budget category. Only employees on the selected applicant(s)'s payroll should be included in the Personnel budget category.

2. **Supplies, Materials, & Equipment:** specify item(s) and cost. The budget narrative should include the anticipated cost of each item, a detailed explanation of the item's purpose, and how it relates to the project being funded. Be as detailed as possible.

3. **Contractual Services:** these services must be competitively bid. Individuals that are not on selected applicant(s)'s payroll, e.g., independent contractors, individuals receiving a Form 1099, temporary workers, etc., must be placed under **Contractual Services**. When competitive selection is not feasible or practical, the selected applicant(s) agrees to obtain the written approval of the Grant Administrator before making a sole source selection. Selected applicant(s) must provide a copy of contracts, memoranda of understanding or agreements signed by selected applicant(s) and contractors.

Selected applicant(s) assumes responsibility to select subcontractors on a competitive basis. A minimum of three (3) bids must be solicited and proposals must include, at a minimum:

(1) name of selected applicant(s), grant number, and grant period; and (2) the type, number, and description of projects as described in the proposal.

Selected applicant(s) must provide the Grant Administrator with the solicitation, list of vendor responses (including amounts), and name of the selected vendor. Selected applicant(s) must maintain bids on file at their place of business according to Section II-B, Records Maintenance, Inspection, Examination, Audit and Monitoring. The Grant Administrator will reserve the right to request a copy of all bids for services that are competitively bid.

Selected applicant(s) must award the project to the lowest bid unless the Grant Administrator has given prior written approval for selection of a higher bid. Selected applicant(s) must provide a written justification for the selection of a higher bid. When awarding subcontracts, the selected applicant(s) must ensure that preference is given to products manufactured in or services offered by Michigan-based firms.

4. **Travel:** in the budget include the name, job title and official workstation for each staff member that will be traveling. Selected applicant(s) must follow the State of Michigan Standardized Travel Regulations (www.michigan.gov/dtmb/0,5552,7-150- 9141_13132---,00.html). The State will reimburse for mileage, lodging, and meals, refer to the current State travel rates. Meals and lodging must be supported by itemized, legible receipts and reasons for travel. Itemized meal receipts must include a list of each item purchased; receipts for payments made by credit card that are not itemized will not be accepted.

   Mileage must be supported by travel log(s) with beginning and ending addresses, mileage total, and reason for travel. Grantees will be provided a travel log example. Out-of-state travel must be directly related to the grant project and approved by the Grant Administrator prior to travel. Travel expenses listed in the travel budget category are strictly for individuals listed on the budget under Personnel. Per Diem payments and alcoholic beverage reimbursements are not allowed.

5. **Other Expenses:** This category is solely for use by organizations charging a per-case fee for work performed by subunits or internal agencies within the organization that do not require a competitive bid, i.e. contract, memorandum of understanding or any other type of signed agreement.

6. **Indirect Costs:** Indirect costs are costs not directly or specifically related to the grant program. Indirect costs are costs of administering the organization and must be spread over a number of products, services, or grant programs proportionately. Examples include office supplies and equipment, utilities, rent, maintenance and repair, insurance, accounting and bookkeeping services, and legal services. Non-cash expenses like depreciation, amortization, and depletion are not allowable indirect costs under this grant. **Total administrative and indirect costs must be identified, labeled clearly, and may not exceed 10% of the overall grant.**

   Selected applicant(s) will be reimbursed for its proportional share of indirect costs. This means the MRA should be allocated a portion of the selected applicant(s)'s indirect costs and not 100% of the organization's total indirect cost.

   Indirect costs should be displayed on the face of the budget on a single line item and the indirect rate should be rounded to six (6) decimal places. The budget narrative should contain a list of indirect costs, how the selected applicant(s) determined its indirect costs, and the percentage rate calculation for reimbursable indirect costs. Selected applicant(s) is not required to provide documentation supporting indirect

costs; however, documentation verifying the costs must be retained by the selected applicant(s).

v. To ensure efficient review and approval of grant expenditures, selected applicant(s) will be provided additional guidelines to assist with calculating and determining accurate and appropriate grant expenditures.

vi. Each budget category should have a subtotal displaying the total anticipated amount to be expended, and the budget should include a subtotal for total direct project costs and a sum of total project costs.

vii. After grants are approved by the MRA, modifications of proposals and budgets may be necessary. If the MRA does not approve the total amount requested in the original proposal, selected applicant(s) will be required to submit a revised proposal, budget and budget narrative for the purpose of entering into a Grant Agreement. New line items to the revised budget are not allowed.

viii. Selected applicant(s) assumes the responsibility of ensuring all unexpended grant funds are returned to the State of Michigan at the end of the grant period. Failure to do so may render selected applicant(s) ineligible for future grant awards and/or subject to legal action.

ix. Selected applicant(s) may not commingle grant award funds with current or future grant awards. All funding sources must be managed and accounted for separately.

BEGIN APPLICANT RESPONSE

BUDGET NARRATIVE

Of note, the budget for the proposed Supplement Study is completely separate from the Parent Study. Therefore, the proposed budget and narrative outlined below pertains *only* to the Supplement Study and will be kept 100% separate from the Parent Study and any other studies.

Key Personnel (All personnel work 40-hr work weeks)

Hilary Marusak, Ph.D., Co-Principal Investigator (Assistant Professor, tenure-track) is a tenure-track Assistant Professor in the Department of Psychiatry and Behavioral Neurosciences (DPBN) at Wayne State University (WSU), and directs the Trauma History Investigation of Neurodevelopment in Kids (THINK) lab. Dr. Marusak has >11 years of experience conducting neuroimaging research in patients with trauma exposure and psychiatric disorders, especially anxiety and posttraumatic stress disorder (PTSD). Her lab uses a variety of structural and functional magnetic resonance imaging (MRI) techniques to study neurobiological mechanisms leading to the development of anxiety and PTSD, and recently, her lab has focused on the role of cannabinoids in modulating neurodevelopment and risk of anxiety and PTSD. Along with Co-PI Woodcock, Dr. Marusak will provide overall scientific direction, lead the research team, and coordinate the design, implementation and quality control of data collected for the proposed study. Dr. Marusak will also oversee the MRI methods proposed for this study, including sequence preparation and testing, data analysis and secure data storage, and coordination with the MR Research Facility, with support from Dr. Rabinak (Co-I). She will oversee protocol and data integrity, analyses, interpretation, and presentation of study results, communicate with LARA/MRA and the IRB, coordinate with the Parent Study team, present these findings at scientific conferences, and prepare manuscripts for submission. She will devote 30% effort, or 12 hours per week, to the work in the proposed supplement.

Eric Woodcock Ph.D., Co-Principal Investigator (Assistant Professor, tenure-track) is a tenure-track Assistant Professor in the DPBN at WSU, and directs the Woodcock Lab. Dr. Woodcock has >10 years of experience conducting psychiatric research and >10 years of experience conducting neuroimaging research in patients with psychiatric disorders. His research has focused on the investigation of neurobiological mechanisms underlying psychiatric disorders, especially substance use disorders (SUDs), using multimodal in vivo neuroimaging techniques. Recently, his lab has focused on studying the role of neuroimmune signaling in SUDs using proton magnetic resonance spectroscopy (^{1}H MRS) and positron emission tomography (PET) imaging. Dr. Woodcock has the scientific expertise necessary to acquire and quantify PET [^{11}C]AMT imaging data for this proposal and will oversee all of the PET imaging methods proposed for this study with support from Dr. Muzik (Co-I). In particular, Dr. Woodcock will oversee PET methods preparation and testing, data quality control evaluation, data analysis and secure storage, and coordination with the WSU PET Imaging Center. Along with Co-PI Marusak, Dr. Woodcock will provide the overall scientific direction, lead the research team, and coordinate the design, implementation and quality control of data collected for the proposed study. He will oversee protocol and data integrity, analyses, interpretation, and presentation of study results, communicate with LARA/MRA and the IRB, coordinate with the Parent Study team, present these findings at scientific conferences, and prepare manuscripts for submission. He will devote 30% effort, or 12 hours per week, to the work in the proposed supplement.

Leslie Lundahl, Ph.D., Co-Investigator (Associate Professor, tenured) is a licensed clinical psychologist and an experienced psychopharmacologist in the Human Pharmacology Laboratory within the Substance Abuse Research Division of the DPBN at WSU. Dr. Lundahl has over 20 years of experience in designing, conducting, and publishing behavioral pharmacology clinical research studies. Dr. Lundahl is the Lead Principal Investigator of the Parent VMR Study, which includes communication with LARA/MRA, FDA, DEA, WSU IRB and compliance with their monitoring and reporting requirements, including filing protocols under her FDA IND for marijuana (#75,596). Dr. Lundahl's effort on the proposed supplement will include overseeing the overall scientific direction of this research program, including achieving research objectives and study milestones, coordinating between the Supplement Study methods and team and the Parent Study, assisting with safety and clinical oversight of all participants, and assisting with LARA/MRA and WSU IRB communications, manuscript writing, and dissemination of results. She will devote 5% effort, or 2 hours per week, to the work proposed in the supplement.

David Ledgerwood, Ph.D., Co-Investigator (Professor, tenured) a licensed clinical psychologist and experienced clinical scientist in the Substance Abuse Research Division of the DPBN at WSU. He is also the Director of the Nicotine and Tobacco Research Division in the DPBN. Dr. Ledgerwood has extensive experience conducting studies that examine the efficacy and effectiveness of clinical interventions and is skilled in clinical trial methodology. Dr. Ledgerwood is the Co-Principal Investigator of the Parent VMR Study, and his role includes overseeing clinical trials design and the naturalistic observational study. Dr. Ledgerwood's effort on the proposed supplement will include overseeing the overall scientific direction of this research program, including achieving research objectives and study milestones, coordinating between the Supplement Study methods and team and the Parent Study, assisting with safety and clinical oversight of all participants, and assisting with IRB communications, manuscript writing, and dissemination of results. He will devote 3% effort, or 1.2 hours per week, to the work proposed in the supplement.

Christine Rabinak, Ph.D., Co-Investigator (Associate Professor, tenured) is the Director of Translational Neuropsychopharmacology Lab within the Department of Pharmacy Practice at WSU. Dr. Rabinak completed her postdoctoral training in the Mental Health Service, specifically the PTSD Clinic, at the Ann Arbor Veteran Affairs Healthcare System and the Department of Psychiatry at the University of Michigan. During her training, she was involved in a clinical trial of sertraline in veterans with PTSD returning from Operation Iraqi Freedom and Operation New Dawn and has several peer-reviewed publications from this work. Since then, Dr. Rabinak has established an internationally-recognized, productive, comprehensive and continuously funded research program in translational psychiatric neuroscience. Dr. Rabinak's expertise is in PTSD, cannabinoids, fMRI, and fear learning. Therefore, she will assist Dr. Marusak the development and implementation of MRI

methods, programming of experiments, data processing, interpretation of findings, manuscript writing, and overseeing the secure neuroimaging server. She will devote 10% effort, or 4 hours per week, to the work proposed in this supplement.

Otto Muzik, Ph.D., Co-Investigator (Professor, tenured) is a Professor in the Departments of Radiology and Pediatrics at Wayne State University. Dr. Muzik is an expert in Positron Emission Tomography (PET) imaging and pharmacokinetic data analysis techniques with 25+ years of experience. Pertinent to this project, Dr. Muzik is a world-renowned expert in the application of PET [^{11}C]AMT imaging to study psychiatric and neurological disorders with more than 20 years and 1000 patient scans of experience using PET [^{11}C]AMT imaging. Dr. Muzik will provide guidance for the acquisition and analysis of PET [^{11}C]AMT data throughout the Supplement study. He will devote 10% effort, or 4 hours per week, to the work proposed in this supplement.

Nick Mischel, M.D., Ph.D. (Assistant Professor) is a board-certified psychiatrist at WSU and faculty in the DPBN. Mischel provides outpatient psychiatric consultation for patients in medication-assisted treatment (MAT) with suboxone and methadone, and has also treated patients with alcohol, opiate, tobacco, cocaine, benzodiazepine, cannabis, other stimulant, and other psychedelic use disorders in both acute inpatient detoxification and rehabilitation centers. Dr. Mischel will review EKGs, labs, and perform physicals to determine subject eligibility for the Parent Study (and thus, by extension, the proposed Supplement), contribute to interpretation of findings and manuscript preparation, as well as provide medical coverage during cannabis administration sessions and oversight throughout the Parent Study trial. These duties are covered on the Parent Study and therefore no effort is requested here (0% FTE; Note: As no effort is requested, Dr. Mischel does not appear in our Budget).

Andy King, M.D. (Assistant Professor) is an Emergency Department physician who also sees patients in our on-site methadone clinic. He will provide backup to Dr. Mischel for medical monitoring and oversight, oversee the study nurse (Ms. Gwen DeWalt), and assist with interpretation of findings and manuscript preparation. These duties are covered on the Parent Study and therefore no effort is requested here (0% FTE; Note: As no effort is requested, Dr. King does not appear in our Budget).

Biostatistics Core

Samiran Ghosh, Ph.D. (Professor, tenured) is a Biostatistician with significant experience in designing and running randomized intervention trial. He has experience writing and supporting trials similar to the proposed project and has also actively developed novel statistical methods for adaptive and Bayesian RCT. As a core leader of Biostatistics, Epidemiology and Research Design (BERD a core facility) at WSU, he will work with the Co-PIs and their team for successful completion of the project. For this project, he will oversee implementation of statistical analyses and interpretation of findings. He is currently working with Drs. Marusak, Lundahl, and Ledgerwood on the Parent VMR Study, and on several other NIH-funded awards with our team. He will commit 2% effort, or 0.8 hours per week, to the proposed Supplement.

Other Personnel

Research Technologist/Data Manager, TBN. The data manager will have Bachelor's or Master's degree in computer science, engineering, or a related field, experience with coding (e.g., Python, MATLAB), and evidence of strong organizational and data management skills. This individual's primary responsibility will be the secure storage, management, processing, and backup of all neuroimaging data collected for this study. The data manager will coordinate with the study team and with the MRI and PET imaging centers at WSU to securely transfer data, maintain HIPAA compliance, establish quality assurance and processing pipelines, oversee the processing of data, and assisting with preparation for dissemination (e.g., publication, conference presentations). The data manager will also be responsible for implementing and maintaining software systems on the server, installing and maintaining new hardware and software on all computers within the lab, and

coordinating with WSU IT and other technical staff. The data manager will commit 100% effort, or 40 hours per week, to this study.

Professional Research Assistant, TBN. This research assistant will be directly supervised by Dr. Marusak and will be responsible for managing all day-to-day project needs, including scheduling and screening participants for the supplement study, making pre-visit reminder phone calls and text messages to maximize participation rates, tracking enrollment milestones, creating digital data collection protocols and questionnaires, conducting study assessments and collecting data, coordinating with the research team and scheduling/payments with the WSU MRI center, assisting with IRB communications and submissions, and administering participant payments. This individual will meet regularly with the Co-PIs to assure quality control and maintenance of study records, provide summaries, track milestones, and assist in preparing data for presentations and publications. The research assist will devote 50% effort, or 20 hours per week, throughout this 5-year project.

Professional Research Assistant, TBN. This research assistant will be directly supervised by Dr. Woodcock and will assist Dr. Woodcock with implementation of PET imaging methods and acquisition of PET imaging data proposed for this study. This research assistant will be responsible for managing all day-to-day project needs, including scheduling and screening participants for the supplement study, making pre-visit reminder phone calls and text messages to maximize participation rates, creating digital data collection protocols and questionnaires, tracking enrollment milestones, conducting study assessments and collecting data, coordinating with the research team and scheduling/payments with the WSU PET imaging center, assisting with IRB communications and submissions, and administering participant payments. This individual will meet regularly with the Co-PIs to assure quality control and maintenance of study records, provide summaries, and track study milestones. The research assist will devote 50% effort, or 20 hours per week, throughout this 5-year project.

Postdoctoral Research Fellow, TBN. This postdoctoral research fellow will have a PhD in Neuroscience, Psychology, or a related field. This individual will be directly supervised by Dr. Marusak and will work closely with and oversee the research assistants and data manager, including data collection, archiving, quality checking, and analysis. This individual will also work closely with Dr. Marusak and be responsible for the MRI aspects of the study, including processing all behavioral and structural and functional MRI scans collected for this study, statistical analysis, including applying advanced network-level analyses to the MRI data, generating figures and data visualization methods, and preparing MRI data for presentations and publication. This postdoc will be hired in Year 3 and will devote 100% effort, or 40 hours per week, for Years 3-5 of this 5-year project.

Postdoctoral Research Fellow, TBN. This postdoctoral research fellow will have a PhD in Neuroscience, Psychology, or a related field. This individual will be directly supervised by Dr. Woodcock and will work closely with and oversee the research assistants and data manager, including data collection, archiving, quality checking, and analysis. This individual will also work closely with Dr. Woodcock and be responsible for the PET imaging aspects of the study, including processing PET [^{11}C]AMT imaging data, generating PET imaging figures and data visualization methods, and preparing PET data for presentations and publication. This postdoc will be hired in Year 3 and will devote 100% effort, or 40 hours per week, for Years 3-5 of this 5-year project.

Clara Zundel, Ph.D. (Postdoctoral Research Fellow). Dr. Zundel earned a PhD in Behavioral Neuroscience from Boston University and has extensive experience in clinical neuroscience research. Her graduate work focused on Gulf War veterans who were exposed to neurotoxicants (e.g., sarin nerve gas, pesticides) while in theatre, and characterizing the longitudinal effects of neurotoxicant exposures on PTSD symptoms, brain structure, and other health outcomes over time. Dr. Zundel has been working as postdoc in Dr. Marusak's lab for the past year, where she has gained experience and expertise in the development and implementation of structural and functional MRI approaches to study neurobiological mechanisms leading to psychiatric symptoms, including anxiety and PTSD. For the proposed project, Dr. Zundel will assist with the research assistant and postdoc on the MRI methods, including best practices for collecting and processing of MRI and behavioral data. Also, given her extensive experience working with U.S. armed forces veterans in neuroimaging research, Dr. Zundel will advise the study team on safety measures, including screening

practices. She will also lead analyses linking neurotoxicant exposures to neuroinflammation and neurobiological markers that will be collected in this study, including manuscript writing and subsequent grant applications. She will devote 10% effort, or 4 hours per week, to this proposed project.

Pavan Jella, M.S. (MR Technician). Mr. Jella has a Master's degree in Biomedical Engineering and has been working as an MRI Chief Technologist in the WSU MR Research Facility for the past 8 years. Mr. Jella has extensive experience and expertise performing a variety of MR-based studies, including structural and functional MRI. He has been the MRI technician on several of Dr. Marusak's past and ongoing studies, including her currently funded NIH project. Mr. Jella will be the MR Technologist on the proposed supplement project. His primary duty will be to acquire MRI data for this study and to screen participants for safety for MR imaging. He will also assist with sequence development and testing, provide guidance on MR parameters, denoising strategies, and analysis of structural and functional MR data, coordinate billing and scheduling with the study team, and MRI data image reconstruction and transfer via secure server to the neuroimaging server. He will devote 10% effort, or 4 hours per week, to the proposed project.

Administrative Personnel

Jennifer Ballard-Traynor (Administrative Director). Jennifer will provide financial oversight on this study. She will review all personnel charges and expenses on this study for compliance. She will monitor expenditures and report to the Co-PIs on a regular basis. Review and coordinate close out documents with the Sponsored Program Administrative Office. She will contribute 10% effort, or 4 hours per week throughout this 5-year project.

Cordell Crutchfield (Grants and Contracts Administrator). Cordell will coordinate the pre-award aspects for this project to ensure compliance with University and sponsor. He will review budget proposals and justifications each award period and coordinate documentation required by granting agency. His will contribute 5% effort, or 2 hours per week, throughout this 5-year project.

Fringe Benefits

Fringe benefits are calculated on requested salary per the University's policy. The fringe rates are set and charged by the University based on pay classification. These amounts are subject to change on a fiscal year basis (Oct to Sep). The current rate for faculty is 27.4% (Marusak, Woodcock, Lundahl, Ledgerwood, Rabinak, and Muzik), the rate for research personnel is 30.4%, and the rate for administrative personnel is 29.4% (Ballard-Traynor, Crutchfield).

Other Direct Costs

***Laptop Computers*:** In year one, we will need to purchase 2 laptop computers ($1,500 x 2) that will be used for behavioral data collection in the lab, at the MRI Center, and at the PET imaging Center. These will also be used to practice the fMRI tasks that will be completed during fMRI scanning. Two more laptops are requested in Year 4 to replace the original ones bought in Year 1, for a total of $6,000.

Computing Tablets: In year one, we will purchase 2 computing tablets ($500 x 2) to be used for day-to-day tasks, including real-time data collection during study visits and participant scheduling. Two more tablets are requested in Year 4 to replace the original ones bought in Year 1, for a total of $2,000.

Desktop Computers: We will obtain 4 desktop computers with monitors ($1,000 x 4) to be used for day-to-day tasks, including participant tracking and scheduling, processing of behavioral, MRI, and PET imaging data, data visualization, and manuscript and report writing. We are requesting the costs to purchase 2 desktop computers in Year 1 and 2 desktop computers in Year 4, for a total of $4,000.

DMC IRB review: $300 is requested to cover the costs of the Detroit Medical Center IRB review, if needed.

Deep Freezer and Battery Backup: In Year 1, we are requesting funds (total cost of $17,000 including installation and setup) to purchase a hospital-grade -80ºC degree deep freezer, with lock, alarm with temperature display, and battery backup system. This freezer will be used to storage the plasma samples collected during the PET imaging visits for peripheral inflammatory marker and other biomarker analysis.

Centrifuge: In Year 1 we will purchase a centrifuge to process the blood samples collected during the PET imaging visits. Cost: $3,000.

Ferromagnetic Detector for MRI: In Year 1, we will purchase a walk-through ferromagnetic detector (total cost of $25,000, including installation/testing). This detector is essential for performing MRI scans safely in veteran populations, in particular, who are frequently exposed to metal fragments and shrapnel as a part of their active military service, would make them unsafe for the neuroimaging scans. This walk-through detector is the highly sensitive, and will be mounted at the MRI Center to identify ferromagnetic hazards and provide valuable objective data to determine whether participants are safe for scanning. This is the final layer of our 4-tiered MRI safety screening protocol, and participants will walk through this detector at the MRI center before each of their scans.

Ferromagnetic Sensor for Screening Visit: In Year 1, we will purchase a hand-held ferromagnetic sensor (total cost of $5,000). This sensor will be used in the initial screening visit of the Parent Study to identify participants who may be eligible for the Supplement Study. The ferromagnetic sensor will provide valuable objective data to determine whether participants are safe for scanning and is the third tier in our 4-tier MRI safety screening protocol.

Neuroimaging Data Storage and Backup Server: The server includes a networked cluster of workstations and storage is provided by a Dell Eight Core, 3.1GHz, 20M, 8.0GT/s, Turbo+ with 128GB, DDR3 RDIMM Memory, three 2TB 3.5" STAT 6GB/s hard drives, RAID 5, with 16 1GbE Ports. In addition, 30TB of hard drives and NAS server to provide completely redundant data storage. In addition to RAID redundancy, nightly incremental and weekly full backups occur for non-RAIDed storage. A secondary backup system consists of bi-weekly, rotating backup with off-site storage. Archival storage is maintained on CD-ROM and DVD. Analysis packages include Matlab licenses, SPM8, as well as custom software. Secure, high speed networking connects computers of the core with those on campus, but access to the analysis cluster is restricted to ssh and sftp protocols only. This is needed because neuroimaging requires extensive computing capacity and specialized expertise and software, as each scan (PET or MRI) requires upwards of 20GB in storage (for >4TB over the entire study). The server will be used to securely implement preprocessing, quality assurance, and MRI and PET statistical analyses, and will also house the raw (unprocessed) data in addition to a remote server backup. For this study, $25,000 is requested in Year 1 to purchase needed space on the data storage and backup server for the proposed 200 MRI and 200 PET scans. An additional $5,000/year (plus up to 4% inflation) is requested to cover the cost of annual server maintenance and upkeep. The server will be maintained by the data manager in collaboration with Drs. Marusak, Woodcock, and Rabinak and be securely accessed by restricted study personnel who are trained in neuroimaging data management. Therefore, the total anticipated cost across all five years is $45,918.

Urine Drug and Pregnancy Testing: All participants will complete urine drug screening for the presence of drugs of abuse (or metabolites thereof) in urine: one at screening (as part of the Parent Study) and one prior to each neuroimaging session. Additionally, all female participants will complete urine pregnancy test at the initial screening as a part of the Parent Study and one prior to each neuroimaging session, which is consistent with WSU MRI and PET Center policies. It is assumed that 10% of participants screened will be female. Therefore, we anticipate a yearly cost of about $120 (plus up to 4% inflation/year) to cover the costs of urine drug and pregnancy testing, for a total of $637 across all five years.

Printing and Office Supplies: $1,000/yr (plus up to 4% inflation/yr) is requested to cover the costs of printing of study-related documents and office supplies for this study (e.g., pens, binders, notebooks, etc.). Therefore, the total cost across five years is $5,374.

Blood Lab Panels and Peripheral Biomarkers: $200/scan is requested to cover the costs of standard lab panels for plasma samples collected during the PET scan. This includes Lipids, CBCs, and CMPs for a general assessment of peripheral immune function for each subject. Additionally, we will also assay biomarkers directly related to the brain's immune system, and specifically the tryptophan-kynurenine pathway, including peripheral levels of Tryptophan, Kynurenine, Serotonin, Kynurenine Acid, Quinolinic Acid, and Picolinic Acid, as well other inflammatory markers (cytokines/chemokines and C-reactive protein levels) and stress system markers (cortisol and noradrenaline/adrenaline levels). For the 100 scans at baseline and 80 at post-trial, we anticipate that costs will be $7,200/yr (plus up to 4% inflation/yr) for a total of $38,692 across all five years.

Phlebotomy Training and Certification: A total of $1,750 is requested to cover the costs of two research assistants (one during Year 1, one during Year 4 to account for potential staff turnover) in completing a phlebotomy training course and the certification exam.

Water, Snacks, and Lunch for Participants. The proposed study sessions will last about 6.5 hours each, and will require that participants to eat breakfast and intake caffeine prior to the 8:30 AM arrival, as they must be fasted for at least 5 hours prior to the PET scan (which starts at 1:30 PM). Therefore, we are requesting funds to cover the costs of water bottles for the study visit, and to offer participants snacks and their choice of lunch at the Detroit Medical Center (DMC) food court directly after the completion of their PET scan (~2:30 PM). Participants will be able to eat their lunch in a private room while awaiting their transportation (personal vehicle or Uber/taxi) or discharged immediately upon receipt of study payment (subject preference). We anticipate that this will be about $15/participant/session, or $540/yr (plus up to 4% inflation/yr), for a total of $2,902 across all five years.

Participant Transportation to and from Study Visits. We will offer transportation via Uber, Lyft, or Taxi to and from study visits for participants who require transportation. We anticipate that fewer than half (~40 participants) may need assistance with transportation. We are requesting $1,200/yr (plus up to 4% inflation/yr) to assist with transportation to and from baseline and post-trial scan sessions, for a total of $6,449 across all five years.

PET Scan Hours: The current hourly rate for one 60-minuate PET [^{11}C]AMT scan at the WSU PET Imaging Center is $3,000. This includes radiotracer biosynthesis, quality control, and radiotracer injection, scanner time, PET technician and nurse time, and plasma radiotracer concentration analysis. Each participant will be scanned twice (once at baseline and once at post trial) for a total of 2 PET [^{11}C]AMT scan hours or $6,000. Per the WSU PET Center policy, we will not be charged for unsuccessful scans. Therefore, we request $108,000/yr (plus up to 4% inflation/yr), for a total of $584,963 across all five years.

MRI Scan Hours: The current hourly rate for scanning at the WSU MR Research Facility $650. This includes scanner time, technician time, miscellaneous supplies, usage of acquisition hardware and software, and image reconstruction by the technologist. The proposed MRI scan protocol is estimated to last 1 hr/session, and each participant is scanned twice (once at baseline, once at post trial = 2 hrs). Per the WSU MR Research Facility policy, we will not be charged for unsuccessful scans. Therefore, we request $23,400 (plus up to 4% inflation/yr), for a total of $126,742 across all five years.

Participant Incentives: Participants will receive up to $500 for completing each scanning session, including bonus payments for performance tasks (Balloon Analogue Risk task and Monetary Incentive Delay Task), for a total of up to $1,000 for completing the proposed Supplement Study (and perfect performance on the two bonus payment tasks). Therefore, total requested amount for the 180 sessions (100 pre- and 80 post-scan sessions) is $90,000 across all five years. In addition, we expect that up to 10% (10 participants) may pass all but the final

tier of MRI safety screening (i.e., walk-through metal detector). These participants will be considered "screen fails" and compensated $50 for their time. Therefore, total requested amount for the 180 sessions (100 pre- and 80 post-scan sessions) plus the 10 potential screen fails is $90,500 across all five years.

Clincard Fees to Administer Participant Payments: We will be using the Clincard system to pay all research subjects. This is the same system used in the Parent Study and therefore participants will be familiar. There are physical card costs of $4.95/card and a load fees of $1.15/card loaded. We will ask participants to bring back their cards to avoid additional card fees. Cards are loaded with payments as participants complete each milestone. Therefore, we are requesting the costs to load participants' Clincards for 180 sessions, which is $42/yr (plus up to 4% inflation/yr) for a total of $226 across all five years.

Software Fees: In Year 1, we will purchase MATLAB and Millisecond software. These are one-time fees and used to process the neuroimaging data and administer and analyze the in-lab behavioral task data, respectively. In Years 1-5, we will purchase yearly software licenses for SPSS, Adobe Photoshop, and Neurobehavioral Systems Presentation software, which are used for statistical analyses, image editing and presentation, and fMRI task administration, respectively. We will also purchase yearly Biorender lab license for Years 2-5, which will be used for data visualization and creation of high-quality figures to be used in presentations and publications. Therefore, total requested amount is $19,442 across all five years.

Manuscript Publication Costs: We anticipate publishing at least 3 manuscripts/yr (about $2,000/publication) during Years 3-5 of the project period. Manuscripts will be submitted to high-quality peer-reviewed journals related to cannabis and cannabinoids, trauma and PTSD, or psychiatric outcomes. Therefore, total requested amount is $18,000 across all five years.

Occupancy Costs: The study sessions will begin and end at our Tolan Park Medical Building, located at 3901 Chrysler Dr. Detroit, MI 48201. Participant sessions will occur in our Warrior Care Center, which is space designated to conduct our current, ongoing LARA/CRA-funded cannabis trial. The Warrior Care Center is housed on the first floor of the Tolan Park Medical Building, and comprises a reception area, small kitchen, conference room, and two private interview rooms for testing. Drs. Marusak, Woodcock, Lundahl, and Ledgerwood also have offices and laboratory space on the 2nd floor of the Tolan Park Medical Building, in the Human Pharmacology Laboratory or the Detroit Trauma Project. The total estimated cost of using the two private testing rooms for this study is $2,540/yr (plus up to 4% inflation/yr), for a total of $13,755 across all five years. This cost includes includes rent, maintenance, utilities, and property taxes. Rent is paid to Wells Fargo Bank Northwest, maintenance and utilities is paid to Colliers, our property management company, and property taxes to the City of Detroit.

<u>Other Expenses</u>

Consulting Fees & Travel to Assist with MRI Setup & Analysis: We are requesting funds to cover the costs of an MR imaging expert (e.g., Dr. Prantik Kundu from the Icahn School of Medicine at Mount Sinai) to visit to assist with the development and testing of the most up-to-date optimized MRI parameters for this study in veterans. The consultant will also review our MRI safety protocol, particularly safety protocol, prior to the study starting, and advise on our overall methods for collecting, processing, analyzing, and interpreting MRI data collected for this study. $2,000 is requested during Year 1 for the proposed in-person set-up visit (within the first 3 months), which will cover flight and lodging. The consultant will review study procedures with the research team and provide a seminar on the most up-to-date MR imaging methods to the study of psychiatric illness, including depression and PTSD. During Years 1-5, we request costs to cover 4 consulting hrs/yr at $200/hr. Therefore, total requested amount is $6,000 across all five years.

Consulting Fees & Travel to Assist with PET Analysis & Interpretation: We are requesting funds to cover the costs of a PET imaging expert (e.g., Dr. Kelly Cosgrove or Ansel Hillmer from Yale School of Medicine) to consult on the PET Imaging Methods proposed for this study. The consultant will review our PET safety

protocol, advise on study methods, and evaluate our data analysis processing pipelines and statistical methods. This individual will also be involved to an on-site visit during Year 1 to review study procedures with the research team and provide a seminar on the most up-to-date PET imaging methods to the study neuroinflammation in psychiatric illness, including PTSD. $2,000 is requested during Year 1 for the proposed on-site visit (during Year 1), which will cover flight and lodging. During Years 1-5, we request costs to cover 4 consulting hrs/yr at $200/hr. Therefore, total requested amount is $6,000 across all five years.

Indirect Costs: Indirect costs are limited to **<10%** of the overall grant.

END APPLICANT RESPONSE

V-I Additional Information and Comments

Include in this section any other information that is believed to be pertinent but not specifically requested elsewhere in this RFP.

BEGIN APPLICANT RESPONSE

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Neuroimaging studies are extremely expensive and challenging. Scan rates typically exceed $3,000 per PET scan, and >$650 per MRI scan. They also require extensive personnel (e.g., PET and MRI technicians), specialized expertise and software, and extensive computing capacity, with each scan (PET or MRI) requiring upwards of 20GB in storage for a total of >4TB for the entire study. A *de novo* study of this size and scope would typically cost upwards of $8M.

Fortunately, we have designed a novel, highly efficient study that capitalizes on our ongoing Parent VMR study and neuroimaging infrastructure at WSU; thus, minimizing costs. We have taken several measures to keep costs low, including leveraging already-established recruitment processes, neuroimaging processing pipelines, and server storage, buying scans in bulk, and minimizing administrator costs that are already covered by the Parent Study.

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END APPLICANT RESPONSE

Indirect Costs: Indirect costs are limited to **<10%** of the overall grant.

END APPLICANT RESPONSE

V-I Additional Information and Comments

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BEGIN APPLICANT RESPONSE

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Neuroimaging studies are extremely expensive and challenging. Scan rates typically exceed $3,000 per PET scan, and >$650 per MRI scan. They also require extensive personnel (e.g., PET and MRI technicians), specialized expertise and software, and extensive computing capacity, with each scan (PET or MRI) requiring upwards of 20GB in storage for a total of >4TB for the entire study. A *de novo* study of this size and scope would typically cost upwards of $8M.

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END APPLICANT RESPONSE

V-J Certification of Proposal

Please sign the proposal including the following language:

I certify that all information contained in the proposal is true to the best of my knowledge and belief, and that the organization is in compliance and agreement with all sections of the Request for Proposal.
Failure to comply with grant terms may result in termination.

Certified by: Sophia Johnson-Parks Grant & Contract Officer IV 5.25.2022

Authorized Signatory and Title Date

Name of Organization

Wayne State University

Wayne State VMR 2022-02

CORRECTED BUDGET - 8.22.22 (ALL VALUES ROUNDED TO NEAREST DOLLAR)

Line Item	Budget Category						
1	**Administrative Expenses**						
2	**Administrative Personnel (Grant Administration Staff)**	**2022-2023**	**2022-2024**	**2022-2025**	**2022-2026**	**2022-2027**	**TOTAL**
3	*Salary*						
4	Jennifer Ballard-Traynor, Administrative Director	$9,981	$10,280	$10,589	$10,906	$11,233	$52,989
5	Cordell Crutchfield, Grant & Conract Administrator	$3,098	$3,190	$3,286	$3,385	$3,486	$16,445
6	**Total Salary**	$13,079	$13,470	$13,875	$14,291	$14,719	$69,434
7	*Fringe Benefits*						
8	Jennifer Ballard-Traynor, Administrative Director	$2,934	$3,022	$3,113	$3,206	$3,303	$15,578
9	Cordell Crutchfield, Grant & Conract Administrator	$911	$938	$966	$995	$1,025	$4,835
10	**Total Fringe Benefits**	$3,845	$3,960	$4,079	$4,201	$4,328	$20,413
11	***Total Administrative Personnel***	$16,924	$17,430	$17,954	$18,492	$19,047	$89,847
12	**Administrative Supplies, Materials, and Equipment**						
13	Does not apply	$ -	$ -	$ -	$ -	$ -	$ -
14	***Total Administrative Supplies, Materials & Equipment***	$ -	$ -	$ -	$ -	$ -	$ -
15	**Administrative Contractual Services**						
16	Does not apply	$ -	$ -	$ -	$ -	$ -	$ -
17	***Total Administrative Contractual Services***	$ -	$ -	$ -	$ -	$ -	$ -
18	**Administrative Travel (Grant Administration Staff)**						
19	Does not apply	$ -	$ -	$ -	$ -	$ -	$-
20	***Total Administrative Travel***	$ -	$ -	$ -	$ -	$ -	$-
21	**Total Administrative Expenses**	**$16,924**	**$17,430**	**$17,954**	**$18,492**	**$19,047**	**$89,847**
22	**VMR Program Expenses**						
23	**VMR Program Staff**						
24	*Salary*						
25	Leslie Lundahl, Ph.D., Co-Investigator	$10,968	$11,297	$11,636	$11,985	$12,344	$58,230
26	David Ledgerwood, Ph.D., Co-Investigator	$6,140	$6,324	$6,514	$6,709	$6,911	$32,598
27	Hilary Marusak, Ph.D., Co-Principal Investigator	$38,597	$39,755	$40,947	$42,176	$43,441	$204,916
28	Eric Woodcock, Ph.D.,Co-Principal Investigator	$39,552	$40,739	$41,961	$43,220	$44,516	$209,988
29	Christine Rabinak, Ph.D., Co-investigator	$14,530	$14,966	$15,415	$15,877	$16,354	$77,142
30	Otto Muzik, Ph.D., Co-Investigator	$19,711	$20,303	$20,912	$21,539	$22,185	$104,650
31	Samiran Ghosh, Ph.D., Biostatistician	$3,785	$3,898	$4,015	$4,135	$4,260	$20,093
32	**Total Salary**	$133,283	$137,282	$141,400	$145,641	$150,011	$707,617
33	*Fringe Benefits*						
34	Leslie Lundahl, Ph.D., Co-Investigator	$3,005	$3,095	$3,188	$3,284	$3,382	$15,954
35	David Ledgerwood, Ph.D., Co-Investigator	$1,682	$1,733	$1,785	$1,838	$1,894	$8,932
36	Hilary Marusak, Ph.D., Co-Principal Investigator	$10,576	$10,893	$11,220	$11,556	$11,903	$56,148
37	Eric Woodcock, Ph.D.,Co-Principal Investigator	$10,837	$11,162	$11,497	$11,842	$12,197	$57,535
38	Christine Rabinak, Ph.D., Co-investigator	$3,981	$4,101	$4,224	$4,350	$4,481	$21,137
39	Otto Muzik, Ph.D., Co-Investigator	$5,401	$5,563	$5,730	$5,902	$6,079	$28,675
40	Samiran Ghosh, Ph.D., Biostatistician	$1,037	$1,068	$1,100	$1,133	$1,167	$5,505
41	**Total Fringe Benefits**	$36,519	$37,615	$38,744	$39,905	$41,103	$193,886
42	***Total VMR Program Staff***	$169,802	$174,897	$180,144	$185,546	$191,114	$901,503

43	**VMR Personnel Program Staff**						
44	*Salary*						
45	TBD, Professional Research Assistant (Marusak)	$20,000	$20,600	$21,218	$21,855	$22,510	$106,183
46	TBD, Professional Research Assistant (Woodcock)	$20,000	$20,600	$21,218	$21,855	$22,510	$106,183
47	TBD, Research Technologist/Data Manager	$55,000	$56,650	$58,350	$60,100	$61,903	$292,003
48	TBD, Postdoctoral Research Fellow (Marusak)	$0	$0	$55,000	$56,649	$58,350	$169,999
49	TBD, Postdoctoral Research Fellow (Woodcock)	$0	$0	$55,000	$56,649	$58,350	$169,999
50	Clara Zundel, Ph.D., Postdoctoral Research Fellow	$5,648	$5,817	$5,992	$6,172	$6,357	$29,986
51	Pavan Jella, MRI Technician	$7,393	$7,615	$7,843	$8,078	$8,321	$39,250
52	**Total Salary**	$108,041	$111,282	$224,621	$231,358	$238,301	$913,603
53	*Fringe Benefits*						
54	TBD, Professional Research Assistant (Marusak)	$6,080	$6,262	$6,450	$6,644	$6,843	$32,279
55	TBD, Professional Research Assistant (Woodcock)	$6,080	$6,262	$6,450	$6,644	$6,843	$32,279
56	TBD, Research Technologist/Data Manager	$16,720	$17,222	$17,738	$18,270	$18,819	$88,769
57	TBD, Postdoctoral Research Fellow (Marusak)	$0	$0	$16,720	$17,222	$17,738	$51,680
58	TBD, Postdoctoral Research Fellow (Woodcock)	$0	$0	$16,720	$17,222	$17,738	$51,680
59	Clara Zundel, Ph.D., Postdoctoral Research Fellow	$1,717	$1,769	$1,822	$1,876	$1,932	$9,116
60	Pavan Jella, MRI Technician	$2,247	$2,315	$2,384	$2,456	$2,529	$11,931
61	**Total Fringe Benefits**	$32,844	$33,830	$68,284	$70,334	$72,442	$277,734
62	***Total VMR Personnel Program Staff***	$140,885	$145,112	$292,905	$301,692	$310,743	$1,191,337
63	***VMR Supplies, Materials, & Equipment***						
64	4 Laptops	$3,000	$ -	$ -	$3,000	$ -	$6,000
65	4 Tablets	$1,000	$ -	$ -	$1,000	$ -	$2,000
66	4 Desktop Computers	$2,000	$ -	$ -	$2,000	$ -	$4,000
67	DMC IRB	$300	$ -	$ -	$ -	$ -	$300
68	Deep Freezer & Battery Backup	$17,000	$ -	$ -	$ -	$ -	$17,000
69	Centrifuge	$3,000	$ -	$ -	$ -	$ -	$3,000
70	Ferromagnetic Detector for MRI	$25,000	$ -	$ -	$ -	$ -	$25,000
71	Ferromagnetic Sensor for Screening Visit	$5,000	$ -	$ -	$ -	$ -	$5,000
72	Data storage and server management	$25,000	$5,000	$5,150	$5,304	$5,464	$45,918
73	Urine drug and pregnancy tests (MRI & PET)	$120	$124	$127	$131	$135	$637
74	Printing and Lab/Office Supplies	$1,000	$1,030	$1,071	$1,114	$1,159	$5,374
75	Blood Lab Panels and Peripheral Biomarkers	$7,200	$7,416	$7,712	$8,021	$8,342	$38,691
76	Phlebotomy Supplies for PET	$500	$515	$536	$557	$579	$2,687
77	Phlebotomy Training and Certification	$850	$ -	$ -	$900	$ -	$1,750
78	Water, Snacks, and Lunch for Participants	$540	$556	$578	$602	$626	$2,902
79	Participant Transportation to and from Study Visits	$1,200	$1,236	$1,285	$1,337	$1,390	$6,448
80	PET Scan Hours	$108,000	$112,320	$116,813	$121,485	$126,345	$584,963
81	MRI Scan Hours	$23,400	$24,336	$25,309	$26,322	$27,375	$126,742
82	Participant Payments Sessions	$18,100	$18,100	$18,100	$18,100	$18,100	$90,500
83	Clincard Fees for Participant Payments	$42	$43	$45	$47	$49	$226
84	Software Fees	$7,665	$2,815	$2,899	$2,986	$3,076	$19,441
85	Manuscript Publication Costs	$ -	$ -	$6,000	$6,000	$6,000	$18,000
86	Occupancy Costs	$2,539	$2,641	$2,747	$2,857	$2,971	$13,755
87	***Total VMR Supplies, Materials, & Equipment***	$252,456	$176,132	$188,372	$201,763	$201,611	$1,020,334
88	**VMR Contractual Services**						
89	Does not apply	$ -	$ -	$ -	$ -	$ -	$ -
90	***Total VMR Contractual Services***	$ -	$ -	$ -	$ -	$ -	$ -

91	**VMR Travel (VMR Staff)**						
92	Does not apply	$ -	$ -	$ -	$ -	$ -	$ -
93	***Total VMR Travel (VMR Staff)***	$ -	$ -	$ -	$ -	$ -	$ -
94	**VMR Other**						
95	Consulting Fees & Travel to Assist with MRI Setup & Analysis	$2,800	$800	$800	$800	$800	$6,000
96	Consulting Fees & Travel to Assist with PET Analysis & Interpretation	$2,800	$800	$800	$800	$800	$6,000
97	***Total EAP Other***	$5,600	$1,600	$1,600	$1,600	$1,600	$12,000
98	**Total VMR Program Expenses**	$585,667	$515,171	$680,975	$709,093	$724,115	$3,215,021
99	**Total Direct Cost**	$585,667	$515,171	$680,975	$709,093	$724,115	$3,215,021
100	*Indirect Cost (0.0.10000028)*	$58,567	$51,517	$68,098	$70,909	$72,412	$321,503
101	**TOTAL PROJECT COST**	$644,234	$566,688	$749,073	$780,002	$796,527	$3,536,524

Attachment B2 - Compressed Budget

Compressed Budget VMR - Wayne State VMR 2022-02	
Budget Category	**Original**
Administrative Personnel Expenses	
Administrative Personnel	$89,847.00
Administrative Supplies, Materials, and Equipment	$0.00
Administrative Contractual Services	$0.00
Administrative Travel (Grant Administration Staff)	$0.00
Administrative Expenses Total	**$89,847.00**
VMR Program Expenses	
VMR Program Staff Total	**$901,503.00**
VMR Personnel Program Staff	
VMR Personnel Program Staff Total	**$1,191,337.00**
VMR Supplies, Materials, & Equipment	
VMR Supplies Materials & Equipment Total	**$1,020,334.00**
VMR Other	
EAP Other Total	**$12,000.00**
VMR Program Expenses Total	**$3,215,021.00**
Total Direct Cost	**$3,215,021.00**
Indirect Cost (0.10000028)	**$321,503.00**
TOTAL PROJECT COST	**$3,536,524.00**

DEPARTMENT OF TECHNOLOGY, MANAGEMENT & BUDGET,
VEHICLE AND TRAVEL SERVICES
SCHEDULE OF TRAVEL RATES FOR CLASSIFIED AND UNCLASSIFIED EMPLOYEES
Effective January 1, 2022

MICHIGAN SELECT CITIES *

	Individual	Group Meeting (pre-arranged and approved)
Lodging**	$85.00	$85.00
Breakfast	$10.25	$13.25
Lunch	$10.25	$13.25
Dinner	$24.25	$27.25

MICHIGAN IN-STATE ALL OTHER

	Individual	Group Meeting (pre-arranged and approved)
Lodging**	$85.00	$85.00
Breakfast	$ 8.50	$11.50
Lunch	$ 8.50	$11.50
Dinner	$19.00	$22.00
Per Diem	**$87.00**	
Lodging	$51.00	
Breakfast	$ 8.50	
Lunch	$ 8.50	
Dinner	$19.00	

OUT-OF-STATE SELECT CITIES *

	Individual	Group Meeting (pre-arranged and approved)
Lodging**	Contact Conlin Travel	Contact Conlin Travel
Breakfast	$13.00	$16.00
Lunch	$13.00	$16.00
Dinner	$25.25	$28.25

OUT-OF-STATE ALL OTHER

	Individual	Group Meeting (pre-arranged and approved)
Lodging**	Contact Conlin Travel	Contact Conlin Travel
Breakfast	$10.25	$13.25
Lunch	$10.25	$13.25
Dinner	$23.50	$26.50
Per Diem	**$95.00**	
Lodging	$51.00	
Breakfast	$10.25	
Lunch	$10.25	
Dinner	$23.50	

Incidental Costs Per Day (with overnight stay) $5.00

Mileage Rates

Premium Rate	$0.585 per mile
Standard Rate	$0.360 per mile

* See Select Cities Listing

** Lodging available at State rate, or call Conlin Travel at 877-654-2179 or www.somtravel.com

SELECT HIGH COST CITY LIST

TRAVEL RATE REIMBURSEMENT FOR CLASSIFIED AND UNCLASSIFIED EMPLOYEES
Effective January 1, 2022

Michigan Select Cities/Counties

Cities	Counties
Ann Arbor, Auburn Hills, Beaver Island, Detroit, Grand Rapids, Holland, Leland, Mackinac Island, Petoskey, Pontiac, South Haven, Traverse City	All of Grand Traverse, Oakland and Wayne

Out of State Select Cities/Counties

State	City/County
Arizona	Phoenix, Scottsdale, Sedona
California	Los Angeles (Los Angeles, Orange, Mendocino & Ventura Counties, and Edwards AFB), Eureka, Arcata, Mckinleyville, Mammoth Lakes, Mill Valley, San Rafael, Novato, Monterey, Palm Springs, San Diego, San Francisco, Santa Barbara, Santa Monica, South Lake Tahoe, Truckee, Yosemite National Park
Colorado	Aspen, Breckenridge, Grand Lake, Silverthorne, Steamboat Springs, Telluride, Vail
Connecticut	Bridgeport, Danbury
District of Columbia	Washington DC (also the cities of Alexandria, Falls Church and Fairfax, and the counties of Arlington and Fairfax, in Virginia; and the counties of Montgomery and Prince George's in Maryland) (See also Maryland and Virginia)
Florida	Boca Raton, Delray Beach, Jupiter, Fort Lauderdale, Key West
Georgia	Jekyll Island, Brunswick
Idaho	Sun Valley, Ketchum
Illinois	Chicago (Cook and Lake counties)
Kentucky	Kenton
Louisiana	New Orleans
Maine	Bar Harbor, Kennebunk, Kittery, Rockport, Sanford
Maryland	Counties of Montgomery & Prince Georges, Baltimore City, Ocean City
Massachusetts	Boston (Suffolk), Burlington, Cambridge, Woburn, Martha's Vineyard
Minnesota	Duluth, Minneapolis/St. Paul (Hennepin and Ramsey Counties)
Nevada	Las Vegas
New Mexico	Santa Fe
New York	Lake Placid, Manhattan (the borough of Manhattan, Brooklyn, Bronx, Queens and Staten Island), Riverhead, Ronkonkoma, Melville, Suffolk County, Tarrytown, White Plains, New Rochelle
Ohio	Cincinnati
Pennsylvania	Bucks County, Pittsburgh
Rhode Island	Bristol, Jamestown/Middletown/ Newport (Newport County) Providence
Texas	Austin, Dallas, Houston, L.B. Johnson Space Center
Utah	Park City (Summit County)
Vermont	Manchester, Montpelier, Stowe (Lamoille County)
Virginia	Alexandria, Falls Church, Fairfax
Washington	Port Angeles, Port Townsend, Seattle
Wyoming	Jackson, Pinedale