



**- STATEMENT OF WORK -
Task Authorization (TA) – 37**

FOR SUBCONTRACT WITH CIMVHR

1. NUMBER – TITLE OF TASK AUTHORIZATION

TA 37 –Role of Neuroinflammation in Mental Disorders: Application of Multimodal Neuroimaging in the Assessment of Military PTSD.

2. VALIDATION OF SCOPE OF CONTRACT

2.1 The following task(s), as written in the SOW of the main contract (W7714-145967/001/SV) apply to this Task Authorization (TA):

- a. **Experimental and Clinical Studies** - Design and conduct of experiments involving both human and animal studies.
- b. **Field Studies and Trials** - Design and conduct studies and trials, including clinical trials.
- c. **Data Analysis** - Perform state of the art analysis of data from experimental studies, clinical trials, field studies or trials, and existing databases.
- d. **Presentations to Government and Health Care System Stakeholders** - Prepare and deliver presentations to Government and Healthcare system stakeholders.

3. ACRONYMS

CAF	Canadian Armed Forces
CAPS	Clinician Administered PTSD Scale
CNS	Central Nervous System
DRDC	Defence Research and Development Canada
DSM	Diagnostic and Statistical Manual
GSH	Glutathione
HPA	Hypothalamic-Pituitary-Adrenal
MAO	Monoamine Oxidase
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
PET	Positron Emission Tomography
PTSD	Post-Traumatic Stress Disorder
SA	Scientific Authority
SGHRP	Surgeon General Health Research Program
TA	Task Authorization
TSPO	18 kDa Mitochondrial Translocator Protein

4. REQUIREMENT

4.1 The following services of the Sub Contractor are required: to conduct a prospective, observational cohort study of Canadian Armed Forces (CAF) personnel and veterans experiencing post-traumatic stress disorder (PTSD); using a multimodal neuroimaging (i.e., PET, MRS, MRI) and multivariate biomolecular analysis approach, to assess brain and blood correlates of PTSD, which could yield both clinical utility and novel mechanistic insights into this condition.

5. BACKGROUND



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5.1 Mental health research is a top priority for the Surgeon General's Health Research Program (SGHRP) and Defence Research and Development Canada (DRDC). In particular, PTSD (with or without comorbid depression) is a debilitating operational stress injury of high concern. Mental illnesses are increasingly recognized as having a biological basis; yet understanding and treatment of psychiatric disorders is hampered by the complexity of the human system and by a lack of validated clinical biomarkers (i.e., altered blood levels of specific proteins, genetic changes, and/or brain abnormalities observed on neuroimaging). Given the potential uses of biomarkers in multiple aspects of prevention and treatment of mental disorders — such as risk factor assessment, diagnosis, prognosis, treatment selection, drug discovery, and more — efforts to uncover biomarkers of psychiatric illness have been expanding. Recent advances in neuroimaging, including functional and structural magnetic resonance imaging (fMRI, sMRI), magnetic resonance spectroscopy (MRS), and nuclear imaging using positron emission tomography (PET) are bringing us closer to the goal of developing objective brain-based markers of the neural functions and neuropathology that underlie many mental disorders. The integration of multiple imaging modalities, such as functional MRI, MRS and PET is becoming an increasingly well used research strategy for studying human brain disorders.

5.2 One biological process that has been well interrogated is the inflammatory response, as it has a clear role in the pathophysiology of chronic mental and physical illness. Immune signaling contributes to the regulation of the hypothalamic-pituitary-adrenal (HPA) axis and other neurobiological processes that modulate affective behavior in the face of stressor exposure. Indeed, exposure to traumatic and stressful events results in HPA axis reactivity, activation of the immune system, and the release of pro-inflammatory mediators. Over time and with continuous exposure to stressors, both HPA and immune function become dysregulated.

5.3 Neuroinflammation, occurring within the central nervous system (CNS), is implicated in the pathophysiology of a growing number of human disorders, including in the etiology and development of neuropsychiatric conditions, such as major depression and PTSD. As a result, interest in the development of novel methods to investigate neuroinflammatory processes, for the purpose of diagnosis, development of new therapies, and treatment monitoring, has surged in recent years. The effects of neuroinflammation have been linked to both gliosis and oxidative stress leading to neurodegeneration of brain regions involved in memory and mood control, which can result in depression and cognitive impairment. Gliosis is a natural immune response of glial cells (astrocytes and microglia) to brain injury, infection, or disturbed homeostasis and can be both beneficial and detrimental to brain function. Preclinical and clinical data support the idea that the pathophysiology of PTSD can be attributed to altered neuroinflammatory processes. This hypothesis stems from findings from animal models of PTSD, which have shown that the development of anxiety phenotype in rodents following chronic exposure to stressful stimuli is associated with and depends on elevated neuroinflammatory profile (i.e., exacerbation of pro-inflammatory mediators in blood and CNS), macrophage recruitment, astrocyte activation and neuroglia communication. Likewise in humans, persistently altered levels of central and/or peripheral markers of inflammation (e.g., inflammatory cytokines, reactive oxygen species), epigenetic regulation of their expression, the correlations with stress sensitization, and involvement of other immune response genes and subtypes of immune cells have been recently revealed in PTSD. Overall, enhanced or abnormal immune response is suspected to contribute to dysfunction in monoamine and glucocorticoid transmission and neurosteroid activities that parallel clinical symptomatology in PTSD, suggesting that treatment approaches targeting neuroinflammation may be beneficial and neuroprotective in this disorder. However, the mechanism of neuroinflammation in the development of PTSD is unknown and there are no in vivo studies providing proof-of-concept that PTSD is indeed associated with increases in inflammatory and oxidative stress markers within the brain.

5.4 Several state-of-the-art molecular imaging tools exist for studying human neuroinflammation, combining functional and biochemical modalities that target: (1) activation of CNS immunocompetent glial cells with the 18 kDa mitochondrial translocator protein (TSPO) tracer [¹⁸F]FEPPA a second generation PET radioligand; (2) a monoamine oxidase-B (MAO-B) selective tracer [¹¹C]SL25.1188, that can serve to index activated astrocytes where MAO-B is preferentially and highly expressed in the brain; combined with (3) ¹H MRS measurements of myo-inositol concentration, a marker of glial (astrocyte) cell activation and proliferation and with measurement of glutathione (GSH) and index of oxidative stress.



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5.5 The proposed combination of these novel PET imaging tools and MRI/MRS measurements will allow for simultaneous assessment of both microgliosis and astrogliosis (key players of neuroimmune function) in the same participant with PTSD. This comprehensive fusion analysis, will provide a greater understanding of the separate or integrated roles of these two key types of glia in PTSD than that detected by a single imaging modality, which could yield both clinical utility and novel mechanistic insights into this condition.

6. OBJECTIVES

6.1 *The objective of this work is to enhance our understanding of the biological basis of PTSD using specific multimodal neuroimaging techniques (i.e., PET, MRI/MRS) to assess the level of neuroinflammation in CAF personnel and veterans with PTSD.* A greater understanding of objective clinical evaluation tools and fundamental biological mechanisms of PTSD is needed to facilitate early diagnosis and management of this disorder. The development of valid and reliable biomarkers (i.e., brain abnormalities observed in neuroimaging and/or altered expression of specific proteins in the blood) of PTSD is key to improving prevention and treatment.

7. SCOPE

7.1 The Sub Contractor must conduct a prospective, cross-sectional observational cohort study, using multimodal neuroimaging (i.e., PET, MRI/MRS) to investigate the potential role of neuroinflammation in PTSD clinical symptomatology in CAF members and veterans experiencing PTSD.

7.2 To achieve this aim, the Sub Contractor must enrol three (3) groups of study volunteers: two (2) groups will be composed of CAF members/veterans who have experienced at least one potentially traumatic event traumatic event during a deployment (with one group of 15 CAF members/veterans who have been diagnosed with PTSD according to the Clinician Administered PTSD Scale [CAPS] for the DSM-5; and a second group of 15 CAF members/veterans who were exposed to, but without a lifetime history of PTSD); and a third control group of 15 healthy CAF members/veterans not exposed to war-zone deployment and without a lifetime history of PTSD or other current DSM-IV Axis-I psychopathology.

7.3 The scope of work will include the following:

- a. The contactor must conduct of all planning, coordination, training, execution, and implementation necessary to conduct the observational cohort study, including participant recruitment, clinical assessments, neuroimaging, and biological sample collection; and
- b. The Sub Contractor must ensure they have adequate resources for designing, testing, and implementing the trial and are staffed for the data collection, statistical analysis and publication of the resulting research findings.

8. APPLICABLE DOCUMENTS & REFERENCES

None

9. TASKS TO BE PERFORMED

Phase 1 - Study Planning and Scoping

9.1 Prepare Human Subjects Research Ethics Protocols for submission to each of the participating institutional Research Ethics Boards for approval;

9.2 Develop a Research Protocol for a cross-sectional observational cohort study to investigate the clinical trajectory and neuroimaging profile of PTSD in CAF members and veterans (including, but is not limited to: subject recruitment plan with benchmarks; data management plan; blood collection plan; statistical analysis plan);



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9.3 Recruit and train all required staff – including, but not limited to, clinicians, therapists, graduate students/postdoctoral fellows, and technicians in accordance with the approved Research Protocol; and

9.4 Purchase all necessary equipment and clinical/laboratory supplies.

Phase 2 – Subject Testing and Data Collection

9.5 Initiate enrolment of eligible volunteers in accordance with institutional and regulatory guidelines to complete PET, MRI/MRS neuroimaging in CAF members/veterans;

9.6 Monitor participant enrolment and data quality metrics;

9.7 Coordinate participant data collection (i.e., clinical evaluation, neuropsychological testing, imaging analyses, blood sample collection) and establish a database; and

9.8 Coordinate biological specimens storage at Sub Contractor’s site during course of study and shipment of remaining samples to DRDC Toronto for subsequent analysis of selected genomic and proteomic biomarkers.

Phase 3 – Data Analysis and Reporting

9.9 Complete all data analysis, statistical analyses, and tabulation/presentation of results in accordance with standard scientific publishing guidelines;

9.10 Prepare and submit Quarterly Progress Reports summarizing all results/findings to date, and providing conclusions and recommendations with respect to the requirement to pursue the study;

9.11 Prepare and submit a Draft Study Report and a Final Study Report detailing all evidence-based data captured during the conduct of the entire study; including executive summary, background, objectives, methods, results, conclusions, and recommendations for future research directions in this domain;

9.12 Prepare and submit a PowerPoint presentation to present research findings at scientific meetings; and

9.13 Prepare draft scientific manuscripts, in association with the SA and DRDC co-investigators, suitable for publication in the open peer-reviewed literature.

10. DELIVERABLES (DESCRIPTION AND SCHEDULES)

All deliverables must be submitted and completed by March 2019. The Sub Contractor must prepare and submit the following deliverables:

Deliverable Number	Task reference	Description (Quantity and Format) and Schedule
10.1	9.1	Human Subjects Research Ethics Protocols for submission to each of the participating institutional Research Ethics Boards no later than 1 month after the authorization to begin work.
10.2	9.2	Research Protocol to be delivered no later than 2 months after the authorization to begin work.
10.3	9.10	Quarterly Progress Reports to be submitted every 3 months.



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10.4	9.11	Draft Study Report no later than 30 days prior to the end of the work. Draft Study Report no later than 30 days prior to the end of the work. The SA will require no more than 5 business days to provide feedback to the Sub Contractor.
10.5	9.11	A Final Study Report addressing issues and concerns identified by the SA on the Draft Study Report to be submitted within 15 days of receipt of feedback from the SA.
10.6	9.12	PowerPoint presentation no later than 1 month prior to any scientific meeting
10.7	9.13	Draft scientific manuscripts suitable for publication in open literature no later than 30 days prior to the end of the work.

11. MANDATORY SELECTION CRITERIA

11.1 This prospective observational cohort study must be completed by a world-leading Canadian neuroimaging centre (with both PET and MRI/MRS expertise, and exclusive access to the following tracers: [¹⁸F]FEPPA and [¹¹C]SL25.1188) and PTSD clinical and academic investigator group.

12. LANGUAGE OF WORK

12.1 Documentation and deliverables must be submitted in the English language.

13. LOCATION OF WORK

The work must be performed on the Sub Contractor's site.

14. TRAVEL

14.1 This task authorization may include the following domestic travel requirements:

- a. Sub Contractor travel to present research findings at scientific meetings; and
- b. Subjects travel for data collection.

14.2 All travel must have the prior written authorization of the Scientific Authority and the Technical Authority, and must be undertaken in accordance with the *National Joint Council Travel Directive* and with the other provisions of the directive referring to "travellers", rather than those referring to "employees".

15. MEETINGS

None

16. GOVERNMENT SUPPLIED MATERIAL (GSM)

None

17. GOVERNMENT FURNISHED EQUIPMENT (GFE)

None

18. SPECIAL CONSIDERATIONS OR CONSTRAINTS

18.1 See Section 11.



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19. SECURITY

The Sub Contractor will not require access to PROTECTED and/or CLASSIFIED information or asset, nor to restricted access areas.

Not applicable RELIABILITY STATUS PROTECTED A PROTECTED B

20. INTELLECTUAL PROPERTY (IP) OWNERSHIP

The Sub Contractor will own any Foreground IP created by virtue of the main contract (W7714-145967/001/SV).

21. CONTROLLED GOODS

Not applicable
 Applicable

22. BUDGET The Sub Contractor will be paid by CIMVHR as per the terms of Contract # W7714-145967 between Defence Research and Development Canada and CIMVHR. The amount of funding available is allocated by fiscal year (April 1 - March 31st) and is approximately \$408,000 for the duration of the two-year project. Details TBD upon award.

A draft budget must be submitted with the proposal along with a budget justification. A detailed budget will be developed post award in consultation with CIMVHR. Interested parties should request budget documents and information on creating their budget from Jocelyne Halladay.