Funding Award Number: W81XWH-20-1-0141

Project Title: Frontotemporal Dementia: Military Exposures and Disease Characteristics (FTD-MEDIC)

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Contracting organization: University of Utah, Salt Lake City, UT

Report date: March 2022

Type of report: Annual

Prepared for: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

Distribution Statement: Approved for Public Release; Distribution Unlimited

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
March 2022	Annual	01Mar2021 – 28Feb2022

4. TITLE AND SUBTITLE
Frontotemporal Dementia: Military Exposures and Disease Characteristics (FTD-MEDIC)

5a. CONTRACT NUMBER
W81XWH-20-1-0141

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release, Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
Frontotemporal dementia (FTD) is a group of disorders that occur when there is a degeneration in the frontal and temporal lobes of the brain. Unlike Alzheimer's disease, FTD usually does not involve memory impairments, instead exhibit a variety of behavioral symptoms and language problems. Clinical presentation of the disease is heterogeneous and based on the phenotype of FTD. Understanding the epidemiology of FTD and its clinical phenotypes in a population, and the risk factors associated, play an important role in the accurate diagnosis, appropriate management of, and in identifying those at risk for the disease.
Our study has two main aims: first to identify the clinical phenotypes of Frontotemporal dementia (FTD) through natural language processing aided detailed medical chart reviews of post-9/11 era U.S military veterans in Veterans Health Administration care between fiscal years 2002-2015 diagnosed with FTD. Second: Evaluate if the clinical phenotypes of FTD among the post-9/11 era U.S. military veterans diagnosed with FTD vary by exposure to traumatic brain injury (TBI), spinal cord injury and by occupational risk to blast injury. This knowledge is critical for the clinical care of FTD and for planning of health and preventive services as this cohort of Post-9/11 Veterans ages.

15. SUBJECT TERMS
Frontotemporal dementia, traumatic brain injury, epidemiology, natural language processing

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OFABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
					USAMRDC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**	Unclassified	10	**19b. TELEPHONE NUMBER**
Unclassified	Unclassified	Unclassified			

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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1. INTRODUCTION AND BACKGROUND

The proposed project will identify clinical phenotypes of Frontotemporal dementia (FTD) disease among post-9/11 era United States Veterans and identify the association of military exposures with the FTD disease characteristics using data from the Departments of Defense (DoD) and Veterans Affairs (VA). Existing research from animal and human studies suggests that symptomatic FTD patients, both familial and sporadic, can be clinically heterogeneous. Occurrence of FTD and its clinical presentation among military populations is not well studied. While prior studies have examined the associations between Traumatic Brain Injury (TBI) and dementia broadly speaking, little is known about the association of military exposures and injuries to FTD—which is a subtype of the broad category of dementia. This study will address this gap in knowledge through two specific aims. In Aim 1, we will identify cases of FTD from a cohort of all Post-9/11 era Veterans who received VA care (2 or more years 2002-2019); obtain VA and DoD health care system data for these cases; and identify the diverse disease characteristics associated with FTD diagnosis using chart reviews and natural language processing (NLP) in VA data. The NLP software that we are using is called Moonstone. It has been used to assess function before in a VA dataset and is based on semantic, grammar-based rules. In Aim 2, we will identify whether FTD risk and clinical phenotypes vary by exposure to TBI, spinal cord injury or high risk of blast injury. Together these aims address the DoD FY19 PRMRP Topic Area of Frontotemporal Lobe Degeneration by examining FTD disease characteristics among post-9/11 era Veterans in relation to specific military exposures.

KEYWORDS

Frontotemporal dementia, traumatic brain injury, epidemiology, natural language processing

2. AIMS MAJOR TAKS & ACCOMPLISHMENTS

Aim 1: Identify the clinical phenotypes of FTD through detailed medical chart reviews in post-9/11 era U.S military Veterans receiving VHA health care during FY 2002-2019.

- **Major Task 1:** Complete Regulatory Requirements for Study
  - **Subtask 1:** prepare regulatory Documents and Research protocol

  Completion: University of Utah IRB approval on 07-04-2020, SLC VA IRB approval 13-04-2020, HRPO approval 06-10-2020. IRB continuing review was submitted and acknowledged 01/22/2022. IRBNet (IRB application on VA site) application was acknowledged on 03/27/2022.

- **Major Task 2**: Identify cohort, cases, controls, and exposures
  - **Subtask 1:** Obtain VA data for Post 9/11 Era Veterans
  - **Subtask 2:** Identify cases, controls, exposures, and other variables in FY02-FY19 cohort

  Completion: All tasks have been completed. We have compiled data from DoD data sources and identified cases of FTD, sociodemographic characteristics, TBI, deployment status, comorbidities. In table 1, we have matched each person with FTD with four other Veterans of similar age and sex in the same population but with no diagnosis of FTD or other dementias. In Table 1 summarize descriptive information comparing cases with FTD and controls to understand the characteristic of our cohort. In total, we have identified n=203 cases of FTD with n=748 cases of matching controls. Matching controls were more likely to be married (63%), white and non-Hispanic Latino, 77% and 86%, respectively. FTD cases were more likely to be on active duty (56%) and be identified as an officer (14%). This cohort had an equal distribution of males (90%) and females (10%) among both FTD cases and their matching controls. For FTD cases, 36% were identified to have cognitive dysfunction diagnosis between the ages of 25-45 and 62% between the ages of 45-65.

Table1: Sociodemographic Information of cohort including cases of FTD and controls

	Category	Cases FTD	Controls FTD
# Of Cases		**203**	**748**
Marital status N (%)	Married	126 (62%)	468 (63%)
	Never Married	33 (16%)	97 (13%)
	Divorced	33 (16%)	138 (18%)
	Separated	8 (4%)	31 (4%)
	Widowed	2 (1%)	5 (1%)
	Unknown	1 (0%)	9 (2%)
Race N (%)	White	153 (75%)	579 (77%)
	Black	31 (15%)	119 (16%)
	Other	5 (2%)	12 (2%)
	Unknown	6 (3%)	20 (3%)
	Declined to Answer	8 (4%)	18 (2%)
Ethnicity N (%)	Hispanic or Latino	23 (11%)	78 (10%)
	No Hispanic or Latino	169 (83%)	640 (86%)
	Unknown	7 (4%)	26 (4%)
	Declined to Answer	4 (2%)	4 (0%)
Service branch N (%)	Navy/Coast Guard/Air Force	54 (27%)	170 (27%)
	Army/Marines	149 (73%)	575 (73%)
	Unknown	0 (0%)	3 (0%)
Component N (%)	Active duty (Regular)	113 (56%)	`341 (46%)
	Reserved (Activated NG, Activated Reserve)	52 (25%)	229 (31%)
	Unknown	38 (19%)	178 (24%)
Rank N (%)	Enlisted	125 (62%)	559 (75%)
	Officer	58 (14%)	58 (8%)
	Warrant	5 (2%)	15 (2%)
	Unknown	45 (22%)	116 (15%)
Gender N (%)	Male	181 (90%)	671 (90%)
	Female	77 (10%)	77 (10%)
Age at cognitive dysfunction diagnosis N (%)	18-25	3 (1%)	0 (0%)
	25-45	74 (36%)	0 (0%)
	45-65	126 (62%)	0 (0%)

- **Major Task 3:** Identify and abstract clinical characteristics of FTD among cases

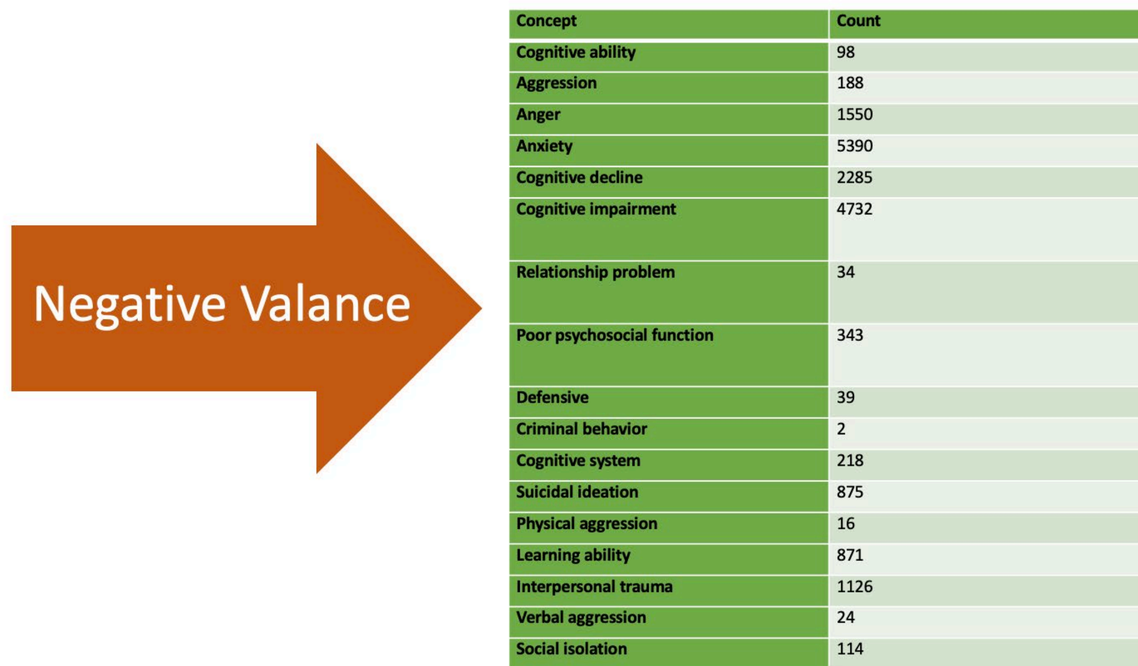
Completion: All tasks have been completed. Table 2 presents the concepts that we have manually reviewed and abstracted at sentence level from the medical records that patients or clinicians use to describe FTD and its symptoms. We have developed and trained on the process for manual chart review which led to the development of these neurobehavioral phenotypes in conjunction with our NLP tool generated data.

Table 2: Concepts from manual chart review of FTD cases	
Factors associated with patient reported positive outcomes	Positive reintegration with family and friends
	Education related success
	Family support
	Participating in therapy
	Motivated to begin therapy
	Compliant w/ treatment plan
	employed
Factors associated with patient reported negative outcomes	Family distress
	Legal problems
	Substance abuse
	Violence/ domestic violence
	PTSD symptoms
	Suicidal ideation
	ETOH/ alcohol use
	TBI symptoms
	Interpersonal/relationship problems
	unemployed
	Financial instability
	Complex medical problems
	Behavioral issues

- **Major Task 4:** Identification of phenotypes of FTD

  Current completion- 50%

  Using the text notes, we have completed the training protocol for annotators and finalized the training protocol for NLP software validation (See Major Task 5). We have also organized the existing software ontology and created new ontology as needed to incorporate the concepts necessary for this study. The otology main concepts were developed using RDOC (research Domain Criteria Initiative) which is the research framework for investigating human behavior and functioning. Based on the RDOC 6 domains we have reorganized the ontology into 6 umbrella concepts of Negative Valence, Positive Valence, Cognitive Systems, Systems for Social Processes, Regulatory systems and Sensorimotor. Cognitive system domain is associated to the concepts related to the symptomology associated with cognitive dysfunction and neurobehavioral characteristics and phenotypes. Some of the concepts related to cognitive decline that the current version of NLP software can identify includes poor executive function, memory deficit, depressive symptoms, isolation, etc. Furthermore, we have modified the current software to work more efficiently with large numbers of documents across many varied concepts. Figure 1 below presents how our NLP programing tool (Moonstone) has identified and counted some of the concepts related to negative valence domain in free text notes from the cases. Concepts including Cognitive impairment, Cognitive decline Anxiety, Anger and Interpersonal trauma had the highest count among the others.



Concept	Count
Cognitive ability	98
Aggression	188
Anger	1550
Anxiety	5390
Cognitive decline	2285
Cognitive impairment	4732
Relationship problem	34
Poor psychosocial function	343
Defensive	39
Criminal behavior	2
Cognitive system	218
Suicidal ideation	875
Physical aggression	16
Learning ability	871
Interpersonal trauma	1126
Verbal aggression	24
Social isolation	114

Figure 1: RDOC Framework Concept of Negative Valance and Moonstone Outcomes in FTD Cases

Over the next 12 months we plan to further evaluate this data and using the Moonstone based concept output (exampled in Figure 1) and the RDOC framework, identify distinct phenotypes of FTD.

- **Major Task 5:** Enhancement of Existing NLP tool with concepts of FTD disease characteristics
  Completion: All tasks have been completed.

We have finalized our training of Moonstone on the neuropsychiatric and psychosocial form text notes of the gold standard cases. This will allow Moonstone to better assess the cases of FTD and ultimately develop phenotypes of FTD based on the Moonstone identified concepts as illustrated in Task 4. We have also verified our NLP tool classifier. We forced our blinded test run on a population with a ratio of 1:4 cases to controls using logistic regression as a classifier (Table 3**)**, Moonstone was able to correctly identify those with FTD 16% of the time among cases and those with non-FTD 72% of the time among the control group. Simultaneously, when we forced our blinded test run on a population with a ratio of 1:4 cases to controls using random forest as a classifier, Moonstone was able to correctly identify those with FTD 13% of the time among cases and those with non-FTD 71% of the time among the control group (Table 4**)**. Therefore, for further analysis, using logistic regression as presented to be more sensitive by correctly identifying 88% of the FTD and non-FTD cases.

Table 3: Results From Logistic Regression Based Classifier for Moonstone Evaluation of FTD Cases

logistic_4Cost (88% correctly identified)	
Case Control	**Count of Subject**
Control	80
FTD	8
NO- FTD	72
Case	20
FTD	16
NO- FTD	4
Grand Total	**100**

Table 4: Results From Random Forest Based Classifier for Moonstone Evaluation of FTD Cases

Random_4Cost (84% identified correctly)	
Row Labels	Count of Subject
Control	80
FTD	9
NO- FTD	71
Case	20
FTD	13
NO- FTD	7
Grand Total	**100**

Aim 2: Evaluate whether the FTD clinical phenotypes in post-9/11 era U.S. military Veterans diagnosed with FTD vary by exposure to traumatic brain injury (TBI), spinal cord injury, and occupational risk to blast injury

- **Major Task 6:** Matched case control analysis
  Completion: Current completion- 50%

We have begun to use the logistic regression model for our Matched case control analysis, we will have the output ready for the next quarterly report

- **Major Task 7:** Complete manuscripts
  Completion: Current completion- 50%

We have begun to write the introduction and methods section in preparation for our first manuscript

Methods

Over the past quarter we have advanced the analysis of our data by applying the logistic regression as a classifier.

Opportunities for Training and Personal Development

While the project was not intended to provide training/professional development, we have provided opportunities for professional development on the team. Jamie Mayo and Lee Christensen provided training for new staff and graduate students, to prepare them for NLP development and case analysis in year two.

Dissemination to Communities of Interest

Nothing to report this quarter.

Plans for Next Reporting Period

Major Tasks 5 and 6: We will complete analysis of contributing factors that are unique to specific phenotypes and complete manuscripts in order to disseminate these findings.

4. IMPACT

Impact On The Development Of The Principal Disciplines Of The Project

None to report this quarter

Impact On Other Disciplines

None to report this quarter

Impact On Technology Transfer

None to report this quarter

Impact On Society Beyond Science And Technology
None to report this quarter

5. CHANGES/PROBLEMS

Changes in approach and reasons for change
There were no problems that arose during this reporting period.

Actual or anticipated problems or delays and actions or plans to resolve them
There were no problems that arose during this reporting period.

Changes that had a significant impact on expenditures
There were no problems that arose during this reporting period.

6. PRODUCTS

Conference Papers and Presentations
None to report this quarter

Papers Submitted
None to report this quarter

Website
We updated our university website to include information on our study and resources for Veterans and Service Members **https://medicine.utah.edu/internalmedicine/epidemiology/research_programs/torch/** .

7. PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS

Organization Name:	Location of Organization:	Organization Contributions:
University of Utah	Salt Lake City, Utah	Collaboration & Facilities

Name:	Project Role:	Researcher Identifier (ORCID):	Percent Effort:	Person Month(s) Worked this Year:
Jamie Mayo	Principal Investigator	0000-0003-4259-4938	50%	6
Mary Jo Pugh	Co-PI	0000-0003-4196-7763	23%	2.76
Lee Christenson	Programmer		45%	5.4
Tyler Cooper	Graduate Research Assistant		50%	6
Samin Panahi	Graduate Research Assistant		50%	6
Sreekanth Kamineni	Research Analyst		10%	1.2

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to Report

What other organizations were involved as partners?
Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS
Quad Chart Attached