



Adverse childhood experience and serotonin transporters: a gene environmental study of the risk of PTSD in soldiers (ACES).

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FINAL REPORT

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DECLARATION OF INTEREST

The views expressed are those of the author and do not reflect the official views or policy of the Department of Defense, Department of Veterans Affairs, or its Components. The voluntary, fully informed consent of the subject used in this research was obtained as required by 32 CFR 219 and DODI 3216.02_AFI40-402. Funding received through the Substance Abuse Working Group (SAWG) of the Joint Program Committee 5 (JPC-5) / Military Operational Medicine Research Program (MOMRP), US Army Medical Research and Materiel Command (USAMRMC), Air Force Research Laboratory FA8650-15-C-6588 P1; Air Force Research Laboratory FA8650-15-C-6588 P2.

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Feasibility of Implementing an Opioid Risk Mitigation System in Military Treatment Facilities to Mitigate Drug Use

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INTRODUCTION

The purpose of the overall protocol was to study the role of early childhood psychological trauma interactions with both adult psychological trauma as well as high risk Post-Traumatic Stress Disorder (PTSD) genotypes in the risk for development of PTSD. This work will highlight how genetic and environmental influences interact to alter the risk for PTSD. This research will provide a more in depth understanding for future studies related to PTSD.

Regulatory:

1. Institutional Review Board (IRB) application
 - IRB approved protocol, ICD, and HIPAA received on 28Aug2014. Annual reviews submitted yearly and are up to date with expiration on 02Oct2018.

Assessments:

2. Questionnaires, blood collection, SNPs and genetic analysis
 - Patients are asked to answer brief, validated, questionnaires
 - 2 tubes (6mL) of blood are collected from each patient.
 - Blood collection attempted on several patients was unsuccessful.
 - CAMD laboratory tested each samples and delivered the SNP risk factors identified for this protocol for each subject.
 - CRD laboratory tested each sample for genetic details.
 - Genetic data stored for future studies.
3. Recruitment:
 - Population targeted for this research study is soldiers who served in OEF/OIF/OND and witnessed combat (per subject's perspective).
 - Multiple locations utilized to increase patient recruitment efforts.
 - Total enrollment as of today is 321 patients out of the 510 needed for the study.
 - Enrollment continues as of 13Mar2018.

TABLE 1

| Subject # | Informed Consent and HIPPA Signed | Rand/ Enrollment Date | Number of blood samples collected | Completion or Disc. Date | Number of Visits Attended | SA E | Reason for Discontinuation if applicable |
|-----------|-----------------------------------|-----------------------|-----------------------------------|--------------------------|---------------------------|------|---|
| 140001 | Y | 12/9/2015 | 2 | | 1 | N | |
| 140002 | Y | 12/9/2015 | 2 | | 1 | N | |
| 140003 | Y | 12/9/2015 | 2 | | 1 | N | |
| 140004 | Y | 12/9/2015 | 2 | | 1 | N | |
| 140005 | Y | 12/9/2015 | 2 | | 1 | N | |
| 140006 | Y | 12/9/2015 | 2 | | 1 | N | |
| 140007 | Y | 12/9/2015 | 2 | | 1 | N | |
| 140008 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140009 | Y | 12/9/2015 | 2 | | 1 | N | |
| 140010 | Y | 12/9/2015 | 2 | | 1 | N | |
| 140011 | Y | 12/9/2015 | 2 | | 1 | N | |
| 140012 | Y | 12/9/2015 | 2 | | 1 | N | |
| 140013 | Y | 1/25/2016 | 2 | | 1 | N | |
| 140014 | Y | 1/25/2016 | 2 | | 1 | N | |
| 140015 | Y | 1/25/2016 | 2 | | 1 | N | |
| 140016 | Y | 1/25/2016 | 2 | | 1 | N | |
| 140017 | Y | 1/25/2016 | 2 | | 1 | N | |
| 140018 | Y | 1/25/2016 | 2 | | 1 | N | |
| 140019 | Y | 1/25/2016 | 2 | | 1 | N | |
| 140020 | Y | 1/25/2016 | 2 | | 1 | N | |
| 140021 | Y | 1/25/2016 | 2 | | 1 | N | |
| 140022 | Y | 1/25/2016 | 2 | | 1 | N | |
| 140023 | Y | | 2 | 1/25/2016 | 1 | N | DUAL ENROLLEE - 140224 (data for 140023 not utilized for study) |
| 140024 | Y | 1/25/2016 | 2 | | 1 | N | |
| 140025 | Y | 1/25/2016 | 2 | | 1 | N | |
| 140026 | Y | 1/25/2016 | 2 | | 1 | N | |
| 140027 | Y | 1/25/2016 | 2 | | 1 | N | |
| 140028 | Y | 1/26/2016 | 2 | | 1 | N | |
| 140029 | Y | 1/26/2016 | 2 | | 1 | N | |
| 140030 | Y | 1/26/2016 | 2 | | 1 | N | |
| 140031 | Y | 1/26/2016 | 2 | | 1 | N | |
| 140032 | Y | 1/26/2016 | 2 | | 1 | N | |

| | | | | | | | |
|--------|---|-----------|---|-----------|---|---|---|
| 140033 | Y | 1/26/2016 | 2 | | 1 | N | |
| 140034 | Y | 1/26/2016 | 2 | | 1 | N | |
| 140035 | Y | 1/26/2016 | 2 | | 1 | N | |
| 140036 | Y | 1/26/2016 | 2 | | 1 | N | |
| 140037 | Y | 1/26/2016 | 2 | | 1 | N | |
| 140038 | Y | 1/26/2016 | 2 | | 1 | N | |
| 140039 | Y | 1/26/2016 | 2 | | 1 | N | |
| 140040 | Y | 1/26/2016 | 2 | | 1 | N | |
| 140041 | Y | | 2 | 1/26/2016 | 1 | N | DUAL ENROLLEE - 140237 (data for 140041 not utilized for study) |
| 140042 | Y | 1/26/2016 | 2 | | 1 | N | |
| 140043 | Y | 1/26/2016 | 2 | | 1 | N | |
| 140044 | Y | 1/26/2016 | 2 | | 1 | N | DUAL ENROLLEE - 140223 |
| 140045 | Y | 1/26/2016 | 2 | | 1 | N | |
| 140046 | Y | 1/26/2016 | 2 | | 1 | N | |
| 140047 | Y | 1/26/2016 | 2 | | 1 | N | |
| 140048 | Y | 1/26/2016 | 2 | | 1 | N | |
| 140049 | Y | | 2 | 1/26/2016 | 1 | N | DUAL ENROLLEE - 140231 (data for 140049 not utilized for study) |
| 140050 | Y | 1/26/2016 | 2 | | 1 | N | |
| 140051 | Y | 1/26/2016 | 2 | | 1 | N | |
| 140052 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140053 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140054 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140055 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140056 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140057 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140058 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140059 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140060 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140061 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140062 | Y | 5/10/2016 | 2 | | 1 | N | |

| | | | | | | | |
|--------|---|-----------|---|-----------|---|---|----------------------|
| 140063 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140064 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140065 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140066 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140067 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140068 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140069 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140070 | Y | | 0 | 5/10/2016 | 1 | N | DNQ - abnormal CT |
| 140071 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140072 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140073 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140074 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140075 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140076 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140077 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140078 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140079 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140080 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140081 | Y | 3/29/2016 | 2 | | 1 | N | |
| 140082 | Y | 3/29/2016 | 2 | | 1 | N | |
| 140083 | Y | 3/29/2016 | 2 | | 1 | N | |
| 140084 | Y | 3/29/2016 | 2 | | 1 | N | |
| 140085 | Y | 4/5/2016 | 2 | | 1 | N | |
| 140086 | Y | 4/5/2016 | 2 | | 1 | N | |
| 140087 | Y | 4/5/2016 | 2 | | 1 | N | |
| 140088 | Y | 4/5/2016 | 2 | | 1 | N | |
| 140089 | Y | 4/5/2016 | 2 | | 1 | N | |
| 140090 | Y | 4/12/2016 | 2 | | 1 | N | |
| 140091 | Y | 4/12/2016 | 2 | | 1 | N | |
| 140092 | Y | 4/12/2016 | 2 | | 1 | N | |
| 140093 | Y | 4/12/2016 | 2 | | 1 | N | |
| 140094 | Y | 4/12/2016 | 2 | | 1 | N | |
| 140095 | Y | 4/12/2016 | 2 | | 1 | N | |
| 140096 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140097 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140098 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140099 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140100 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140101 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140102 | Y | 5/17/2016 | 2 | | 1 | N | |

| | | | | | | | |
|--------|---|-----------|---|-----------|---|---|---|
| 140103 | Y | 5/17/2016 | 2 | | 1 | N | |
| 140104 | Y | 5/17/2016 | 2 | | 1 | N | |
| 140105 | Y | 5/17/2016 | 2 | | 1 | N | |
| 140106 | Y | 5/17/2016 | 2 | | 1 | N | |
| 140107 | Y | 5/31/2016 | 2 | | 1 | N | |
| 140108 | Y | 5/31/2016 | 2 | | 1 | N | |
| 140109 | Y | 5/31/2016 | 2 | | 1 | N | |
| 140110 | Y | 5/31/2016 | 2 | | 1 | N | |
| 140111 | Y | 5/31/2016 | 2 | | 1 | N | |
| 140112 | Y | | 0 | 5/31/2016 | 1 | N | DNQ - unallowed medication |
| 140113 | Y | 6/7/2016 | 2 | | 1 | N | |
| 140114 | Y | 6/7/2016 | 2 | | 1 | N | |
| 140115 | Y | 6/7/2016 | 2 | | 1 | N | |
| 140116 | Y | 6/7/2016 | 2 | | 1 | N | |
| 140117 | Y | 6/7/2016 | 2 | | 1 | N | |
| 140118 | Y | 6/7/2016 | 2 | | 1 | N | |
| 140119 | Y | 6/21/2016 | 2 | | 1 | N | |
| 140120 | Y | 6/21/2016 | 2 | | 1 | N | |
| 140121 | Y | 6/21/2016 | 2 | | 1 | N | |
| 140122 | Y | 6/21/2016 | 2 | | 1 | N | |
| 140123 | Y | 6/21/2016 | 2 | | 1 | N | |
| 140124 | Y | 6/21/2016 | 2 | | 1 | N | |
| 140125 | Y | 6/21/2016 | 2 | | 1 | N | |
| 140126 | Y | 6/21/2016 | 2 | | 1 | N | |
| 140127 | Y | 6/21/2016 | 2 | | 1 | N | |
| 140128 | Y | 6/21/2016 | 2 | | 1 | N | |
| 140129 | Y | 7/12/2016 | 2 | | 1 | N | |
| 140130 | Y | 7/12/2016 | 2 | | 1 | N | |
| 140131 | Y | 7/12/2016 | 2 | | 1 | N | |
| 140132 | Y | 7/19/2016 | 2 | | 1 | N | |
| 140133 | Y | 7/19/2016 | 2 | | 1 | N | |
| 140134 | Y | 7/19/2016 | 2 | | 1 | N | |
| 140135 | Y | 7/19/2016 | 2 | | 1 | N | |
| 140136 | Y | 7/19/2016 | 2 | | 1 | N | |
| 140137 | Y | | 2 | 7/19/2016 | 1 | N | DUAL ENROLLEE - 140166 (data for 140137 not utilized for study) |

| | | | | | | | |
|--------|---|-----------|---|-----------|---|---|---|
| 140138 | Y | 7/19/2016 | 2 | | 1 | N | |
| 140139 | Y | 7/26/2016 | 2 | | 1 | N | |
| 140140 | Y | 7/26/2016 | 2 | | 1 | N | |
| 140141 | Y | 8/2/2016 | 2 | | 1 | N | |
| 140142 | Y | 8/2/2016 | 2 | | 1 | N | |
| 140143 | Y | 8/2/2016 | 2 | | 1 | N | |
| 140144 | Y | 8/2/2016 | 2 | | 1 | N | |
| 140145 | Y | 8/2/2016 | 2 | | 1 | N | |
| 140146 | Y | 8/2/2016 | 2 | | 1 | N | |
| 140147 | Y | 8/2/2016 | 2 | | 1 | N | |
| 140148 | Y | 8/2/2016 | 2 | | 1 | N | |
| 140149 | Y | | 0 | 8/2/2016 | 1 | N | DNQ - abnormal CT |
| 140150 | Y | 8/9/2016 | 2 | | 1 | N | |
| 140151 | Y | 8/9/2016 | 2 | | 1 | N | |
| 140152 | Y | 8/9/2016 | 2 | | 1 | N | |
| 140153 | Y | 8/9/2016 | 2 | | 1 | N | |
| 140154 | Y | 8/9/2016 | 2 | | 1 | N | |
| 140155 | Y | 8/9/2016 | 2 | | 1 | N | |
| 140156 | Y | 8/9/2016 | 2 | | 1 | N | |
| 140157 | Y | 8/23/2016 | 2 | | 1 | N | |
| 140158 | Y | 8/23/2016 | 2 | | 1 | N | |
| 140159 | Y | 8/30/2016 | 2 | | 1 | N | |
| 140160 | Y | 8/30/2016 | 2 | | 1 | N | |
| 140161 | Y | 5/10/2016 | 2 | | 1 | N | |
| 140162 | Y | 5/16/2016 | 2 | | 1 | N | |
| 140163 | Y | 5/16/2016 | 2 | | 1 | N | |
| 140164 | Y | 5/16/2016 | 2 | | 1 | N | |
| 140165 | Y | | 0 | 5/16/2016 | 1 | N | DNQ - did not return questionnaire and no blood collected |
| 140166 | Y | 5/16/2016 | 2 | | 1 | N | DUAL ENROLLEE - 140137 |
| 140167 | Y | 5/16/2016 | 2 | | 1 | N | |
| 140168 | Y | 5/16/2016 | 2 | | 1 | N | |
| 140169 | Y | 5/16/2016 | 2 | | 1 | N | |
| 140170 | Y | 5/16/2016 | 2 | | 1 | N | |
| 140171 | Y | 5/16/2016 | 2 | | 1 | N | |
| 140172 | Y | 5/17/2016 | 2 | | 1 | N | |

| | | | | | | | |
|--------|---|-----------|---|-----------|---|---|---|
| 140173 | Y | 5/17/2016 | 2 | | 1 | N | |
| 140174 | Y | 5/17/2016 | 2 | | 1 | N | |
| 140175 | Y | 5/17/2016 | 2 | | 1 | N | |
| 140176 | Y | 5/17/2016 | 2 | | 1 | N | |
| 140177 | Y | 5/24/2016 | 2 | | 1 | N | |
| 140178 | Y | 5/24/2016 | 2 | | 1 | N | |
| 140179 | Y | | 2 | 5/25/2016 | 1 | N | DUAL ENROLLEE - 140303 / DNQ - unallowed medication |
| 140180 | Y | 5/25/2016 | 0 | | 1 | N | |
| 140181 | Y | 5/25/2016 | 2 | | 1 | N | |
| 140182 | Y | 5/25/2016 | 2 | | 1 | N | |
| 140183 | Y | 5/25/2016 | 2 | | 1 | N | |
| 140184 | Y | 5/25/2016 | 2 | | 1 | N | |
| 140185 | Y | 5/25/2016 | 2 | | 1 | N | |
| 140186 | Y | 5/25/2016 | 2 | | 1 | N | |
| 140187 | Y | 5/25/2016 | 2 | | 1 | N | |
| 140188 | Y | 5/25/2016 | 2 | | 1 | N | |
| 140189 | Y | 5/25/2016 | 2 | | 1 | N | |
| 140190 | Y | 5/25/2016 | 0 | | 1 | N | |
| 140191 | Y | 5/25/2016 | 2 | | 1 | N | |
| 140192 | Y | 5/25/2016 | 2 | | 1 | N | |
| 140193 | Y | 5/25/2016 | 2 | | 1 | N | |
| 140194 | Y | 5/25/2016 | 2 | | 1 | N | |
| 140195 | Y | | 0 | 5/25/2016 | 1 | N | DNQ - unallowed medication |
| 140196 | Y | 5/25/2016 | 2 | | 1 | N | |
| 140197 | Y | 5/25/2016 | 2 | | 1 | N | |
| 140198 | Y | 5/25/2016 | 2 | | 1 | N | |
| 140199 | Y | 5/25/2016 | 2 | | 1 | N | |
| 140200 | Y | 5/25/2016 | 0 | | 1 | N | |
| 140201 | Y | 7/13/2016 | 2 | | 1 | N | |
| 140202 | Y | 7/13/2016 | 2 | | 1 | N | |
| 140203 | Y | 7/13/2016 | 2 | | 1 | N | |
| 140204 | Y | 7/13/2016 | 2 | | 1 | N | |
| 140205 | Y | 7/13/2016 | 2 | | 1 | N | |
| 140206 | Y | 7/13/2016 | 2 | | 1 | N | |
| 140207 | Y | 3/8/2016 | 2 | | 1 | N | |

| | | | | | | | |
|--------|---|------------|---|------------|---|---|--|
| 140208 | Y | 8/3/2016 | 2 | | 1 | N | |
| 140209 | Y | 8/3/2016 | 2 | | 1 | N | |
| 140210 | Y | 8/3/2016 | 0 | | 1 | N | |
| 140211 | Y | 8/3/2016 | 2 | | 1 | N | |
| 140212 | Y | 8/3/2016 | 2 | | 1 | N | |
| 140213 | Y | 8/3/2016 | 2 | | 1 | N | |
| 140214 | Y | 11/14/2016 | 2 | | 1 | N | |
| 140215 | Y | 11/14/2016 | 2 | | 1 | N | |
| 140216 | Y | 11/14/2016 | 2 | | 1 | N | |
| 140217 | Y | 11/14/2016 | 2 | | 1 | N | |
| 140218 | Y | | 0 | 11/14/2016 | 1 | N | DUAL ENROLLEE - 140302 (data for 140218 not utilized for study) |
| 140219 | Y | 11/15/2016 | 0 | | 1 | N | |
| 140220 | Y | 11/15/2016 | 2 | | 1 | N | |
| 140221 | Y | 11/21/2016 | 2 | | 1 | N | |
| 140222 | Y | 11/21/2016 | 2 | | 1 | N | |
| 140223 | Y | | 2 | 11/21/2016 | 1 | N | DUAL ENROLLEE - 140044 (data for 140223 not utilized in the study) |
| 140224 | Y | 11/21/2016 | 2 | | 1 | N | DUAL ENROLLEE - 140023 |
| 140225 | Y | 11/21/2016 | 2 | | 1 | N | |
| 140226 | Y | 11/21/2016 | 2 | | 1 | N | |
| 140227 | Y | 11/21/2016 | 2 | | 1 | N | |
| 140228 | Y | 11/22/2016 | 2 | | 1 | N | |
| 140229 | Y | 11/22/2016 | 2 | | 1 | N | |
| 140230 | Y | 11/22/2016 | 2 | | 1 | N | |
| 140231 | Y | 11/22/2016 | 2 | | 1 | N | DUAL ENROLLEE - 140049 |
| 140232 | Y | 11/22/2016 | 2 | | 1 | N | |
| 140233 | Y | 11/22/2016 | 2 | | 1 | N | |
| 140234 | Y | 11/22/2016 | 2 | | 1 | N | |

| | | | | | | | |
|--------|---|------------|---|------------|---|---|-----------------------------------|
| 140235 | Y | 11/22/2016 | 2 | | 1 | N | |
| 140236 | Y | 11/22/2016 | 2 | | 1 | N | |
| 140237 | Y | 1/26/2016 | 2 | | 1 | N | DUAL ENROLLEE - 140041 |
| 140238 | Y | 2/7/2017 | 2 | | 1 | N | |
| 140239 | Y | 2/7/2017 | 2 | | 1 | N | |
| 140240 | Y | 2/7/2017 | 2 | | 1 | N | |
| 140241 | Y | 8/30/2016 | 2 | | 1 | N | |
| 140242 | Y | 8/30/2016 | 2 | | 1 | N | |
| 140243 | Y | 8/30/2016 | 2 | | 1 | N | |
| 140244 | Y | 8/30/2016 | 2 | | 1 | N | |
| 140245 | Y | 9/20/2016 | 2 | | 1 | N | |
| 140246 | Y | | 0 | 9/20/2016 | 1 | N | DNQ - prior loss of consciousness |
| 140247 | Y | 9/20/2016 | 2 | | 1 | N | |
| 140248 | Y | | 0 | 9/20/2016 | 1 | N | DNQ - unallowed medication |
| 140249 | Y | 9/27/2016 | 2 | | 1 | N | |
| 140250 | Y | 9/27/2016 | 2 | | 1 | N | |
| 140251 | Y | 9/27/2016 | 2 | | 1 | N | |
| 140252 | Y | 9/27/2016 | 2 | | 1 | N | |
| 140253 | Y | 10/4/2016 | 2 | | 1 | N | |
| 140254 | Y | | 0 | 10/4/2016 | 1 | N | DNQ - unallowed medication |
| 140255 | Y | 10/4/2016 | 2 | | 1 | N | |
| 140256 | Y | 10/11/2016 | 2 | | 1 | N | |
| 140257 | Y | 10/11/2016 | 2 | | 1 | N | |
| 140258 | Y | | 0 | 10/11/2016 | 1 | N | DNQ - abnormal MRI |
| 140259 | Y | 10/11/2016 | 2 | | 1 | N | |
| 140260 | Y | 10/11/2016 | 2 | | 1 | N | |
| 140261 | Y | 10/11/2016 | 2 | | 1 | N | |
| 140262 | Y | 10/11/2016 | 2 | | 1 | N | |
| 140263 | Y | 11/1/2016 | 2 | | 1 | N | |
| 140264 | Y | 11/1/2016 | 2 | | 1 | N | |
| 140265 | Y | 11/8/2016 | 2 | | 1 | N | |
| 140266 | Y | 11/8/2016 | 2 | | 1 | N | |
| 140267 | Y | 11/15/2016 | 2 | | 1 | N | |

| | | | | | | | |
|--------|---|------------|---|------------|---|---|-------------------------------|
| 140268 | Y | 11/15/2016 | 2 | | 1 | N | |
| 140269 | Y | 11/15/2016 | 2 | | 1 | N | |
| 140270 | Y | 11/15/2016 | 2 | | 1 | N | |
| 140271 | Y | 11/15/2016 | 2 | | 1 | N | |
| 140272 | Y | | 0 | 11/15/2016 | 1 | N | DNQ - abnormal radiology read |
| 140273 | Y | 11/29/2016 | 2 | | 1 | N | |
| 140274 | Y | 11/29/2016 | 2 | | 1 | N | |
| 140275 | Y | 11/29/2016 | 2 | | 1 | N | |
| 140276 | Y | 11/29/2016 | 2 | | 1 | N | |
| 140277 | Y | 11/29/2016 | 2 | | 1 | N | |
| 140278 | Y | 12/6/2016 | 2 | | 1 | N | |
| 140279 | Y | 12/6/2016 | 2 | | 1 | N | |
| 140280 | Y | 12/6/2016 | 2 | | 1 | N | |
| 140281 | Y | 12/6/2016 | 2 | | 1 | N | |
| 140282 | Y | 12/6/2016 | 2 | | 1 | N | |
| 140283 | Y | 12/13/2016 | 2 | | 1 | N | |
| 140284 | Y | 12/13/2016 | 2 | | 1 | N | |
| 140285 | Y | 12/13/2016 | 2 | | 1 | N | |
| 140286 | Y | 12/13/2016 | 2 | | 1 | N | |
| 140287 | Y | 12/13/2016 | 2 | | 1 | N | |
| 140288 | Y | 1/10/2017 | 2 | | 1 | N | |
| 140289 | Y | 1/10/2017 | 2 | | 1 | N | |
| 140290 | Y | 1/10/2017 | 2 | | 1 | N | |
| 140291 | Y | 1/10/2017 | 2 | | 1 | N | |
| 140292 | Y | 1/10/2017 | 2 | | 1 | N | |
| 140293 | Y | 1/10/2017 | 2 | | 1 | N | |
| 140294 | Y | 1/17/2017 | 2 | | 1 | N | |
| 140295 | Y | 1/17/2017 | 2 | | 1 | N | |
| 140296 | Y | 1/17/2017 | 2 | | 1 | N | |
| 140297 | Y | 1/17/2017 | 2 | | 1 | N | |
| 140298 | Y | 1/17/2017 | 2 | | 1 | N | |
| 140299 | Y | 1/17/2017 | 2 | | 1 | N | |
| 140300 | Y | 1/17/2017 | 2 | | 1 | N | |
| 140301 | Y | 1/17/2017 | 2 | | 1 | N | |
| 140302 | Y | 1/17/2017 | 2 | | 1 | N | DUAL ENROLLEE - 140218 |
| 140303 | Y | | 0 | 1/17/2017 | 1 | N | DUAL ENROLLEE - 140179 / |

| | | | | | | | |
|--------|----|-----------|---|-----------|---|---|---|
| | | | | | | | DNQ - unallowed medication |
| 140304 | Y | 1/24/2017 | 2 | | 1 | N | |
| 140305 | Y | 1/24/2017 | 2 | | 1 | N | |
| 140306 | Y | 1/24/2017 | 2 | | 1 | N | |
| 140307 | Y | 1/24/2017 | 2 | | 1 | N | |
| 140308 | Y | 1/24/2017 | 2 | | 1 | N | |
| 140309 | Y | 1/31/2017 | 2 | | 1 | N | |
| 140310 | Y | 1/31/2007 | 2 | | 1 | N | |
| 140311 | Y | 1/31/2017 | 2 | | 1 | N | |
| 140312 | Y | 2/8/2017 | 2 | | 1 | N | |
| 140313 | Y | 2/14/2017 | 2 | | 1 | N | |
| 140314 | Y | | 0 | 2/14/2017 | 1 | N | DNQ - unallowed medication |
| 140315 | Y | 2/14/2017 | 2 | | 1 | N | |
| 140316 | Y | 2/14/2017 | 2 | | 1 | N | |
| 140317 | Y | 2/21/2017 | 2 | | 1 | N | |
| 140318 | NO | | 0 | | 1 | N | PIN # designated to patient, but patient took home ICD to review and declined participation |
| 140319 | Y | 2/21/2017 | 2 | | 1 | N | |
| 140320 | Y | 2/21/2017 | 2 | | 1 | N | |
| 140321 | Y | 2/21/2017 | 2 | | 1 | N | |
| 140322 | Y | 2/21/2017 | 2 | | 1 | N | |
| 140323 | Y | 2/28/2017 | 2 | | 1 | N | |
| 140324 | Y | 2/28/2017 | 2 | | 1 | N | |
| 140325 | Y | 2/28/2017 | 2 | | 1 | N | |
| 140326 | Y | 3/21/2017 | 2 | | 1 | N | |
| 140327 | Y | 3/21/2017 | 2 | | 1 | N | |
| 140328 | Y | 4/4/2017 | 2 | | 1 | N | |
| 140329 | Y | | 0 | 4/4/2017 | 1 | N | DNQ - unallowed medication |
| 140330 | Y | 4/4/2017 | 2 | | 1 | N | |

| | | | | | | | |
|--------|---|-----------|---|-----------|---|---|-----------------------------------|
| 140331 | Y | | 0 | 5/9/2017 | 1 | N | DNQ - abnormal radiology read |
| 140332 | Y | 8/22/2017 | 2 | | 1 | N | |
| 140333 | Y | 8/22/2017 | 2 | | 1 | N | |
| 140334 | Y | 11/6/17 | 2 | | 1 | N | |
| 140401 | Y | | 0 | 5/16/2017 | 1 | N | DNQ - prior loss of consciousness |
| 140402 | Y | 5/16/2017 | 2 | | 1 | N | |
| 140403 | Y | 5/16/2017 | 2 | | 1 | N | |
| 140404 | Y | 5/17/2017 | 2 | | 1 | N | |
| 140405 | Y | 5/17/2017 | 2 | | 1 | N | |
| 140406 | Y | 5/17/2017 | 2 | | 1 | N | |
| 140407 | Y | 5/31/2017 | 2 | | 1 | N | |
| 140408 | Y | 5/31/2017 | 2 | | 1 | N | |
| 140409 | Y | 5/31/2017 | 2 | | 1 | N | |

4. Analysis:

- Genetic analysis: At time of report, 273 subjects had been analyzed. Key hypotheses tested included correlations of PTSD diagnosis with combat exposure scale, adverse childhood experiences. Similar analysis was also performed on outcome variable of PTSD checklist – military (PCL-M). Additionally the presence of sensitizing single nucleotides polymorphisms were also tested for the correlation with PTSD diagnosis. Both combat exposure scores and adverse childhood experience scores significantly increased risk for diagnosis of PTSD with correlations of .262, $p < 0.001$ and .147, $p < 0.0147$. The presence SNP of rs7209436 (part of the hypothalamic-pituitary-adrenal pathway) significantly increased risk of PTSD diagnosis after combat. The odds of being diagnosed for PTSD for those with 1 in Rs7209436 was 53% less than that for those with 2 in Rs7209436 (OR = 0.47, 95% CI: 0.24-0.92, $p = 0.03$) after adjusted for age and sex. Similarly, ACE scores and CES also significantly correlated with symptoms of PTSD as measure via PCL-M. CES and ACES scores had significant association of PCL-M scores ($p = 0.0004$ and $p = 0.0012$).
- Methylation Analysis: 170 subjects underwent methylation analysis, with 70 subjects having a diagnosis of PTSD. Significant methylation differences were found across all assays and CpG sites for BDNF and NR3C1 with lower methylation levels seen in PTSD cases when compared to controls, ($p=0.0001$ –

0.031). No significant differences were found between PTSD and non-PTSD groups for SKA2, IL-18, MAN2C1 and SLC6A4, however a minor trend in the PTSD group showed lower methylation levels within these genes. There were no significant findings when assessing methylation levels by age, gender or ethnicity. Higher anti-depressant use was found amongst non-PTSD subjects. 2 way ANCOVA showed that when controlling for anti-depressant use, lower methylation levels within BDNF and NR3C1 remained significant in the PTSD group versus the non-PTSD subjects. Higher PCL-M scores were highly correlated with PTSD diagnosis. Higher ACE scores across all subjects (n=170) were associated with increased methylation (the only trend in all analyses that showed increased methylation) however this trend was only significant for position 2 within SLC6A4.

- Autonomics Analysis: Pending analysis

5. Interpretation:

- Primary Hypothesis: This study identified that experience, both in the form of adverse childhood experience and combat exposure significantly increased risk for PTSD following combat exposure. The only genetic marker with significant risk of PTSD diagnosis was associated with the glucocorticoid receptor pathway with preferential transcription in brain. Further work is necessary to determine pathophysiology of this risk factor as well as explore pharmacologic interventions that may mitigate this risk.
- Methylation Analysis: This study identified epigenetic changes (decreased methylation) significantly correlated with a diagnosis of post-traumatic stress disorder in both a gene that effects neuronal function and synaptic transmission (BDNF) as well the gene of a ubiquitously distributed glucocorticoid receptor (NR3C1) to which cortisol and other stress hormones bind. Additionally, regardless of the diagnosis of PTSD, adverse childhood experiences, had a trend of increased methylation at all methylation sites tested. Both results suggest a complex interplay between early childhood traumatic experiences and combat exposure to produce epigenetic changes within service members. To gain further insight into the significance of these findings and develop possible targeted treatments and biomarkers for post-traumatic stress disorder, future efforts will need to quantify the biochemical effect of such changes in methylation and correlate them with clinical pathology.
- Autonomics Analysis: Pending analysis

6. Manuscript preparation and results dissemination:

- No publications to date
- 3 manuscripts in preparation
- 4 poster presentations at MHSRS

KEY RESEARCH ACCOMPLISHMENTS:

- Over 300 subjects recruited.
- Repository of genetic data for future PTSD studies established
- 4 resident sub-projects performed with 3 manuscripts in preparation for peer review journals.

REPORTABLE OUTCOMES:

- Pending final analysis of data.

CONCLUSION:

- Risk factors for PTSD in this cohort of service members appears to be dominated by experience. However risk factors from changes in the glucocorticoid receptor pathway appear to alter risk while the diagnosis of PTSD may alter methylation of several key neurotransmitter systems. This cohort data will be used to develop a prospective trial to study how experience interacts with genetics to produce changes in methylation patterns and PTSD risk following trauma.

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APPENDICES:

| LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS | |
|--|--|
| ACES | Adverse Childhood Experience Scores |
| ANCOVA | Analysis of covariance |
| BDNF | Brain-derived neurotrophic factors |
| CES | Combat Exposure Scale |
| CpG | Cytosine and guanine separated by only one phosphate |
| IL-18 | Interleukin 18 |
| MAN2C1 | Mannosidase alpha class 2c member 1 |
| NR3C1 | Glucocorticoid receptor |
| PCL-M | PTSD Checklist - Military |
| PTSD | Post-traumatic Stress Disorder |
| SKA2 | Spindle and kinetochore associated complex subunit 2 |
| SLC6A4 | Serotonin transporter |