Seeking Risk and Resilience Factors for PTSD: The Marine Resiliency Study

Dewleen G. Baker M.D.
Professor, Department of Psychiatry
University of California San Diego
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Lifetime</th>
<th>12-Month</th>
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<tbody>
<tr>
<td>Any psychiatric disorder</td>
<td>48.0</td>
<td>29.5</td>
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<tr>
<td>Any affective disorder</td>
<td>19.3</td>
<td>11.3</td>
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<tr>
<td>Major depressive disorder</td>
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<td>Dysthymia</td>
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<td>Manic episode</td>
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<td>Any anxiety disorder</td>
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<td>7.1</td>
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<td>Simple phobia</td>
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<td>Panic disorder</td>
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<td>Post-Traumatic Stress Disorder</td>
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<td>Any substance abuse/dependence</td>
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<td>Alcohol abuse w/o dependence</td>
<td>9.4</td>
<td>2.5</td>
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<tr>
<td>Alcohol dependence</td>
<td>14.1</td>
<td>7.2</td>
</tr>
</tbody>
</table>

(Kessler RC et al, 1994; Narrow et al, 2002; Ruscio et al, 2007)
DSM-V Trauma/Stress Disorders

- Reactive Attachment Disorder (Infants/Children)
- Disinhibited Social Engagement Disorder
- Post-traumatic Stress Disorder
- Acute stress disorder
- Adjustment Disorders
- Other Specified Trauma- and Stressor-Related Disorder
Trauma/Stress Disorders

**DSM-V Diagnosis – Trauma/Stressor Criteria**
Criteria apply to adults, adolescents, children older than 6 years

• Exposure to actual or threatened death, serious injury, or sexual violation in one (or more) of the following ways:
  – Directly experiencing the traumatic event(s).
  – Witnessing, in person, the event(s) as it occurred to others.
  – Learning that the event(s) occurred to a close family member or close friend. **Note:** In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.
Trauma/Stress Disorders

**DSM-V Diagnosis – Trauma/Stressor Criteria**

- Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains, police officers repeatedly exposed to details of child abuse).

  - **Note:** This does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.
Posttraumatic Stress Disorder

**DSM-V Diagnosis**

- Presence of one (or more) **intrusion symptoms** associated with the traumatic event(s), beginning after the traumatic event(s) occurred: (re-experiencing)
- Persistent **avoidance** of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following: avoidance of thoughts/feelings, avoidance of external reminders
- **Negative alterations in cognitions and mood** associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following: difficulty remembering, exaggerated negative beliefs/expectations, distorted cognitions, anhedonia, etc.
- Marked **alterations in arousal and reactivity** associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following: irritable behavior and angry outbursts, reckless or self destructive behavior, hypervigilance, etc.
- Duration of the disturbance (Criteria B, C, D, and E) is more than 1 month.
Posttraumatic Stress Disorder

**DSM-V Diagnostic Features**

- Prevalence among recently exposed populations varies by nature of the event and the context within which it is assessed

- Common rates in the US
  - Projected lifetime risk (under DSM-IV criteria) at age 75 is 8.7% for the general population
  - Reported risk for the Iraq/Afghanistan combatants varies by the publication source, ranging from 5% to 20%

PTSD confers higher risk for a number of Medical Conditions

- PTSD is associated with an increased risk for:
  - Atherosclerotic cardiovascular disease
  - Inflammatory and autoimmune disorders
  - Metabolic syndrome
  - Dementia
Historical Background

*Post-Vietnam to the Iraq/Afghanistan Wars*

*Cross-sectional Areas of Research*

- PTSD risk/resilience factors (psychosocial)
  - Childhood adversity
  - Level of (index) trauma burden
  - Neurological intactness/IQ
  - Social support

- PTSD – biological system abnormalities
In individuals with a diagnosis of PTSD, peripheral and Cerebrospinal fluid studies give evidence for abnormalities associated with:

- The central nervous system (hyperarousal)
- HPA axis
- Autonomic nervous system
- Inflammatory markers
Historical Background

Stress and Immune Physiology

- Serial cerebral spinal fluid study
  - Recruitment of healthy individuals
    - Non-smokers
    - No past alcohol dependence and no current abuse
    - No medications or wash-out for at least 5 half-lives prior to procedure
  - Standardized Diet for duration of Study – set meals/calories
  - Controlled environment – no radio, television
  - Subarachnoid catheter placement at 8AM – 3 hours of rest prior to CSF sampling
  - 24 (every hour) basal samples of CSF and plasma (11AM to 11AM) assayed for NPY concentration or measured using direct radioimmunoassay or for cortisol concentration
Historical Background

Stress and Immune Physiology

Increased CNS NE and CRF

Geracioti et al., 2001

Baker et al., 1999
Historical Background

Stress and Immune Physiology
Abnormal HPA response to stress

Following Trauma-related (vs neutral) video:
- Significant decline in CSF CRF levels following trauma-related video
- Significant decline in Plasma cortisol levels following trauma video

Geracioti et al., 2001
Historical Background

**Stress and Immune Physiology**

**Abnormal HPA response to stress**

Following Trauma-related (vs neutral) video:
- Significant decline in CSF CRF levels following trauma-related video
- Significant decline in Plasma cortisol levels following trauma video

Geracioti et al., 2001
Historical Background

Stress and Immune Physiology
Abnormal Autonomic Response
to stress & increasing evidence
for chronic inflammation

Diminished vagal activity and blunted diurnal variation of heart rate
dynamics in posttraumatic stress disorder

AGORASTOS AGORASTOS\textsuperscript{1,2}, JUDITH A. BOEL\textsuperscript{3}, PIA S. HEPPNER\textsuperscript{4,5}, TORBEN HAGER\textsuperscript{3},
TOBIAS MOELLER-BERTRAM\textsuperscript{1,4,5}, UZAIR HAJI\textsuperscript{5}, ARAME MOTAZED\textsuperscript{1,5},
MATTHEW A. YANAGI\textsuperscript{1}, DEWLEEN G. BAKER\textsuperscript{1,4,5,*}, & OLIVER STIEDL\textsuperscript{3,*}

\textsuperscript{1}Veterans Affairs Center of Excellence for Stress and Mental Health, VA San Diego, CA, USA, \textsuperscript{2}Department of Psychiatry and
Psychotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, \textsuperscript{3}Behavioral Neuroscience Group, Departments of
Functional Genomics and Molecular and Cellular Neurobiology, Center for Neurogenomics and Cognitive
Research, Neuroscience Campus Amsterdam, VU University, Amsterdam, The Netherlands, \textsuperscript{4}Department of Psychiatry,
University of California, San Diego, CA, USA, and \textsuperscript{5}VA San Diego Healthcare System, San Diego, CA, USA

(Received 14 June 2012; accepted 12 November 2012)
Marine Resiliency Study

Dewleen G. Baker M.D.
Caroline Nievergelt Ph.D.
Victoria Risbrough Ph.D.
Mark Geyer Ph.D.
Marine Resiliency Study

Field Study: 1st Marine Division
• Infantry Battalions, Combat Engineers
• Explosive Ordinance Device (EOD)
Participants: Marines, Navy Personnel

Setting
• Marine Corps Air Ground Combat Center - 29 Palms
• Camp Pendleton

Six-wide semi-permanent data collection trailer at MCAGCC 29 Palms
Marine Resiliency Study


- **Pre-Deployment**
  - Visit 0
  - 7 months
  - N = 2593

- **Post-Deployment**
  - Visit 1: 1 week
  - Visit 2: 3 months
  - Visit 3: 6 months
  - N = 2231
  - N = 1898
  - N = 1645

- **Post Second Deployment**
  - Visit 4
  - N = 203


- **Cohorts 11-12**
  - Pre-Deployment
    - Visit 0
    - 7 months
    - N = 1190
  - Post-Deployment
    - Visit 1
    - N = 886

- **Cohort 13 (control group)**
  - No Deployment
  - Visit 0
  - 7 months
  - N = 195
  - Visit 1
  - N = 163

Timeline and Enrollment
MRS Longitudinal Data Sources

Psychological and Behavioral assessments

Psychiatric and medical
- Clinical interviews: PTSD/TBI

Historical
- Self-report questionnaires

Neuropsychological
- ANAM + Penn Battery

Biological assessments

Biomarkers
- e.g. NPY, CRP, Alpha-amylase, Catecholamines, Cortisol

Hemodynamics
- Pulse and blood pressure

Psychophysiology
- EMG, PPG

Metabolomics
- Imaging (MEG/DTI)

Career History Archival Medical and Personnel System database

Military archives
- Medical diagnoses
- Hospitalizations
- Outpatient healthcare visits
- Duty status
- Separation date and reason

Biobank

Biological samples
- Blood (whole blood, plasma)
- Saliva
- Urine
- DNA / RNA

Genomics*

- GWAS (complete data)
- Methylome (subset, pre-post)
- Transcriptome (subset, pre-post)

*GWAS UCSD, NIH R0-1 Caroline Nievergelt PI
*Gene expression, UCSD, R21 Ming Tsuang PI
*Methylome, RNA-seq C Nievergelt MRS-II

- N=640 Army soldiers, Iraq 2003-2004
- Combat/combat support
- Combat Experience Score Mean(SD) = 34.7(10.4)
Deployment-related TBI endorsement was variable across deployments, but was high in some battalions.

<table>
<thead>
<tr>
<th>Combat Experience Scale</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>6.5</td>
<td>6.9</td>
<td>13.2</td>
<td>22.7</td>
<td>12.9</td>
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</table>
Clinician Administered PTSD Scale (CAPS)

- The MRS uses the CAPS as the primary measure of PTSD symptoms and total symptom burden.
- The CAPS is a structured interview designed to provide both continuous and dichotomous data about symptoms.

<table>
<thead>
<tr>
<th>4 Symptom Clusters</th>
<th>CAPS Scale Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-experiencing</td>
<td>0-40</td>
</tr>
<tr>
<td>Avoidance</td>
<td>0-32</td>
</tr>
<tr>
<td>Emotional Numbing</td>
<td>0-24</td>
</tr>
<tr>
<td>Hyperarousal</td>
<td>0-40</td>
</tr>
<tr>
<td>Total score</td>
<td>0-136</td>
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</table>
ZINB Distribution

- CAPS total score is not a normally distributed trait in MRS. The trait cannot simply be transformed to normality because there are too many zero value scores.
- Zero inflated negative binomial (ZINB) distribution: ZINBR best statistical model.

Histogram of CAPS score at V2

N subjects

CAPS total score
Grouping subjects using CAPS DSM-IV diagnosis:

- Alternatives to modeling based upon raw score (CAPS total), we can use diagnosis to group subjects and use ordered logistic regression to model the data.
- There are 3 groups in order of severity: No diagnosis, partial PTSD diagnosis (stringent or lenient criteria), or the DSM-IV based PTSD diagnosis.

**Quantity of subjects within each CAPS group at V2**

- No PTSD Dx: N=1471
- Partial PTSD Dx: N=277
- Full PTSD Dx: N=117
Prospective analysis of deployment-related combat stress and TBI on Post-deployment PTSD

- Age
- AFQT
- Pre-deployment PTSD symptoms
- Pre-deployment TBI
- Cohort (Battalion)

Combat Experiences

Combat-related TBI

3-months post-deployment PTSD symptoms

7 months deployment

Pre-deployment

Post-deployment
Original Investigation

Association Between Traumatic Brain Injury and Risk of Posttraumatic Stress Disorder in Active-Duty Marines

Kate A. Yurgil, PhD; Donald A. Barkauskas, PhD; Jennifer J. Vasterling, PhD; Caroline M. Nievergelt, PhD; Gerald E. Larson, PhD; Nicholas J. Schork, PhD; Brett T. Litz, PhD; William P. Nash, MD; Dewleen G. Baker, MD; for the Marine Resiliency Study Team

Published online December 11, 2013.
Prospective Associations Between Traumatic Brain Injury and Postdeployment Tinnitus in Active-Duty Marines

Kate A. Yurgil, PhD; Royce E. Clifford, MD, MPH; Victoria B. Risbrough, PhD; Mark A. Geyer, PhD; Mingxiong Huang, PhD; Donald A. Barkauskas, PhD; Jennifer J. Vasterling, PhD; MRS Team; Dewleen G. Baker, MD

Cardio-Metabolic function before and after combat stress

Dynapulse station

Daniel T. O’Connor
Samples collected and processed on site:

- **Urine**: 6x 2ml cryovials with almost 2ml urine

- **Saliva**: 4x 2ml cryovials with at least 1ml saliva

- **Blood**:
  - **Plasma samples**: 2x 4ml Lithium Heparin tubes (green tops); 4 aliquots
  1x 6ml EDTA tubes (purple tops); 2 aliquots
  Plasma samples are centrifuged at 4°C, 3000rpm for 15 min; keep supernatant

- **RNA samples**: 1x 10ml EDTA tubes (purple tops) for RNA processing (Ming Tsuang –lab)

- **DNA whole-blood samples**: 1x 10ml EDTA tubes (purple tops) for whole blood DNA (6/4 cryovials with ~1ml blood)

Samples are kept on dry ice during processing and stored in freezer at -80°C
Salivary cortisol: Circadian Rhythm

ANOVA: dependent = logCortisol
N= 1695
R= -0.25; p<0.00001
Age-adjusted

No significant correlation with dynapulse time was found for:
- log Salivary Cotinine: p>0.68
- log Plasma CRP: p>0.71
- log Salivary Alpha-amylase: p>0.36
Assessment of Plasma C-Reactive Protein as a Biomarker of Posttraumatic Stress Disorder Risk

Main Outcomes and Measures  Severity of PTSD symptoms 3 months after deployment assessed by the Clinician-Administered PTSD Scale (CAPS).

Conclusions and Relevance  A marker of peripheral inflammation, plasma CRP may be prospectively associated with PTSD symptom emergence, suggesting that inflammation may predispose to PTSD.
Genomic Predictors of Combat Stress Vulnerability in U.S. Marines: Genome-wide Association Studies across Multiple Ancestries Identify Novel Risk Factors for PTSD

Caroline Nievergelt Ph.D.
Department of Psychiatry, UCSD
Associate Director of Neuroscience Center of Excellence for Stress and Mental Health, VA SD (CESAMH)
MRS: Genetic Ancestry

~62% European American

- Bayesian based cluster methods (STRUCTURE) to generate ancestry estimates based on HGDP reference populations and AIMS
- Determination of main ancestral groups (<5% admixture)
- Visual inspection: PCA with reference populations and color coding for main ancestral groups
Genomic predictors of combat stress vulnerability and resilience in U.S. Marines: A genome-wide association study across multiple ancestries implicates PRTFDC1 as a potential PTSD gene

Caroline M. Nievergelt, Adam X. Maihofer, Maja Mustapic, Kate A. Yurgil, Nicholas J. Schork, Mark W. Miller, Mark W. Logue, Mark A. Geyer, Victoria B. Risbrough, Daniel T. O’Connor, Dewleen G. Baker
The catecholamine biosynthetic enzyme dopamine β-hydroxylase (DBH): first genome-wide search positions trait-determining variants acting additively in the proximal promoter

Maja Mustapic1,2,4, Adam X. Maihofer1, Manjula Mahata2, Yuqing Chen2, Dewleen G. Baker1,3, Daniel T. O’Connor2 and Caroline M. Nievergelt1,3,*
MRS Genomic and Data Integration

- DNA and RNA isolated from peripheral blood leukocytes
- 60 (future) PTSD cases and 60 trauma-exposed controls
- Timepoints: at pre-deployment, and 3- and 6-months post-deployment
- Epigenome: Genome-wide methylation (Illumina 450K)
- Transcriptome: Genome-wide gene expression (RNAseq)
- Transcriptome 2: RNA array data on additional MRS subjects
MRS Longitudinal Data Sources

**Psychological and Behavioral assessments**
- **Psychiatric and medical**
  - Clinical interviews
- **Historical**
  - Self-report questionnaires
- **Neuropsychological**
  - ANAM + Penn Battery

**Biological assessments**
- **Biomarkers**
  - e.g. NPY, CRP, Alpha-amylase, Catecholamines, Cortisol
- **Hemodynamics**
  - Pulse and blood pressure
- **Psychophysiology**
  - EMG, PPG
- **Metabolomics**
  - Imaging (MEG/DTI)

**Career History Archival Medical and Personnel System database**
- **Military archives**
  - Medical diagnoses
  - Hospitalizations
  - Outpatient healthcare visits
  - Duty status
  - Separation date and reason

**Biobank**
- **Biological samples**
  - Blood (whole blood, plasma)
  - Saliva
  - Urine
  - DNA / RNA

**Genomics**
- **GWAS** (complete data)
- **Methylome** (subset, pre-post)
- **Transcriptome** (subset, pre-post)

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*GWAS UCSD, NIH R0-1
Caroline Nievergelt PI
*Gene expression, UCSD, R21 Ming Tsuang PI
*Methylome, RNA-seq
C Nievergelt MRS-II
# Psychophysiology and Neurocognitive Projects

Directors: Vickie Risbrough and Mark Geyer

<table>
<thead>
<tr>
<th>Construct/Task</th>
<th>Collaborators</th>
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<tbody>
<tr>
<td>Fear Conditioning and Extinction/FPS</td>
<td>Dean Acheson</td>
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<tr>
<td>Startle Threshold/EMG</td>
<td>Dan Glenn</td>
</tr>
<tr>
<td>Prepulse Inhibition/EMG</td>
<td>Dean Acheson</td>
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<tr>
<td>Heart Rate Variability/PPG</td>
<td>Arpi Minassian</td>
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<td>Reaction time/ANAM+Penn Battery</td>
<td>Gur, Moore, Vasterling</td>
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<td>Attention/CPT, Go-NoGo</td>
<td>Ruben Gur, Tyler Moore</td>
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<tr>
<td>Attention Set Shifting</td>
<td>Ruben Gur, Tyler Moore</td>
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<tr>
<td>Verbal, Spatial, Facial Memory</td>
<td>Ruben Gur, Tyler Moore</td>
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<td>Spatial and Verbal Reasoning</td>
<td>Ruben Gur, Tyler Moore</td>
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<tr>
<td>Working Memory</td>
<td>Ruben Gur, Tyler Moore</td>
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</table>
Example Aims

• Identify psychophysiological predictors of PTSD
• Identify deployment-related TBI effects on changes in neurocognition
• Identify potential mechanism of TBI-induced increases in risk for PTSD
• Identify overlapping genetic mechanisms of PTSD risk and endophenotypes (fear conditioning, extinction and prepulse inhibition, HRV)
Poor safety signal learning and extinction are biobehavioral markers of PTSD

Conditioned fear and extinction learning performance and its association with psychiatric symptoms in active duty Marines.
Psychoneuroendocrinology 51:495-505
Pre-trauma low HRV is associated with PTSD risk

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
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<tbody>
<tr>
<td>Trauma exposure</td>
<td>2.84</td>
<td>2.15-3.74</td>
<td>&lt;0.001</td>
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<tr>
<td>LF: HF ratio</td>
<td>1.47</td>
<td>1.10-1.98</td>
<td>0.01</td>
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Association of predeployment heart rate variability with risk of postdeployment Posttraumatic Stress Disorder in active-duty Marines
**Psychological, Behavioral and Physiological assessments**

**Mental and Physical Health**
- Deployment related TBI predictors PTSD – Follow-up data collection

**Psychophysiology and Neurocognition**
- Pre-deployment HRV predicts PTSD
- Sensorimotor gating and cue discrimination may be resiliency factors for PTSD

**Biological assessments**

**Biomarkers**
- Pre-deployment immune activation state predicts PTSD – replicate findings, integrate analysis with HRV

**Imaging**
- Development of diagnostic MEG signatures for mTBI

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**Actionable Results**

**MRS Secure database**

**Career History Archival Medical and Personnel System database**
- VA and military service database information in follow-up data collection and analysis

**Biobank**
- Stored samples for future analyses and collaborations

**Genomics**
- PGC PTSD GWAS consortium
- PGC PTSD EWAS consortium
- Active replication of GWAS and EWAS study findings in collaboration with PRISMO, Army STARRS, Grady Trauma Cohort

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**UCSD**

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Ongoing and Future Directions

- **Integrated data analyses of MRS data sources**, e.g. behavior, genomics, metabolomics, physiology, imaging

- **Future data collection: MRS-III 5-year follow up**
  - **Funded:** CDMRP (DoD), FY 2016-2019, PI: Baker, TBI/Tinnitus Study
  - Long term outcomes – hearing, tinnitus, health
  - Better understand HPA axis/autonomic – vagal/immune system relationships in PTSD – TLR-4, TLR-9, α7 nicotinic receptor

- **TBI/PTSD Imaging Biomarker Validation and Development**
  - **Funded:** Investigating the Neurologic Effects of Training Associated Blast (I-TAB) study
  - Longitudinal imaging of blast-exposed trainees