Advancing Precision Medicine for PTSD in Civilians and the Military

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- **Consultant:** Served as a PTSD Fellow for the George W. Bush Institute

- **Other Commercial Interest:** Serves on the scientific advisory board and has equity in Receptor Life Sciences
Examine the role of precision medicine in the optimal management of PTSD.
Limitations of Current Symptom-Based Classification

- Heterogeneity in symptom presentation, course, and response to treatment
- Heterogeneity in biology complicates biomarker discovery
- Fuzzy boundaries with comorbid disorders
- Age, genetic ancestry, culture, gender and ethnicity contribute to variations in biology and symptom expression
- Self-report bias
  - over and under reporting
Next Generation Taxonomy

- Address biological and clinical heterogeneity
- Base in measurable behavior and brain behavior relationships
- Framework for linking animal and human studies
- Framework for accelerating biomarker discovery
- Framework for accelerating discovery of targets for experimental therapeutics
PTSD Intermediate Phenotypes

- Neurocircuit phenotypes
- Molecular phenotypes
- Behavioral phenotypes
Amygdala activation to threat modulated by –
- Medial prefrontal cortex
- Dorsolateral prefrontal cortex
- Dorsal anterior cingulate
- Insula

Mediated by the amygdala, dorsal Anterior Cingulate (dACC) and insula cortex

Modulated by regulatory control mechanisms involving the hippocampus and medial and lateral prefrontal cortex regions

PTSD Neural Circuit Phenotypes

Contextual Processing

- Diminished capacity to use safety context to modulate fear expression\(^1\)
- Diminished capacity to use danger signals adaptively\(^1\)
- Deficits in context updating\(^2\)
- Hippocampal dependent process with insula and PFC\(^2\)

PTSD Neural Circuit Phenotypes

- Orchestrated by central nucleus of amygdala
- Outputs to sympathetic and parasympathetic systems including cardiovascular and respiratory reactions, and activation of the hypothalamic-pituitary-adrenal (HPA) axis
- Behavioral responses include defensive fight, flight, startle and freezing behaviors, and changes in information processing
- Modulated by baso-lateral amygdala, hippocampus, insula and prefrontal structures

PTSD Molecular Phenotypes

- Genetic
- Genomic
- Endocrine
- Metabolomic
- Proteomic
### Systems Biology Consortium - PTSD Associated with Cardio-Metabolic Syndrome Between-Group Differences

<table>
<thead>
<tr>
<th></th>
<th>N (-/ +)</th>
<th>PTSD (-) Mean ± SD</th>
<th>PTSD (+) Mean ± SD</th>
<th>Statistic¹</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Glucose</td>
<td>51/51</td>
<td>79 ± 11.5</td>
<td>91 ± 16.2</td>
<td>t = 3.92</td>
<td>.001</td>
</tr>
<tr>
<td>Insulin</td>
<td>51/51</td>
<td>12.16 ± 10.44</td>
<td>19.18 ± 16.96</td>
<td>F = 3.16</td>
<td>.08</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>51/51</td>
<td>2.65 ± 3.41</td>
<td>4.66* ± 4.75</td>
<td>F = 4.54</td>
<td>.04</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>51/51</td>
<td>171.2 ± 26.5</td>
<td>175.4 ± 35.3</td>
<td>F = 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>51/51</td>
<td>107.7 ± 110.4</td>
<td>121.2 ± 62.3</td>
<td>F = 1.71</td>
<td>.19</td>
</tr>
<tr>
<td>BMI</td>
<td>51/51</td>
<td>28.3 ± 4.2</td>
<td>29.9 ± 5.1</td>
<td>t = 1.95</td>
<td>.06</td>
</tr>
<tr>
<td>Weight</td>
<td>51/51</td>
<td>190.4 ± 32.2</td>
<td>206.1 ± 39.6</td>
<td>t = 2.20</td>
<td>.03</td>
</tr>
<tr>
<td>Pulse</td>
<td>51/50</td>
<td>64 ± 11</td>
<td>71 ± 12</td>
<td>F = 9.24</td>
<td>.003</td>
</tr>
</tbody>
</table>

**METABOLIC SYNDROME TOTAL SCORE***

|                  | 51/51    | -0.84 ± 3.12       | 0.84 ± 3.15        | T = 2.70   | .008 |

¹ Independent t-tests used unless covariates (age and/or BMI) applied, in which case ANCOVA used. Raw data presented in Table, but data were transformed to achieve normal distributions before analysis, when required. As an exploratory study, significance values are not corrected for multiple comparisons, but to limit Type I errors, subsequent analyses use the Metabolic Syndrome Total Score.

*METABOLIC SYNDROME TOTAL SCORE = Sum of standardized z-scores of: HOMA-IR, BMI, Diastolic BP, LDL and Pulse.


## Systems Biology Consortium - Pro-Inflammatory Cytokines are Elevated in PTSD

<table>
<thead>
<tr>
<th>Cytokine (pg/ml)</th>
<th>PTSD (-) (N = 51)</th>
<th>PTSD (+) (N = 51)</th>
<th>t-test</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-γ</td>
<td>0.58 (0.45-0.69)</td>
<td>0.76 (0.42-1.42)</td>
<td>2.04</td>
<td>.001</td>
</tr>
<tr>
<td>TNF-α</td>
<td>2.98 (2.52-3.51)</td>
<td>3.69 (2.48-4.49)</td>
<td>1.93</td>
<td>.058</td>
</tr>
<tr>
<td>IL-1b</td>
<td>0.08 (0.05-0.13)</td>
<td>0.10 (0.05-0.18)</td>
<td>0.93</td>
<td>.354</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.51 (0.44-0.76)</td>
<td>0.79 (0.60-1.12)</td>
<td>2.92</td>
<td>.004</td>
</tr>
<tr>
<td>IL-10</td>
<td>1.53 (1.26-1.87)</td>
<td>1.56 (1.25-2.32)</td>
<td>0.89</td>
<td>.373</td>
</tr>
<tr>
<td>hs CRP</td>
<td>1.00 (0.40-1.80)</td>
<td>1.33 (0.50-3.95)</td>
<td>1.95</td>
<td>.054</td>
</tr>
<tr>
<td><strong>Total Pro-Inflammatory Score</strong></td>
<td><strong>-1.32 (-2.54 - -0.05)</strong></td>
<td><strong>0.83 (-1.24 - -3.56)</strong></td>
<td><strong>3.58</strong></td>
<td><strong>.001</strong></td>
</tr>
</tbody>
</table>

*Total Pro-Inflammatory Score= Sum of standardized z-scores of: IL6, IL1b, TNFa, IFNg and CRP. Values = Medians + Inter-Quartile range. T tests are based on Ln.; (Extreme values excluded if distribution not normalized by Ln- transformation). As an exploratory study, significance values are not corrected for multiple comparisons.

**Systems Biology Consortium - Natural Killer Cell Senescence in PTSD**

Fluorescence-Activated Cell Sorting

<table>
<thead>
<tr>
<th>%NK Cell</th>
<th>PTSD (-) (N = 39)</th>
<th>PTSD (+) (N = 37)</th>
<th>t (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i CD16⁻CD56⁺ (Ln)</td>
<td>1.97 ± 0.63</td>
<td>1.73 ± 0.49</td>
<td>1.93 (p &lt; .06)</td>
</tr>
<tr>
<td>&quot;Bright&quot;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>h CD16⁺CD56⁻ (Ln)</td>
<td>1.83 ± 0.72</td>
<td>2.14 ± 0.69</td>
<td>2.02 (p &lt; .05)</td>
</tr>
<tr>
<td>&quot;Dim&quot;</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CD16⁻CD56⁺ ("bright") NK cells** tend to be decreased in PTSD.

**CD16⁺CD56⁻ ("dim") NK cells** are significantly increased in PTSD, conducive to a pro-inflammatory state and suggesting NK cell aging.

Evidence of Mitochondrial Dysfunction in PTSD

- **Preclinical Animal Model:**
  - Prolonged stress induced hippocampal apoptosis involving mitochondrial pathways\(^1,2\)

- **Clinical Studies:**
  - Gene expression: DLPFC analysis revealed a high percentage of dysregulated mitochondrial-associated genes\(^3\)
  - Blood-based mitochondria-focused gene cDNA arrays
    - 10 clusters distinguished PTSD from non-PTSD soldiers
    - 20% were significantly correlated with PTSD symptom severity (Zhang et al., 2012 [published poster abstract])

Evidence of Mitochondrial Dysfunction in PTSD

Note: All subjects were NPO and rested when A.M. bloods were collected.

Many pathways converge on mitochondrial metabolism:
- Reduced abundance of mitochondrial metabolites
- Increased abundance of “pre-mitochondrial” metabolites

<table>
<thead>
<tr>
<th>Glycolysis</th>
<th>PTSD CTRL</th>
</tr>
</thead>
<tbody>
<tr>
<td>pyruvate</td>
<td>1.27</td>
</tr>
<tr>
<td>lactate</td>
<td>1.36</td>
</tr>
</tbody>
</table>

Red: Elevated in PTSD
Green: Decreased in PTSD

Presented at APA 2013
Developing Blood Biomarkers for PTSD: Stage 1

- 50 candidate biomarker panels were identified from over a million markers in the discovery cohort
  - 77 cases, 74 controls

- These 50 panels contained 343 unique markers
  - 2 physiological measures
  - 20 clinical lab measures
  - 8 endocrine measures
  - 27 metabolites
  - 156 methylation probes
  - 81 miRNAs
  - 42 proteins
  - 4 small molecules
  - 3 nonlinear feature combinations

Study Cohort

- Cross Sectional: OIF/OEF/OND Veterans
- Initial Award to study 100 PTSD+/100 PTSD– OIF/OEF males
  - Discovery/Training subjects completing blood draw
    - 83 cases and 83 controls
- Second Award to study Validation subjects- OIF/OEF males
  - Validation/Test subjects completing blood draw
    - New: 29 cases and 40 controls
    - Recalls: 30 cases and 29 controls

OIF = Operation Iraqi Freedom; OEF = Operation Enduring Freedom; OND = Operation New Dawn
Stage 2: A Recursive Feature Elimination Approach

Algorithm:

1. Begin with a biomarker panel of all markers (343 features)
2. Remove individual markers, one-by-one, and compute average AUC of \( n-1 \) markers over 50 rounds of biomarker validation using bootstrapped datasets (training=discovery, validation = recalls)
3. Remove the marker resulting in the largest AUC improvement, down-selecting to a panel of size \( n-1 \)
4. Repeat steps 2&3 until only a single biomarker remains
5. The panel with the largest AUC was selected

Stage 3: Most Important Features from Random Forest (Machine Learning Program)

- Sort remaining 77 features based on random forest variable importance
- Select biomarkers with top 30% feature importance
  - 28 markers pass importance threshold
  - Combined multi-omic panel outperforms all individual data types
- Final panel is a diverse, multi-omic panel:
  - 1 physiological measure - HR
  - 3 metabolites – GABR, Lactate/citrate
  - 4 miRNAs – miR – 424-3P (inflammation), miR-9-5 (neurogenesis)
  - 2 clinical lab measures – Insulin, MPV
  - 11 methylation probes – PDE9A gene (monamine neurotransmitters)
  - 7 proteins – PTGDS – AQG (prostaglandin)

Final biomarker panel validation:
- AUC = 0.80
- Accuracy = 81%
- Sensitivity = 85%
- Specificity = 77%

PTSD Behavioral Phenotypes

● Neurocognitive
● Psychophysiology
● Sleep
● Speech
● Wearable devices for measuring behavior
Conclusion

- Clinical phenotypes of PTSD conserved across cultures and time
  - Intrusive recollections
  - Avoidance of reminders
  - Sleep disruptions including nightmares
  - Disillusionment
  - Hyperarousal
Alcohol Use Disorder (AUD) / PTSD Heterogeneity

Biomarker Informed Personalized Medicine

Drug X
Standard Approach

- 20% are responders

NNT for Entire Sample = 20

Drug X
Personalized Medicine Approach

- 80% are responders
- 10% are responders
- 10% are responders

NNT for Subgroup = 2+

NNT = Number needed to treat
Advanced analytics/statistical modelling uses biomarker features to appraise causal treatment differences among likely responders.

**Molecular Markers**
- Six pathways relevant to AUD and PTSD
- GRIK1 genotype

**Clinical Trial**
- Clinical response
- Neurocognitive features

**Circuit Markers**
- Neurocircuit markers of addiction domains (stress, ER, craving)

**Precision medicine (PM)**
- Individualized prediction of probability of TPM response

Advanced analytics/statistical modelling uses biomarker features to appraise causal treatment differences among likely responders.
Gender Moderators of Antidepressant Treatment

Studies in depression:

● Women respond better than men to SSRIs\(^1\)
● Premenopausal women respond better to SSRIs than postmenopausal women & men
● SSRIs + HRT improves response in postmenopausal women\(^2\)
● No sex effects for tricyclic antidepressants (TCS)\(^3\)
● No sex effects for desvenlafaxine\(^4\)
  ➥ Good responses in postmenopausal women & men
● SSRIs decrease sexual dysfunction in women, increase sexual dysfunction in men\(^5\)

Gender Moderators of Antidepressant Treatment (cont.)

Studies in PTSD:

● Sertraline is FDA approved for PTSD

● Good response in multisite randomized controlled trials (RCT) with women survivors of sexual assault

● No separation from placebo in male veterans

Cognitive behavioral therapy (CBT) more effective than other psychotherapies for sexual abuse survivors (Taylor, 2019)

PTSD patients with high symptom burden and low emotion regulation
- Poorest response in exposure therapy
- Moderately well in skills building
- Best in combination of skills building followed by PE

Cognitive processing therapy (CPT) outcomes not moderated by age, number of sessions, or group vs. individual treatment

Females had better outcomes with CPT on secondary measures

Small non-significant superiority of prolonged exposure therapy (PE)/CPT over present-centered therapy (PCT)

No superiority of PE over PCT in veterans and active duty military personnel
Civilians had better outcomes than veterans (Stroud, 2019)

Moderators of Prazosin Treatment for PTSD

- Negative multicenter RCT in veterans\(^1\)
- Greater PTSD symptom reduction associated with higher blood pressure in soldiers\(^2\)
  - Each 10 mmHg higher systolic blood pressure pretreatment associated with 14-point CAPS reduction

What We Know:
- PTSD has cognitive deficits and cognitive network abnormalities. Network architecture has been implicated in cognition in other contexts

Key Questions:
1. How does cognitive network topology relate to cognitive deficits in PTSD?
2. Can this be a biomarker for PTSD or a subtype of it?
3. How do cognition and cognitive networks relate to symptoms and treatment outcome?
4. What are potential molecular mechanisms?
Graph Analytical Methods To Understand Networks

Network segregation

Network integration

**Network Definitions**

- ICA-defined
- In standard MNI space

---

Graph Analytical Methods To Understand Networks: PTSD

Network segregation

Network integration

PTSD:

Network/Cognition Relationships
Some Patients Impaired, Others Intact: Disentangle Heterogeneity


Network integration

- * -  - * -

Efficiency

Healthy
Impaired PTSD
Intact PTSD

Does this replicate?
CVC sample

- * -  - * -

Efficiency

CVC Biomarker Prediction of Outcome

**Graph Description:**
- **Y-axis:** CAPS total score
- **X-axis:** PreTx and PostTx

**Graph Details:**
- **Prolonged Exposure (PE):**
  - Impaired: Arm x Time: \( p < .001 \)
  - Intact: Arm x Time: \( p = .3 \)
- **Wait List (WL):**
  - Impaired: Group x Arm x Time: \( p < .04 \)
  - Intact: Group x Arm x Time: \( p = .6 \)

**Legend:**
- Impaired
- Intact

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Proof of Concept for Advanced Analytics of Precision Medicine Trials Before Pilot Data
Traditional Approach to the Analysis of RCTs
Test Treatment (A) vs. placebo (B)

- **Goal**: Test whether there is a treatment difference on average in the population
- **Test** if Treatment A = Treatment B (not causal because every patient has a different set of features f)
- **Adjust** for a few key prognostic features
  - Mediators, moderators, covariates
- **Seek feature subgroups** that identify responders
  - Usually only if null hypothesis is rejected
New Precision Medicine Approach to the Analysis of RCTs

- **Goal**: Identify likely responder as a function of baseline features and test whether there is a causal treatment difference this group
- **Find function** of features predicting probability of response (POR) and identify group with high POR
- **Test** if Treatment A = Treatment B in matched samples in group with high POR
- **Use** prediction function for individual care
Applying the New Analytic Method to the XBOT Study: Design and Major Finding

- Randomized, unblinded 24-week trial for prevention of relapse, N = 570
- Individuals with OUD after detox
- Compare XR-NTX vs BUP-NX
- **Results:** No difference in time to relapse between treatments in whole study sample
- **Authors’ Conclusion:** “…both medications were equally safe and effective.”

OUD = opioid use disorder; BUP-NX = buprenorphine-naloxone; XR-NTX = extended release naltrexone
Relapse-free Survival and Treatment Effect Over Time For The XR-NTX And BUP-NX Treatment Groups: Full Sample Analysis

Full Sample and Precision Medicine Analysis Quintiles Based On Estimated Por(xr-ntx|f)

Result of pooled analysis in full sample
$H_0$ not rejected—no evidence of a treatment difference

Result of pooled analysis in PM sample
$H_0$ rejected—XR-NTX > BUP-NX

<table>
<thead>
<tr>
<th>Feature</th>
<th>Use XR-NTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASI Psychiatric Composite Score</td>
<td>0.24</td>
</tr>
<tr>
<td>Age</td>
<td>34.81 (10.71)</td>
</tr>
<tr>
<td>DSM-5 Cannabis Diagnosis</td>
<td></td>
</tr>
<tr>
<td>No use</td>
<td>72.51%</td>
</tr>
<tr>
<td>Other</td>
<td>27.49%</td>
</tr>
<tr>
<td>DSM-5 Sedatives Diagnosis</td>
<td></td>
</tr>
<tr>
<td>No use</td>
<td>81.04%</td>
</tr>
<tr>
<td>Other</td>
<td>18.96%</td>
</tr>
<tr>
<td>Current Sedative User</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24.64%</td>
</tr>
<tr>
<td>No</td>
<td>75.36%</td>
</tr>
<tr>
<td>Chronic Pain &gt; 6 Months</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12.8%</td>
</tr>
<tr>
<td>No</td>
<td>87.2%</td>
</tr>
</tbody>
</table>

Applying the New Analytic Method to the EMBARC Study: Design and Major Finding

- Randomized, double blind 8-week trial of sertraline vs placebo for MDD
- 228 chronic, early-onset patients meeting DSM-IV TR criteria for nonpsychotic MDD who had usable EEG data
- **Results:** No difference between sertraline/placebo in HAM-D scores in whole study sample

Based on Expected Change From Baseline in HAM-D 17 scores

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.