Advancing Precision Medicine for PTSD in Civilians and the Military

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Disclosures

- ***Research and Clinical Program Funding (current and last 10 years):*** Bank of America Foundation; Brockman Foundation; City of New York; Cohen Veterans Bioscience; Cohen Veterans Network; Home Depot Foundation; McCormick Foundation; National Institute on Alcohol Abuse and Alcoholism (NIAAA); National Institute of Mental Health (NIMH); Northern California Institute for Research and Education; Robin Hood Foundation; Steven & Alexandra Cohen Foundation; Tilray; U.S. Army Medical Research & Acquisition Activity; U.S. Army Telemedicine & Advanced Technology Research Center; and U.S. Department of Defense
- ***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

Learning Objective 1

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

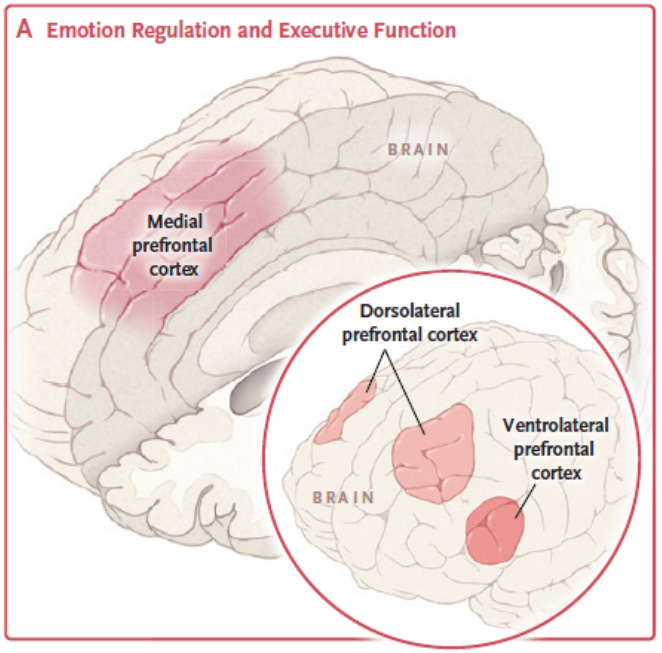
- Address biological and clinical heterogeneity
- Base in measurable behavior and brain behavior relationships
- Framework for linking animal and human studies
- Framework for accelerating biomarker discovery
- Framework for accelerating discovery of targets for experimental therapeutics

PTSD Intermediate Phenotypes

- Neurocircuit phenotypes
- Molecular phenotypes
- Behavioral phenotypes

PTSD Neural Circuit Phenotypes
Emotion Regulation & Executive Function

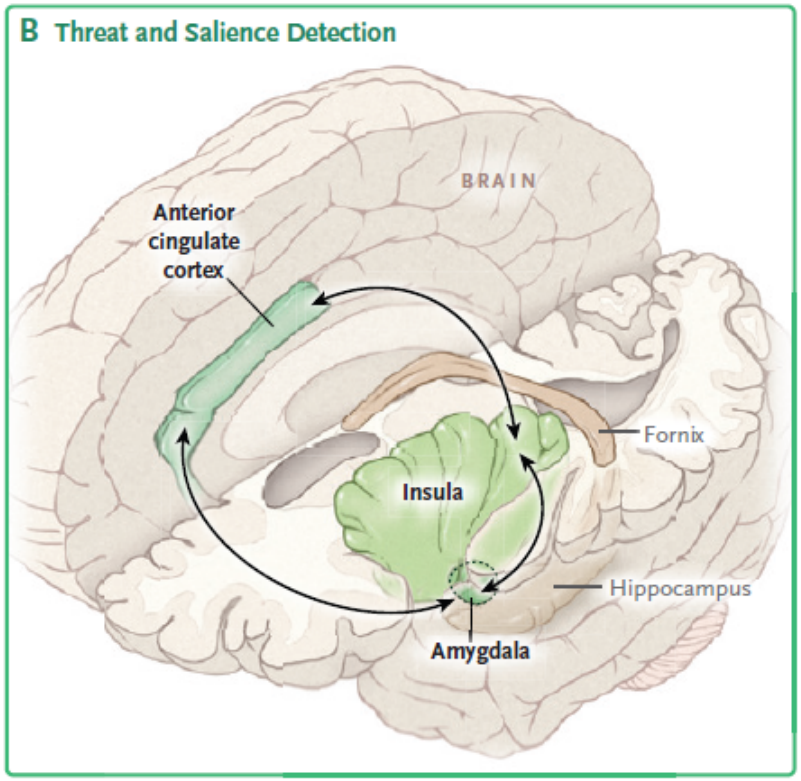
- Amygdala activation to threat modulated by –
  - Medial prefrontal cortex
  - Dorsolateral prefrontal cortex
  - Dorsal anterior cingulate
  - Insula



Shalev A, Liberzon I, Marmar C. *NEJM*. 2017;376(25):2459-2469.

PTSD Neural Circuit Phenotypes Threat and Saline Detection

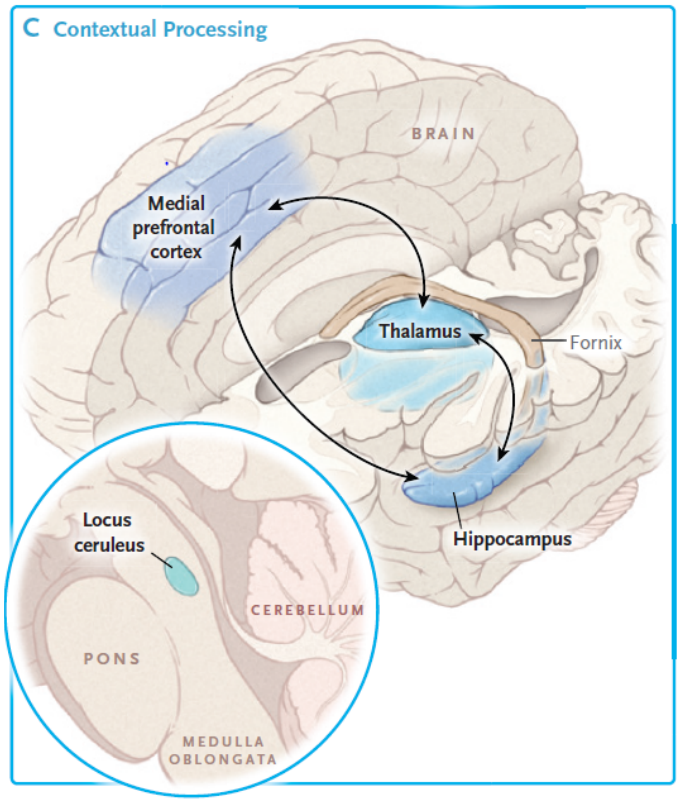
- Mediated by the amygdala, dorsal Anterior Cingulate (dACC) and insula cortex
- Modulated by regulatory control mechanisms involving the hippocampus and medial and lateral prefrontal cortex regions



Shalev A, Liberzon I, Marmar C. *NEJM*. 2017;376(25):2459-2469.

PTSD Neural Circuit Phenotypes Contextual Processing

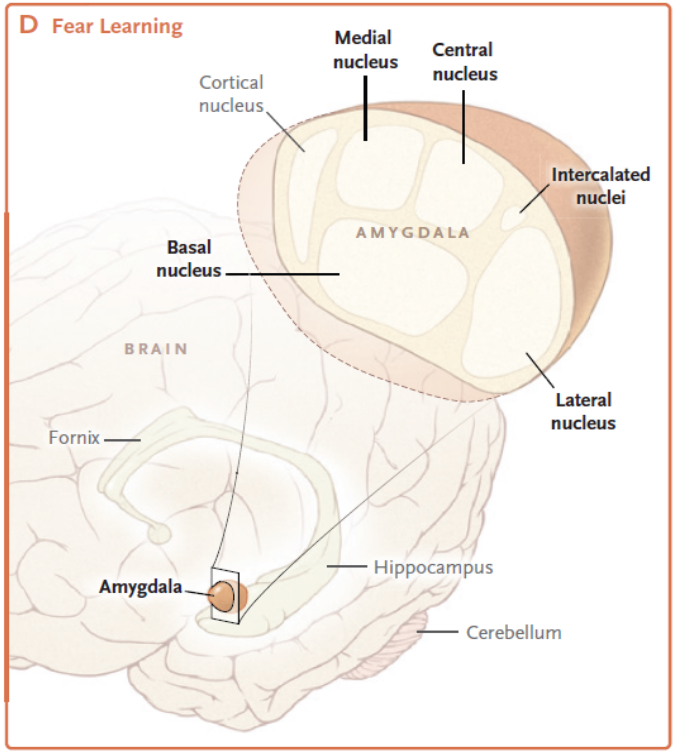
- Diminished capacity to use safety context to modulate fear expression[1]
- Diminished capacity to use danger signals adaptively[1]
- Deficits in context updating[2]
- Hippocampal dependent process with insula and PFC[2]



1. Garfinkel SN, et al. *J Neurosci*. 2014;34(40):13435-13443.; 2. Shalev A, Liberzon I, Marmar C. *NEJM*. 2017;376(25):2459-2469

PTSD Neural Circuit Phenotypes Fear Learning

- 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



Shalev A, Liberzon I, Marmar C. *NEJM*. 2017;376(25):2459-2469.

PTSD Molecular Phenotypes

- Genetic
- Genomic
- Endocrine
- Metabolomic
- Proteomic

Systems Biology Consortium - PTSD Associated with Cardio-Metabolic Syndrome

Between-Group Differences

	N (-/ +)	PTSD (-) Mean ± SD	PTSD (+) Mean ± SD	Statistic[1]	*p*
Fasting Glucose	51/ 51	**79** ± 11.5	**91** ±16.2	t = 3.92	**.001**
Insulin	51/ 51	**12.16** + 10.44	**19.18** + 16.96	F = 3.16	***.08***
HOMA-IR	51/51	**2.65** + 3.41	**4.66*** + 4.75	F = 4.54	**.04**
Cholesterol	51/51	**171.2** ± 26.5	**175.4** ± 35.3	F = 0.05	NS
Triglycerides	51/51	**107.7**± 110.4	**121.2** ± 62.3	F =1.71	*.19*
BMI	51/ 51	**28.3** ± 4.2	**29.9** ± 5.1	t = 1.95	***.06***
Weight	51/ 51	**190.4** ± 32.2	**206.1** ± 39.6	t = 2.20	**.03**
Pulse	51/50	**64** ± 11	**71** ± 12	F = 9.24	**.003**
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.
HOMA-IR= Homeostatic Model Assessment- Insulin Resistance. *HOMA-IR values >3.80 identify Insulin Resistance with high sensitivity.

Mellon SH, et al. *PLoS One.* 2019;14(3):e0213839

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

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

*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.

Mellon SH, et al. *PLoS One.* 2019;14(3):e0213839.

Systems Biology Consortium - Natural Killer Cell Senescence in PTSD

Fluorescence-Activated Cell Sorting

%NK Cell	PTSD (-) (N = 39)	PTSD (+) (N = 37)	t (p)
i $CD16^{-}CD56^{+}$ (Ln) "Bright"	1.97 ± 0.63	1.73 ± 0.49	1.93 **(*p* < .06)**
h $CD16^{+}CD56^{-}$ (Ln) "Dim"	1.83 ± 0.72	2.14 ± 0.69	2.02 **(*p* < .05)**

$CD16^{-}CD56^{+}$ ("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.

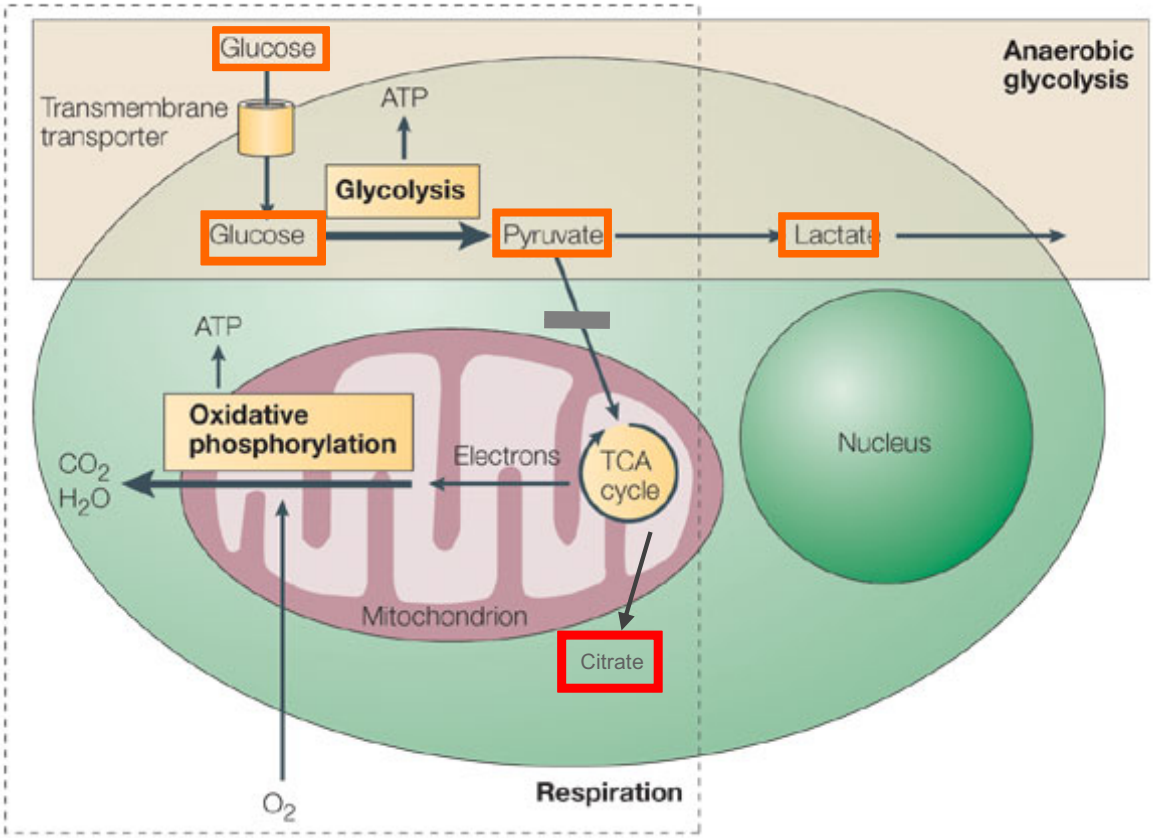
Mellon SH, et al. *PLoS One.* 2019;14(3):e0213839.

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])

1. Li XM, et al. *J Chem Neuroanat*. 2010;40(3):248-255.; 2. Liu D, et al. *BMC Psychiatry*. 2012;12:211.; 3. Su YA, et al. *Int J Biol Sci*. 2008;4(4):223-235.;

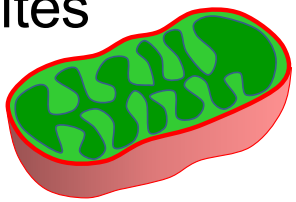
Evidence of Mitochondrial Dysfunction in PTSD

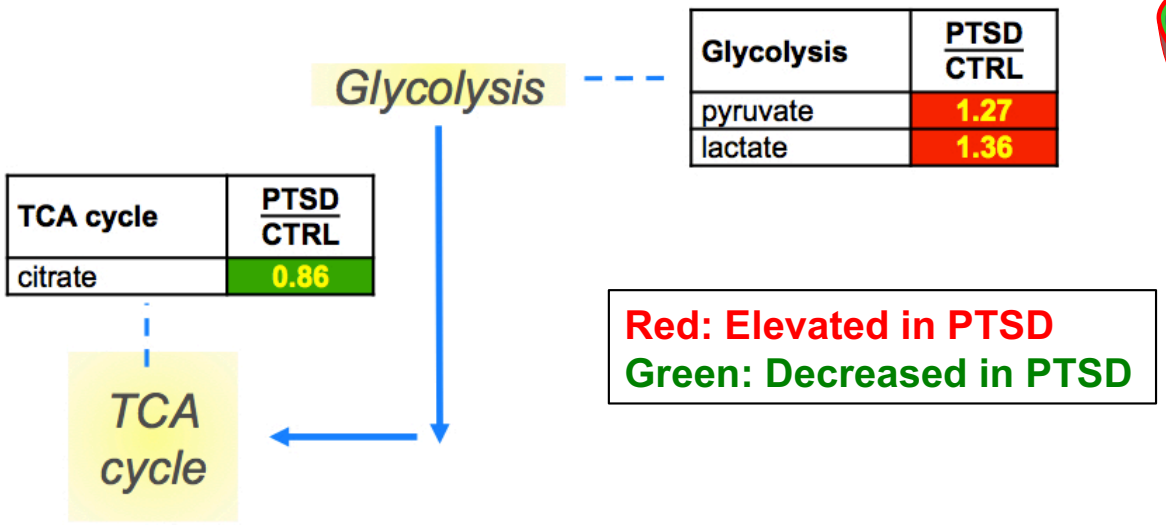


Note: All subjects were NPO and rested when A.M. bloods were collected.

Systems Biology Consortium - Signatures of Mitochondrial Dysfunction in PTSD:
Reduced Citrate and Increased Pyruvate and Lactate

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





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

Dean KR, et al. *Mol Psychiatry.* 2019 Sep 10. doi: 10.1038/s41380-019-0496-z. [Epub ahead of print].

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

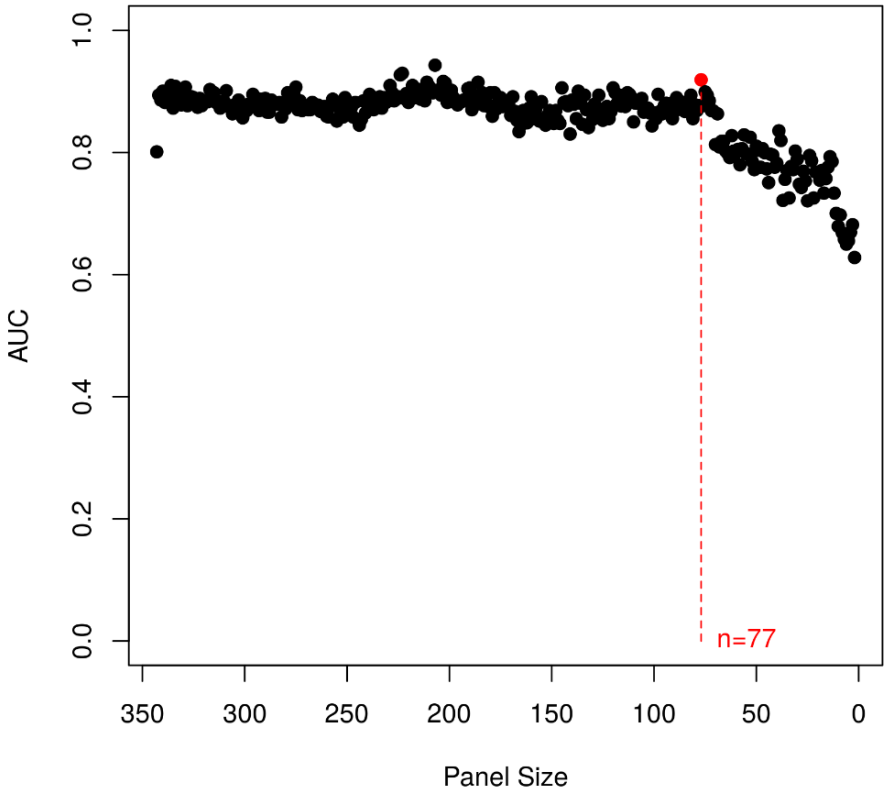
OIF = Operation Iraqi Freedom; OEF = Operation Enduring Freedom; OND = Operation New Dawn

Dean KR, et al. *Mol Psychiatry.* 2019 Sep 10. doi: 10.1038/s41380-019-0496-z. [Epub ahead of print].

Stage 2: A Recursive Feature Elimination Approach

Algorithm:

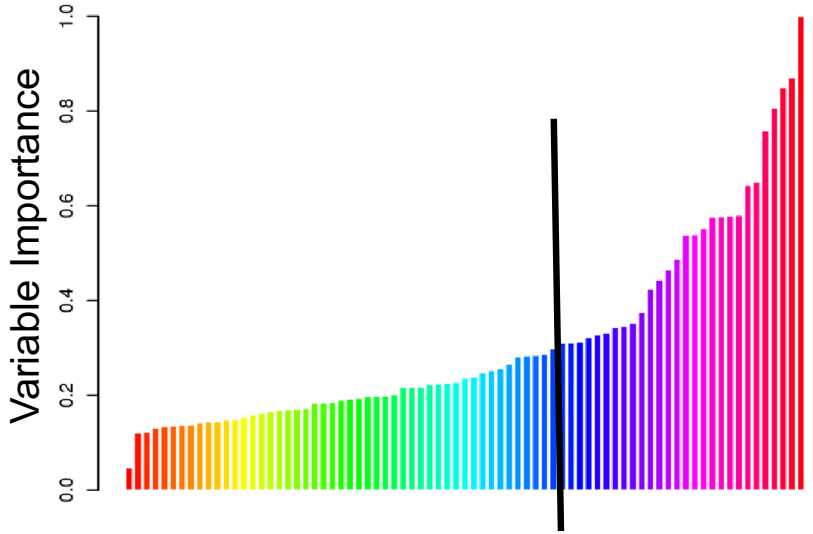
1. Begin with a biomarker panel of all markers (*343* features)
2. Remove individual markers, one-by-one, and compute average AUC of *n-1* markers over 50 rounds of biomarker validation using bootstrapped datasets (training=discovery, validation = recalls)
3. Remove the marker resulting in the largest 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



Dean KR, et al. *Mol Psychiatry.* 2019 Sep 10. doi: 10.1038/s41380-019-0496-z. [Epub ahead of print].

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

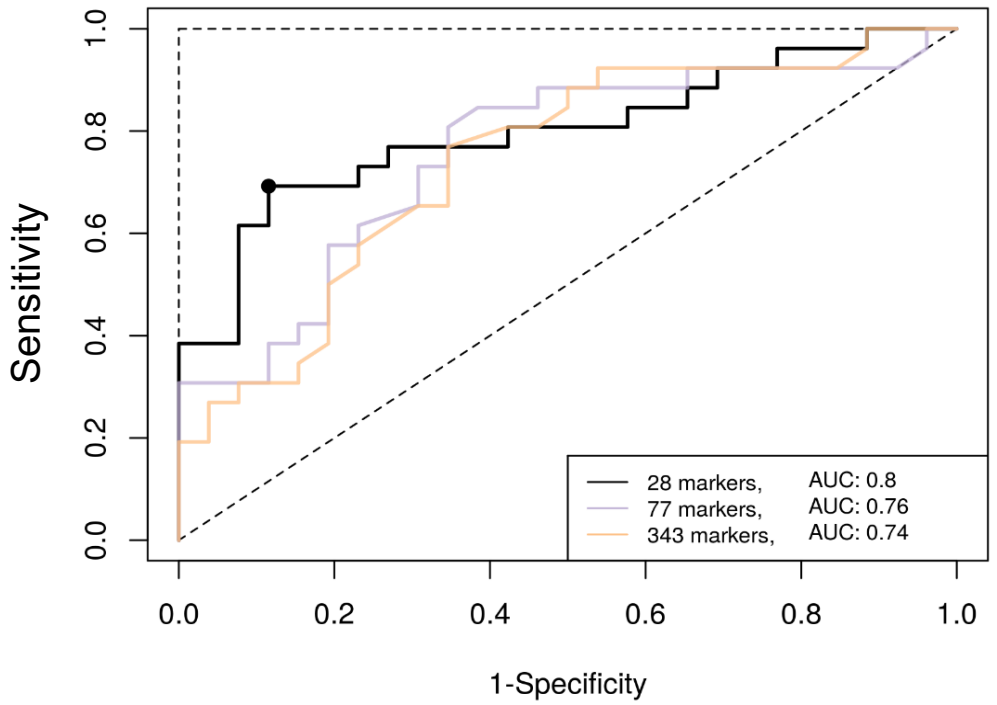


  - 11 methylation probes – PDE9A gene (monamine neurotransmitters)
  - 7 proteins – PTGDS – AQG (prostaglandin)

Dean KR, et al. *Mol Psychiatry.* 2019 Sep 10. doi: 10.1038/s41380-019-0496-z. [Epub ahead of print].

Biomarker Panel Validation

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



Dean KR, et al. *Mol Psychiatry.* 2019 Sep 10. doi: 10.1038/s41380-019-0496-z. [Epub ahead of print].

PTSD Behavioral Phenotypes

- Neurocognitive
- Psychophysiology
- Sleep
- Speech
- Wearable devices for measuring behavior

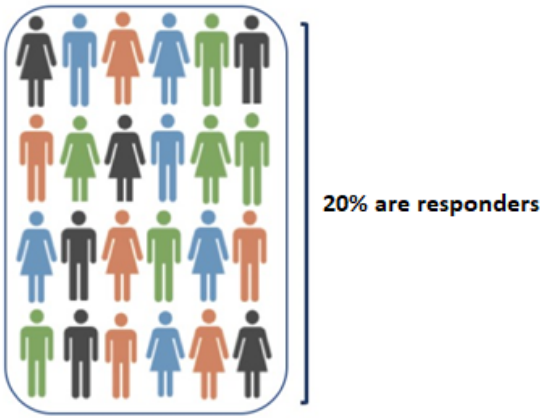
Conclusion

- 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

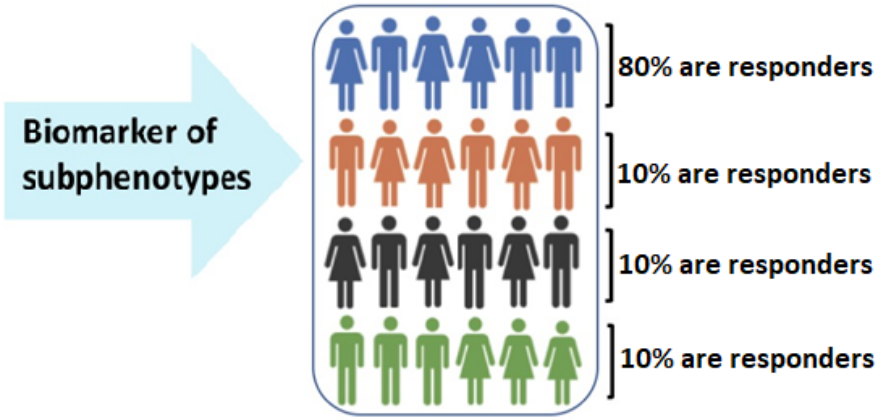
Biomarker Informed Personalized Medicine

Drug X
Standard Approach



NNT for Entire Sample = 20

Drug X
Personalized Medicine Approach



NNT for Subgroup = 2+

NNT = Number needed to treat

Novel Analytic Approaches to Precision Medicine

Molecular Markers

- Six pathways relevant to AUD and PTSD
- GRIK1 genotype

Clinical Trial

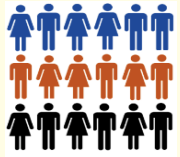
- Clinical response
- Neurocognitive features

Circuit Markers

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

Advanced analytics/statistical modelling uses biomarker features to appraise *causal* treatment differences among likely responders

Precision medicine (*PM*)



Individualized prediction of probability of TPM response

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]

1. Sramek JJ, et al. *Dialogues Clin Neurosci*. 2016;18(4):447-457.; 2. Grigoriadis S, et al. *J Clin Psychopharmacol*. 2003;23(4):405-407.; 3. Wohlfarth T, et al. *Am J Psychiatry*. 2004;161(2):370-372.; Kornstein SG, et al. *Menopause*. 2014;21(8):799-806.; 5. Piazza LA, et al. *Am J Psychiatry*. 1997;154(21):1757-1759.

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

Friedman MJ, Marmar CR, et al. *J Clin Psychiatry*. 2007;68(5):711-720.

Moderators of Evidence-based Psychotherapies for PTSD

- 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[1]
  - 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[2]
- Females had better outcomes with CPT on secondary measures[2]
- Small non-significant superiority of prolonged exposure therapy (PE)/CPT over present-centered therapy (PCT)[3]
- No superiority of PE over PCT in veterans and active duty military personnel
  Civilians had better outcomes than veterans (Stroud, 2019)

1. Cloitre M, et al. *BJPsych Open*. 2016;2(2):101-106.; 2. Asmundson GJG, et al. *Cogn Behav Ther*. 2019;48(1):1-14.; 3. Gerger H, et al. *J Clin* Psychol. 2014;70(7):601-615.; 4. Steenkamp M, et al. *JAMA*. 2020;323(7):656-657.

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

1. Raskind MA, et al. *N Engl J* Med. 2018;378(6):507-517.; 2. Raskind MA, et al. *Biol Psychiatry*. 2016;80(10):736-742.

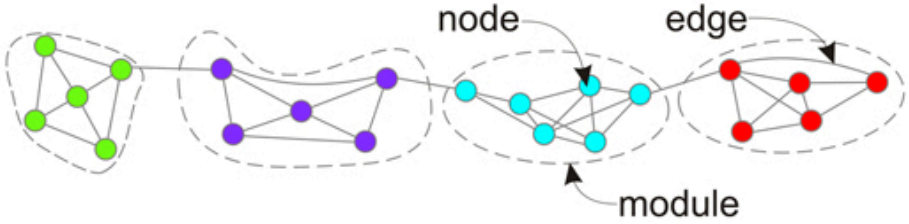
Cohen Veteran Center – Cognition and Neural Networks in PTSD

Amit Etkin MD, PhD

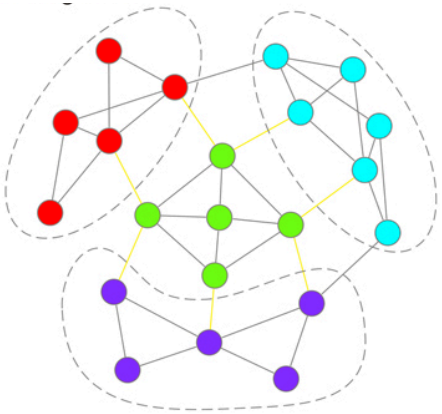
- **What We Know:**
  - PTSD has cognitive deficits and cognitive network abnormalities. Network architecture has been implicated in cognition in other contexts
- **Key Questions:**
  1. How does cognitive network topology relate to cognitive deficits in PTSD?
  2. Can this be a biomarker for PTSD or 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



Etkin A, et al. *Sci Transl Med*. 2019;11(486). Pii.eaal3236. doi: 10.1126/scitranslmed.aal3236.

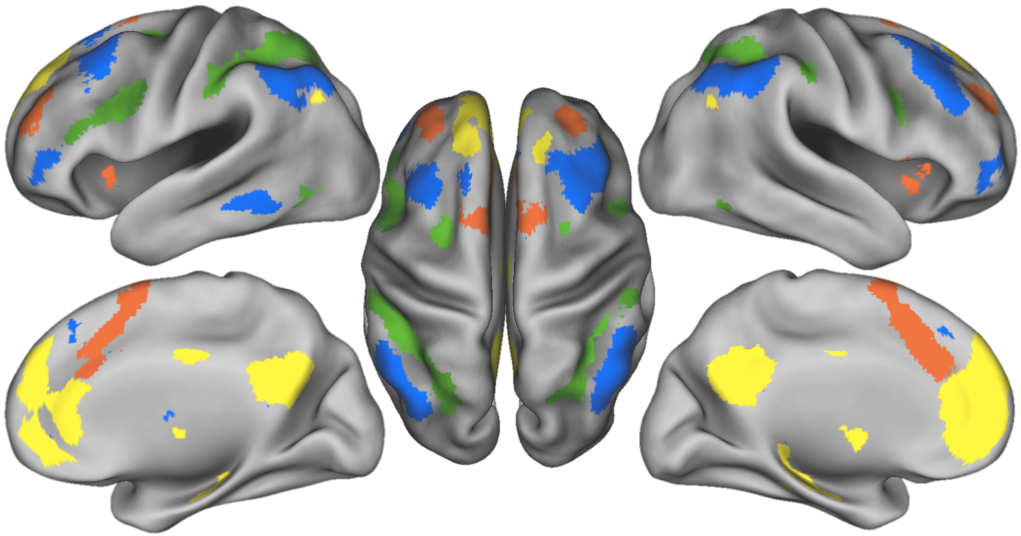
Network Definitions

Cerebral Cortex January 2012;22:158-165
doi:10.1093/cercor/bhr099
Advance Access publication May 26, 2011

Decoding Subject-Driven Cognitive States with Whole-Brain Connectivity Patterns

W. R. Shirer[1], S. Ryali[2], E. Rykhlevskaia[2], V. Menon[2,3] and M. D. Greicius[1,3]

- ICA-defined
- In standard MNI space

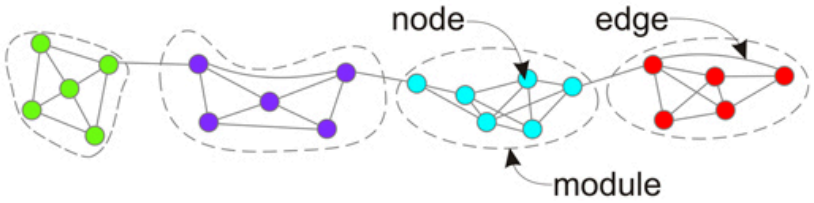


Default mode network (DMN)
Salience network (SN)
Visuospatial network (VS)
Executive control network (ECN)

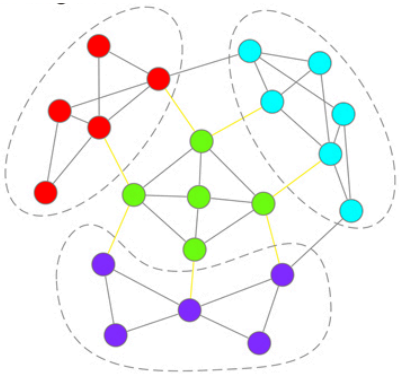
Etkin A, et al. *Sci Transl Med*. 2019;11(486). Pii.eaal3236. doi: 10.1126/scitranslmed.aal3236.; Shirer WR, et al. *Cereb Cortex*. 2012;22(1):158-165.

Graph Analytical Methods To Understand Networks: PTSD

Network segregation



Network integration

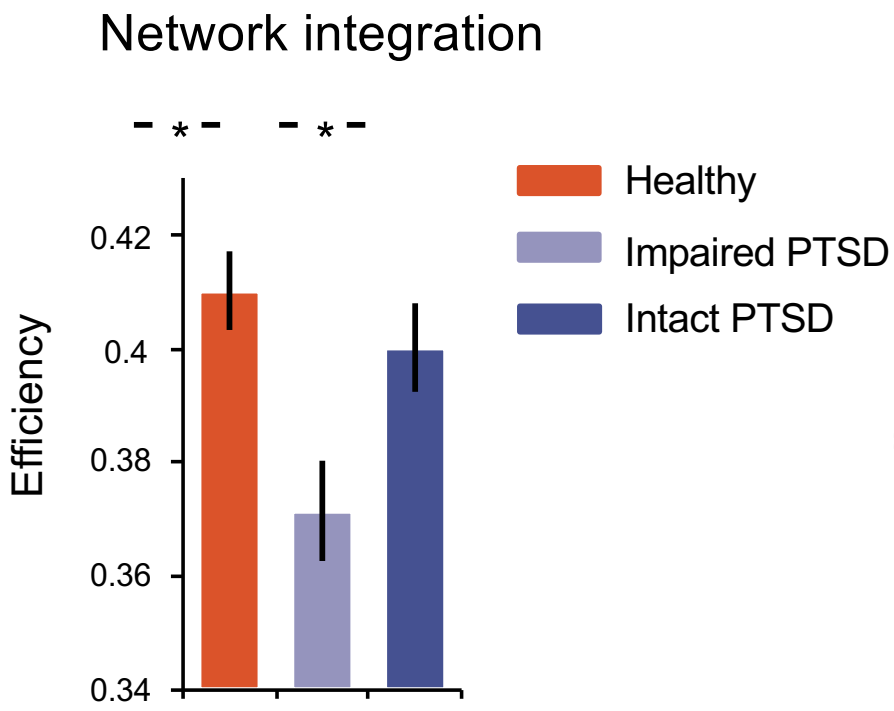


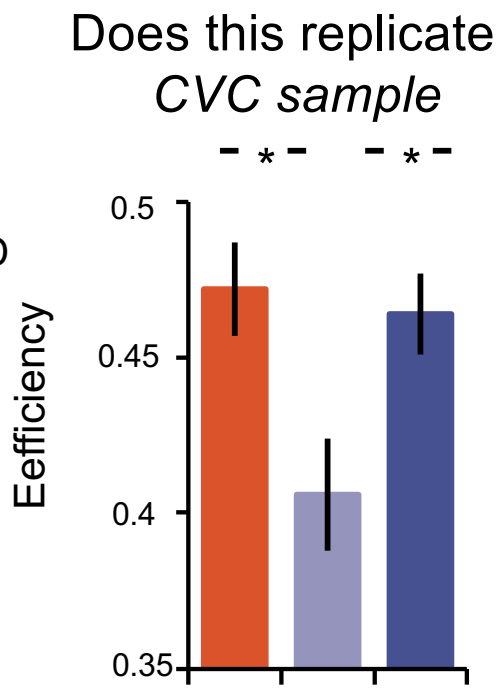
PTSD:

Etkin A, et al. *Sci Transl Med*. 2019;11(486). Pii.eaal3236. doi: 10.1126/scitranslmed.aal3236.

Network/Cognition Relationships

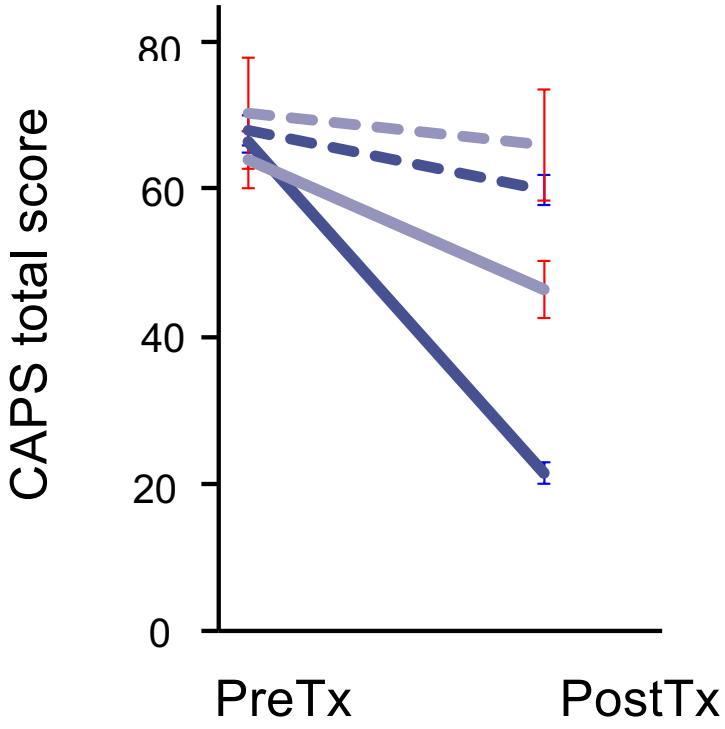
Some Patients Impaired, Others Intact: Disentangle Heterogeneity





Etkin A, et al. *Sci Transl Med*. 2019;11(486). Pii.eaal3236. doi: 10.1126/scitranslmed.aal3236.

CVC Biomarker Prediction of Outcome



Prolonged Exposure (PE)

Impaired

Intact

Wait List (WL)

Impaired

Intact

Arm x Time:
Intact: $p < .001$
Impaired: $p = .3$

Group x Arm x Time: $p < .04$

Etkin A, et al. *Sci Transl Med*. 2019;11(486). Pii.eaal3236. doi: 10.1126/scitranslmed.aal3236.

Proof of Concept for Advanced Analytics of Precision Medicine Trials Before Pilot Data

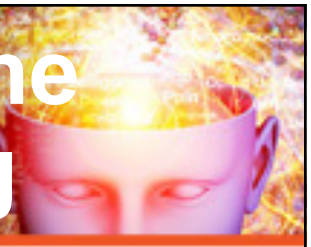
Traditional Approach to the Analysis of RCTs
Test Treatment (A) vs. placebo (B)

- **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

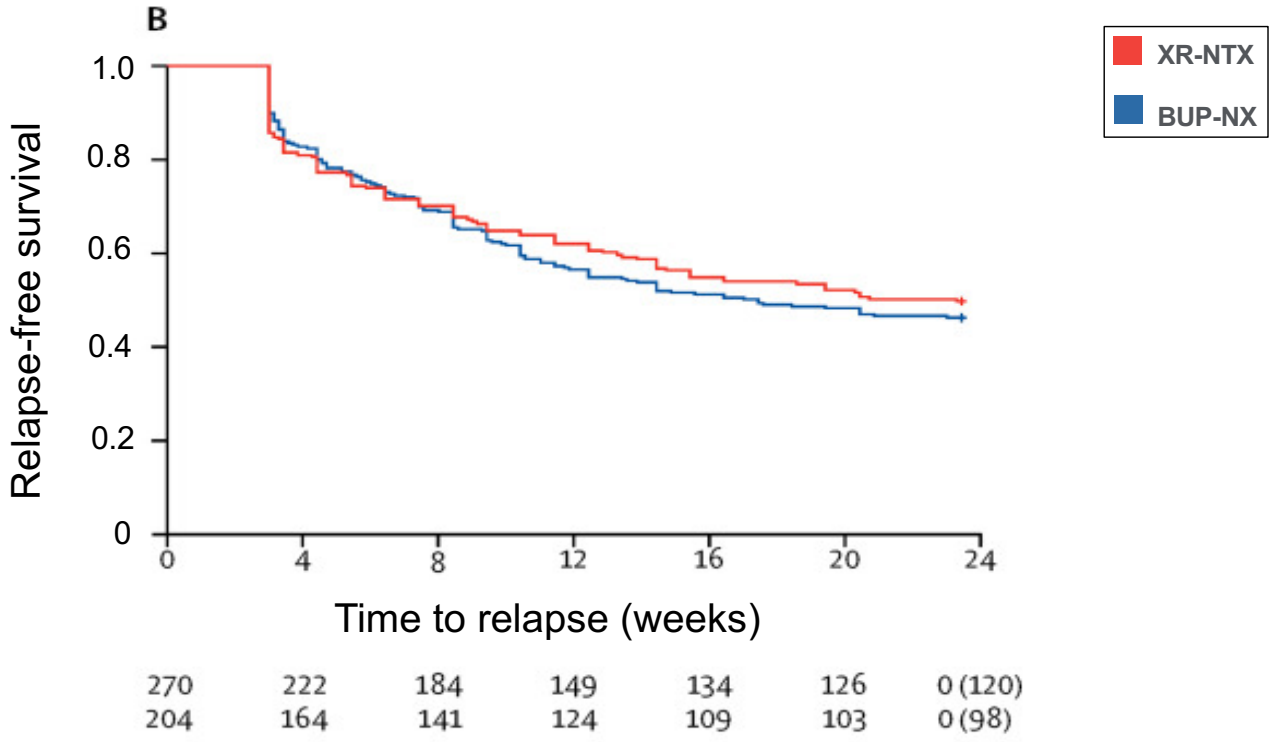


- Randomized, unblinded 24-week trial for prevention of relapse, N = 570
- Individuals with OUD after detox
- Compare XR-NTX vs BUP-NX
- **Results:** No difference in time to relapse between treatments in whole study sample
- **Authors' Conclusion:** "…both medications were equally safe and effective."

OUD = opioid use disorder; BUP-NX = buprenorphine-naloxone; XR-NTX = extended release naltrexone

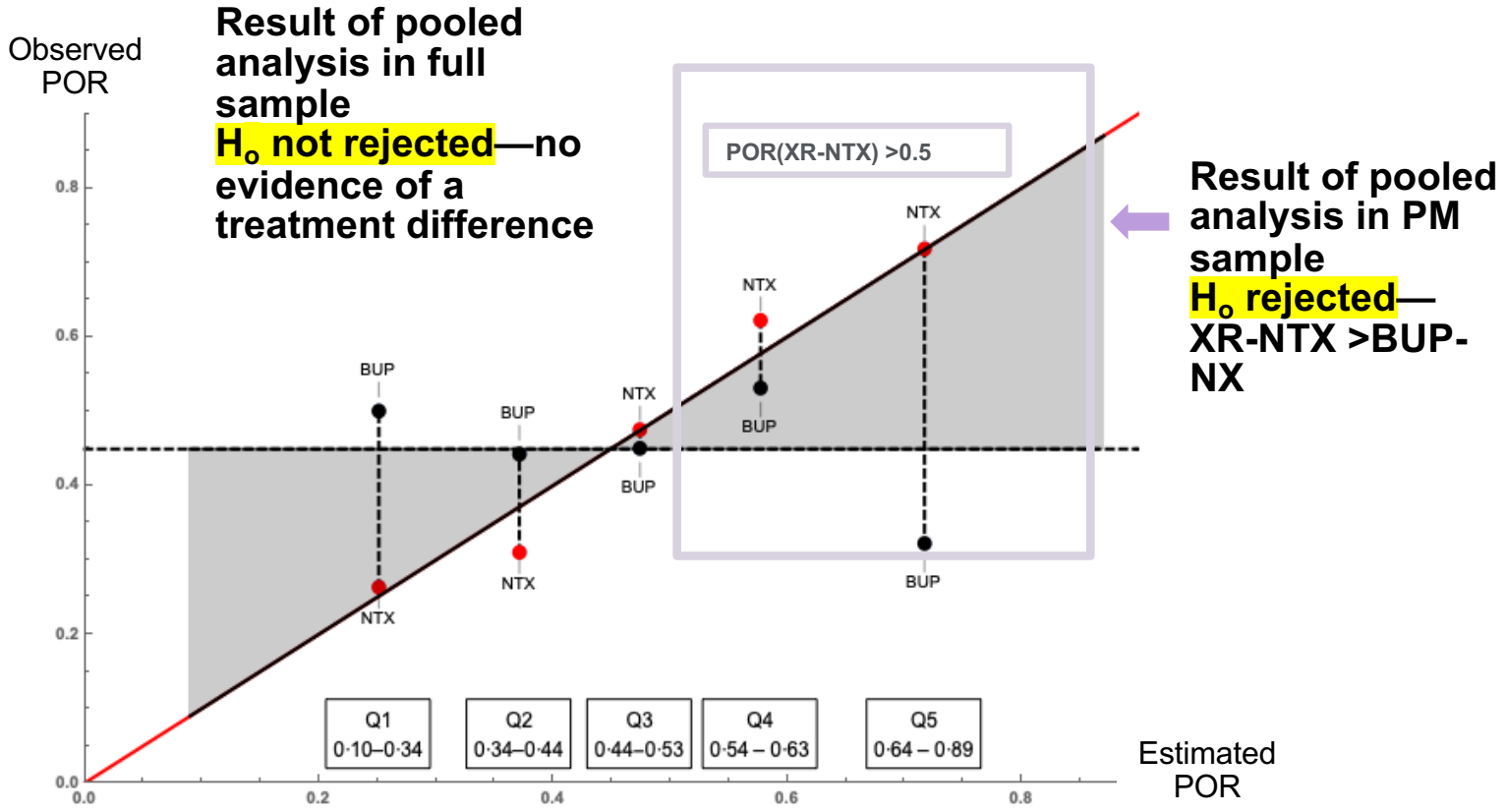
Lee JD, et al. *Lancet* 2018;391:309–318.

Relapse-free Survival and Treatment Effect Over Time For The XR-NTX And BUP-NX Treatment Groups: Full Sample Analysis



Lee JD, et al. *Lancet* 2018;391:309–318.

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



Lee JD, et al. *Lancet* 2018;391:309–318.

Features Guiding Treatment Choice

Feature	Use XR-NTX	
ASI Psychiatric Composite Score	0.24	
Age	34.81 (10.71)	
DSM-5 Cannabis Diagnosis	No use	72.51%
	Other	27.49%
DSM-5 Sedatives Diagnosis	No use	81.04%
	Other	18.96%
Current Sedative User	Yes	24.64%
	No	75.36%
Chronic Pain > 6 Months	Yes	12.8%
	No	87.2%

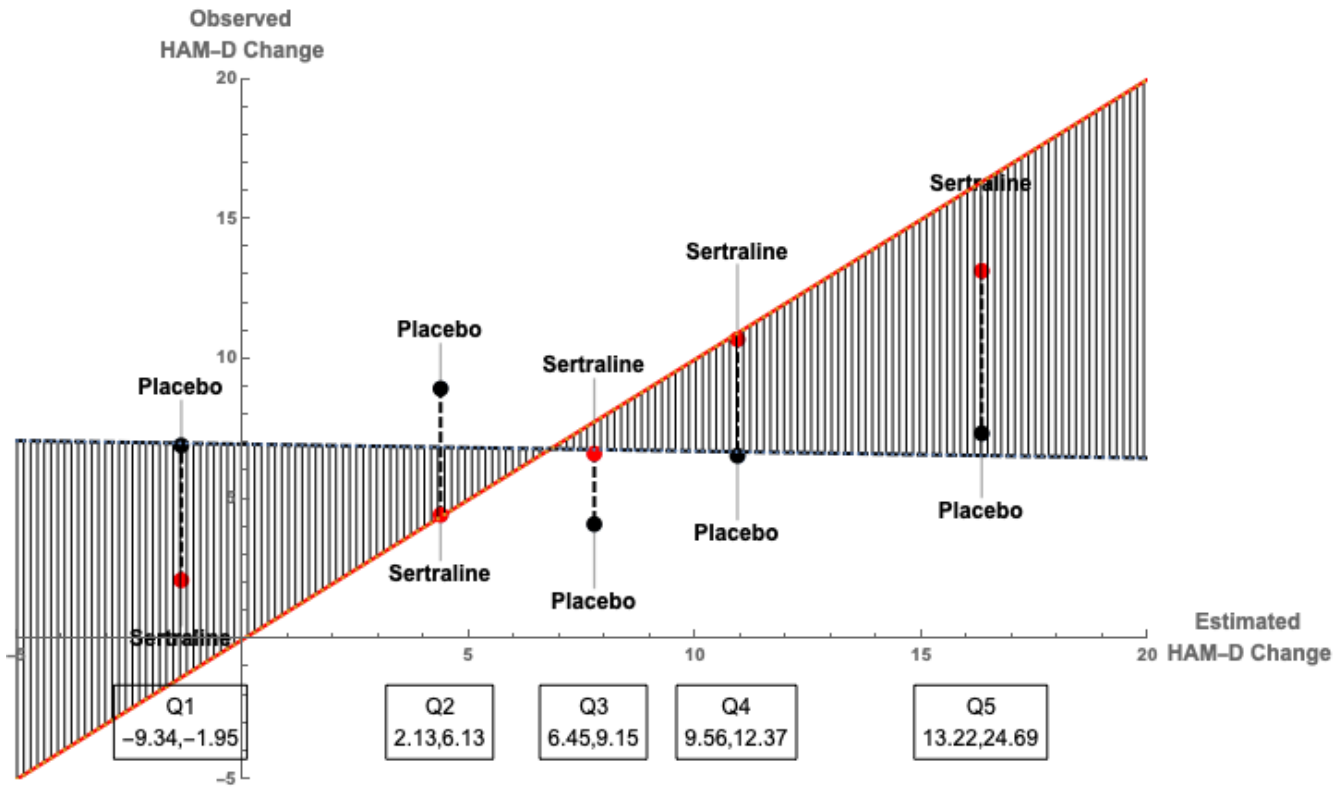
Lee JD, et al. *Lancet* 2018;391:309–318.

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

- Randomized, double blind 8-week trial of wertraline 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

Trivedi MHJ, et al. *Psychiatr Res*. 2016;78:11-23.

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



Trivedi MHJ, et al. *Psychiatr Res*. 2016;78:11-23.

Questions & Answers

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