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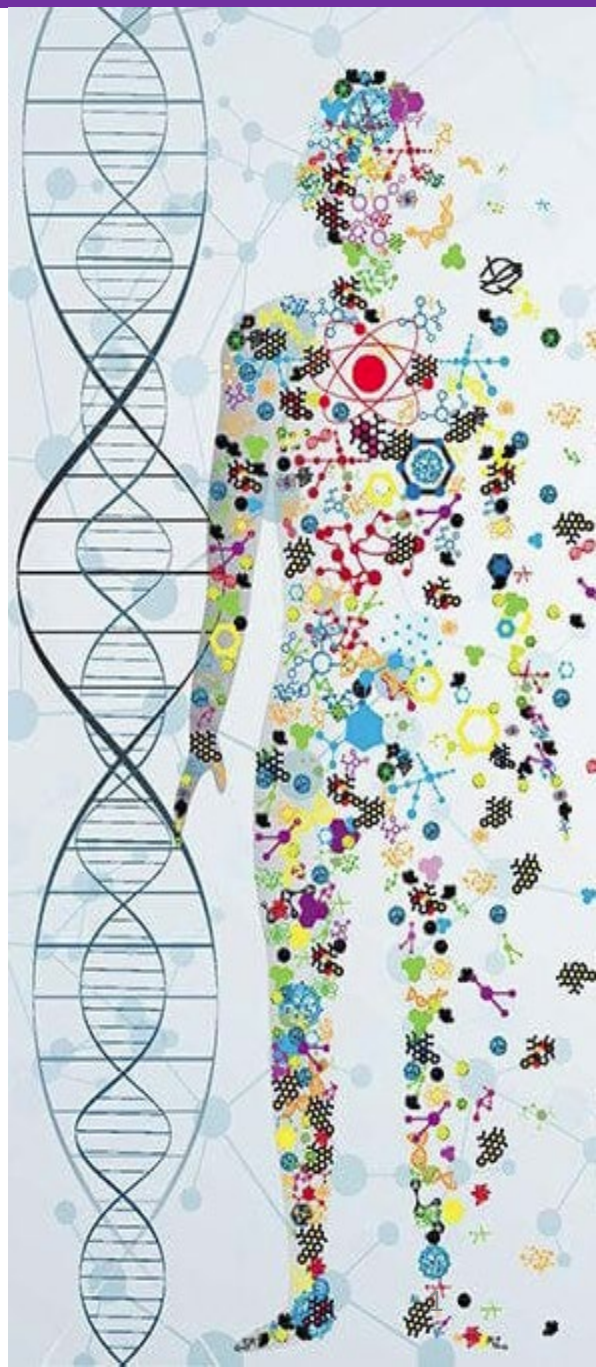
Leveraging Systems Pharmacology and Neurocircuitry to Advance Precision Medicine for AUD and PTSD

ASAM State of the Art 2022



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Disclosures

I serve on Advisory Board of Receptor Life Sciences, Otsuka Pharmaceuticals and Roche Products Limited

I receive support from:

- National Institute on Alcohol Abuse and Alcoholism
- Department of Defense
- Bank of America Foundation
- Brockman Foundation
- Cohen Veterans Bioscience
- Cohen Veterans Network
- Robin Hood Foundation
- McCormick Foundation
- Home Depot Foundation
- New York City Council
- New York State Health
- Mother Cabrini Foundation
- Tilray Pharmaceuticals
- Malin Estate

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

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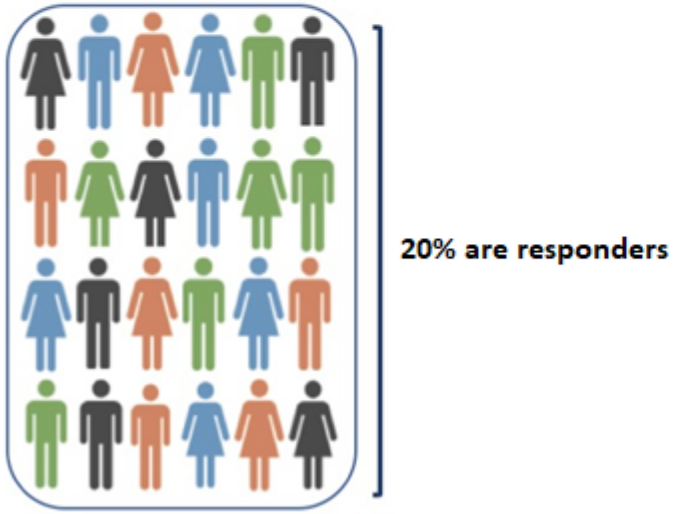
Cohen Veterans Bioscience

AUD/PTSD Heterogeneity

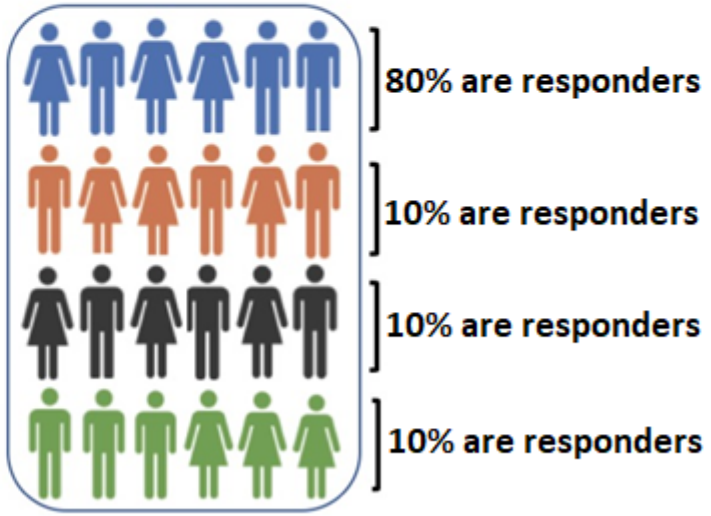
Biomarker informed personalized medicine

Drug X,
standard approach



Biomarker of subphenotypes

Drug X,
personalized medicine approach



NNT for entire sample = 20

NNT for subgroup 2+

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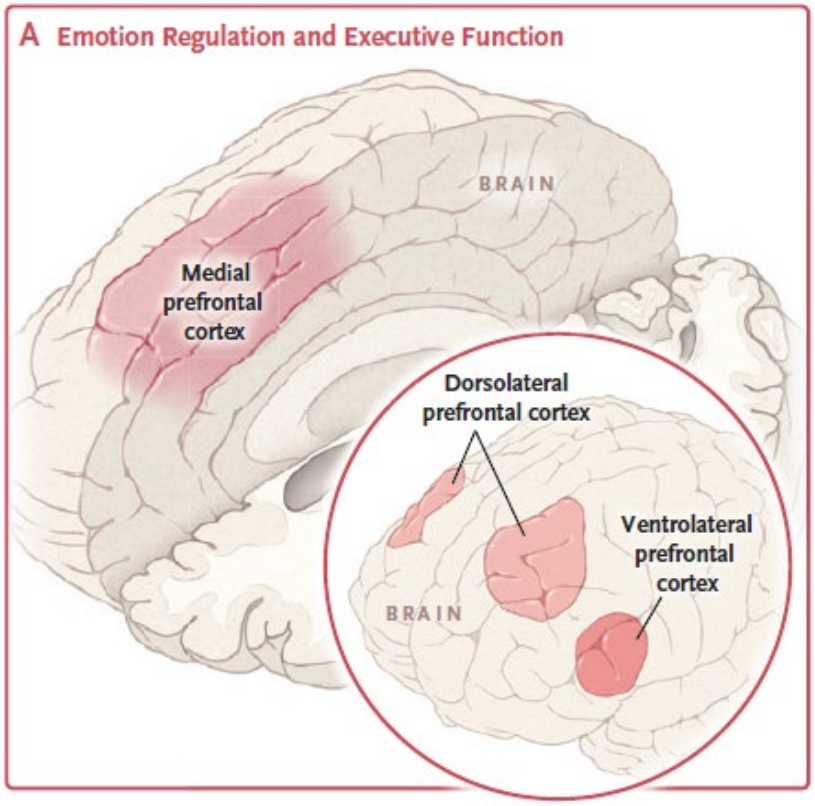
PTSD Neural Circuit Phenotypes
Emotion Regulation & Executive Function

Amygdala activation to threat modulated by –

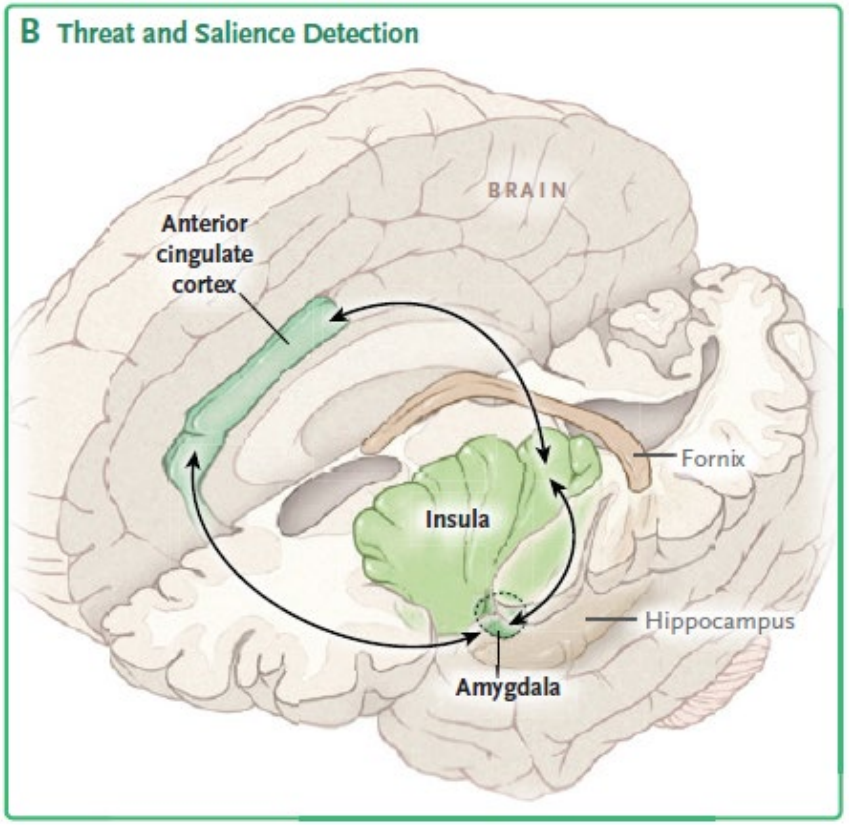
- Medial prefrontal cortex
- Dorsolateral prefrontal cortex
- Dorsal anterior cingulate
- Insula



Shalev, Liberzon and Marmar, N. Eng J Med 2017 377: 1795-6

PTSD Neural Circuit Phenotypes
Threat & 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, Liberzon and Marmar, N. Eng J Med 2017 377: 1795-6

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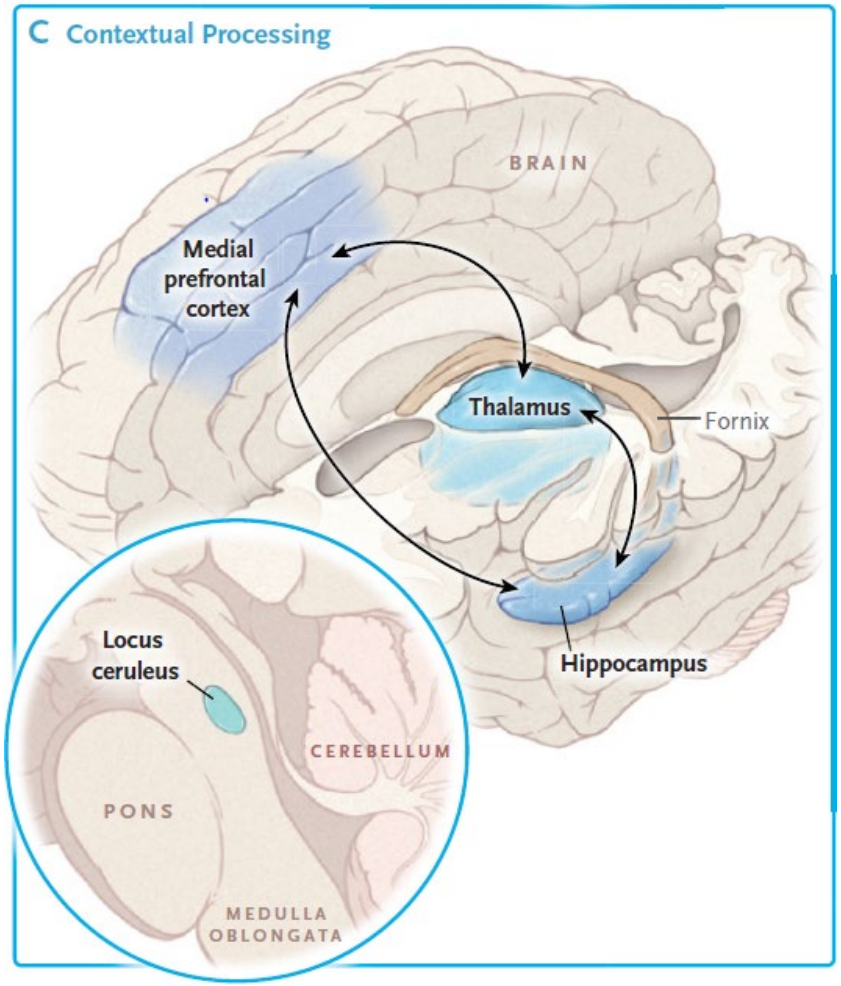
PTSD Neural Circuit Phenotypes
Contextual Processing

- Garfinkel, Abelson, King, Sripada, Wang, Gaines and Liberzon J. Neuroscience, 2014
- Diminished capacity to use safety context to modulate fear expression
- Diminished capacity to use danger signals adaptively
- Deficits in context updating
- Hippocampal dependent process with insula and PFC



Shalev, Liberzon and Marmar, N. Eng J Med 2017 377: 1795-6

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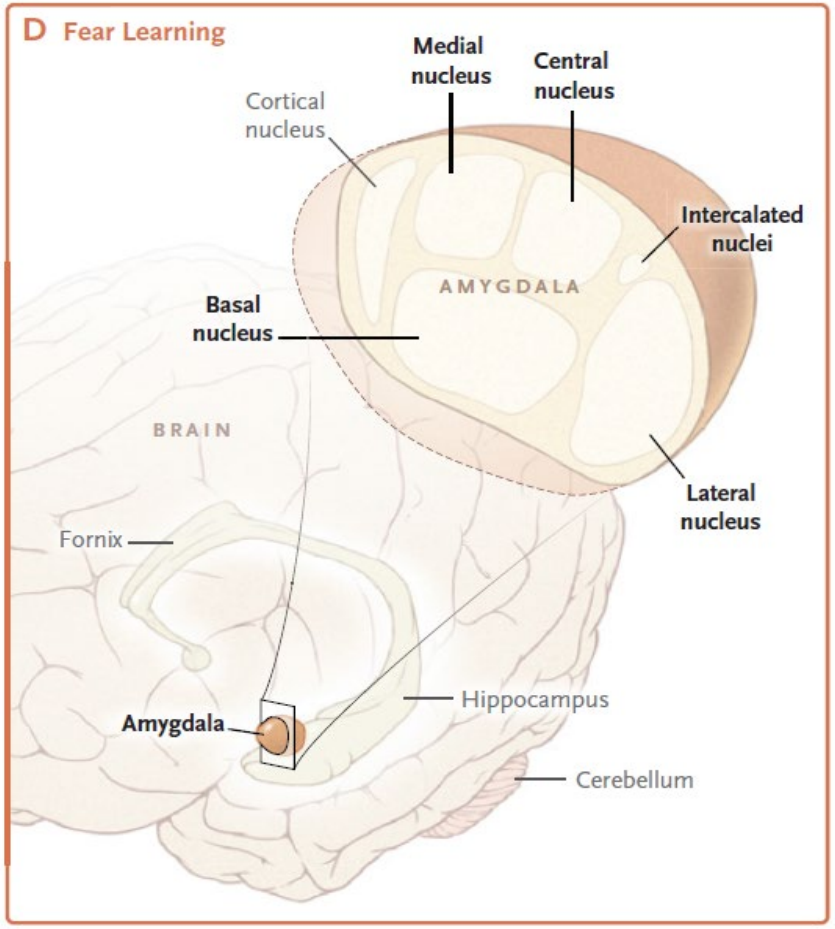
PTSD Neural Circuit Phenotypes
Fear Learning

- 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, Liberzon and Marmar, N. Eng J Med 2017 377: 1795-6

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PTSD Molecular Phenotypes

- Genetic
- Genomic
- Endocrine
- Metabolomic
- Proteomic

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 markers
  - 27 metabolites
  - 156 methylation probes
  - 81 miRNAs
  - 42 proteins
  - 4 small molecules
  - 3 nonlinear feature combinations

Dean KR, Hammamieh R,…Marmar CR et al. Multi-omic biomarker identification and validation for diagnosing warzone-related post-traumatic stress disorder. Mol Psychiatry. 2019 Sep 10. doi: 10.1038/s41380-019-0496-z.

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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;

Dean KR, Hammamieh R,…Marmar CR et al. Multi-omic biomarker identification and validation for diagnosing warzone-related post-traumatic stress disorder. Mol Psychiatry. 2019 Sep 10. doi: 10.1038/s41380-019-0496-z.

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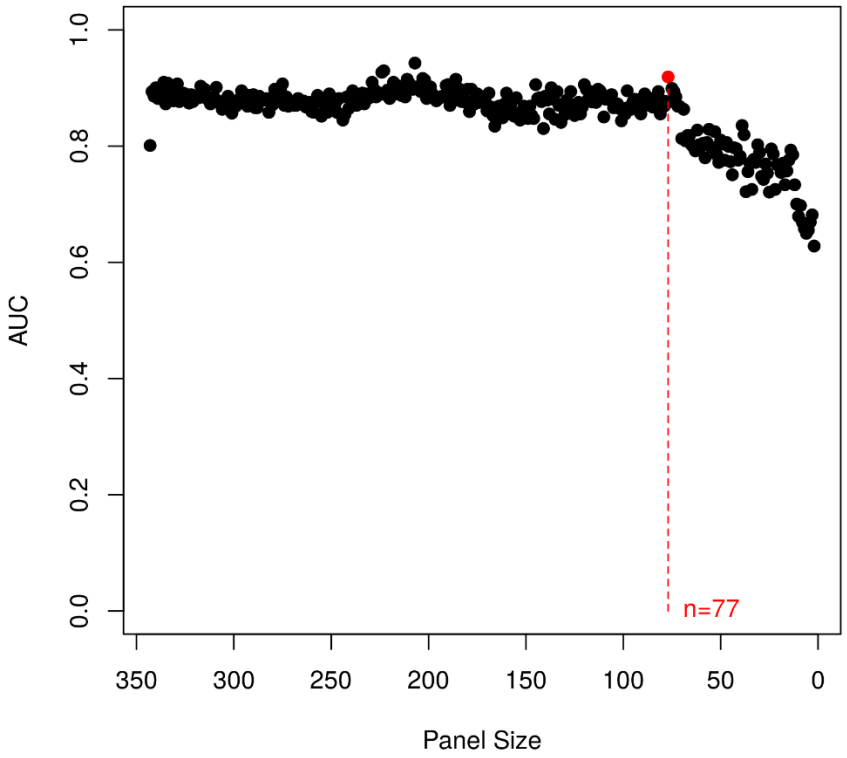
Stage 2: A recursive feature elimination approach

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



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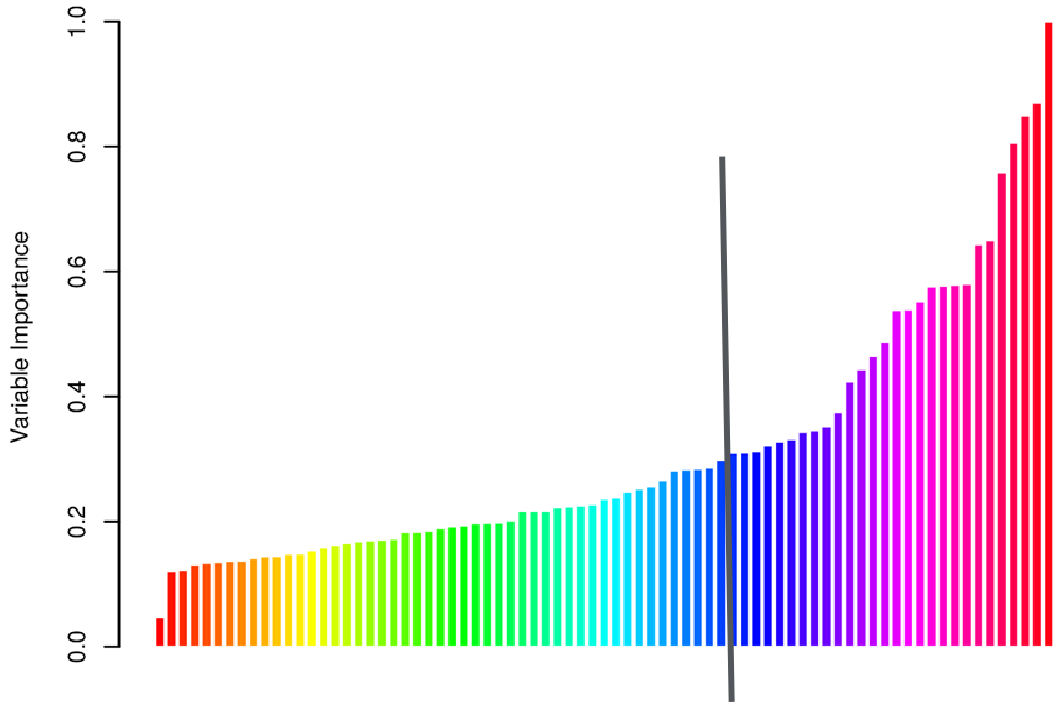
Stage 3: Most Important Features from Random Forest (Machine Learning Program)

- 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-9-5P (Neurogenesis)
  - 2 clinical lab measures – Insulin, MPV
  - 11 methylation probes – PDE9A gene (Monamine neurotransmitters)
  - 7 proteins – PTGDS – AQG (Prostaglandin)

Dean KR, Hammamieh R,…Marmar CR et al. Multi-omic biomarker identification and validation for diagnosing warzone-related post-traumatic stress disorder. Mol Psychiatry. 2019 Sep 10. doi: 10.1038/s41380-019-0496-z.

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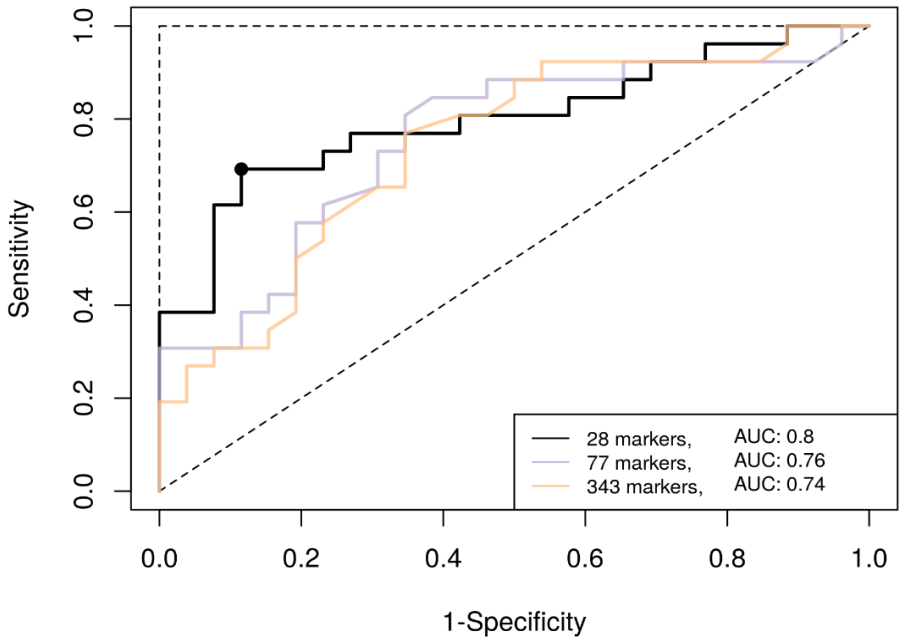
Biomarker Panel Validation

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



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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.

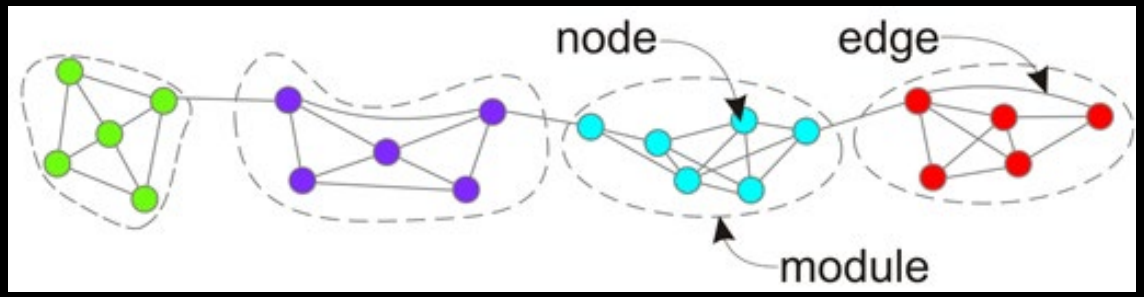
Key Questions:

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?

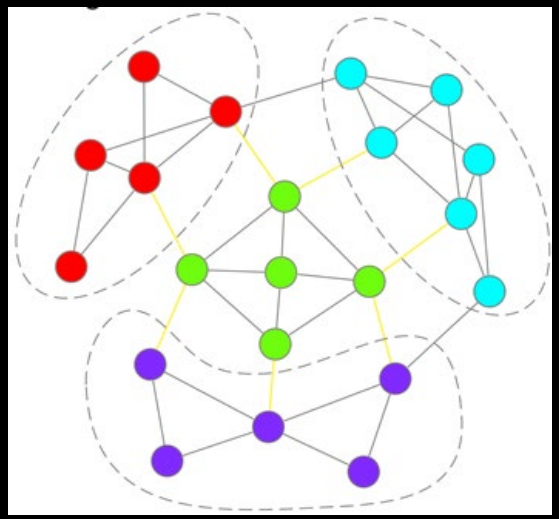
Etkin, Sci. Transl. Med., 2019

Graph analytical methods to understand networks

Network segregation



Network integration



Etkin, Sci. Transl. Med., 2019

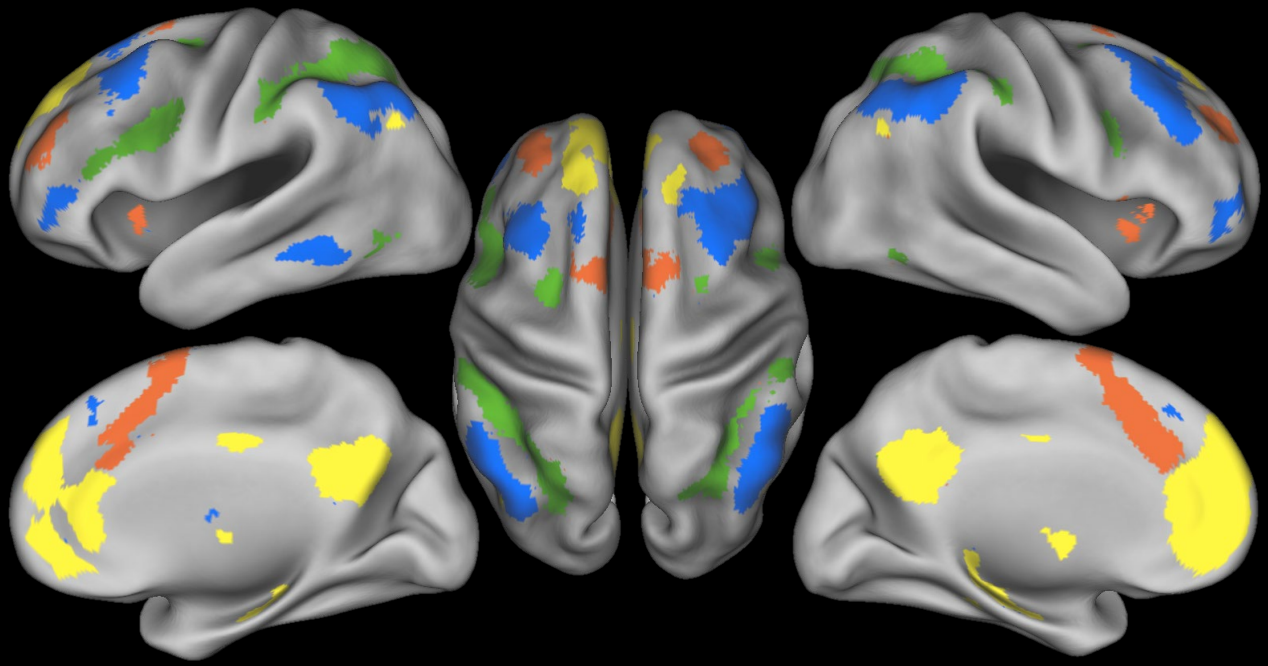
Network definitions

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)

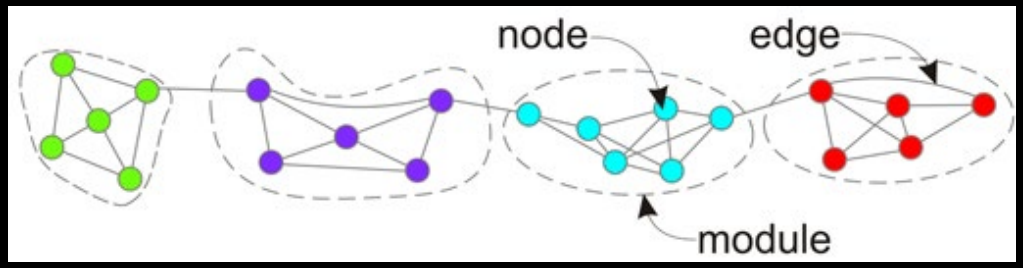
Visuospatial network (VS)

Executive control network (ECN)

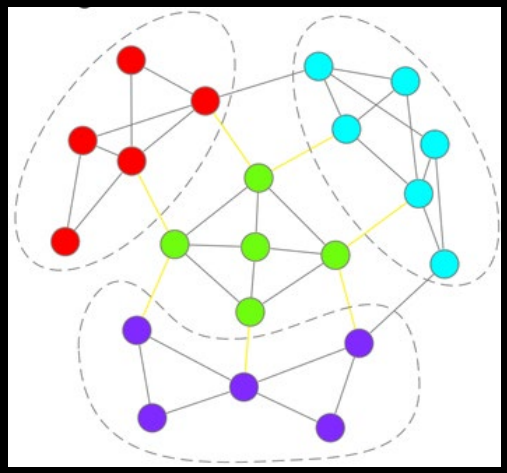
Etkin, Sci. Transl. Med., 2019

Graph analytical methods to understand networks: PTSD

Network segregation



Network integration

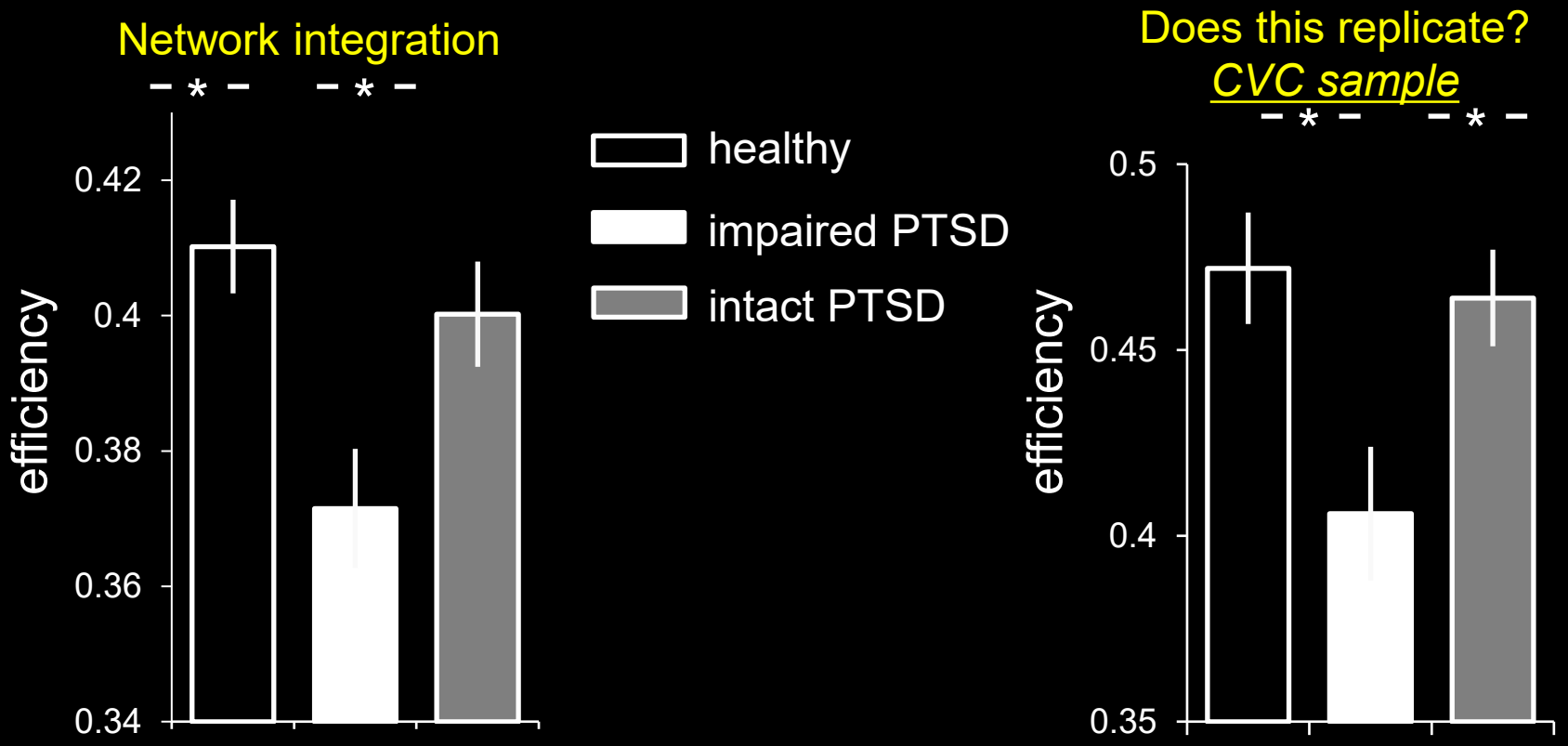


PTSD:

Etkin, Sci. Transl. Med., 2019

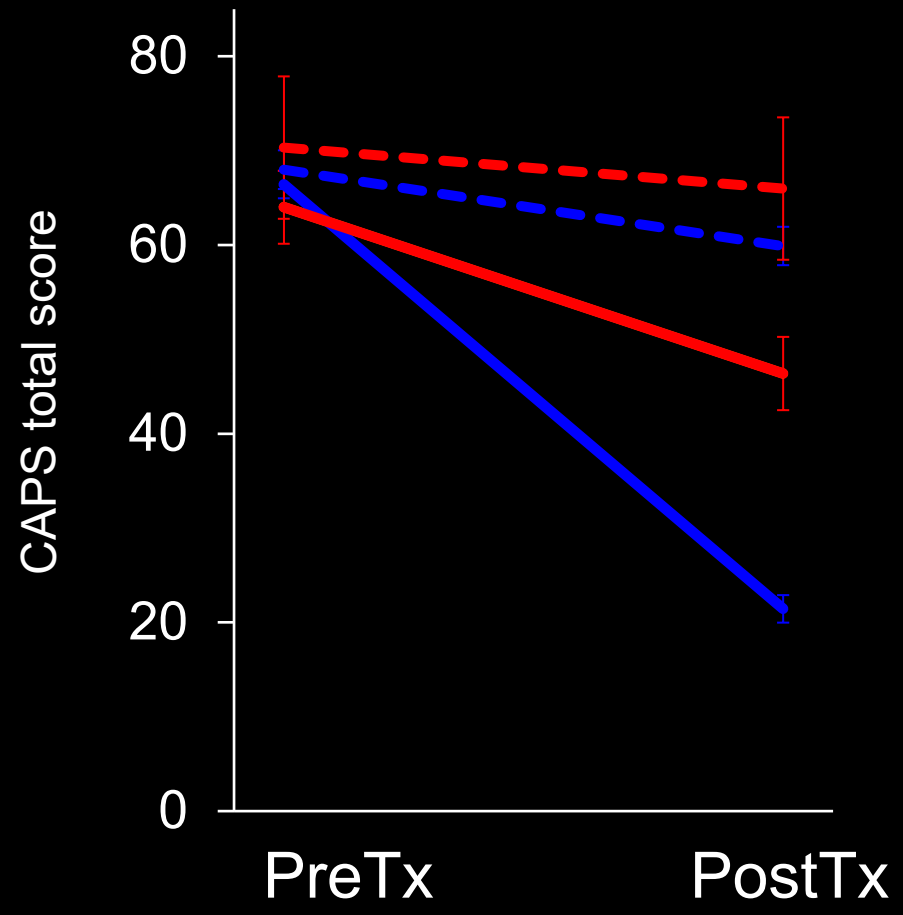
Network/cognition relationships

Some patients impaired, others intact: disentangle heterogeneity



Etkin, Sci. Transl. Med., 2019

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, Sci. Transl. Med., 2019

ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

Vol. 43, No. 1
January 2019

Gabapentin Enacarbil Extended-Release for Alcohol Use Disorder: A Randomized, Double-Blind, Placebo-Controlled, Multisite Trial Assessing Efficacy and Safety

Daniel E. Falk, Megan L. Ryan, Joanne B. Fertig, Eric G. Devine, Ricardo Cruz, E. Sherwood Brown, Heather Burns, Ihsan M. Salloum, D. Jeffrey Newport, John Mendelson, Gantt Galloway, Kyle Kampman, Catherine Brooks, Alan I. Green, Mary F. Brunette, Richard N. Rosenthal, Kelly E. Dunn, Eric C. Strain, Lara Ray, Steven Shoptaw, Nassima Ait-Daoud Tiouririne, Erik W. Gunderson, Janet Ransom, Charles Scott, Lorenzo Leggio, Steven Caras, Barbara J. Mason, Raye Z. Litten, and for the National Institute on Alcohol Abuse and Alcoholism Clinical Investigations Group (NCIG) Study Group

Background: Several single-site alcohol treatment clinical trials have demonstrated efficacy for immediate-release (IR) gabapentin in reducing drinking outcomes among individuals with alcohol dependence. The purpose of this study was to conduct a large, multisite clinical trial of gabapentin enacarbil extended-release (GE-XR) (HORIZANT®), a gabapentin prodrug formulation, to determine its safety and efficacy in treating alcohol use disorder (AUD).

Study Objectives:

1. To conduct the first RCT evaluating the efficacy and safety of GE-XR as a treatment for alcohol use disorder (AUD).
2. Also, the first 6-month, multi-site RCT of a gabapentin formulation adhering to FDA guidelines for pivotal alcohol pharmacotherapy trials.

GE-XR Randomized Controlled Trial for AUD- Methods

- **Participants:** 338 men and women, age 21+, with Moderate/Severe AUD
- **Treatment:** 24 weeks of GE-XR (1-wk titration, 600 mg BID) (n=170); matched placebo (n=168); mITT: took ≥1 pill
- **Behavioral Platform:** *Take Control:* a novel computerized bibliotherapy platform.
- **Recruitment:** 10 academic U.S. sites (June 2015 – February 2017)
- **Key Entry Criteria:**
  - ≥ 21/28 drinks per week (females/males) and 1+ heavy drinking day per week (28 days before consent); ≥ 3 consecutive days of abstinence before randomization
  - No other substance dependence (except nicotine)
  - No major psychiatric disorders (psychotic, bipolar, and eating disorders; major depressive episode) and low suicide risk
  - Normal laboratory values
  - No complicating medical conditions

GE-XR Randomized Controlled Trial for AUD- Conclusions

- GE-XR at 600 mg BID had no therapeutic benefit on measures of alcohol consumption, craving, consequences, or symptoms of protracted abstinence in individuals with AUD.

- GE-XR was well tolerated with generally mild-to-moderate side effects consistent with the product label.

- Evaluation of a higher dose for AUD may be appropriate.

- **Identify subtypes of patients who might be more likely to benefit from this medication**

ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

Vol. **, No. *
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Gabapentin Enacarbil Extended-Release Versus Placebo: A Likely Responder Reanalysis of a Randomized Clinical Trial

Eugene M. Laska, Carole E. Siegel, Ziqiang Lin, Michael Bogenschutz, and Charles R. Marmar

Background: We reanalyzed a multisite 26-week randomized double-blind placebo-controlled clinical trial of 600 mg twice-a-day Gabapentin Enacarbil Extended-Release (GE-XR), a gabapentin prodrug, designed to evaluate safety and efficacy for treating alcohol use disorder. In the original analysis (n = 338), published in 2019, GE-XR did not differ from placebo. Our aim is to advance precision medicine by identifying likely responders to GE-XR from the trial data and to determine for likely responders if GE-XR is causally superior to placebo.

- Study Objective to advance precision medicine by:
  1. Identifying "likely responders" to GE-XR using patient characteristics assessed prior to treatment
  2. Determining if, among the likely responder group, GE-XR is causally superior to placebo on drinking and other outcomes

Methods

Step 1:

Identify Likely Responders (LRs) to GE-XR based on pretreatment clinical features

Step 2:

Causally test whether GE-XR does better than Placebo on reducing number of heavy drinking days - at least a 50% reduction

Step 3:

Determine which specific clinical characteristics have most impact on being a LR among patients receiving GE-XR.

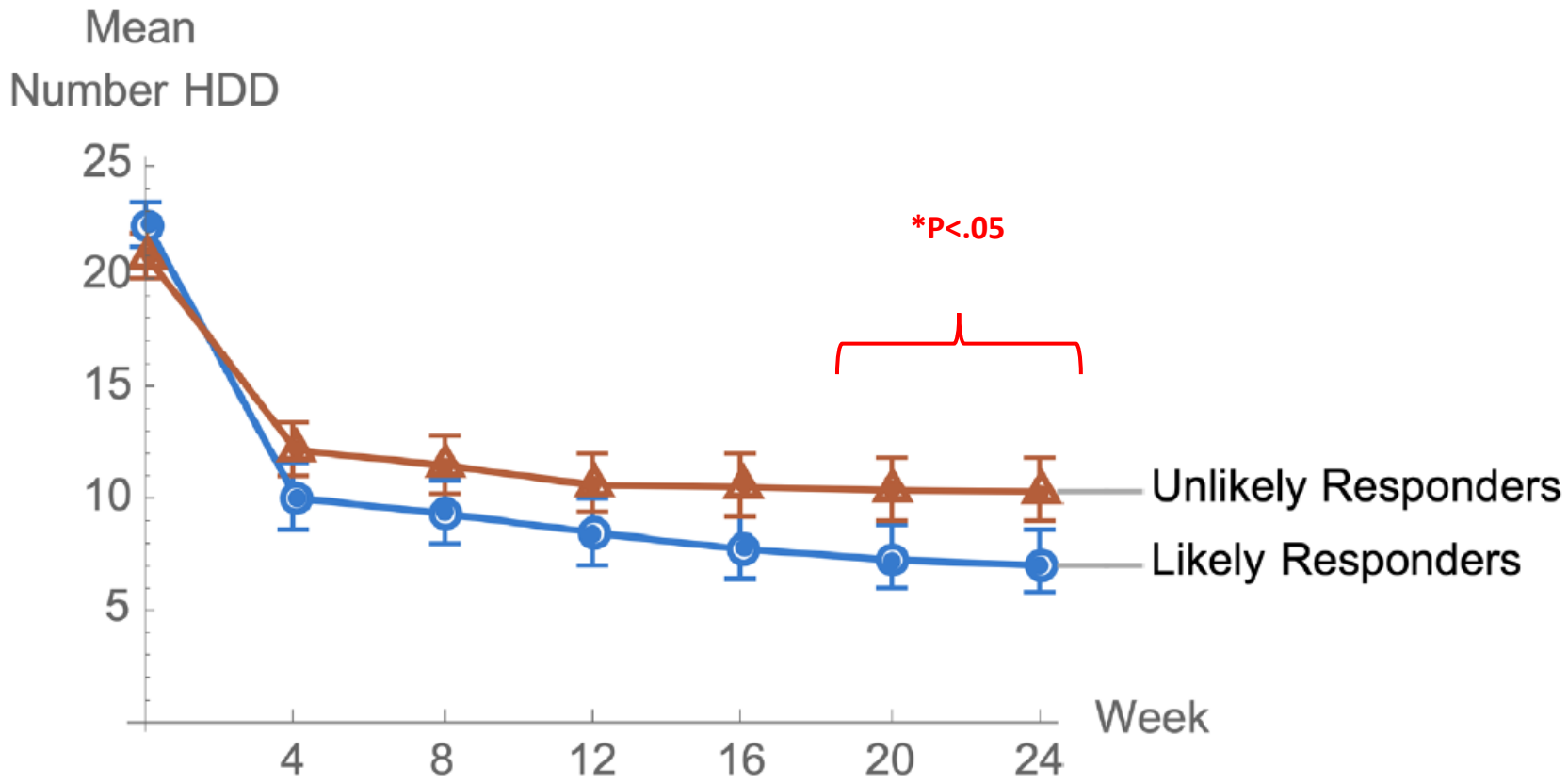
Step 1: Identify Likely Responders (LRs) to GE-XR

- Use random forests (RF, a machine learning technique) to obtain a model for predicting likely responders (LRs) to GE-XR from patient characteristics.
- Build the RF model on GE-XR patients only.
- 223 patient characteristics assessed at baseline entered at same time as predictors in model
    - Demographics
    - Substance use
    - Psychiatric characteristics
  - Outcome modeled: change in heavy drinking days (HDD) from baseline to last month of trial (Month 6)
  - Obtain the predicted change in HDD for both the GE-XR and the placebo patients by pluging the values of their baseline characteristics into the model.
  - **Counterfactual Approach** Ascertain predicted change in HDD for placebo group "as if the placebo patients had received GE-XR"
  - Match GE-XR and placebo patients on the predicted HDD score.
  - Create quintiles for GE-XR and placebo subjects with roughly the same predicted score (response to GE-XR)
  - Likely responders (LR): patients whose ***model-predicted*** change in HDD is at least 14 days (i.e., at least a 50% reduction in HDD)
  - Unlikely responders (ULR): everyone else – predicted change in HDD is less than 50%

Step 2: Causally evaluate treatment effects

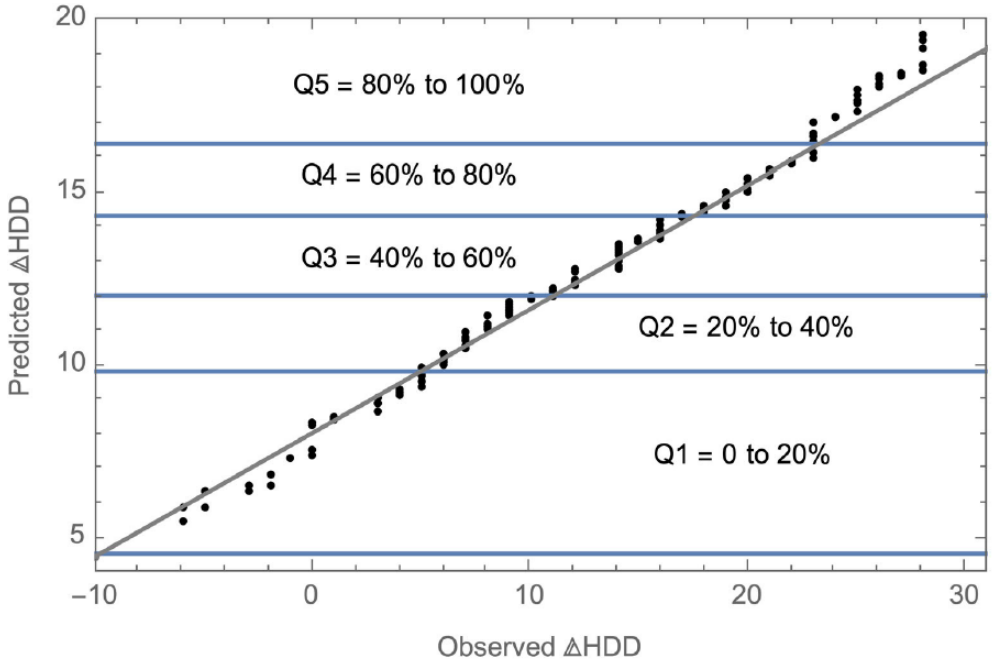
- **Causally test whether GE-XR does better than placebo on observed outcomes (drinking, etc) (within the LR group, UR group, and total sample) during last 4 weeks of trial (Month 6)**
- Based on the **Potential Outcome framework**: the causal effect is the difference between the outcomes that would have been observed had the subject been randomized to GE-XR minus the outcome had the subject been randomized to placebo
- Compare treatment groups using regular statistical analyses (ANCOVA) within each quantile and then pool across quantiles
- Key point: It is legitimate to claim that the treatment group *caused* the difference in outcomes because within each quantile the groups are equivalent with respect to the distribution of important baseline characteristics

LRs have less HDD than URs during last 2 months of trial



Random Forest Model Fit

- r=.42 between predicted and observed change in HDD (R^2 = 17%)
- Good, though suggests other baseline characteristics could be included to account for more explained variance in outcome



Step 3.

- **Determine which specific characteristics have most impact on being a LR among patients receiving GE-XR (important variable)**
- **Estimate the degree of change in HDD induced by a unit change of an important variable**

Go back to random forest model and, for a given characteristic variable, evaluate the average predicted change in HDD caused by a 1 unit increase in the variable, holding all other characteristics constant

Summary

- A machine learning + causal counterfactual/potential outcomes re-analysis of a "negative" RCT identified a fairly large group of likely responders (LRs) (42% of trial patients)
- In this LR group, GE-XR *causally* reduced 3 drinking outcomes compared to placebo.
  - No treatment effect in total sample (consistent with Falk et al., 2019)
  - Opposite treatment effect in UR group (GE-XR worse than placebo) – consistent with a disordinal interaction
- AUD patients with lower levels of internalizing symptoms (anxiety, depression) and higher levels of externalizing problems (cognitive and motor impulsivity) respond better to the gabapentin prodrug*
  - Its anticonvulsant-related mood stabilizing properties may explain why GE-XR is selectively effective for AUD patients with greater cognitive and motor impulsivity.

*comparison of LR vs UR groups on baseline characteristics

Novel Analytic Approaches to Precision Medicine

Molecular Markers

- Six molecular 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

NYU Langone Health

NIAAA funded P01 Clinical Study : Leveraging Biomarkers for Personalized Treatment of AUD Comorbid with PTSD

Phase IV, double-blind, 2-group randomized controlled trial of Topiramate vs. placebo in **150 participants** with moderate to severe AUD comorbid with PTSD or subthreshold PTSD,

- Randomized in a 2:1 ratio to topiramate vs. placebo.
- Drug titrated to a maximum dose of 200 mg over **12 weeks** of treatment, and tapered over a 2-week period (14 weeks total on medication, 24 week follow-up)

Primary Aims

1. Utilize likely responder analyses to **identify pre-treatment predictors of AUD and PTSD/subthreshold PTSD symptom response to topiramate,** including clinical and neurocognitive measures, neuroimaging measures (**fMRI, TMS/EEG**), and multiomic blood biomarkers- **genetic, genomic, metabolomic and proteomic features**.
2. Evaluate the effects **of topiramate on candidate blood and neuro-circuit biomarkers** in patients with AUD and PTSD/subthreshold PTSD.
3. Evaluate the effects of **topiramate on alcohol outcomes and on PTSD symptoms** in patients with AUD and PTSD/subthreshold PTSD.

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Acknowledgments

NYU

- Eugene Laska
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- Ziquang Lin
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- Michelle Jeffries

NIAAA

- Dan Falk
- Raye Litten

NYU Langone Health

Thank You

NYU Langone Health