
Targeting Glutamate to Treat PTSD

A Double-Blind, Randomized, Placebo-Controlled Trial

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- Aptinyx, FSV7, Lundbeck, Janssen, Psilocybin Labs: as consultant, speaker or on advisory board
- Sage Publication: as editor of *Chronic Stress*
- *Patent application (17269470): Anti-inflammatory + antidepressant*

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- Paulo Shiroma (site PI)

CAP

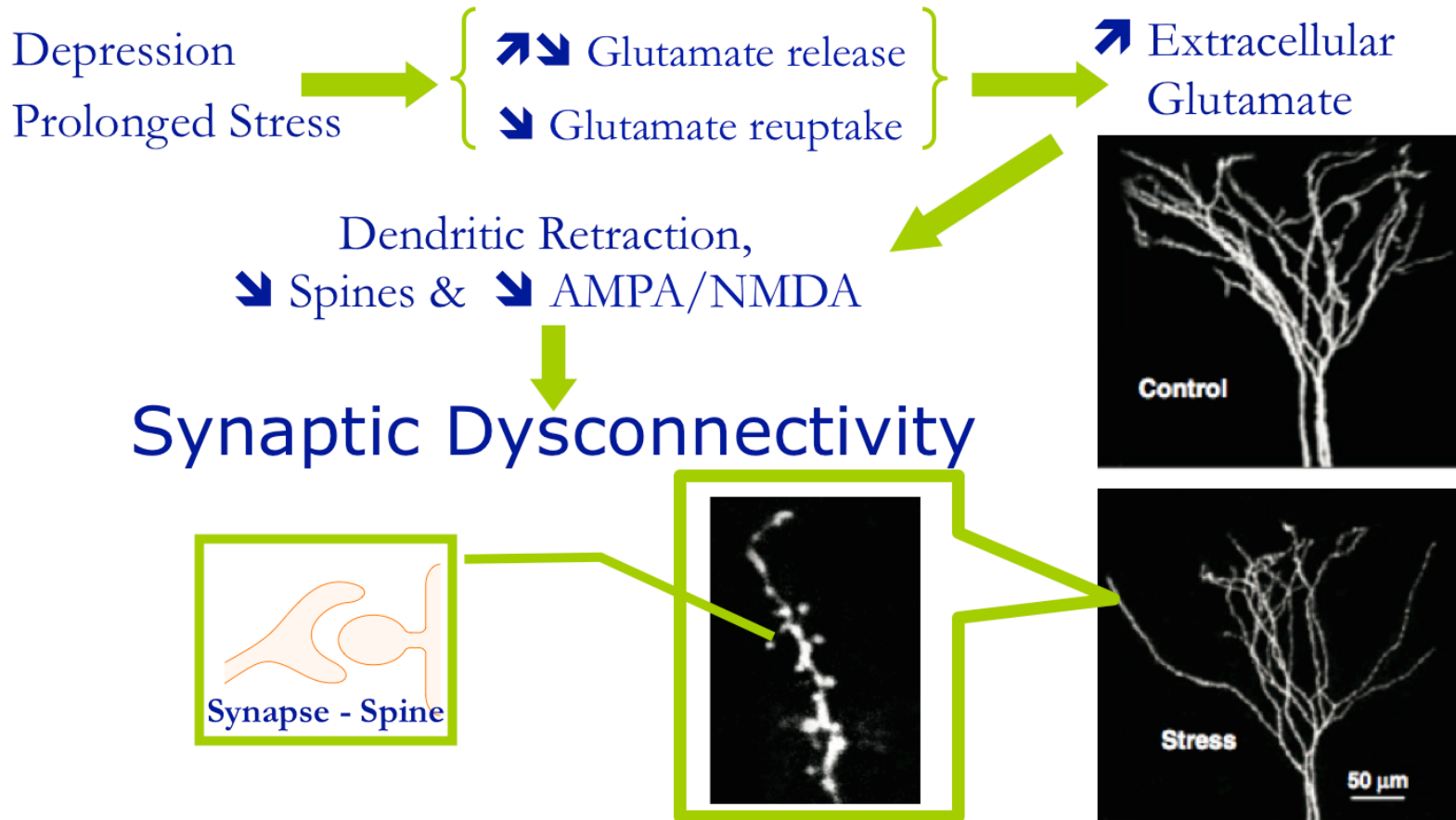
- Alan Peterson (CAP PI), Terry Keane, Barbara Niles, and many others

Note: Fill the blank

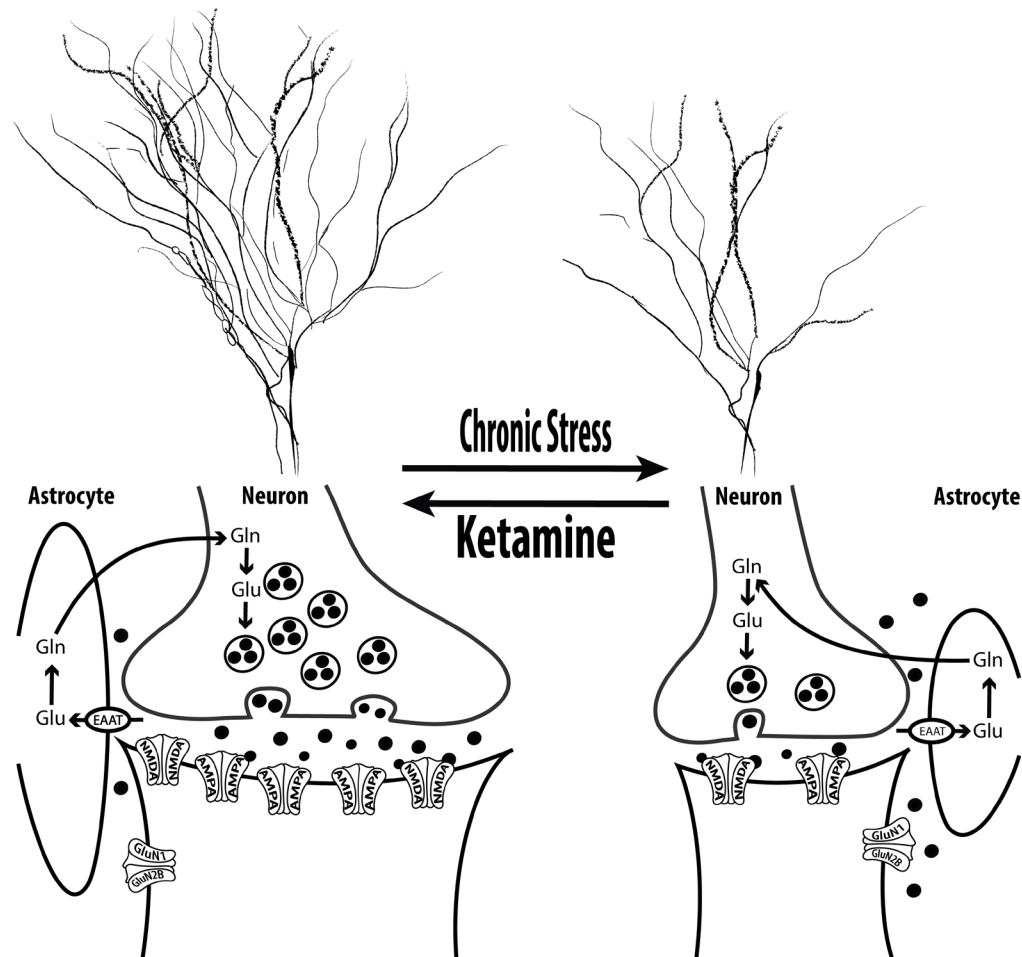
Medications that are effective for depression are often _____ effective in PTSD.

- A. More
- B. Equally
- C. Less
- D. Not

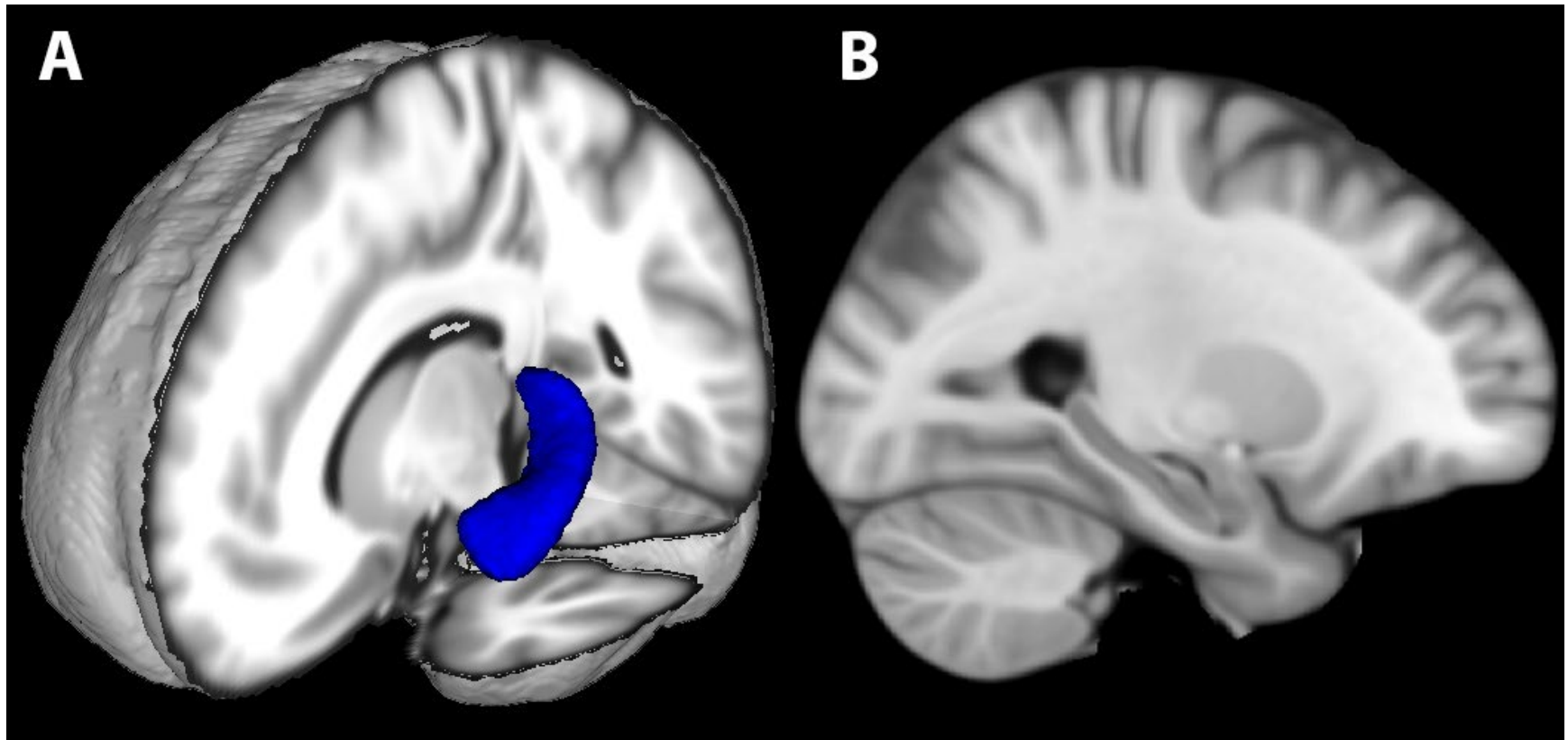
Chronic Stress Pathology (CSP): Aminoacid Based Model



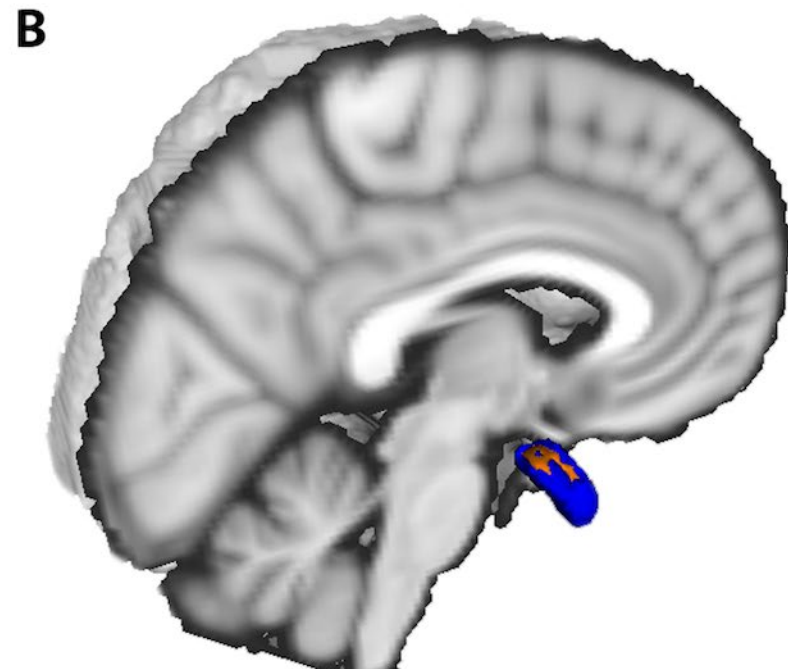
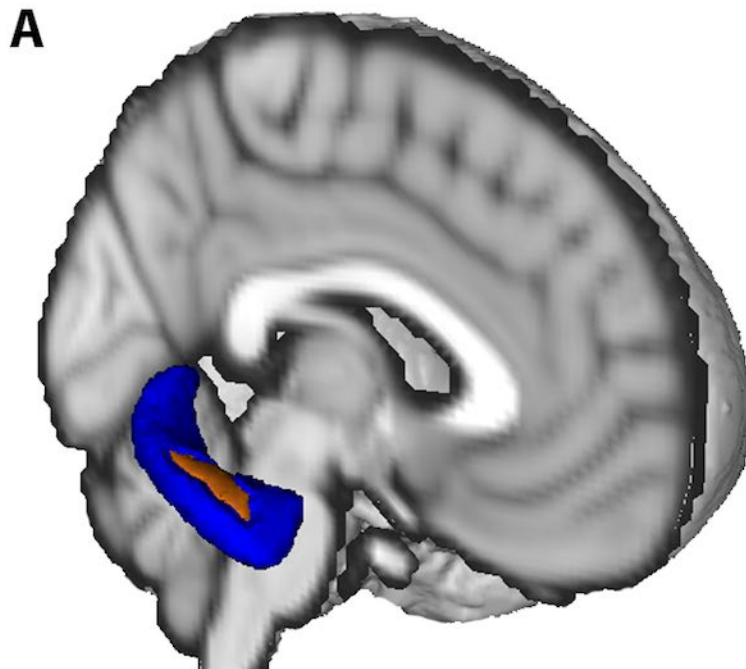
Ketamine as a Treatment: Rapid Reversal of CSP Synaptic Dysconnectivity



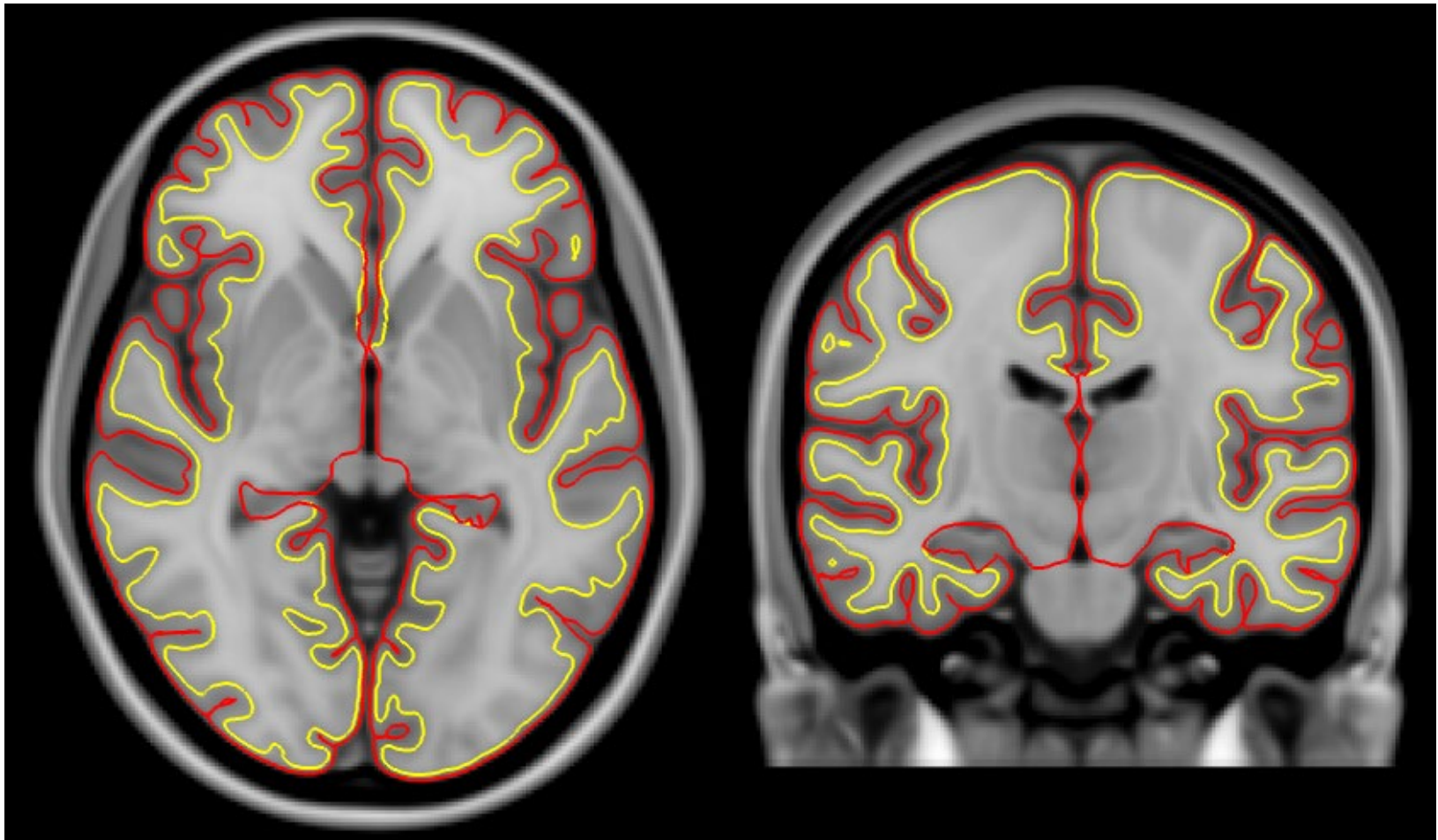
Hippocampal Shape & Volume



PTSD: Hippocampus & Amygdala



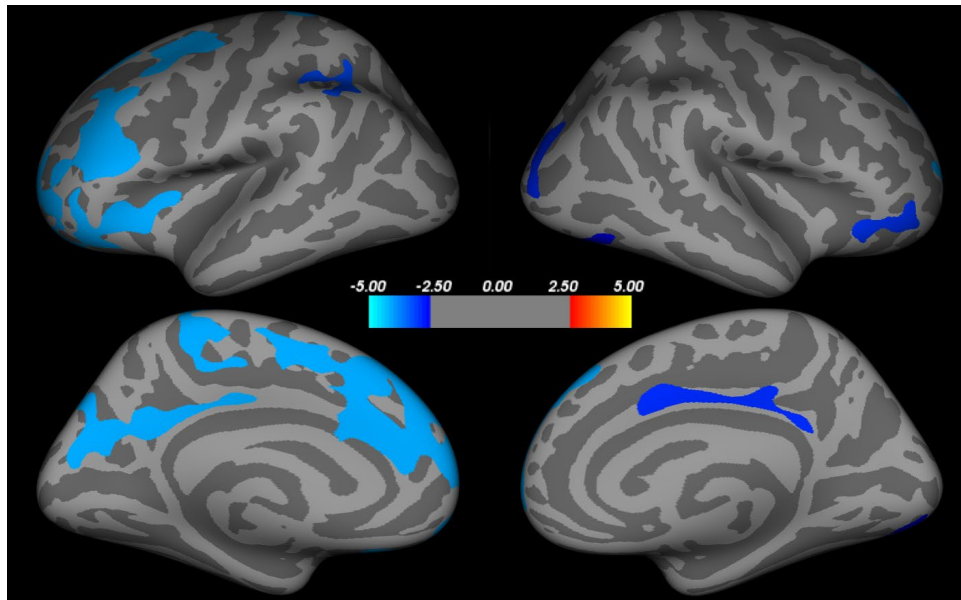
Simple Biomarkers: Gray Matter Morphometry



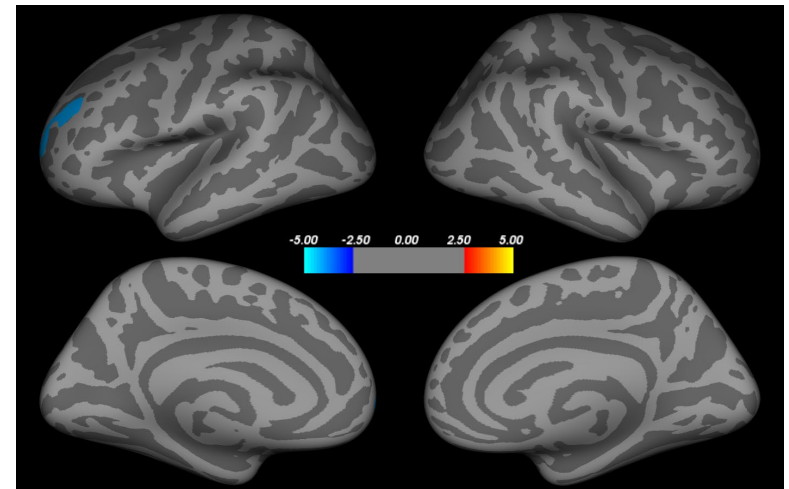
Cortical Thickness Combat-Exposed Veterans (n = 68)



CAPS – PTSD Symptoms

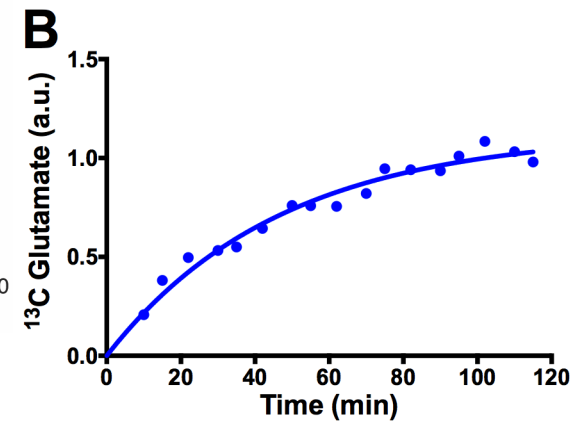
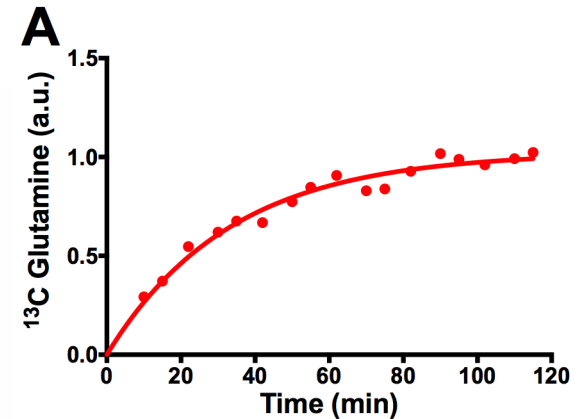
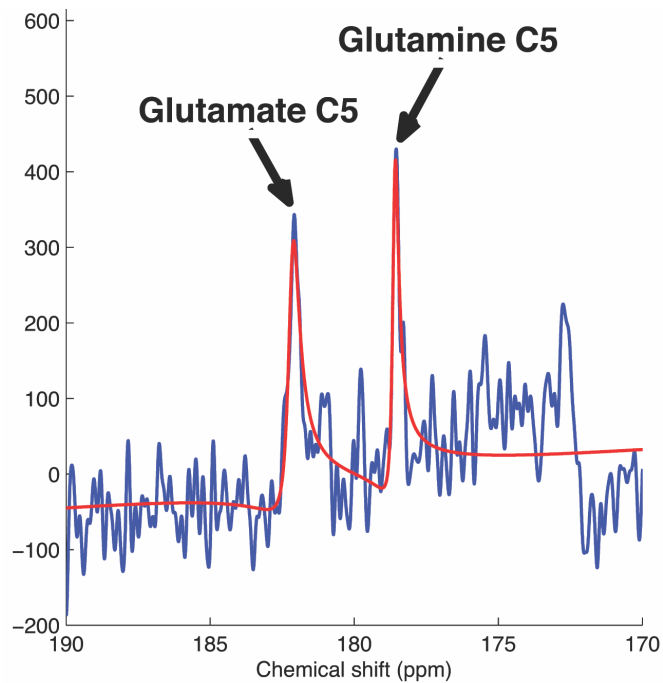
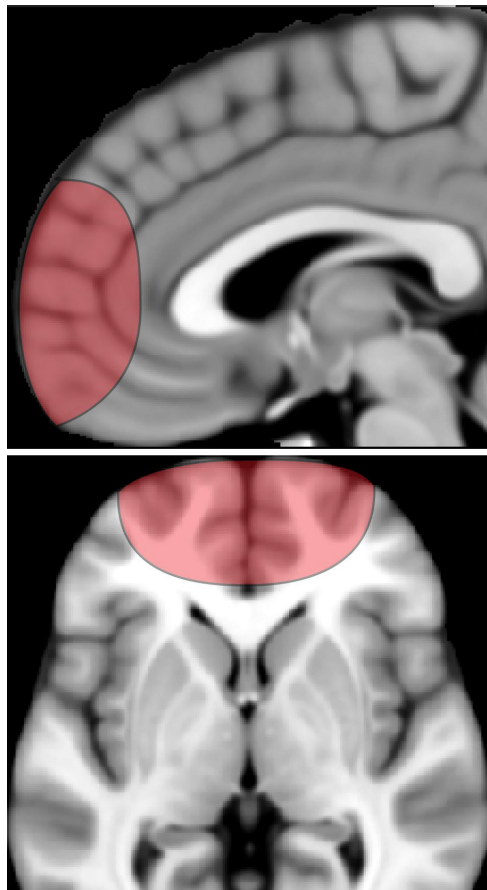


CES – Combat Exposure

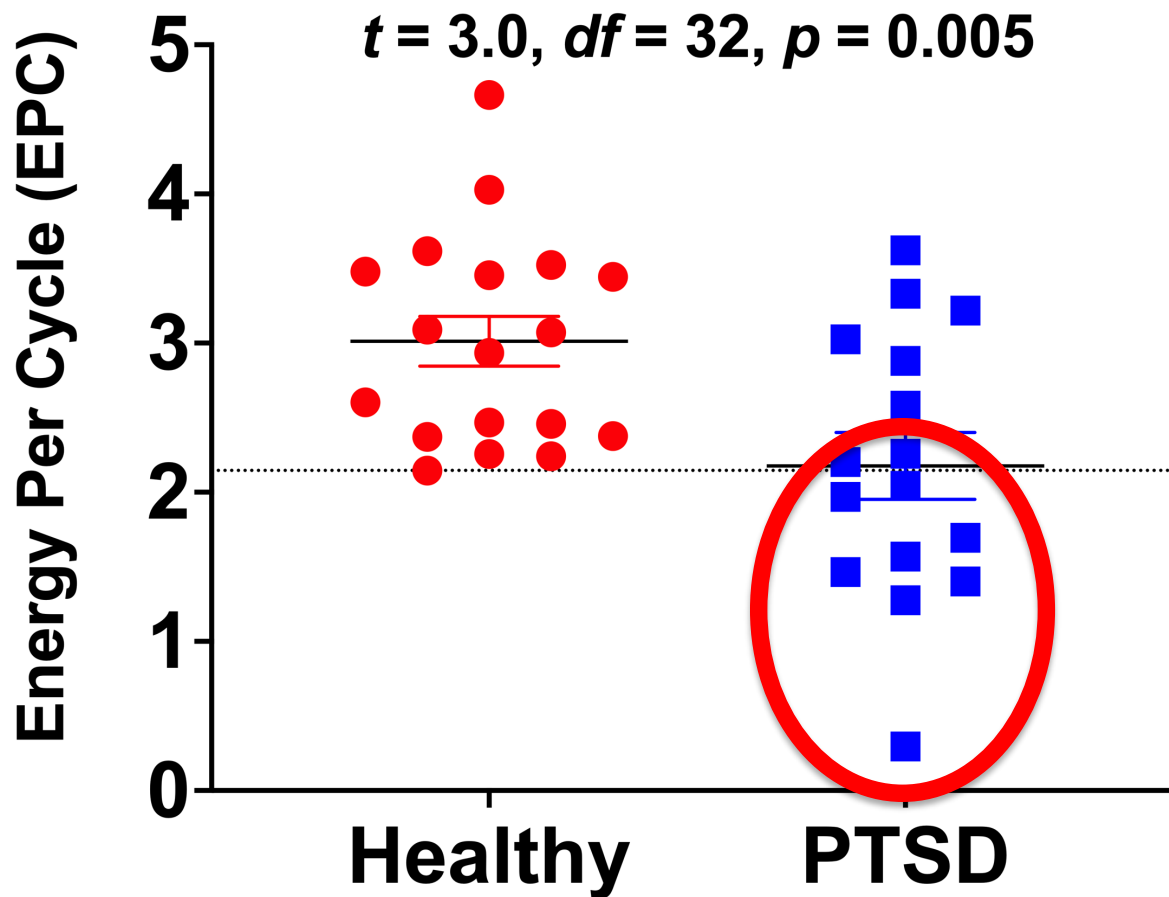


Wrocklage, Averill et al. 2017, Eur. Neuropsychopharm.

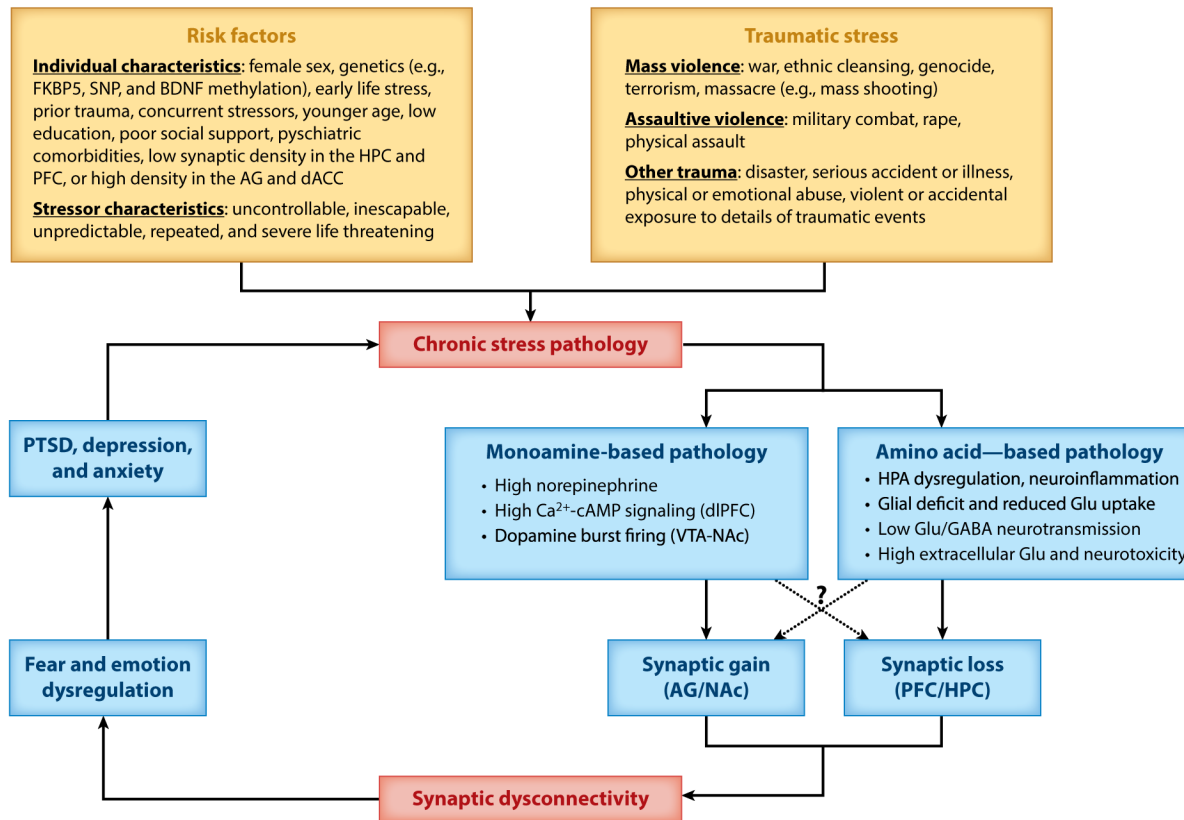
Prefrontal ^{13}C -Acetate MRS



Prefrontal Synaptic Strength



Dual Pathology: A Vicious Cycle

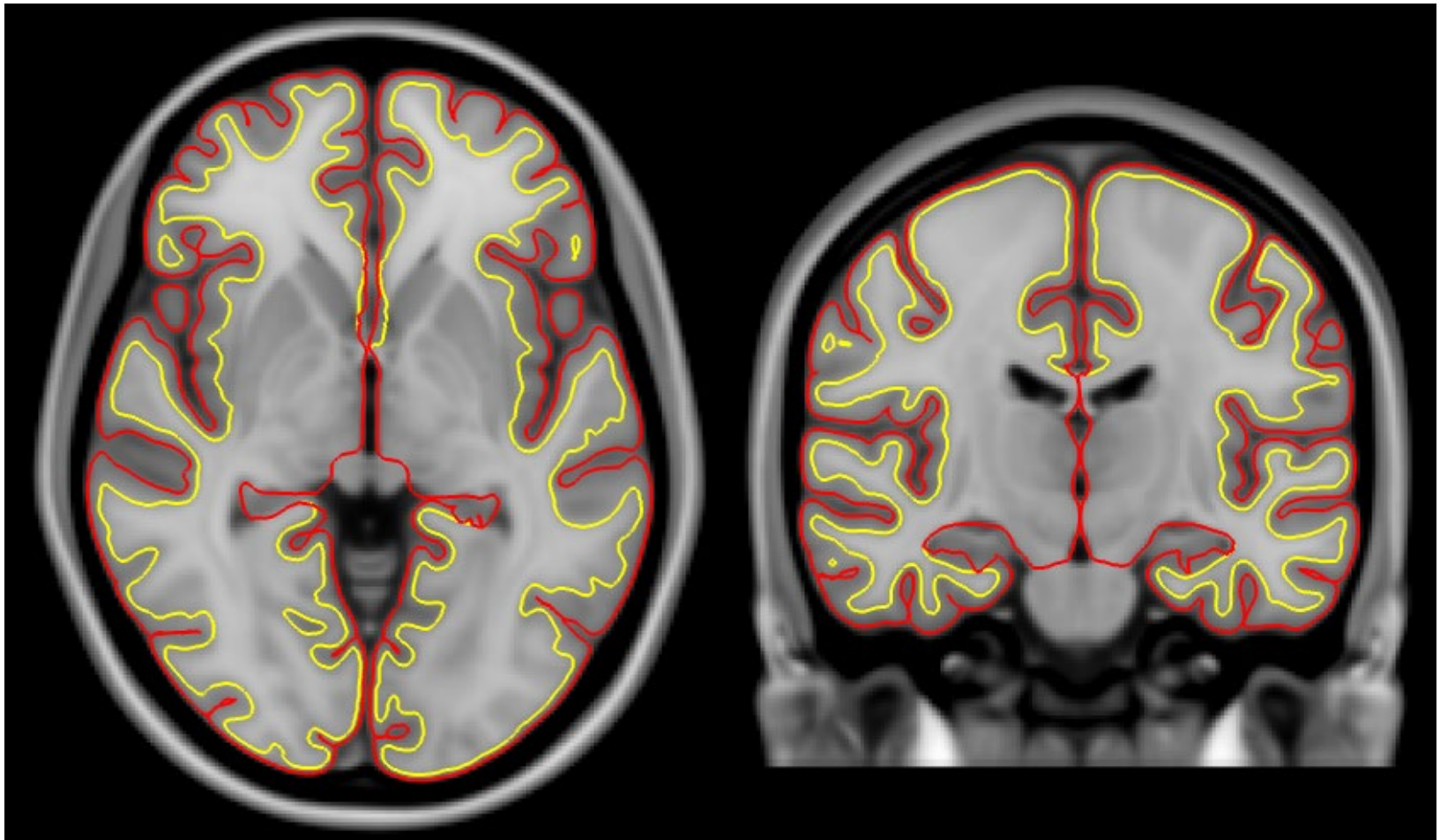


PTSD is not Depression

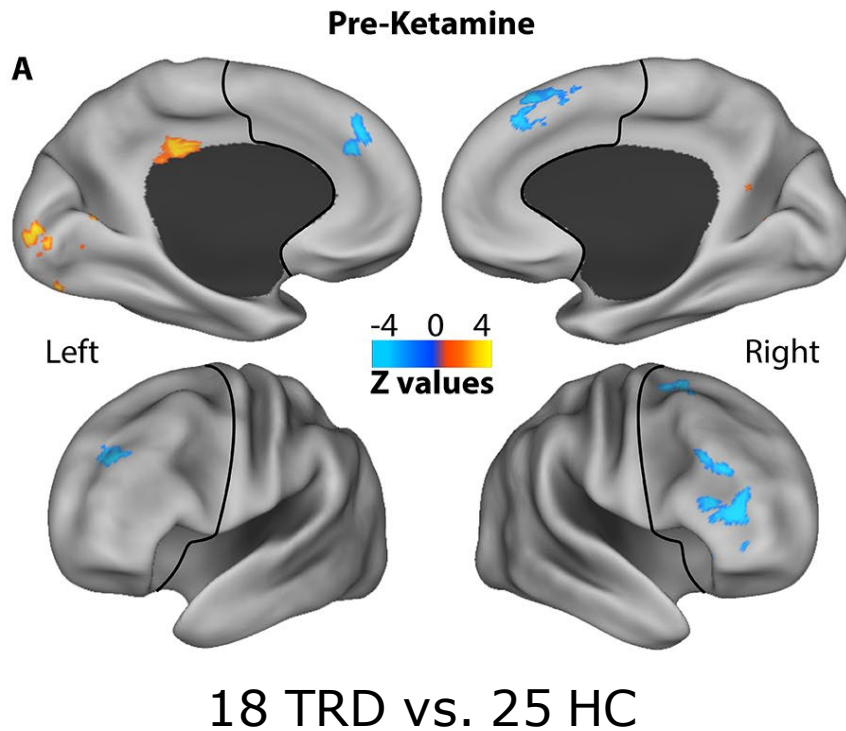
- Common CSP, but different clinical presentations, e.g.:
 - Trauma related
 - Arousal and reexperiencing symptoms
 - Varied response to treatments

- How are they biologically different?
 - Different brain network alterations

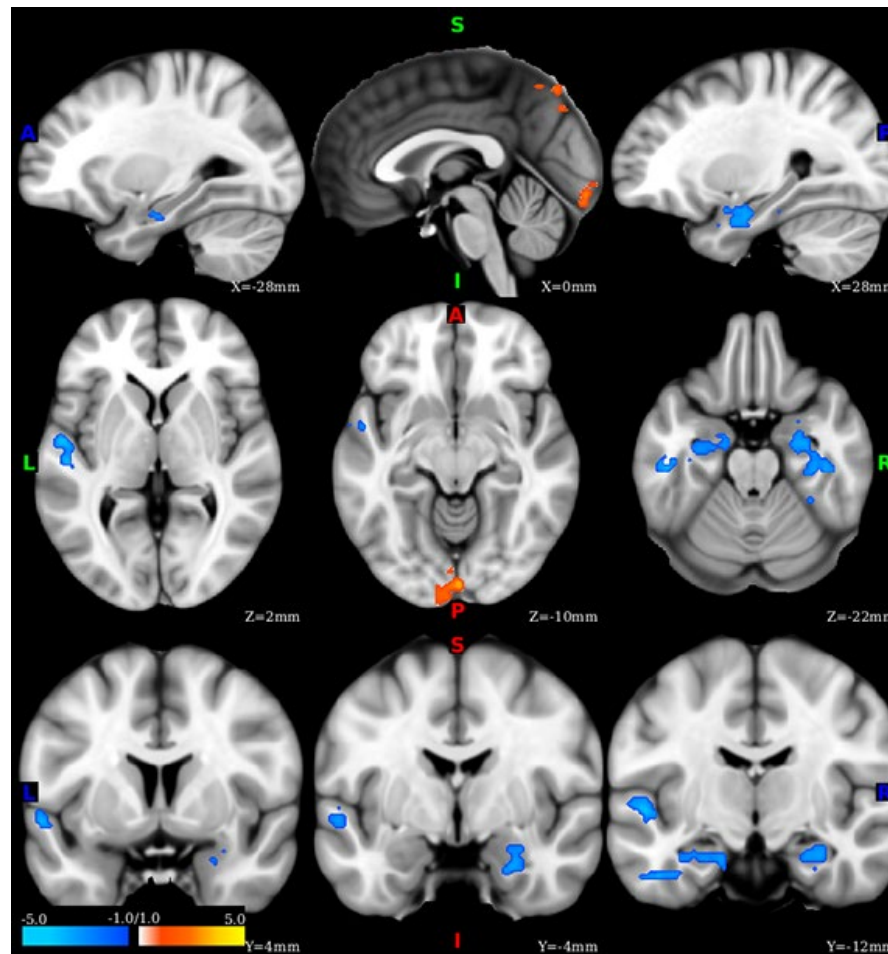
Complex Biomarkers: Functional Brain Connectivity



Global Brain Connectivity (GBC) in MDD

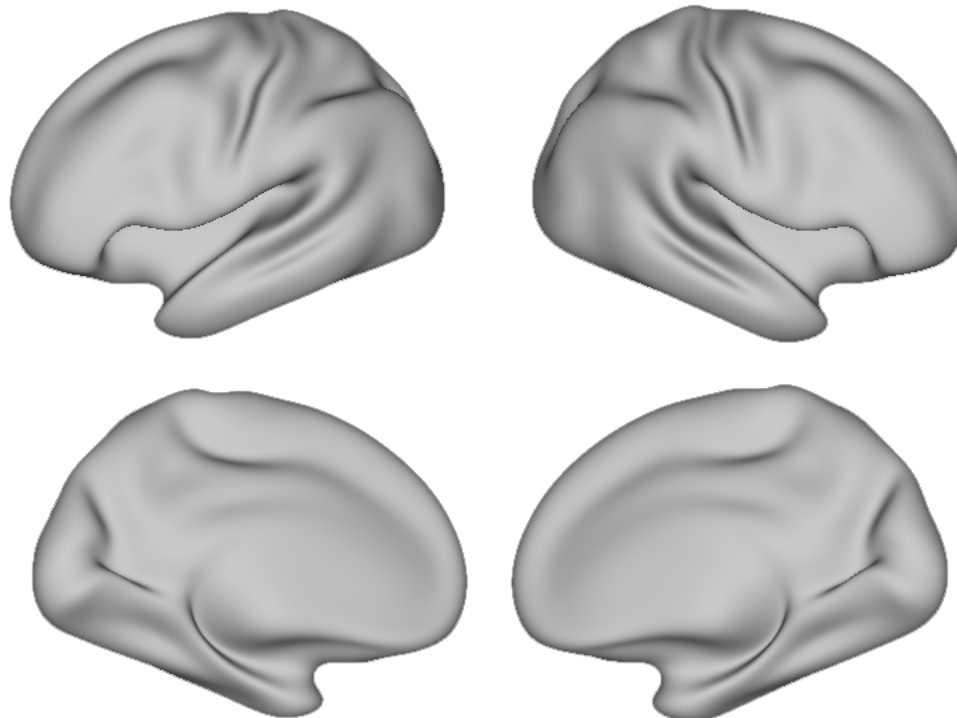


f-GBCr in PTSD Disease Specific Dysconnectivity



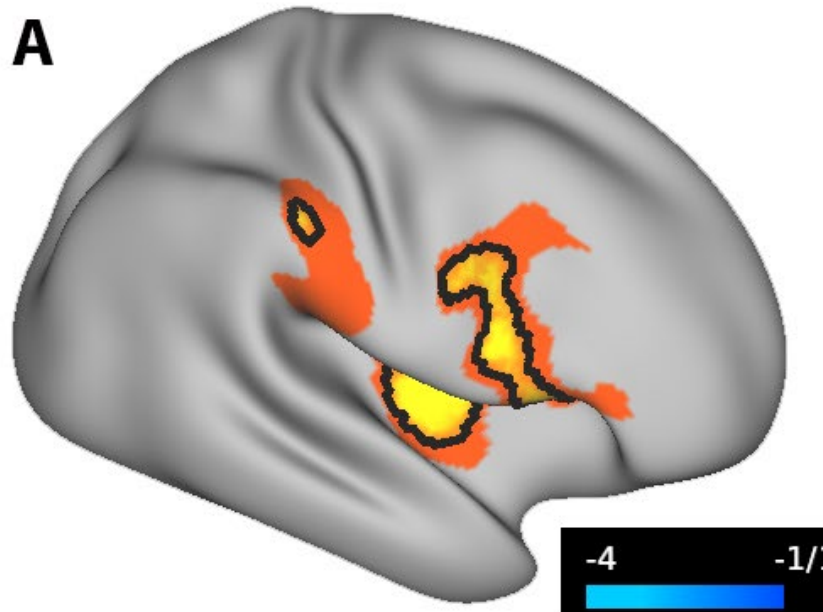
GBC: At Rest

50 PTSD vs. 52 Control

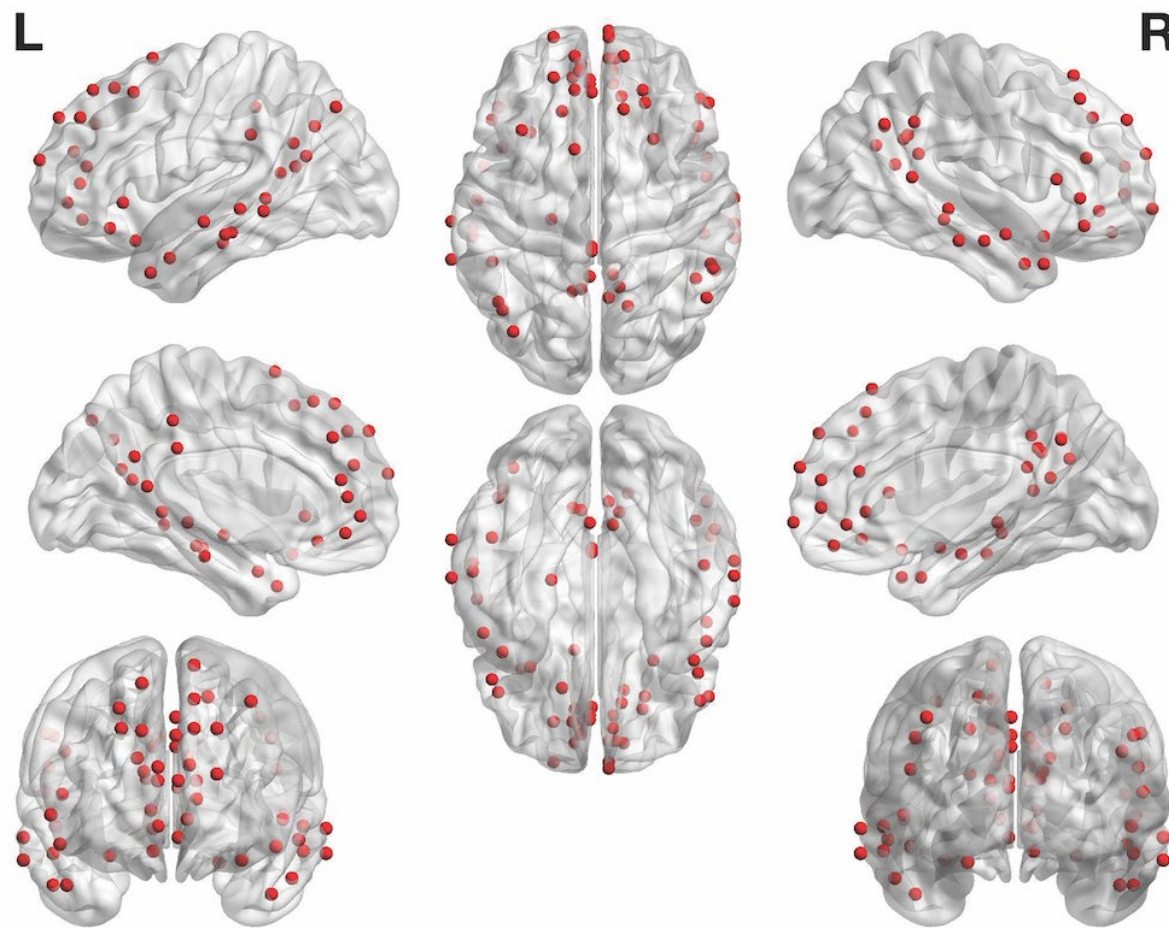


GBC: During Symptoms Provocation

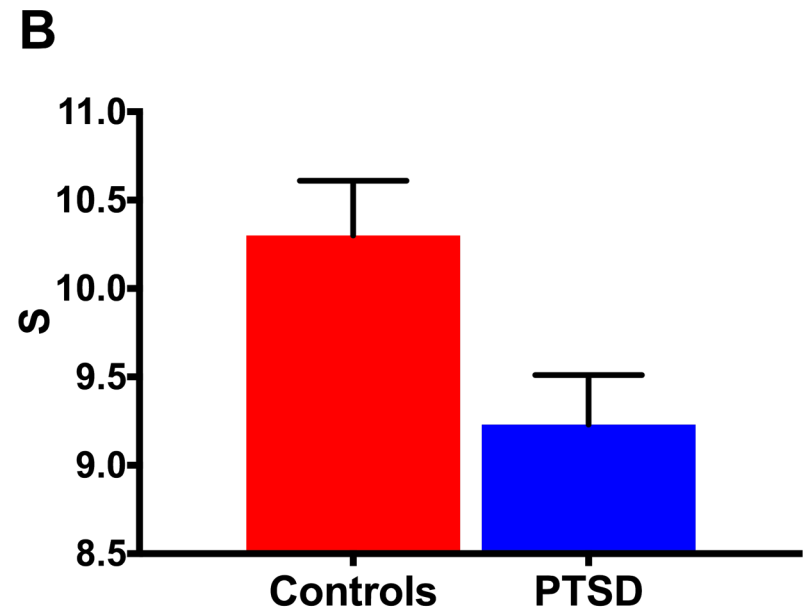
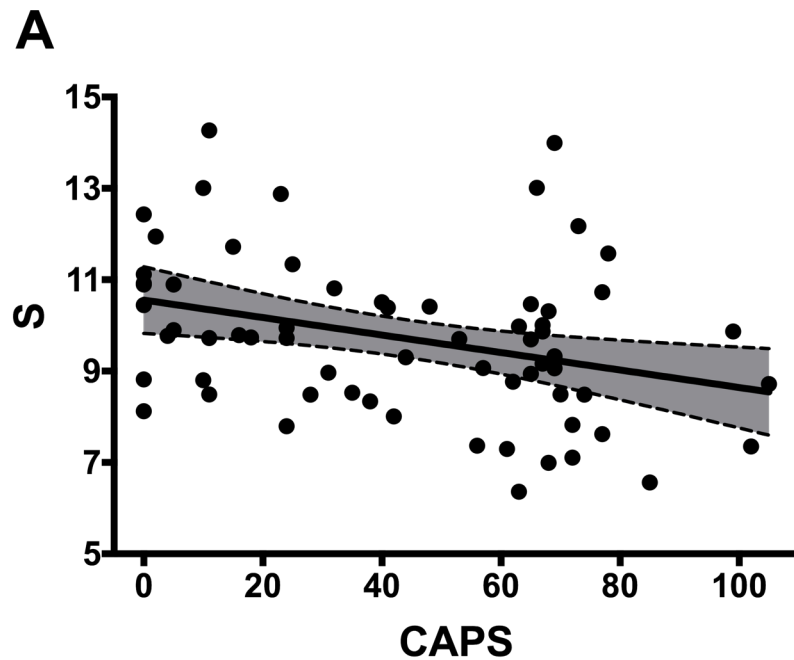
50 PTSD vs. 52 Control



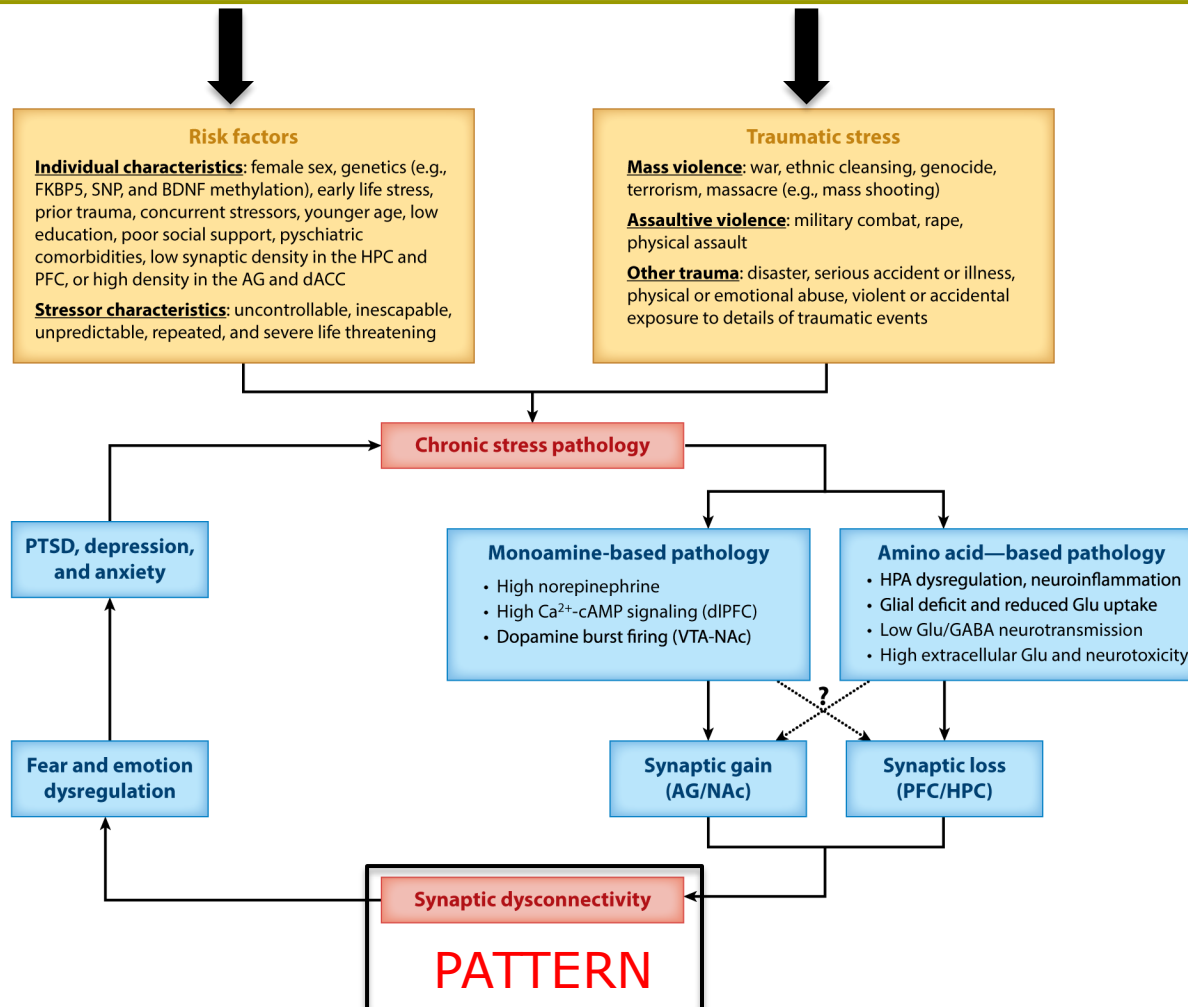
Network-Restricted Strength (NRS)



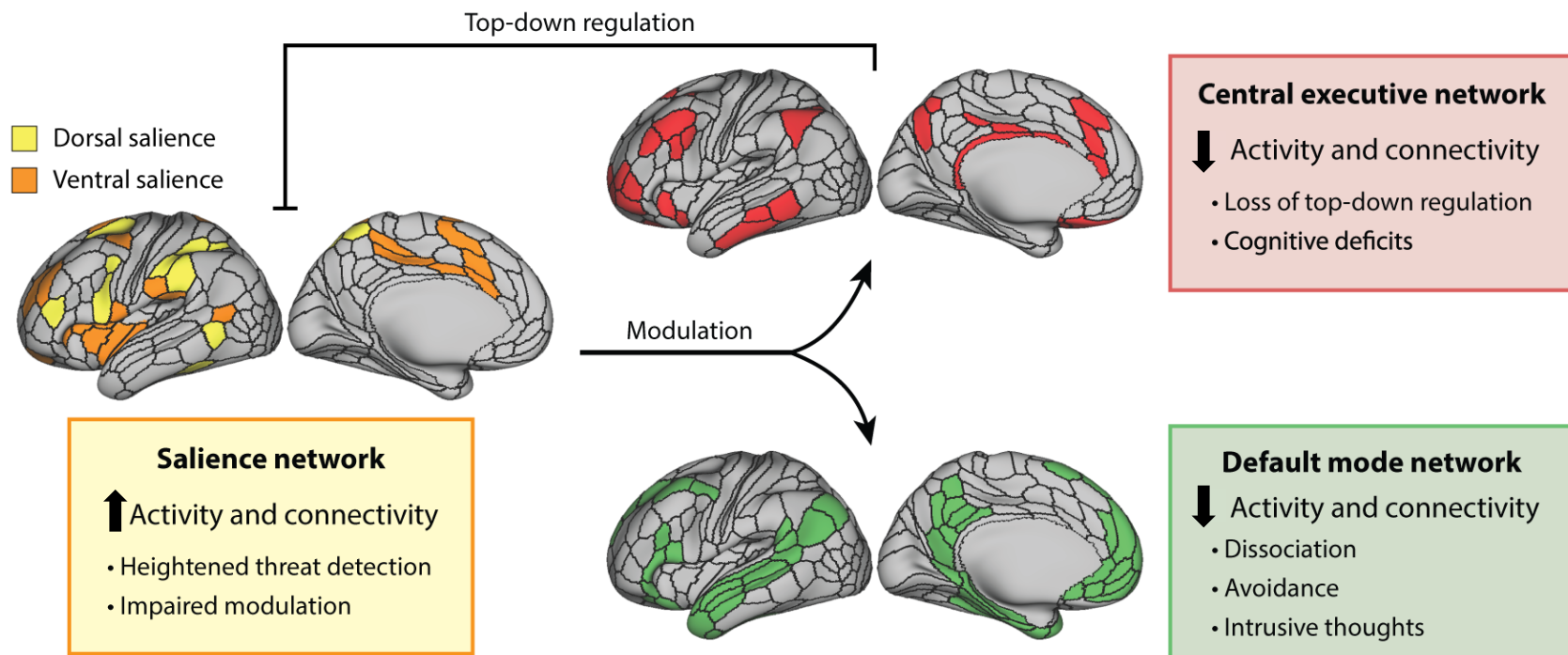
DM in PTSD



Dual Pathology: A Vicious Cycle



Triple Networks Model

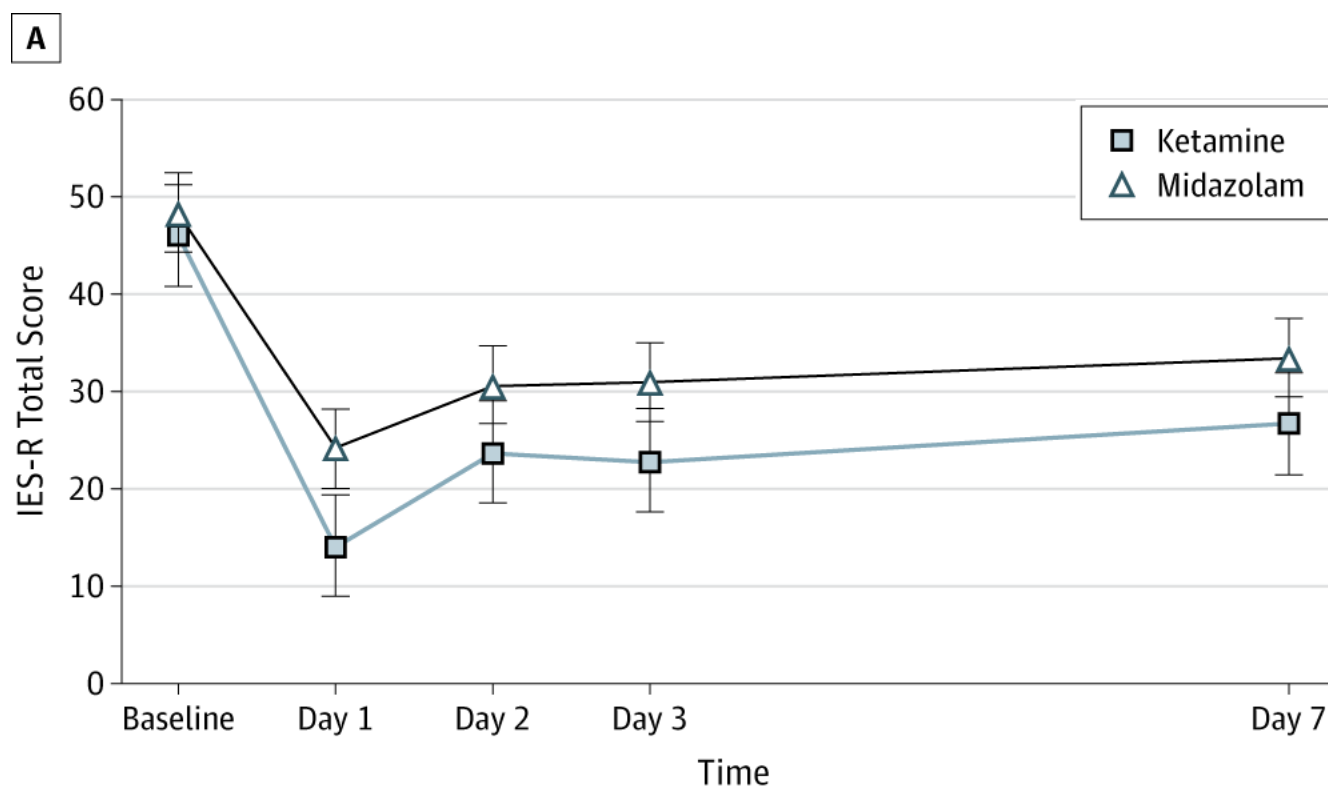


CAP: Consortium to Alleviate PTSD

- 2012: CAP Ketamine in Veterans
 - Randomized Clinical Trial
 - ^{13}C -MRS
 - DWI-fMRI
 - Preclinical
- 2013: CAP funded
- Many years/revisions:
 - Clinical trial (scored 164) → Started in 2016
 - Imaging (scored 144) → Not funded

Proof Concept Study

Ketamine (0.5mg/kg), single dose, n=41, crossover design



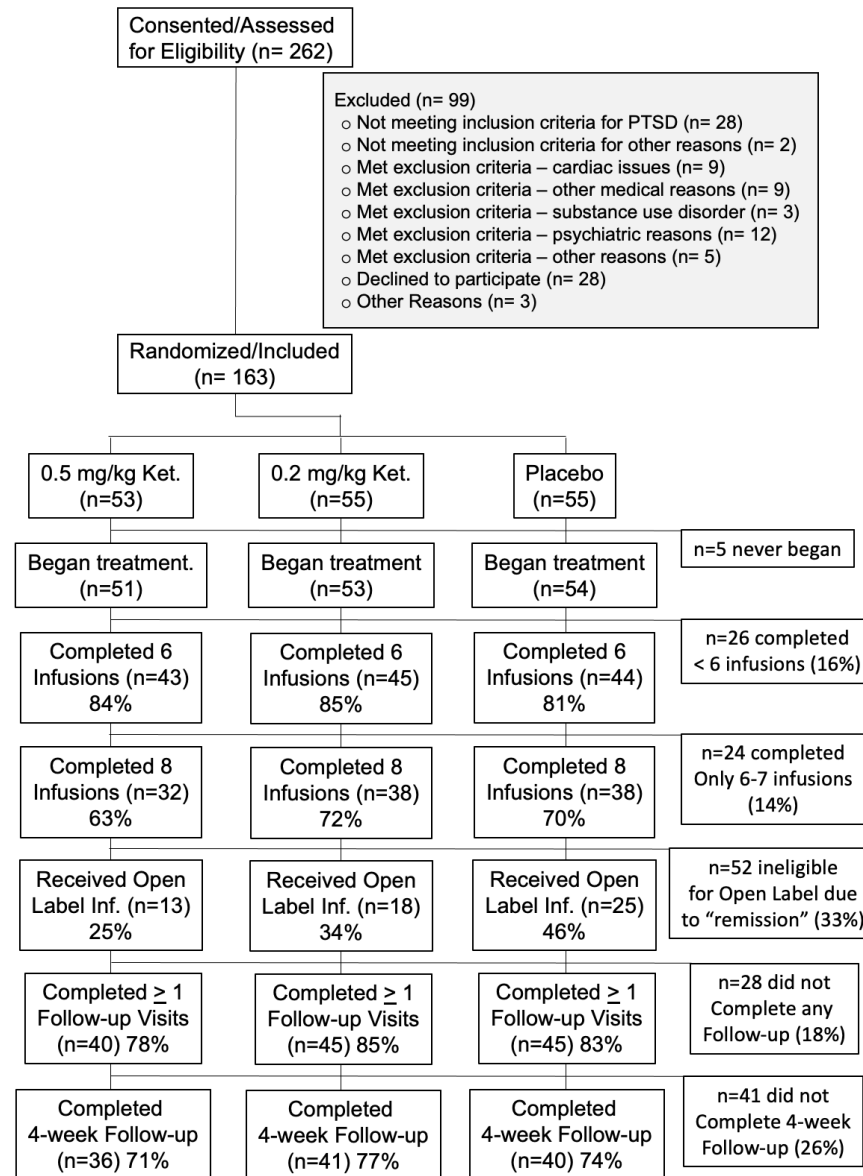
Clinical Trial Design

- Veterans & Active Duty (target n=198)
- Randomized to:
 - Placebo (normal saline)
 - Low dose ketamine (0.2mg/kg)
 - Standard dose ketamine (0.5mg/kg)
- Twice per week for 4 weeks
- Response:
 - <25% improvement → Open-label single infusion of standard dose ketamine
 - >25% improvement → 4 weeks follow-up

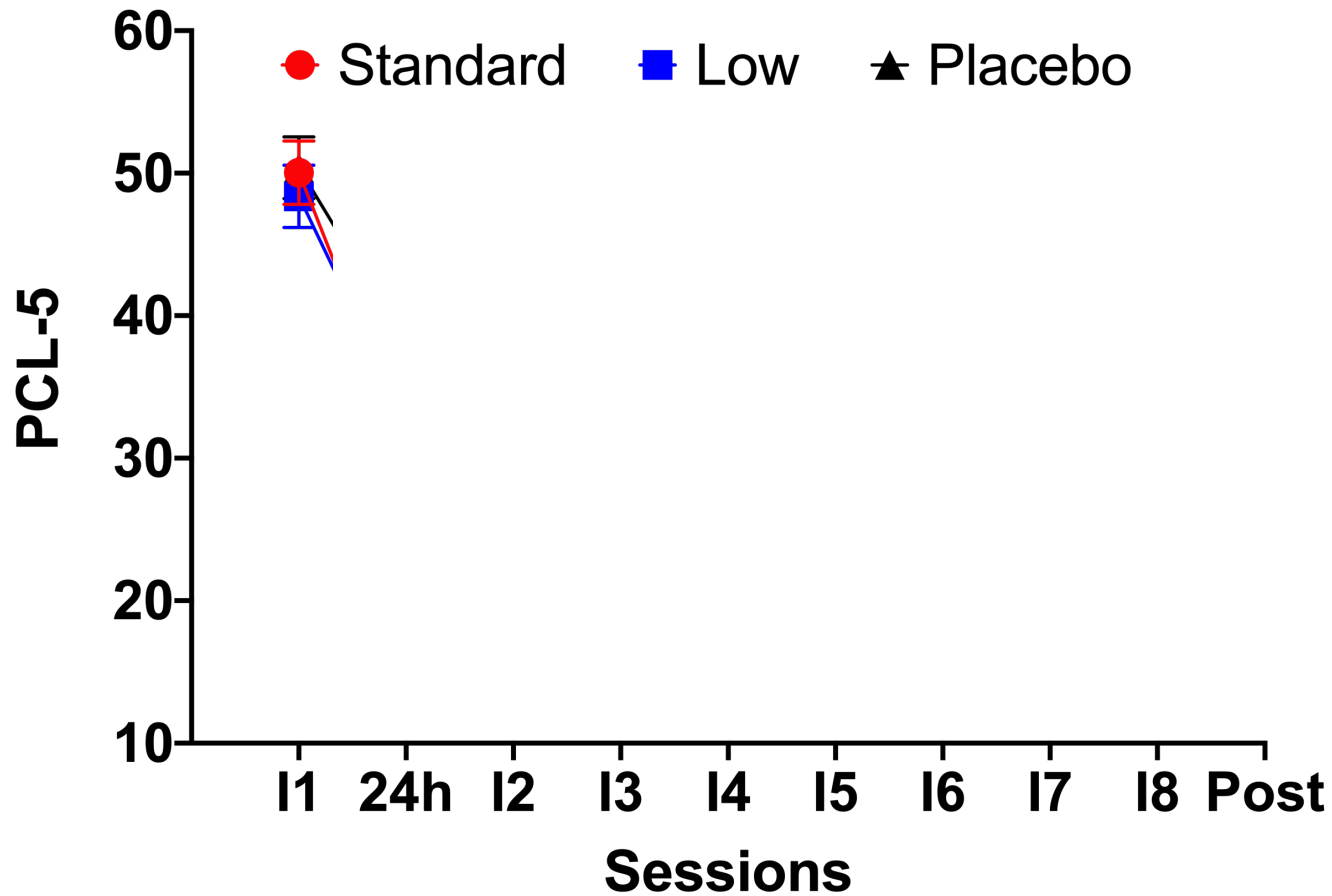
Consort Flow Diagram

COVID-19 Pandemic

The study was prematurely closed due to the restrictions in direct patient care.

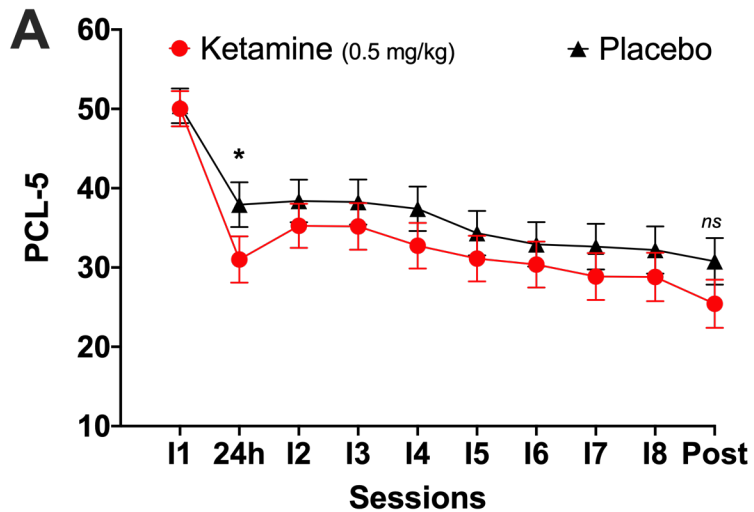


PTSD: Repeated Ketamine

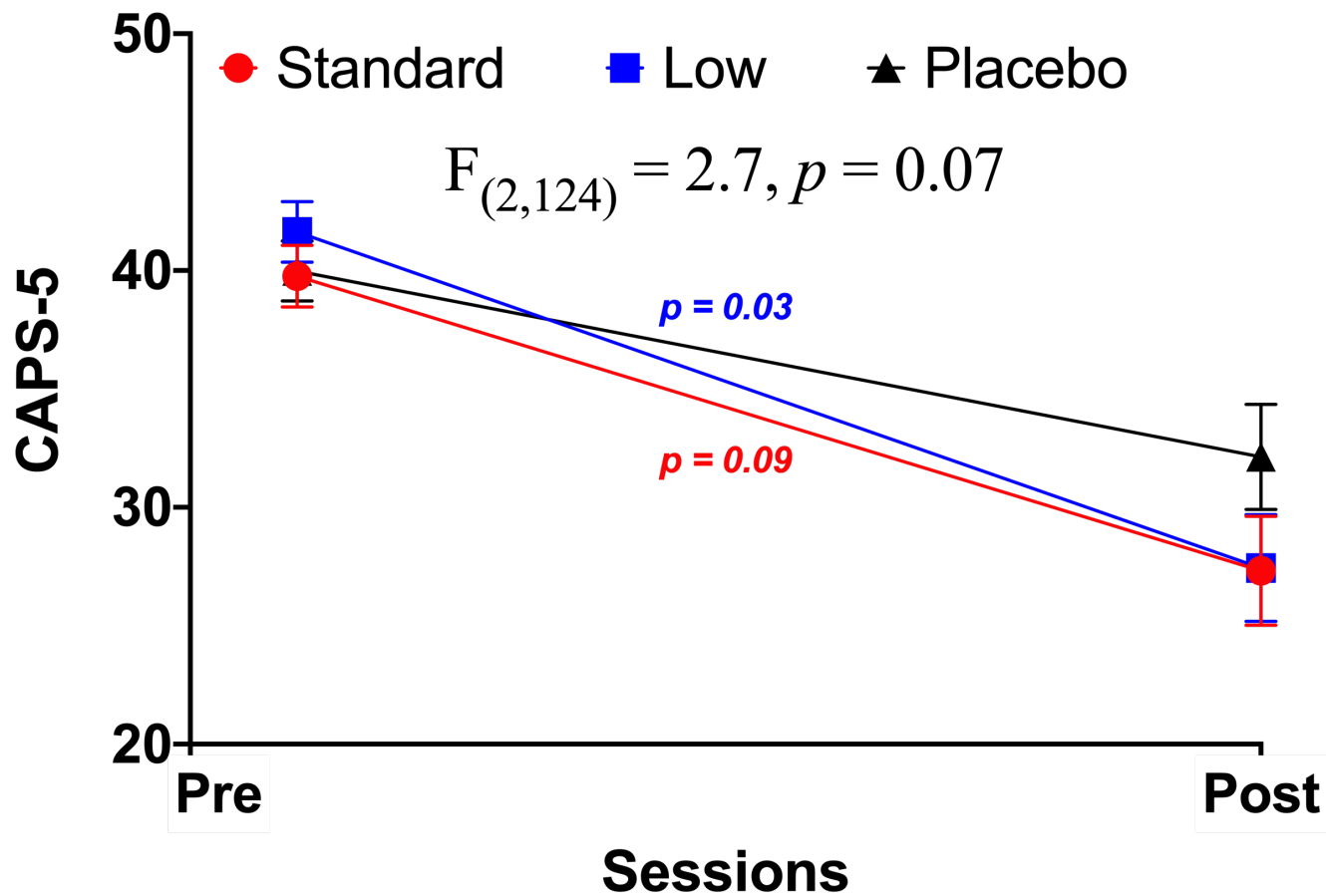


Dose Effects – PTSD Symptoms

Standard Dose

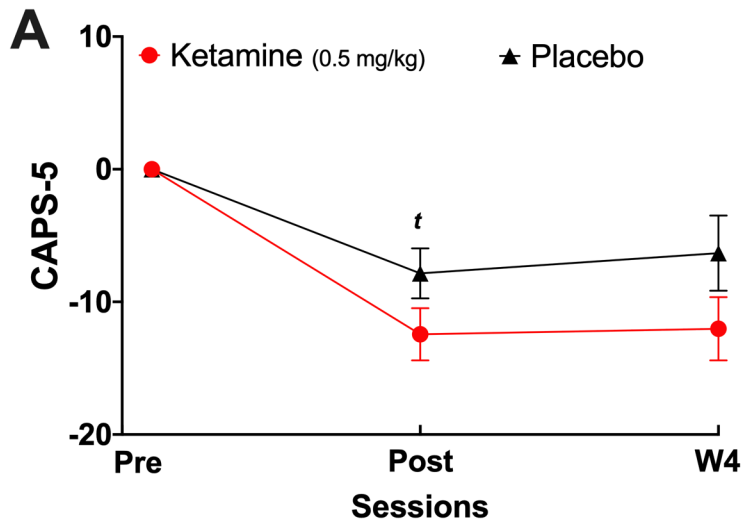


Secondary Outcome

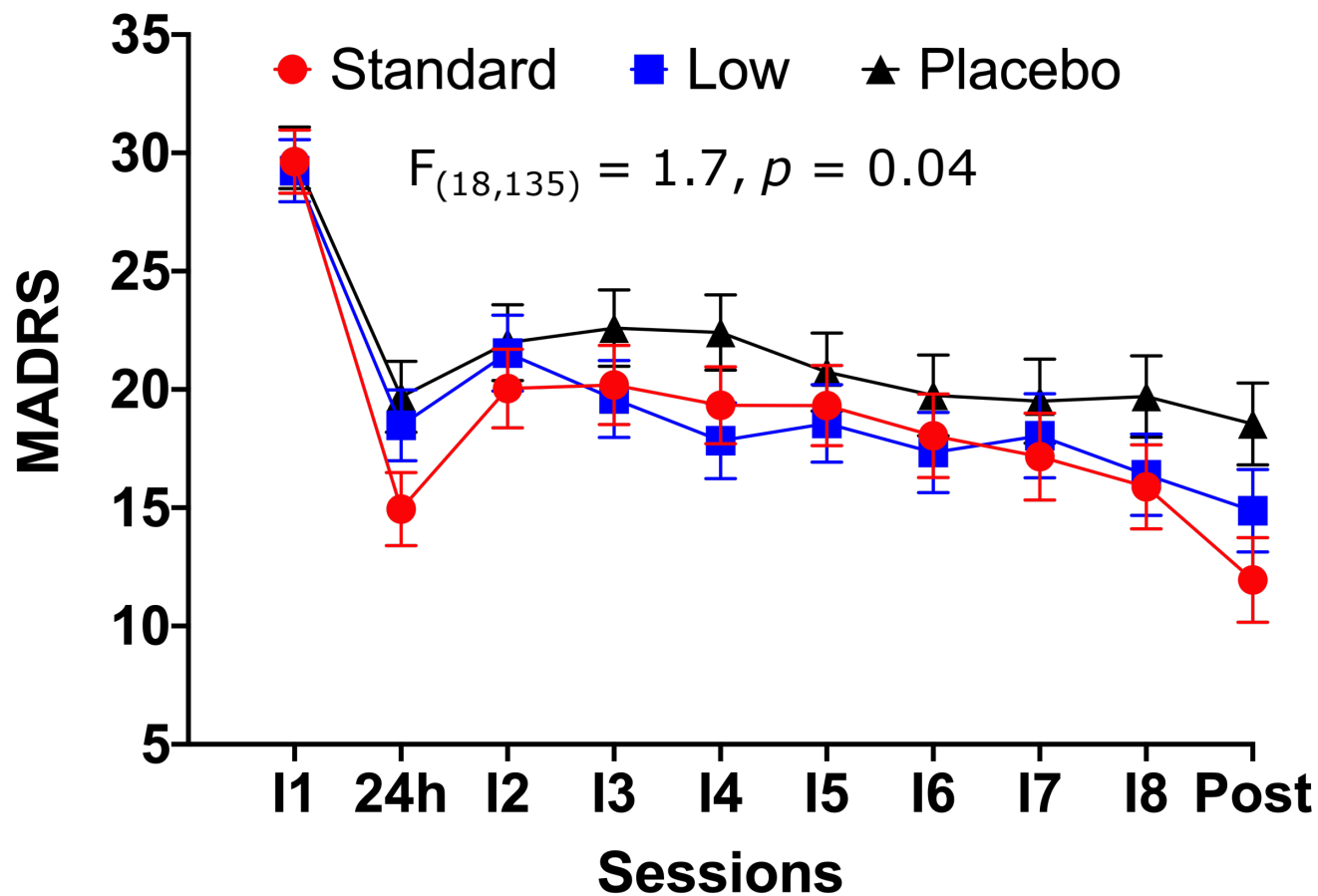


Longevity of Effects

Standard Dose

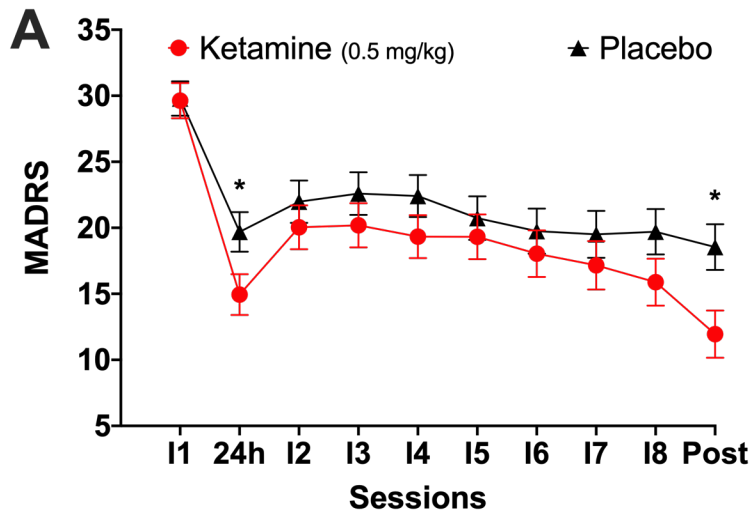


Repeated Ketamine – Depression



Dose Effects – Depression

Standard Dose



Interpretation & Future Directions

- I. Military vs. civilian population
- II. PTSD vs. Depression
- III. Low vs. standard dose
- IV. Frequency of administration
 - Feder et al. 2021: 3 times per week
- V. Consistency of findings:
 - Rapid effects in Feder et al. 2014 & CAP Ketamine
 - No rapid effects in Feder et al. 2021 & Dadabayev et al. 2020

EMERGE Research Program



Thank you