The **endocannabinoid system** a potential buffer against SUD development following **trauma** exposure

Leah Mayo, PhD

Parker Research Chair in Psychedelics
Mathison Centre for Mental Health Research and Education
Hotchkiss Brain Institute
Department of Psychiatry
University of Calgary

LINKÖPING UNIVERSITY

CSAN
Center for Social and Affective Neuroscience

THE MATHISON CENTRE for Mental Health Research & Education

HOTCHKISS BRAIN INSTITUTE

UNIVERSITY OF CALGARY

Email: **leah.mayo@ucalgary.ca** **@MayoOnTheBrain**

Disclosures

C·A·N

The Central Association for Alcohol and Narcotics Information, CAN

BRAIN & BEHAVIOR RESEARCH FOUNDATION

Awarding **NARSAD** Grants

Vetenskapsrådet

Svenska Läkaresällskapet

Ongoing invesigator-initiated clinical trial with Janssen Pharmaceuticals

Does exposure childhood maltreatment (trauma) increase the risk for SUD in adulthood?

Linköping Child and Adolescent Psychiatry - Trauma Unit (est. 1980's)

Regional and National Patient registers

Health care vists (substance dependence clinic)

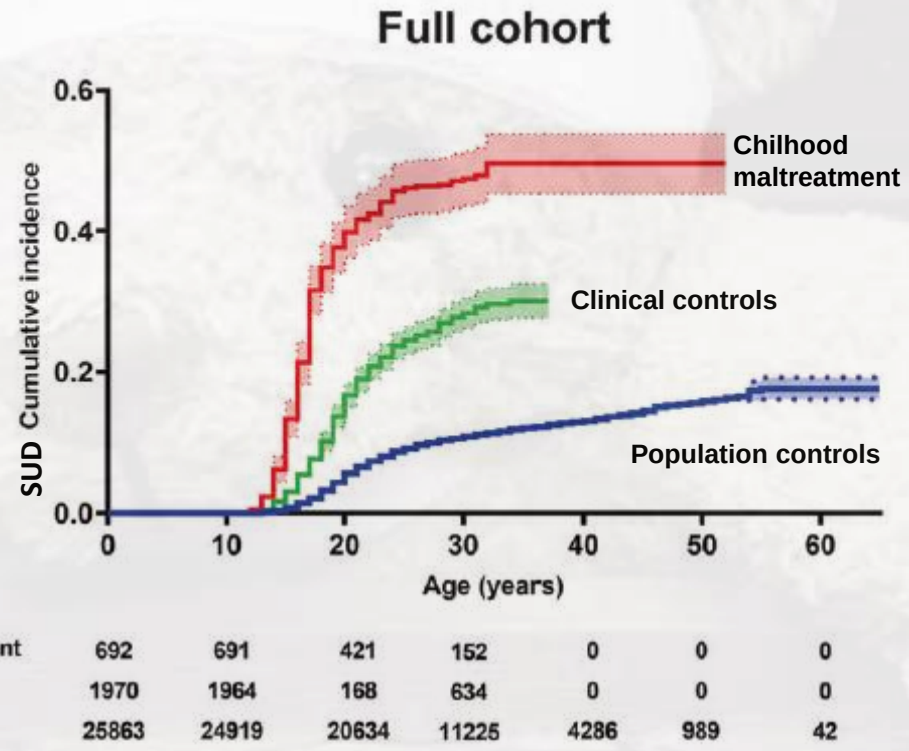
Swedish Multi-Generational register

Parents, half/full siblings, cousins

3-fold increased risk for SUD

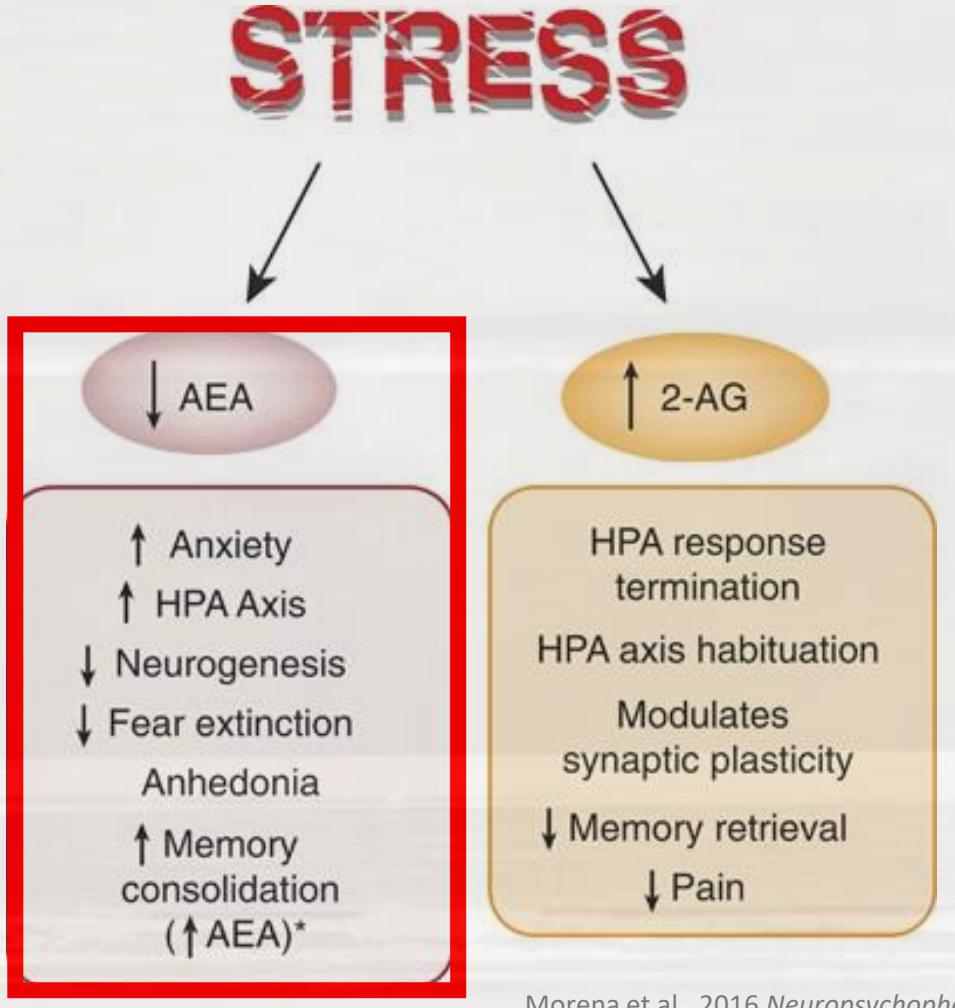
Even when controlling for:

recall bias, familial confounding

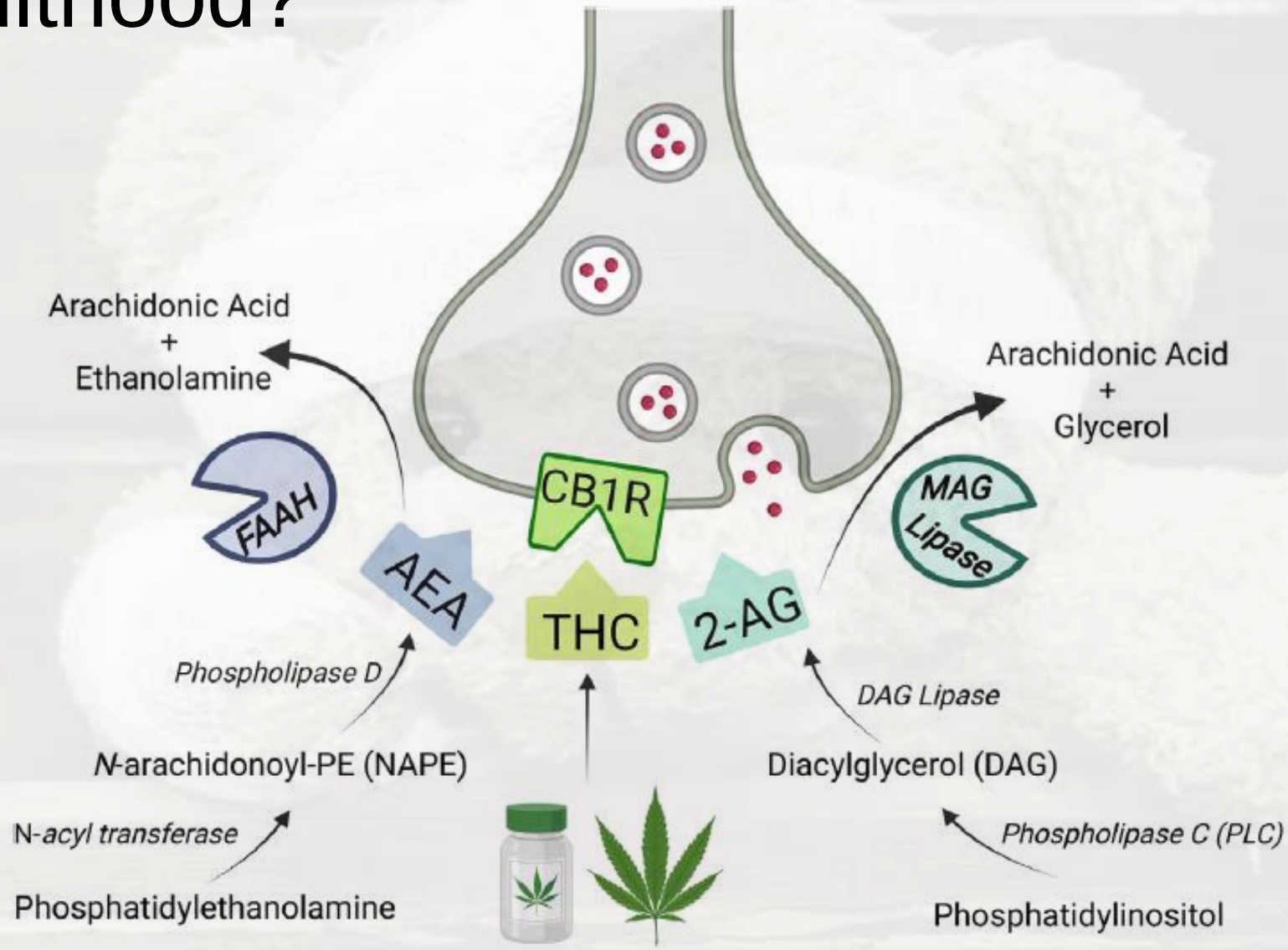


Capusan,…Mayo, Heilig (2021) *Molecular Psychiatry*

How does childhood trauma contribute to SUD development in adulthood?

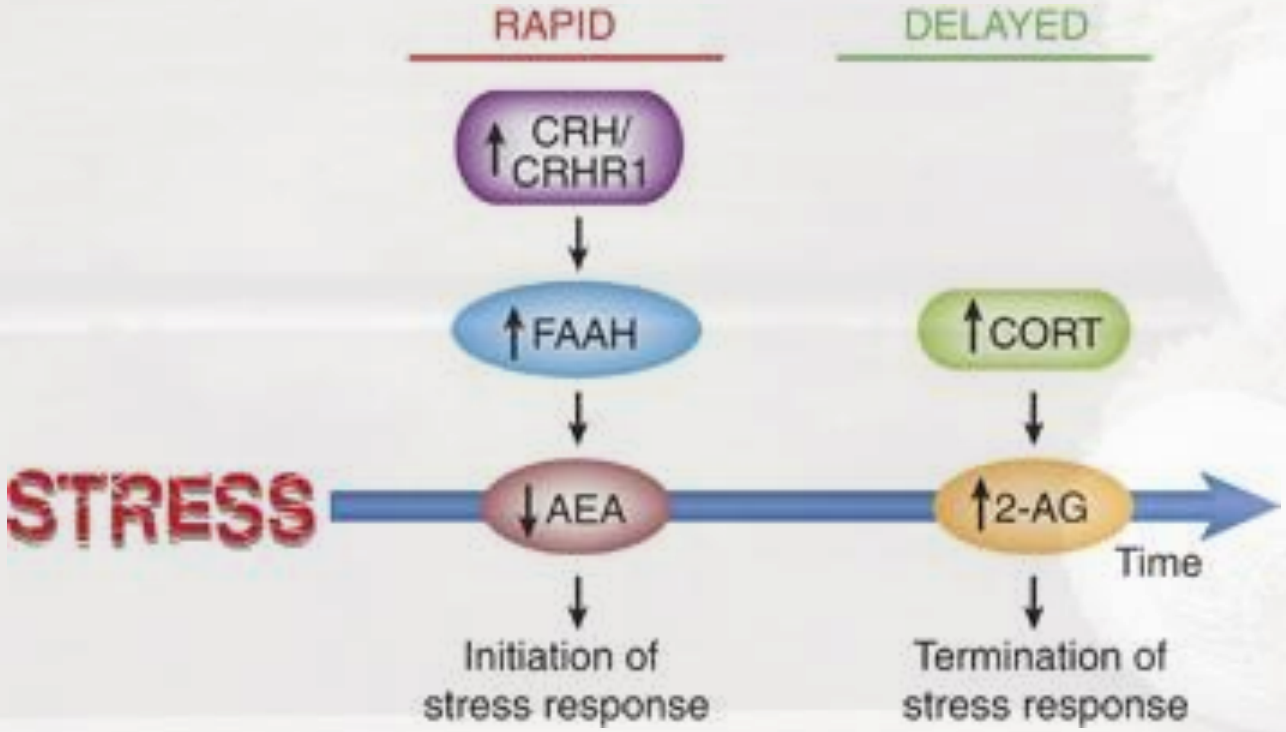


Morena et al., 2016 *Neuropsychopharmacology*

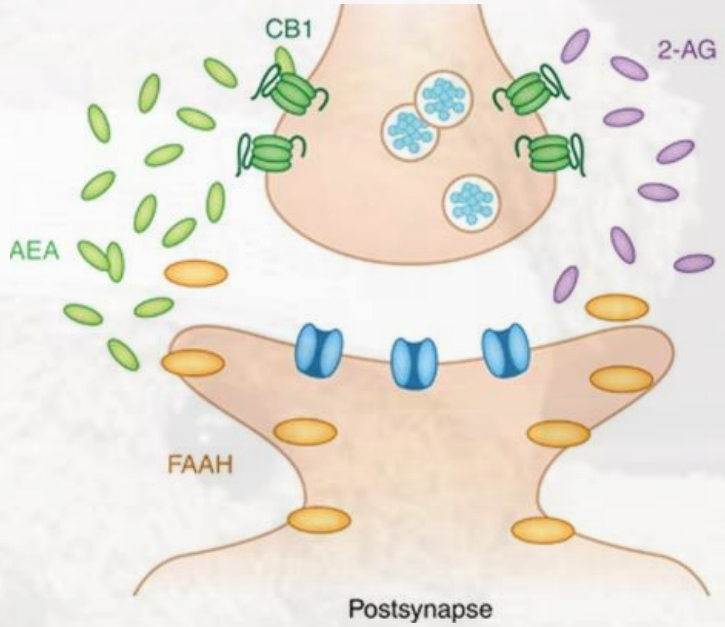


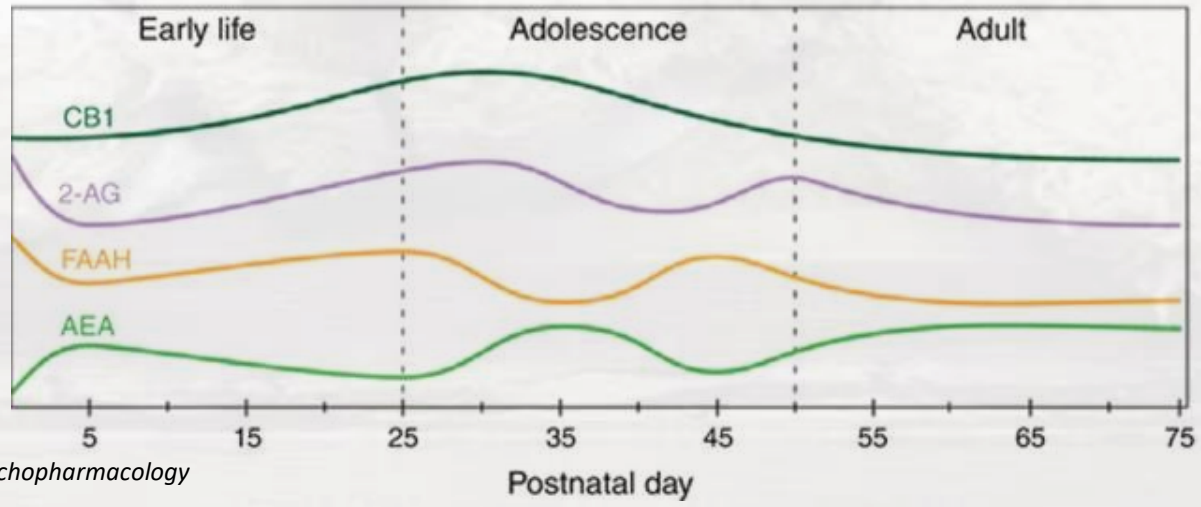
Mayo et al., 2022 *Biological Psychiatry*

How does childhood trauma contribute to SUD development in adulthood?



Morena et al., 2015 *Neuropsychopharmacology*





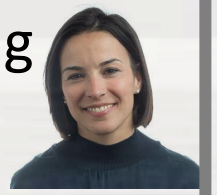
Meyer et al., 2018 *Neuropsychopharmacology*

How does childhood trauma contribute to SUD development in adulthood?

Session 1: Clinical Assessment
- Clinical interview
- **Self-report questionnaires**

Session 2: Behavioral Testing
- **Stress reactivity**
- **Affective processing**
- Fear learning

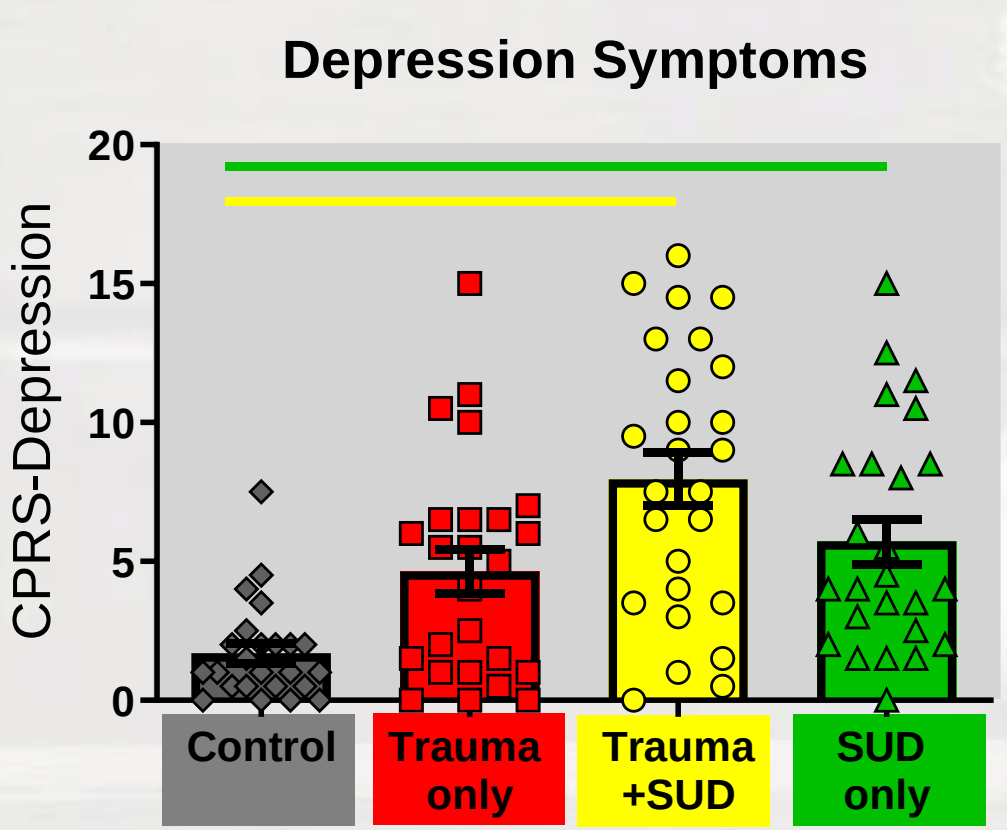
Session 3: Neuroimaging
- **Emotion conflict**
- Threat processing
- Resting state, DTI, ASL



Irene Perini
@NeuroIP

SUBSTANCE USE DISORDER (SUD)	CHILDHOOD TRAUMA: YES	CHILDHOOD TRAUMA: NO
YES	**Trauma+SUD** (N = 26)	**SUD only** (N = 25)
NO	**Trauma only** (N = 26)	**Control** (N = 24)

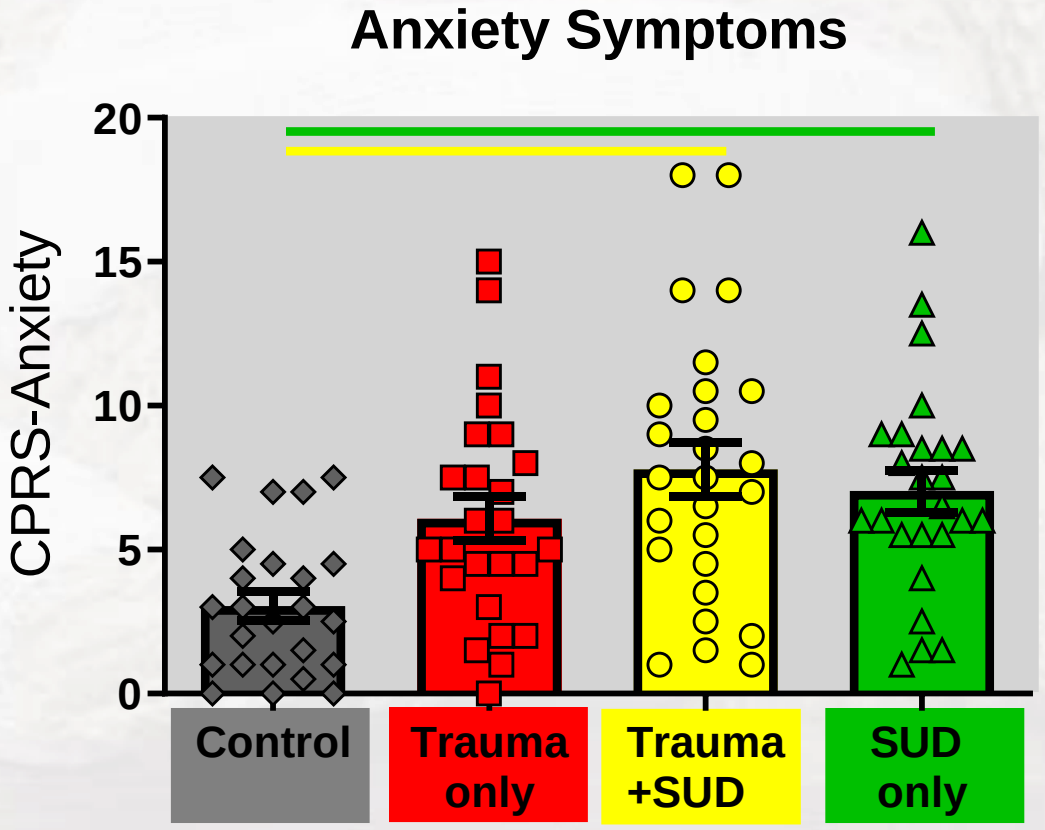
SUD development is associated with greater clinical symptoms than childhood trauma alone



Group p = 0.012; SUD p = 0.016, CM p = 0.090

Trauma + SUD vs control p = 0.026, SUD vs control p = 0.025;

Trauma only vs control p = 0.097



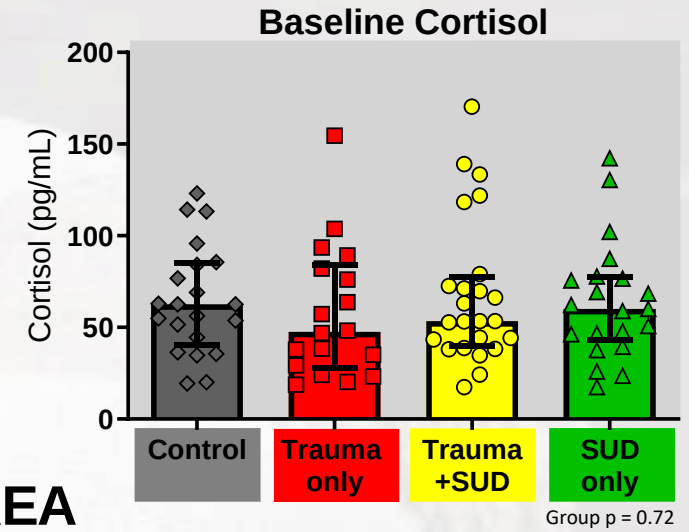
Group p = 0.012; SUD p = 0.008, SUD x CM p = 0.050

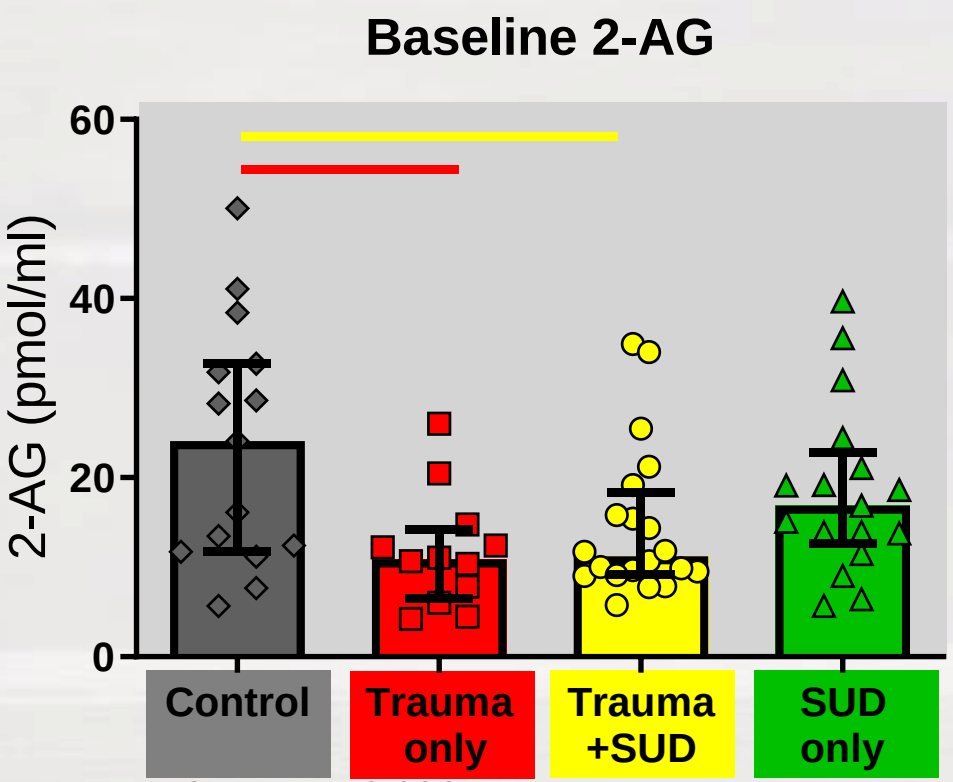
Trauma + SUD vs control p = 0. 0.013, SUD vs control p = 0.010;

Trauma only vs control p = 0.058

Perini*, Mayo* (*in revision*)

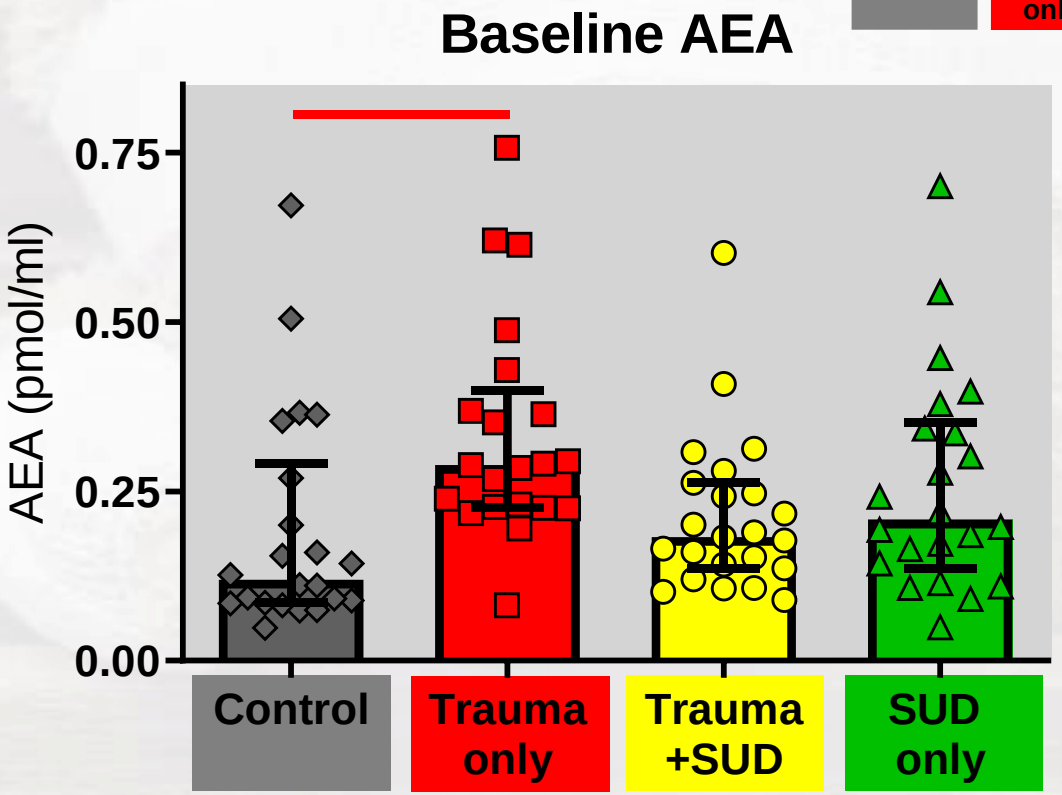
Resilience after childhood trauma is associated with elevated AEA





Group p = 0.006; CM p = 0.038; CM x SUD p = 0.012

Trauma + SUD vs control p = 0.022, Trauma only vs control p = 0.012; SUD vs control p = 0.058



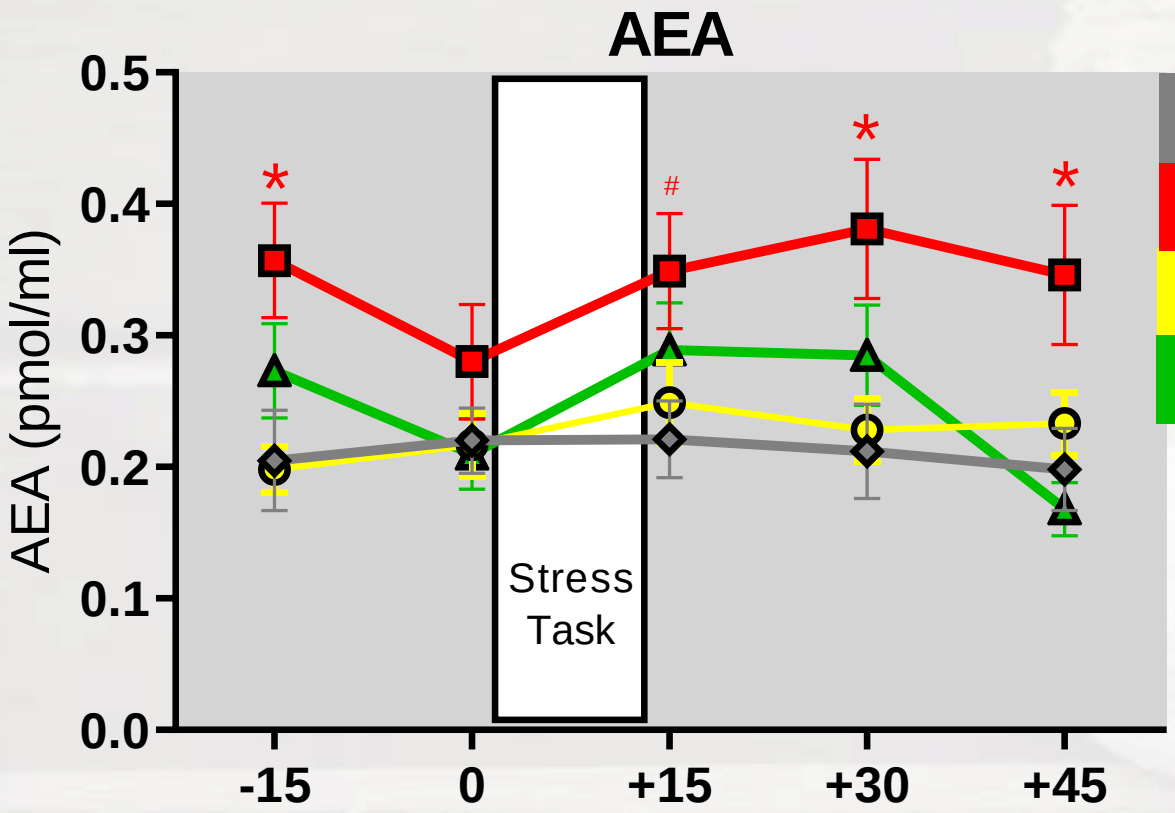
Group p = 0.039; CM x SUD p = 0.021

Trauma only vs control p = 0.037

All data were transformed (natural log) for analysis and back-transformed for plotting

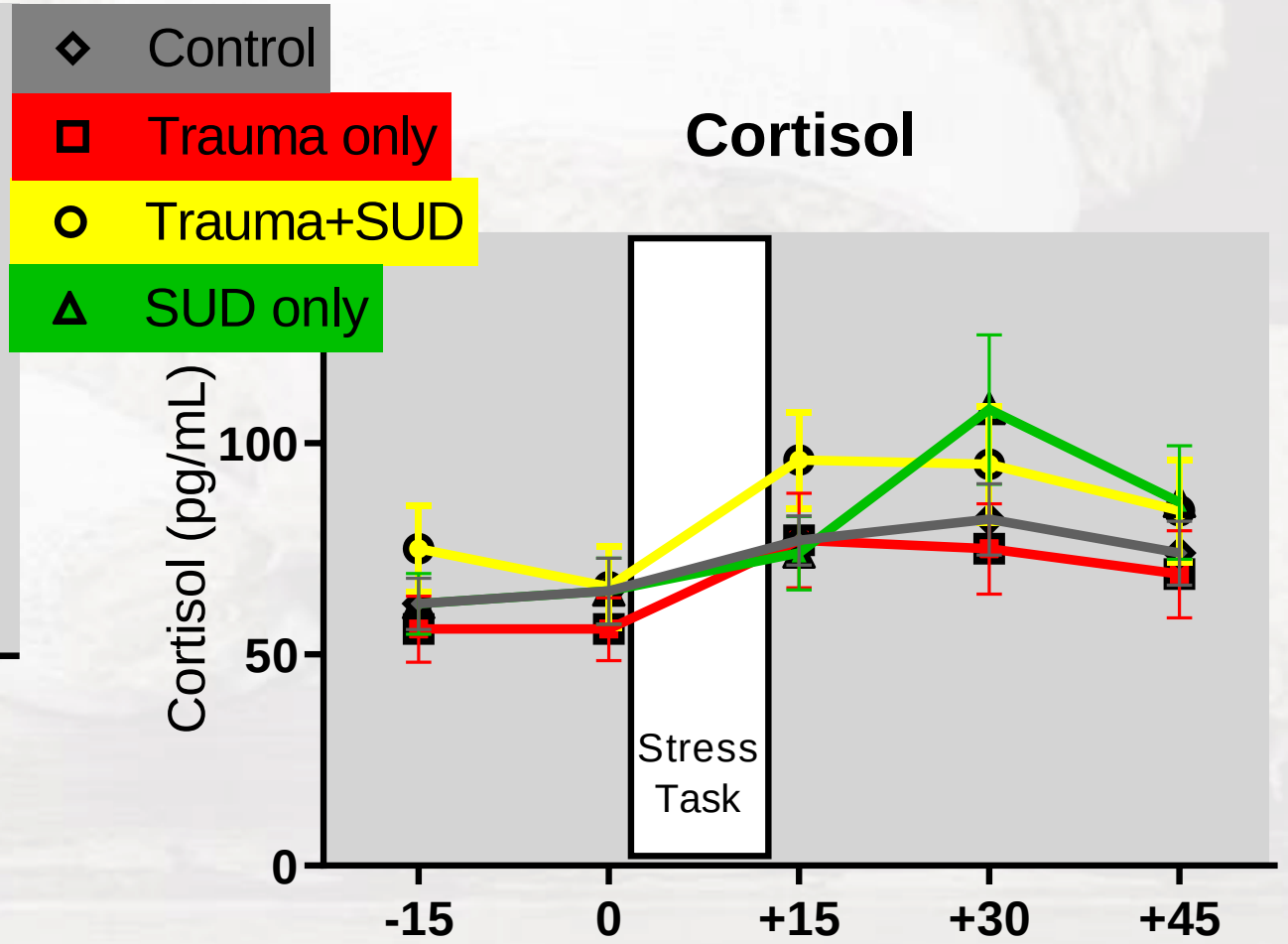
Perini*, Mayo* (*in revision*)

Resilience after childhood trauma is associated with elevated AEA during stress exposure



Effect of time p = 0.025; CM x SUD x Time p = 0.016

CM vs control p = 0.007

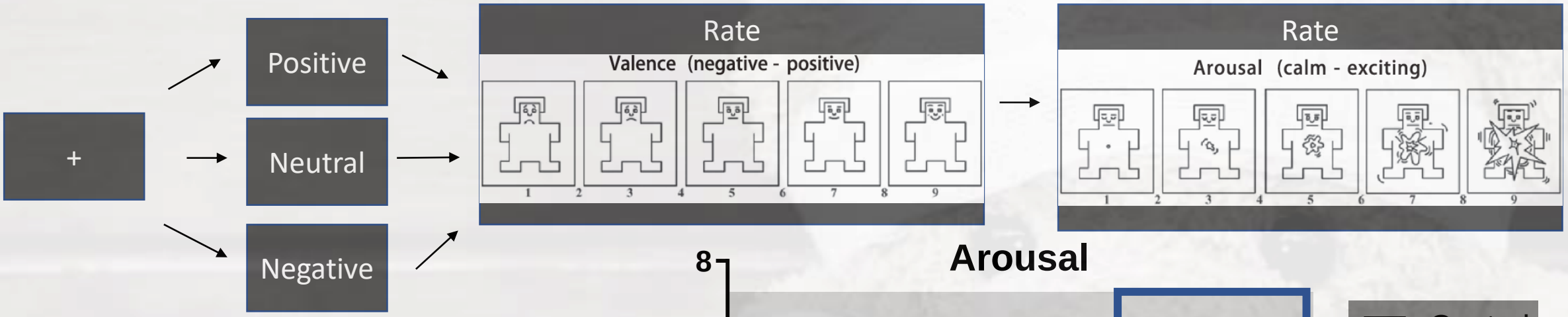


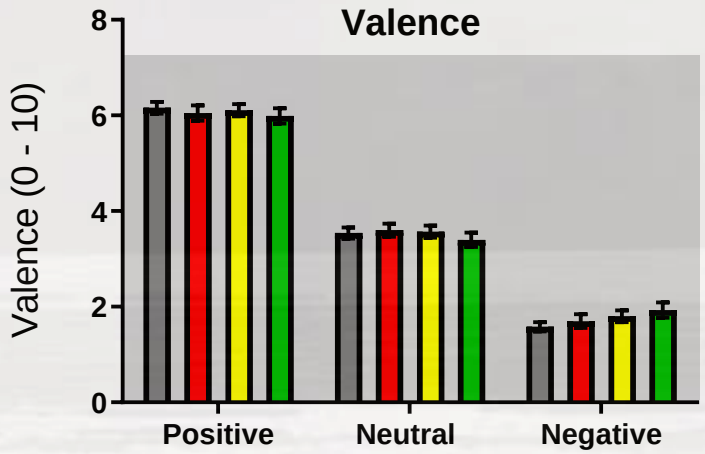
Cortisol: Effect of time: p < 0.001; group p = 0.63; group x time p = 0.67

Perini*, Mayo* (*in revision*)

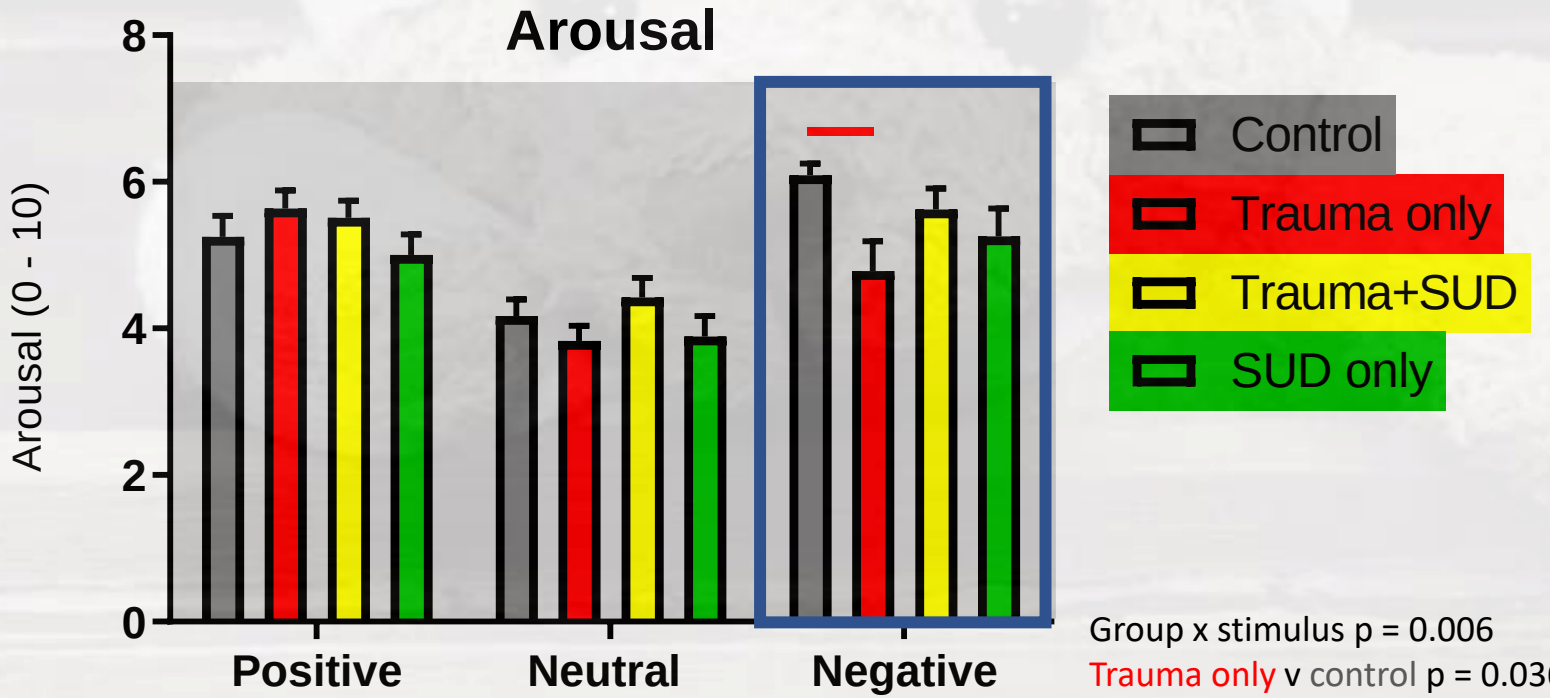
All data were transformed (natural log) for analysis and back-transformed for plotting

Resilience after after childhood trauma is associated with attenuated reactivity to negative affective stimuli





Group p = 0.96; group x stimulus p = 0.38

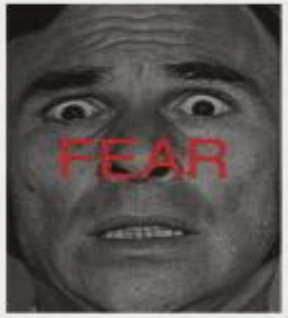


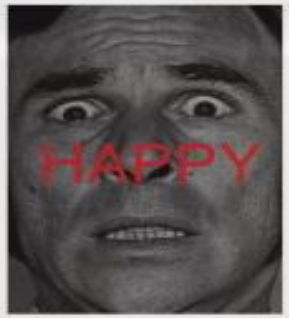
Group x stimulus p = 0.006

Trauma only v control p = 0.036

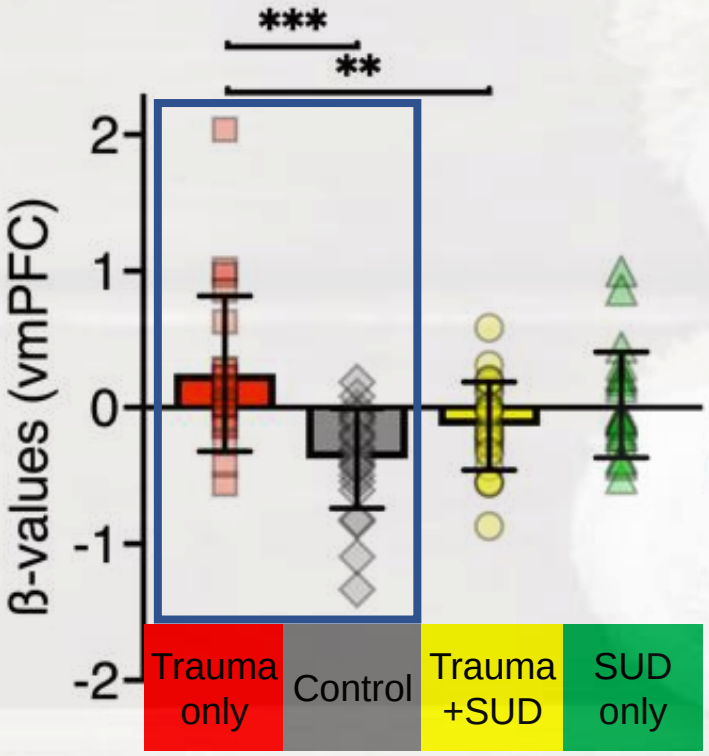
Perini*, Mayo* (*in revision*)

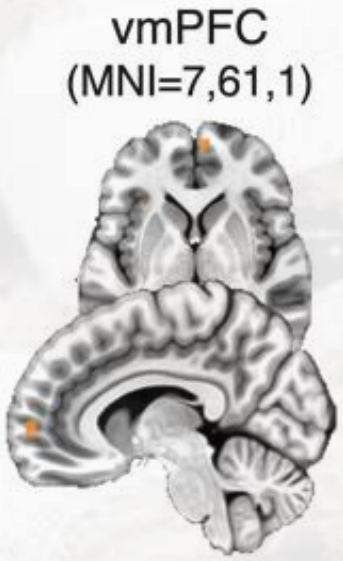
Resilience after childhood trauma is associated with greater activation of emotion regulation & salience processing regions

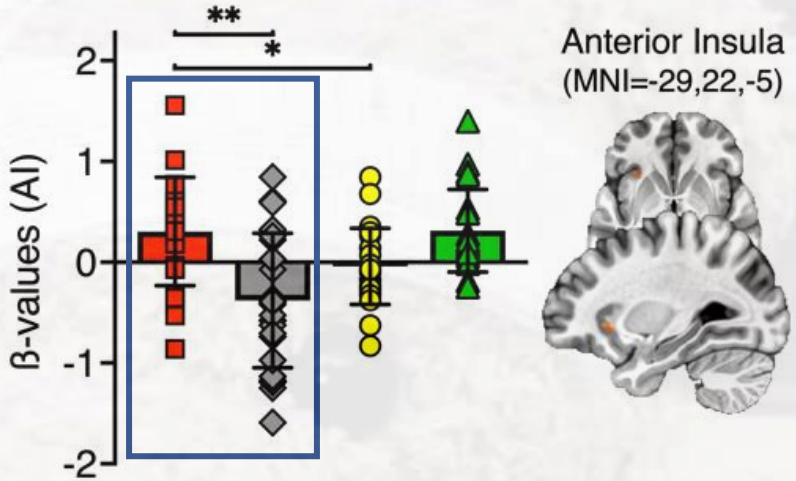


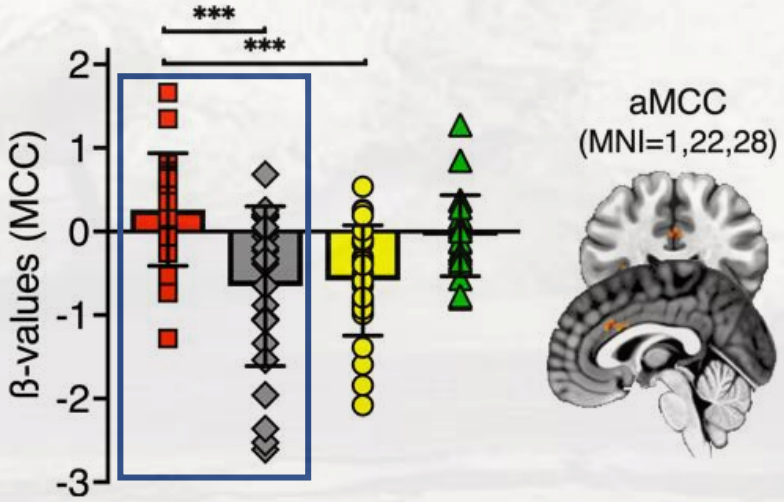


Etkin et al., 2006 *Neuron*









Irene Perini
@NeuroIP

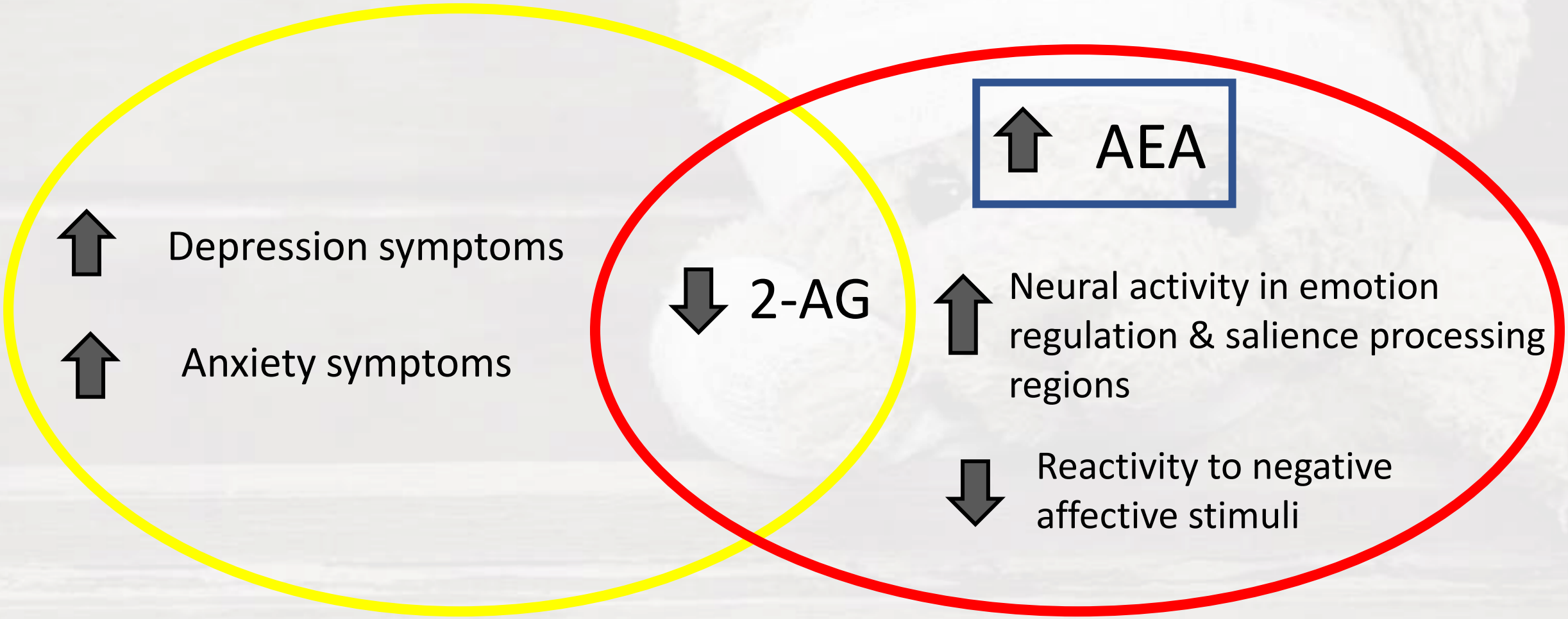
Perini*, Mayo* (*in revision*)

Trauma "Vulnerable"

(Trauma + SUD)

Trauma "Resilient"

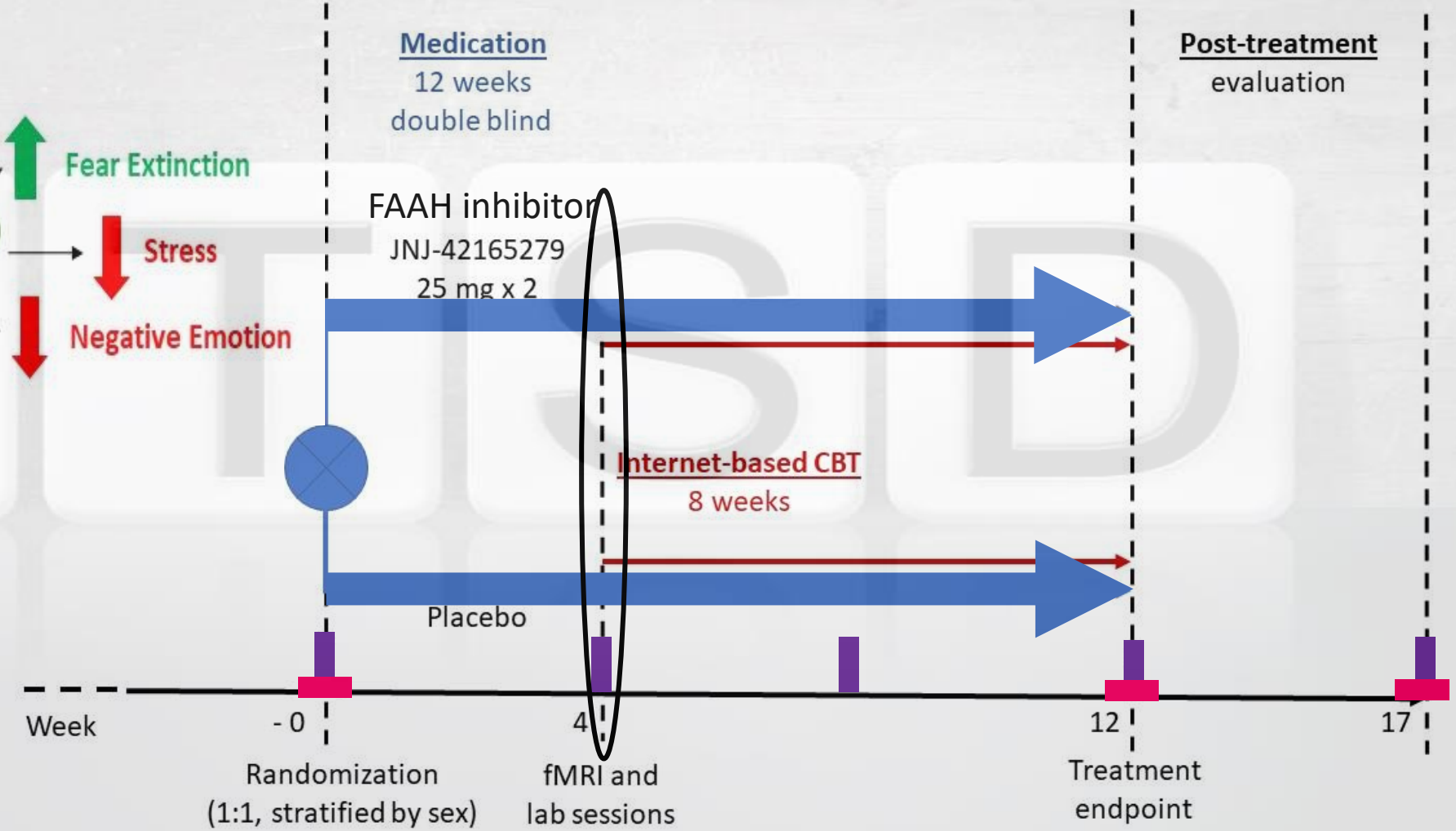
(Trauma only)



Elevating **AEA** via FAAH inhibition in PTSD

Markus Heilig
@Heilig_Lab

Mayo et al., 2020 *Biological Psychiatry*

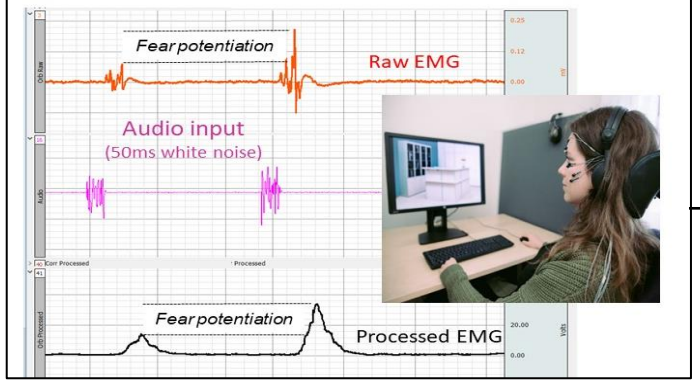


Primary Outcome: CAPS-5 scores

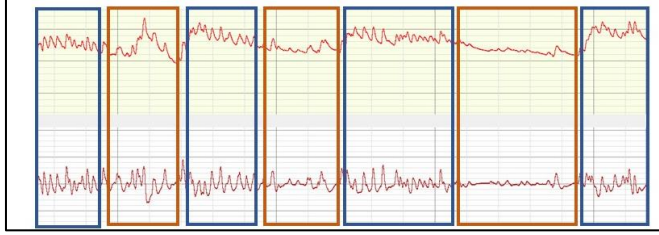
Self-report: PTSD symptoms (PCL-5), sleep (PSQI), anxiety (STAI), mood (POMS) + blood samples

FAAH inhibition in PTSD

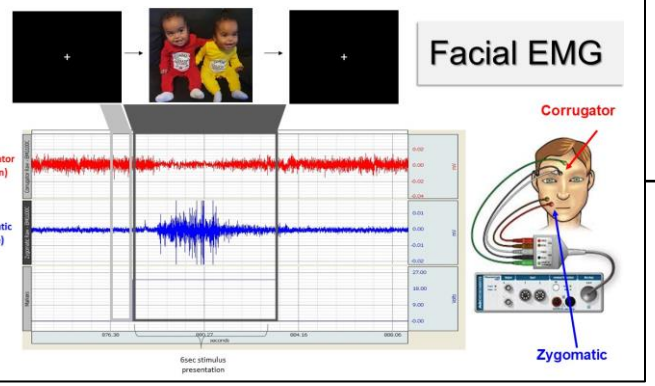
Fear-potentiated startle



Stress Reactivity



Facial EMG

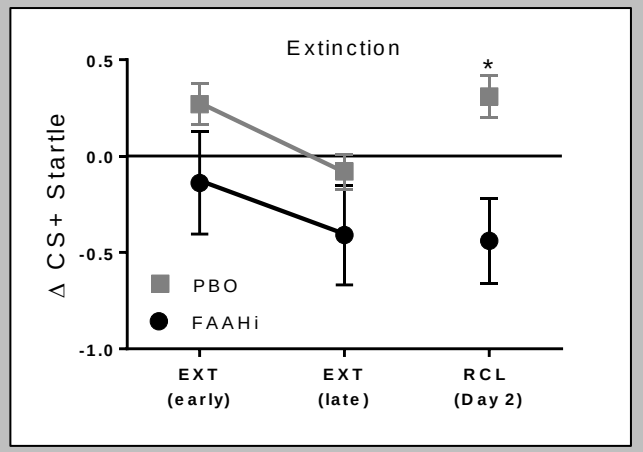


FAAH inhibition in <u>healthy adults</u>

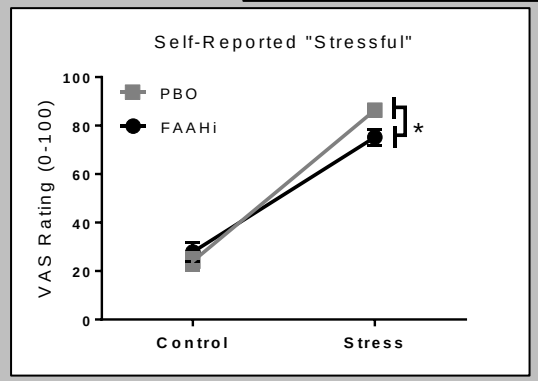
Mayo et al., 2020 *Biological Psychiatry*

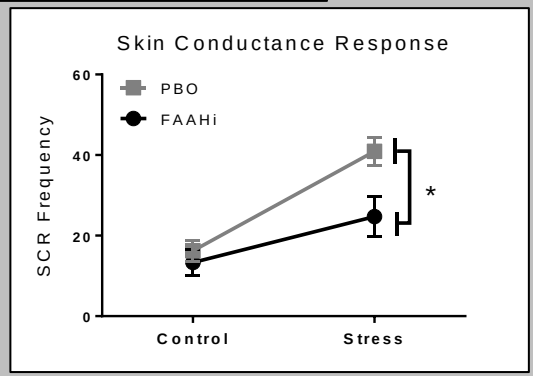
= ⇧ AEA

Greater **recall** of **fear extinction** (24hrs later)

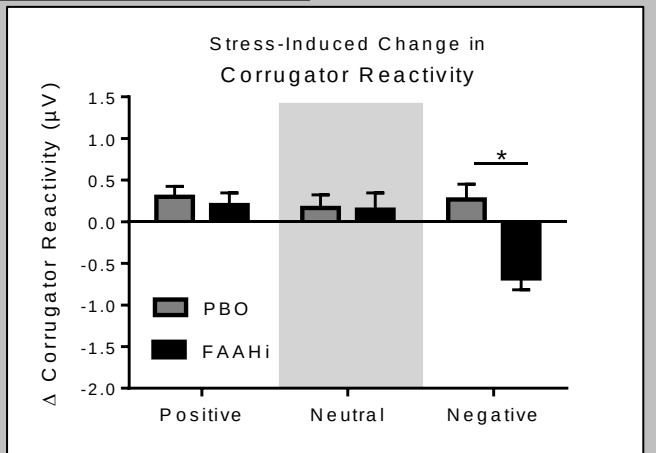


Reduced subjective and autonomic **stress reactivity**



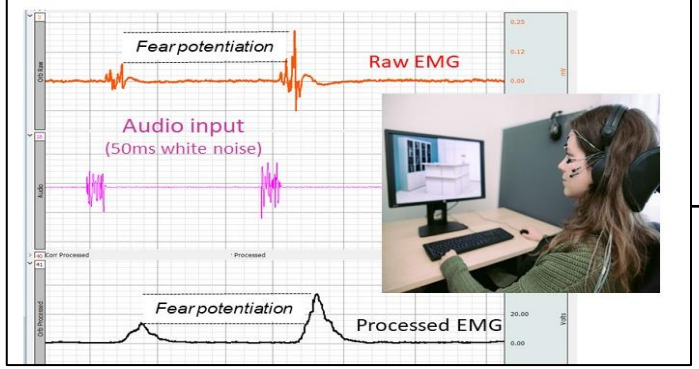


Attenuated stress-induced **negative affect**

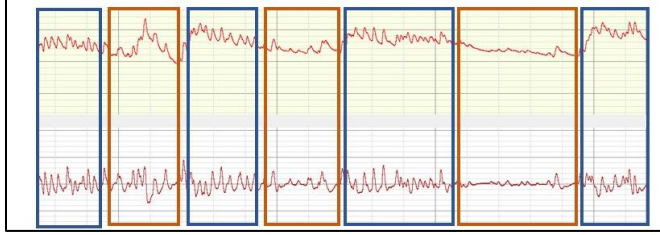


FAAH inhibition in PTSD

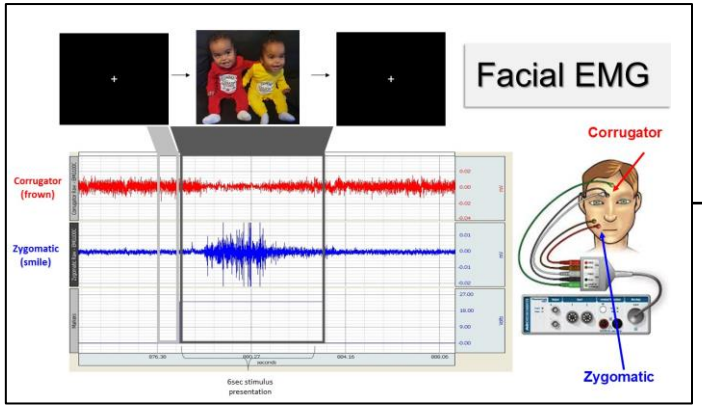
Fear-potentiated startle



Stress Reactivity



Facial EMG



FAAH inhibition in healthy adults

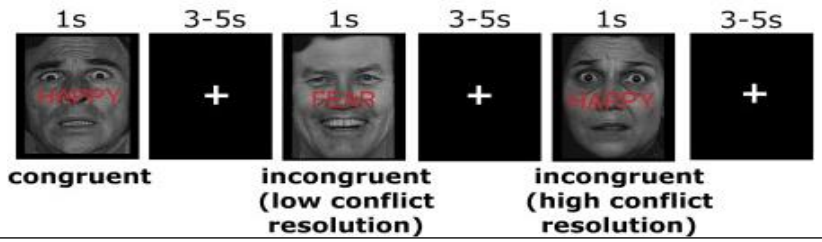
Mayo et al., 2020 *Biological Psychiatry*

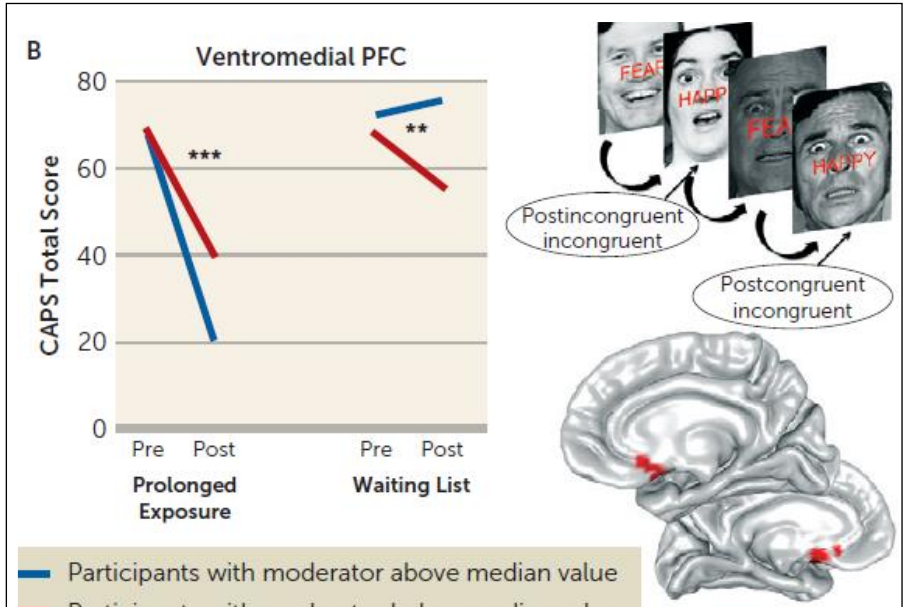
Greater **recall** of **fear extinction** (24hrs later)

Reduced subjective and autonomic **stress reactivity**

Attenuated stress-induced **negative affect**

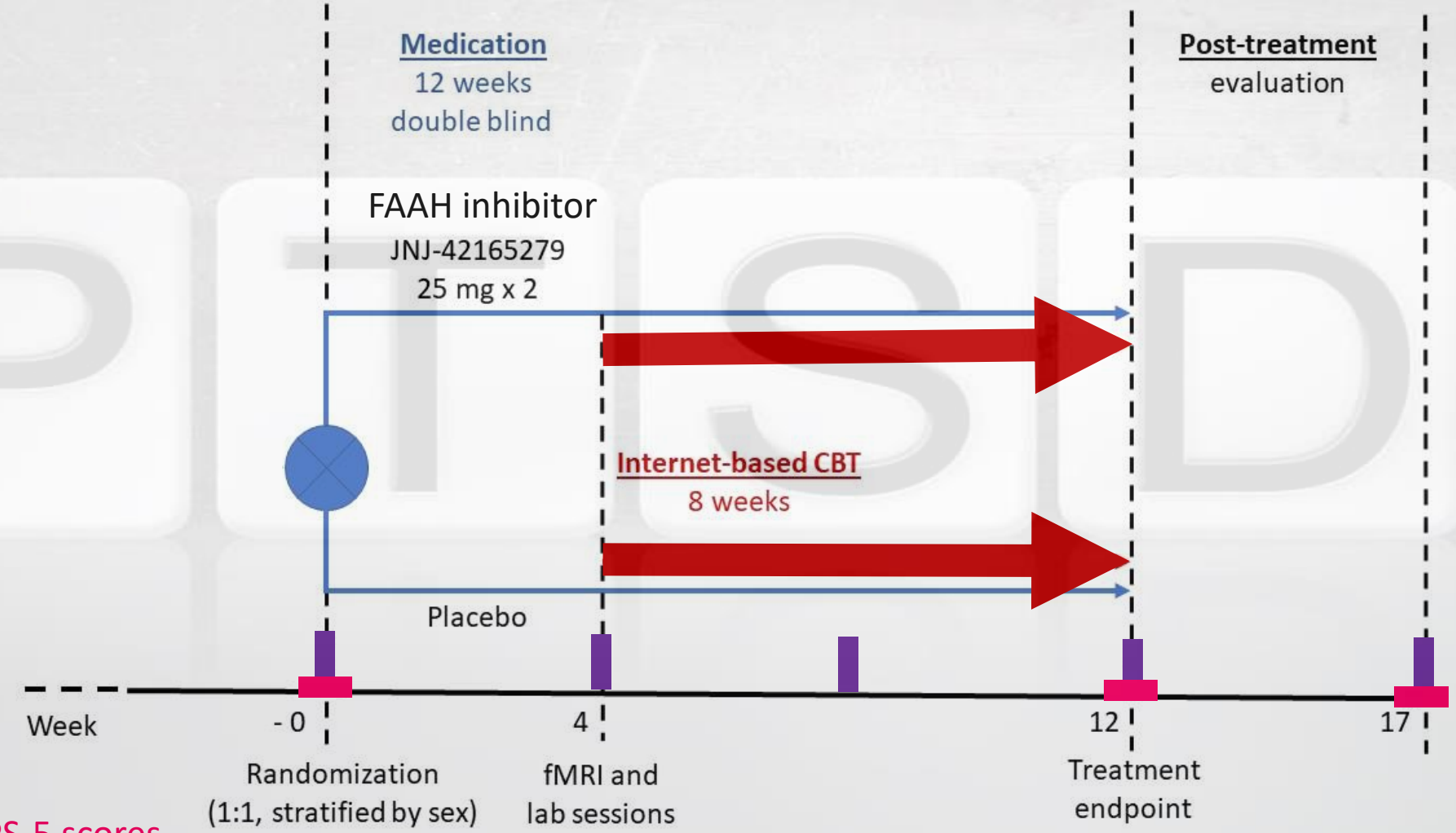
FAAH inhibition in PTSD





Fonzo et al., 2017 *Am J Psychiatry*

Elevating AEA via FAAH inhibition in PTSD

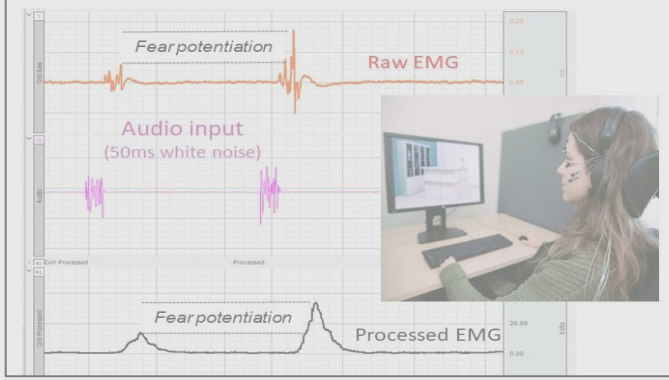


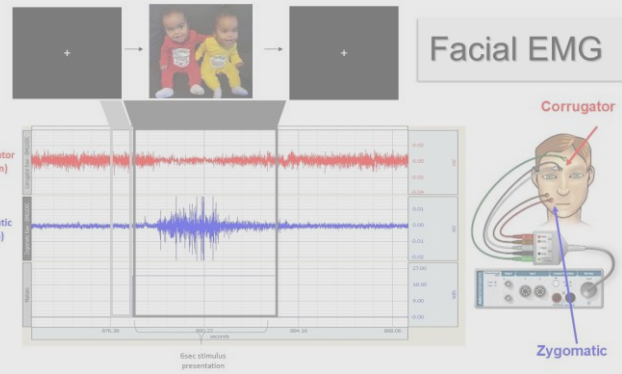
Primary Outcome: CAPS-5 scores

Self-report: PTSD symptoms (PCL-5), sleep (PSQI), anxiety (STAI), mood (POMS) + blood samples

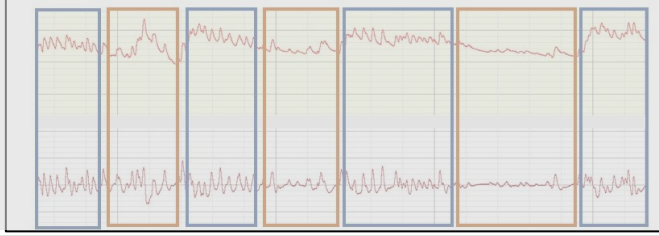
FAAH inhibition in PTSD

Fear-potentiated startle

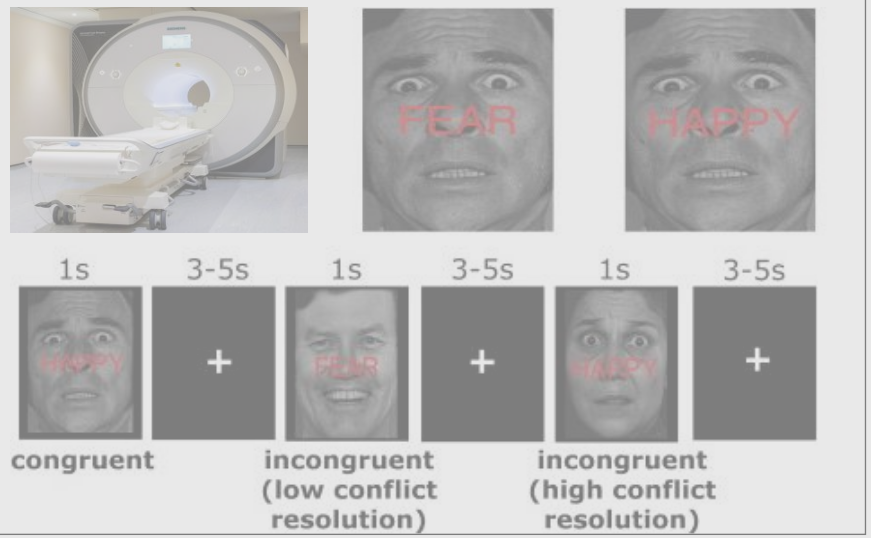


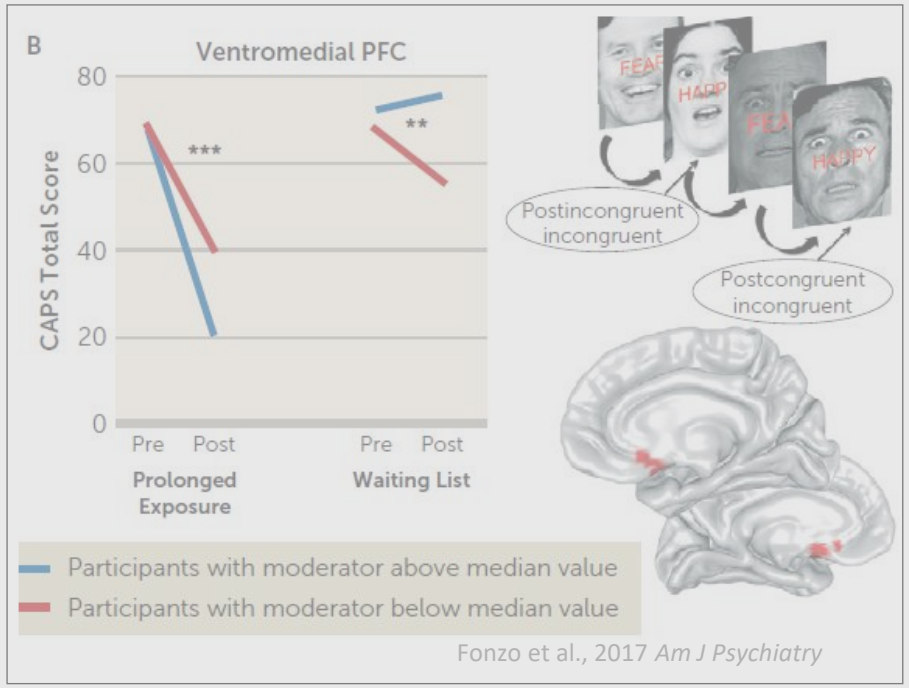


Stress Reactivity



FAAH inhibition in PTSD

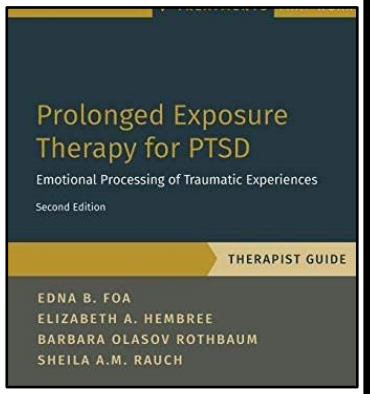




Fonzo et al., 2017 *Am J Psychiatry*

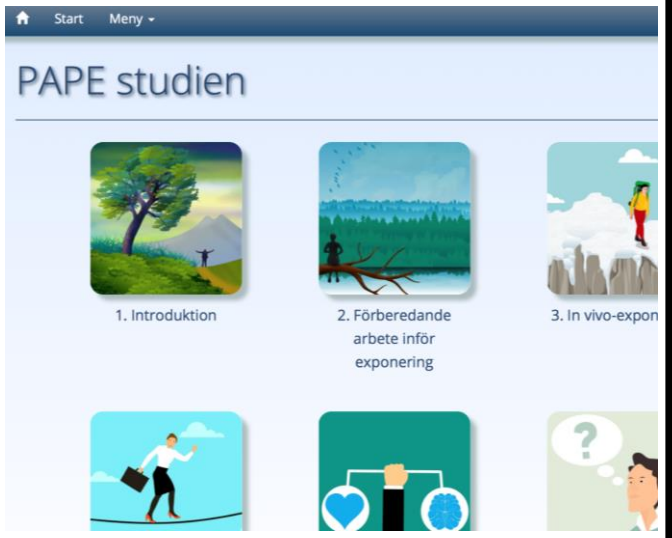
Prolonged Exposure for PTSD

Gerhard Andersson
Linköping University



8-week PE treatment
1 module per week

Modules 3-6: *in vivo* and imaginal exposure

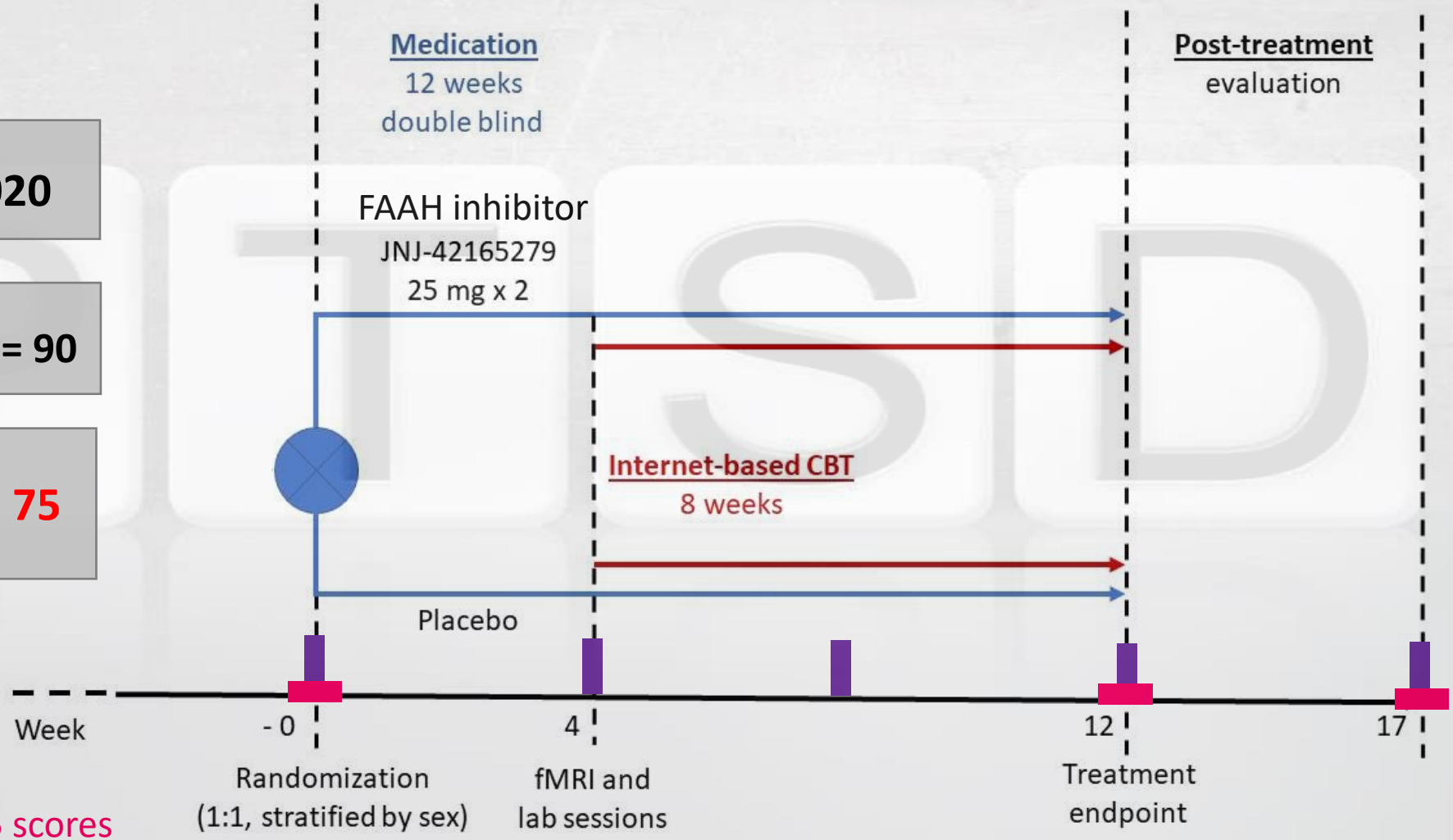


Elevating AEA via FAAH inhibition in PTSD

Start date: Nov 2020

Target Enrollment: N = 90

***Current Status:* N = 75**



Primary Outcome: CAPS-5 scores

Self-report: PTSD symptoms (PCL-5), sleep (PSQI), anxiety (STAI), mood (POMS) + blood samples

Summary & Conclusions

What we [think we] **know**

Elevated **AEA** may *protect against* SUD development following childhood trauma exposure

Center for Social & Affective Neuroscience

Markus Heilig

Andrea Capusan

Irene Perini

Elisabeth Paul

Åsa Axén

Per Gustafsson

Linköping University

Gerhard Andersson

Niclas Stensson

University of Calgary

Matt Hill

The Psychedelic and Cannabinoid Therapeutics (PaCT) Lab

Madeleine Jones (LiU)

Hilda Engelbrektsson (LiU)

Raegan Mazurka (Dalhousie Univ)

Connor Haggarty (Univ of Chicago)

Anisja Hühne (LMU Munich)

@MayoBrainLab

@MayoOnTheBrain

Email: **leah.mayo@ucalgary.ca**

CSAN Center for Social and Affective Neuroscience

Hotchkiss Brain Institute

The Mathison Centre for Mental Health Research & Education

Svenska Läkaresällskapet

Vetenskapsrådet

LINKÖPING UNIVERSITY

UNIVERSITY OF CALGARY

BRAIN & BEHAVIOR RESEARCH FOUNDATION

Awarding NARSAD Grants