Fear and anxiety neural circuits in post-traumatic stress disorder
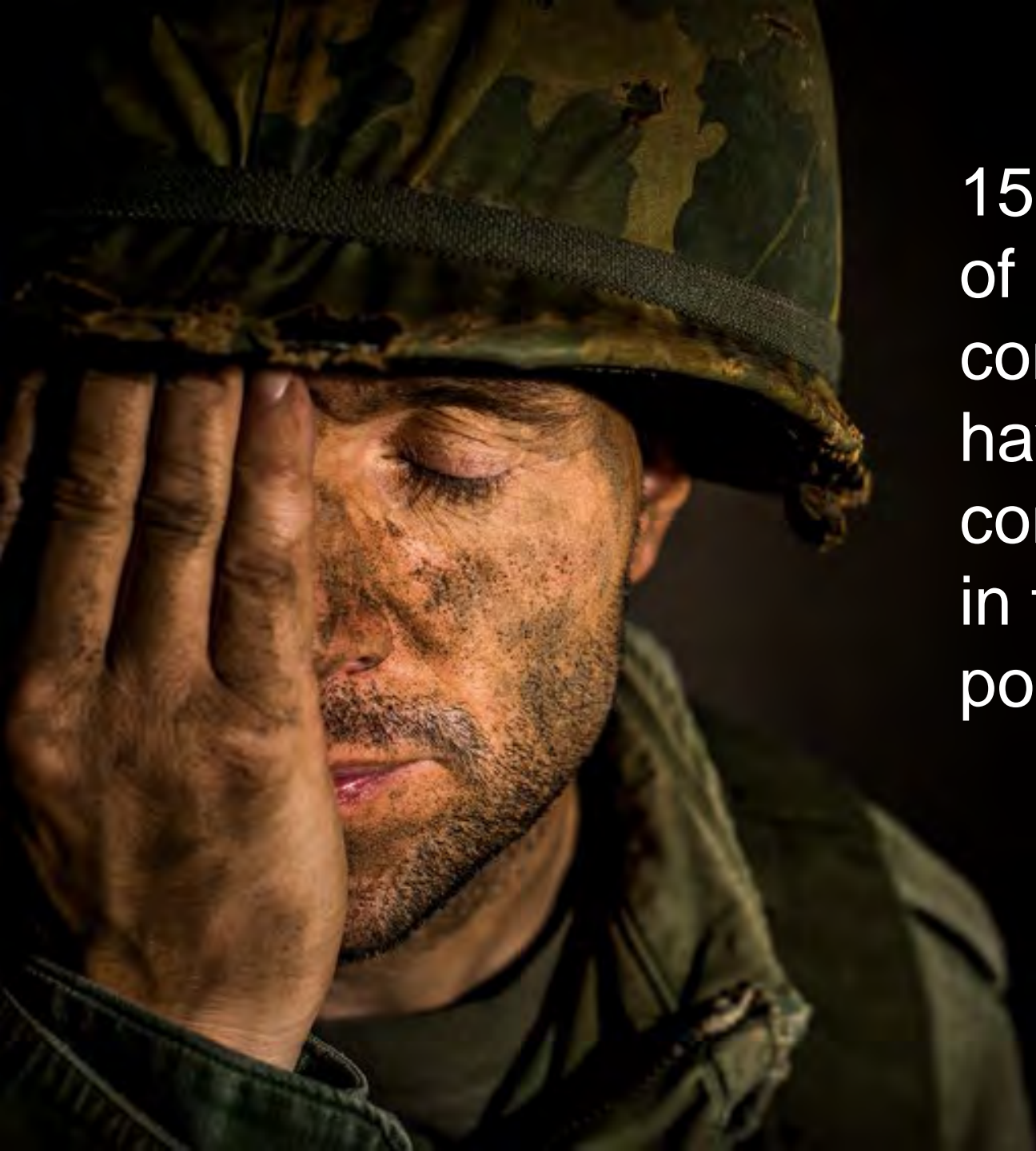
Jenni Blackford, PhD
Hattie B. Munroe Professor and Associate Dean of Research
Munroe-Meyer Institute
University of Nebraska Medical Center

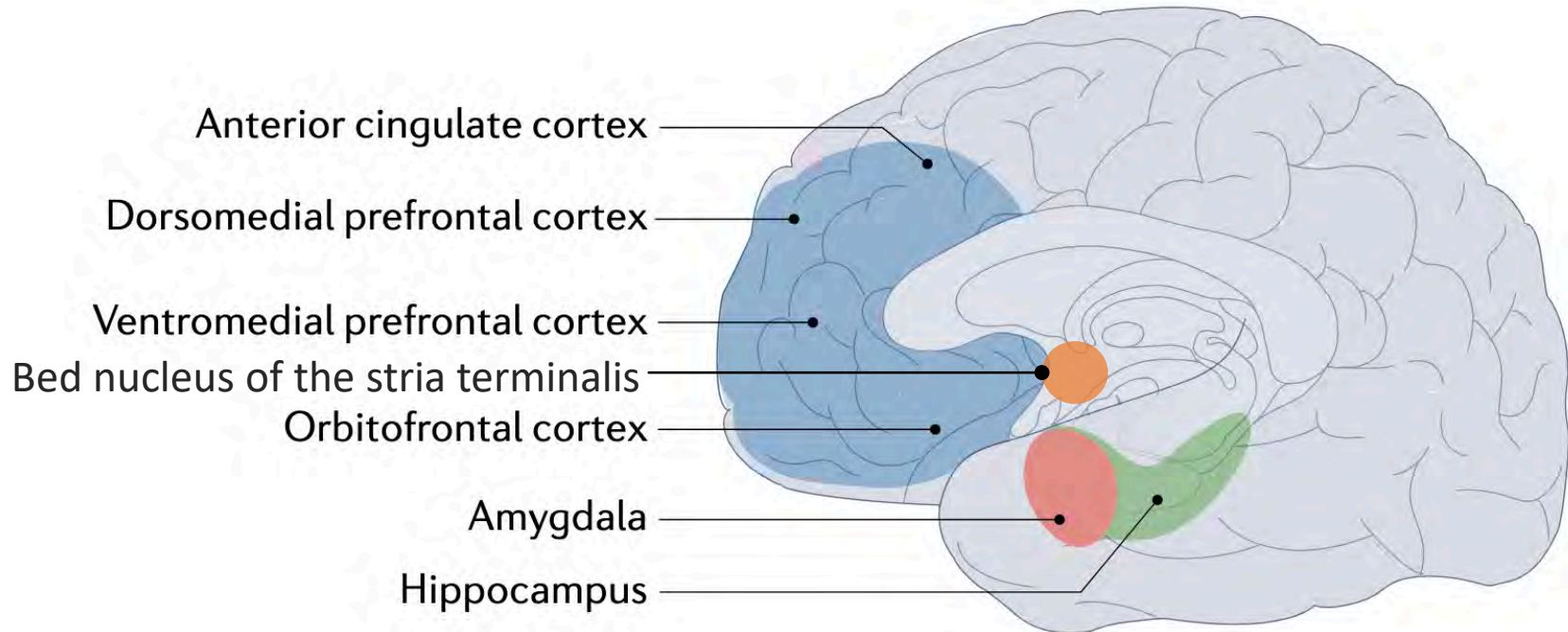# Disclosures

I have nothing to disclose.

15-30%
of people with
combat trauma
have PTSD,
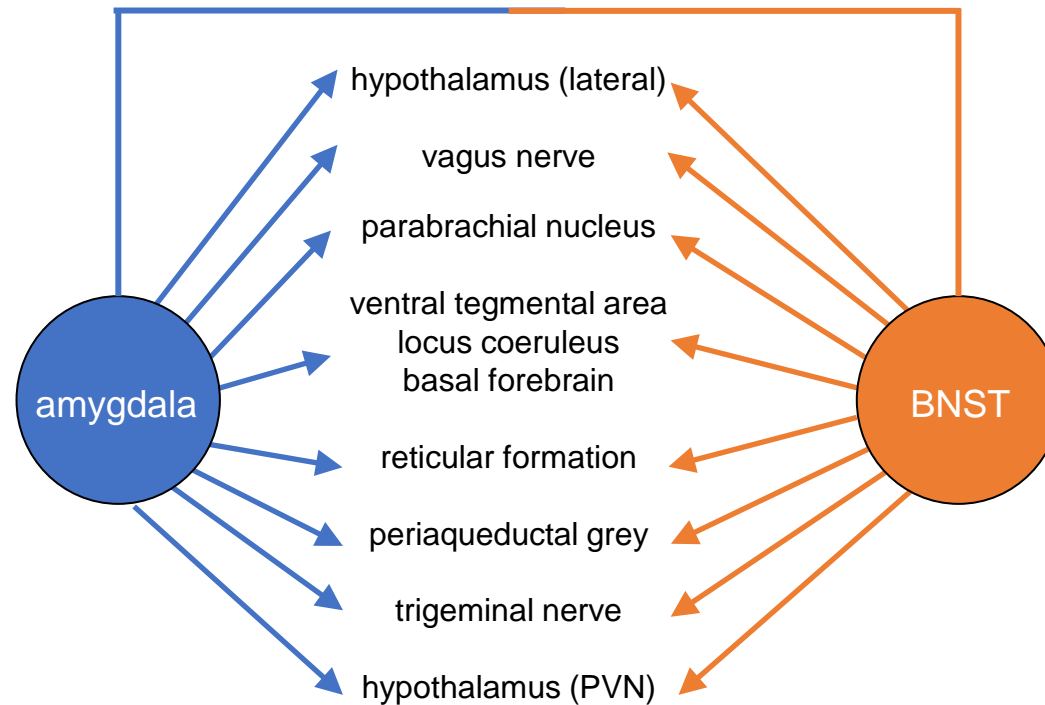compared with 6%
in the general
population

Where should we look?

PTSD neurocircuitry

Anterior cingulate cortex

Dorsomedial prefrontal cortex

Ventromedial prefrontal cortex

Bed nucleus of the stria terminalis

Orbitofrontal cortex

Amygdala

Hippocampus

Amygdala and BNST have the same anatomical targets

Amygdala and BNST have different triggers and responses

amygdala

phobic stimuli

conditioned fear

predictable threat

---

short-lived response

"fight or flight"

fear

BNST

context stimuli

contextual fear

unpredictable threat

---

sustained response

hypervigilance, avoidance

anxiety

Davis, LeDoux, Maren, Walker, Fanselow and others

Role of the Bed Nucleus of the Stria Terminalis in PTSD: Insights From Preclinical Models

Olivia W. Miles* and Stephen Maren

Department of Psychological and Brain Sciences and Institute for Neuroscience, Texas A&M University, College Station, TX, United States

REVIEW

# The Human BNST: Functional Role in Anxiety and Addiction

SN Avery[1,2], JA Clauss[1,2,3] and JU Blackford*[1,4]

[1]Department of Psychiatry, Vanderbilt University School of Medicine, Nashville, TN, USA; [2]Neuroscience Graduate Program, Vanderbilt Brain Institute, Vanderbilt University, Nashville, TN, USA; [3]Vanderbilt School of Medicine, Nashville, TN, USA; [4]Department of Psychology, Vanderbilt University, Nashville, TN, USA

Heightened startle response to unpredictable threat in PTSD

Grillon et al (2009). Biological Psychiatry
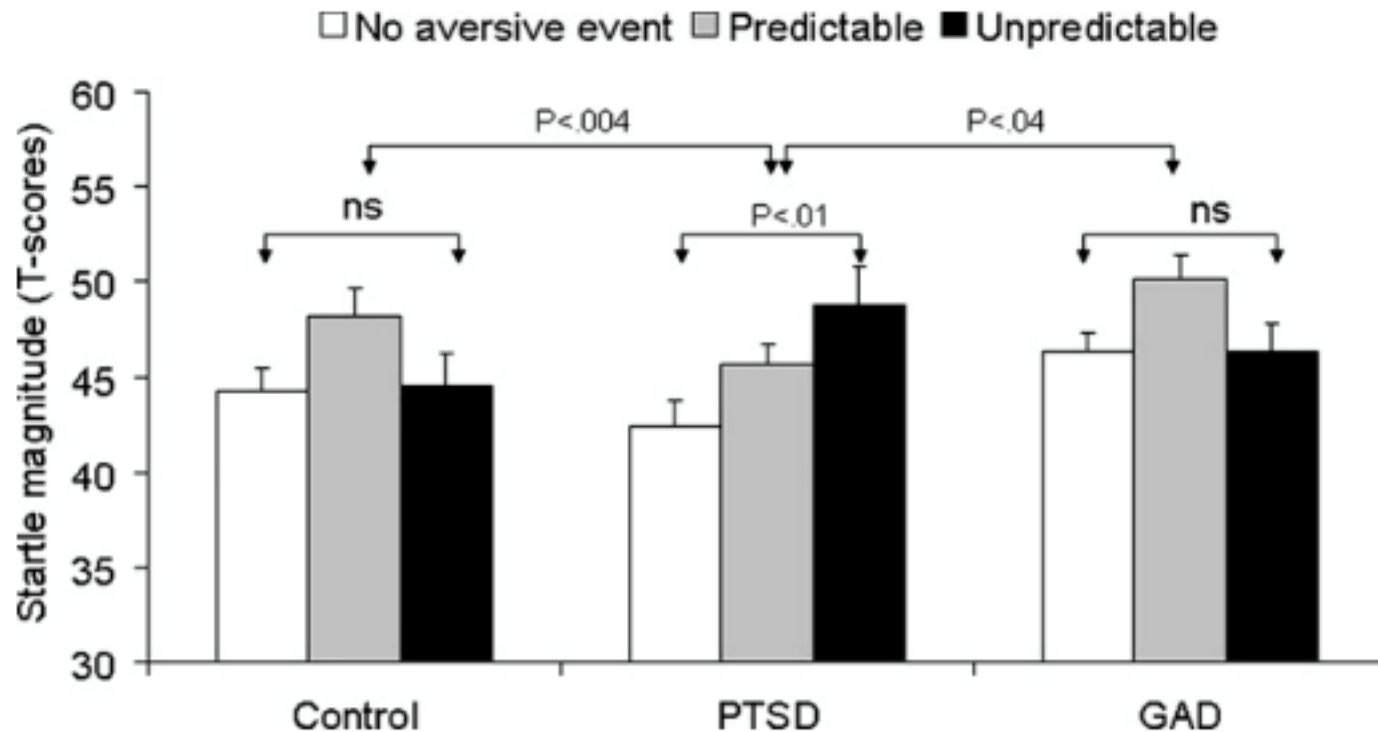
Fear vs anxiety responses may have different responses to treatments

	Fear / Predictable threat	Anxiety / Unpredictable threat
CRF antagonists (rodents)		✓
Benzodiazepines		✓
Alcohol		✓
Escitalopram & citalopram		✓
Mindfulness-based stress reduction		✓
Exercise		✓

Walker et al (2009) Progress in Neuropsychopharmacology & Biological Psychiatry; Hoge…Grillon (2023) Biological Psychiatry; Lago …Grillon (2017) Depression & Anxiety; Grillon et al (2006) Biological Psychiatry; Moberg (2009) J Ab Psych; Grillon (2009), NPP

How can we study the BNST in humans?

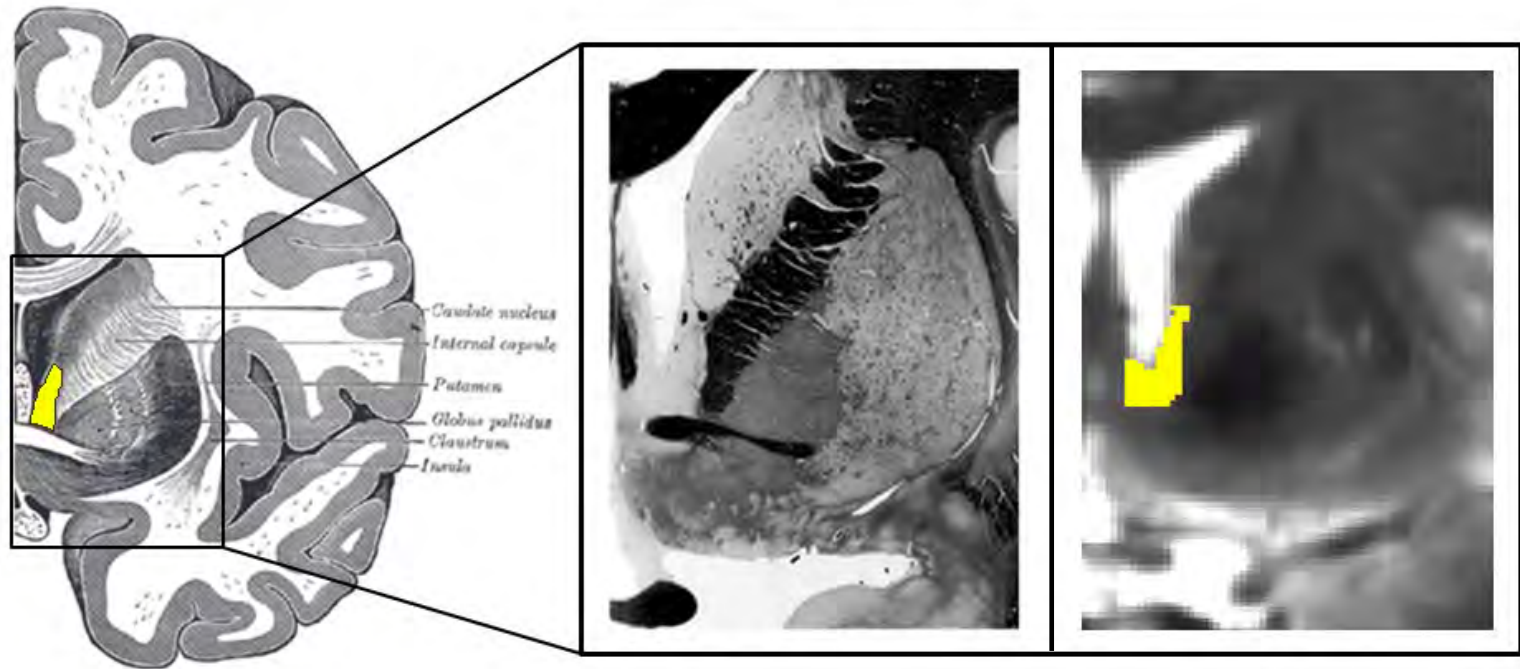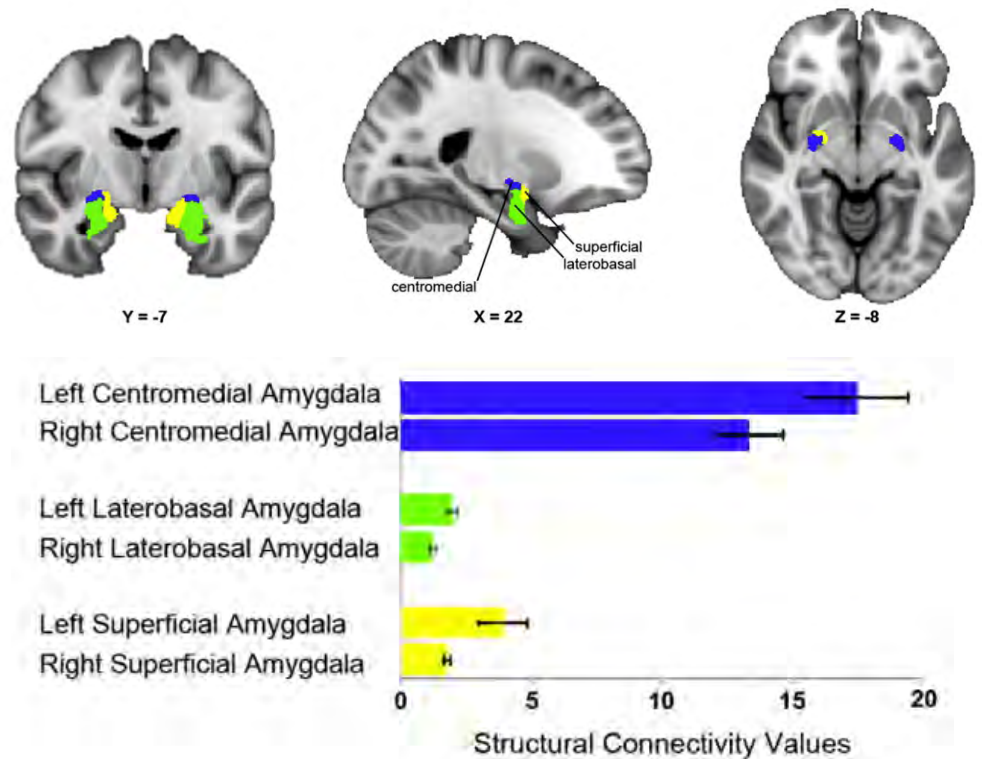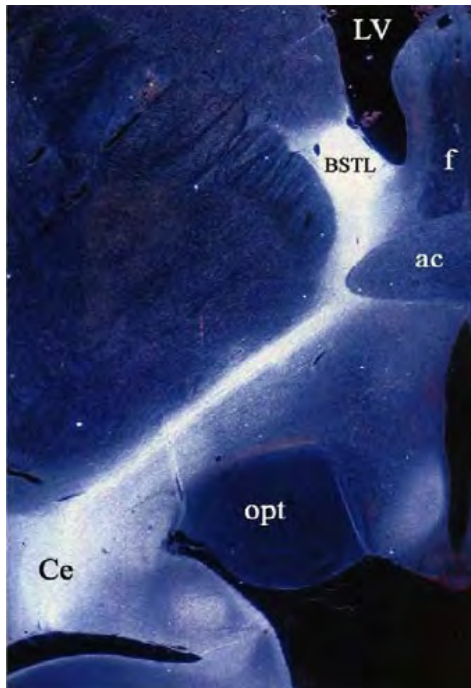# Can we use neuroimaging to study the human BNST?

BNST
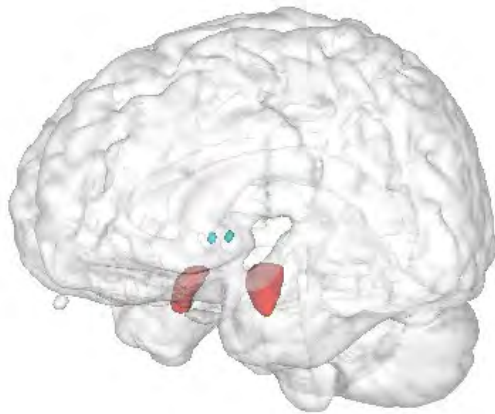
amygdala

1 mm

3 mm

Accurate localization of human BNST with ultra high field imaging and a novel scanner sequence

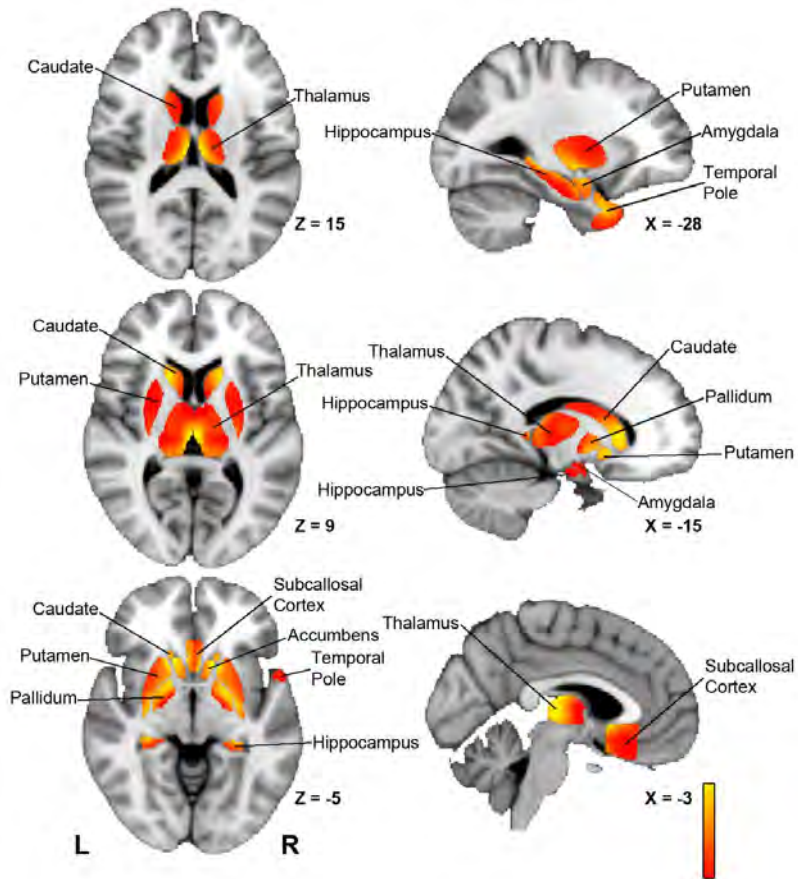# Validate mask by testing for known structural connections

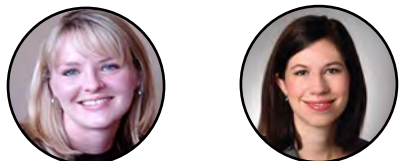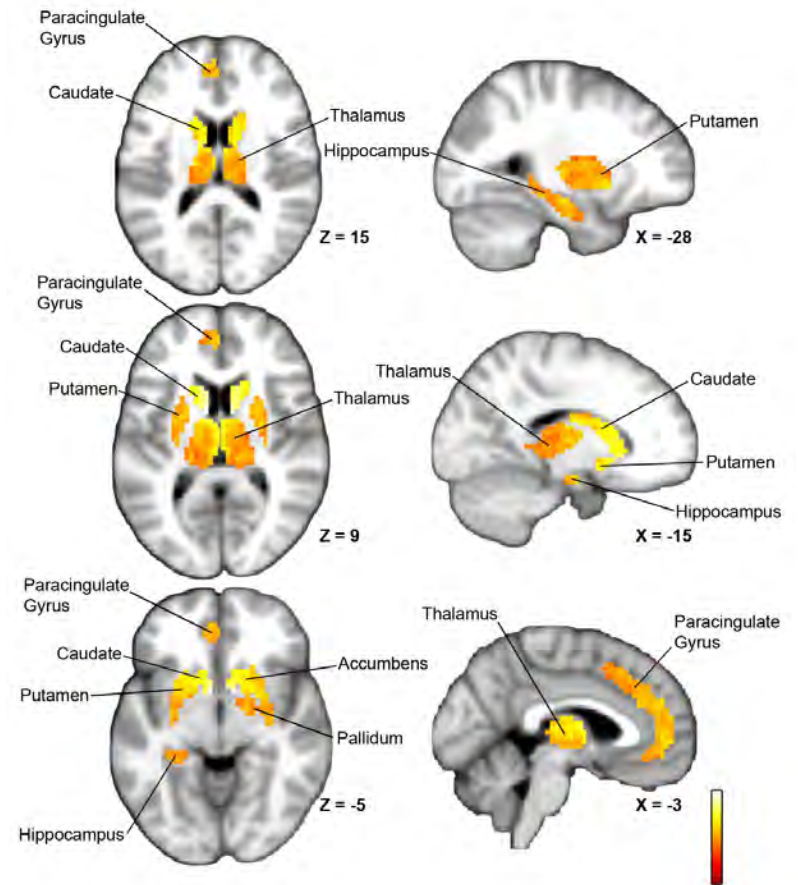Y = -7   X = 22   Z = -8

superficial
laterobasal

centromedial

Left Centromedial Amygdala
Right Centromedial Amygdala

Left Laterobasal Amygdala
Right Laterobasal Amygdala

Left Superficial Amygdala
Right Superficial Amygdala

0   5   10   15   20

Structural Connectivity Values

Suzanne Avery, PhD

Avery, Clauss, Winder, Woodward, Heckers & Blackford (2014). NeuroImage.

Map the BNST network

structural connectivity

functional connectivity

Suzanne Avery, PhD   Jacci Clauss, MD, PhD

Avery, Clauss, Winder, Woodward, Heckers, Blackford (2014) NeuroImage.

Replications

3T

7T

McMennamin et al (2014). Journal of Neuroscience.

Torrisi et al (2015) Human Brain Mapping.
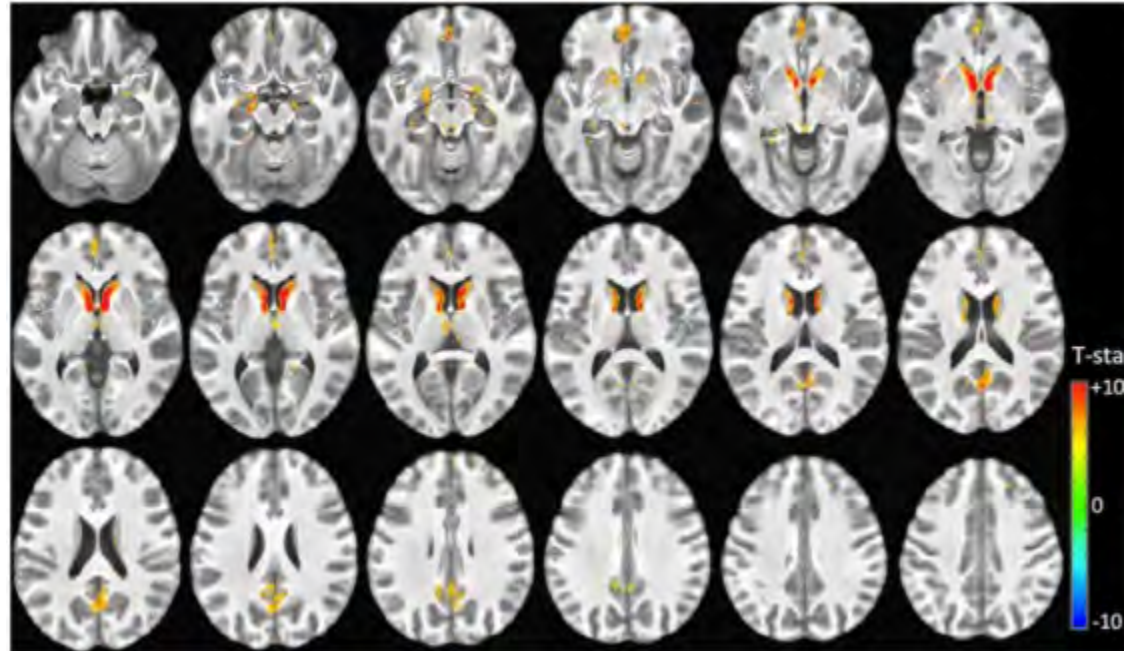
Probabilistic anatomical mask to facilitate further studies

T7
GRASE

3T
T2W

Y = 3   X = 6   Z = 0
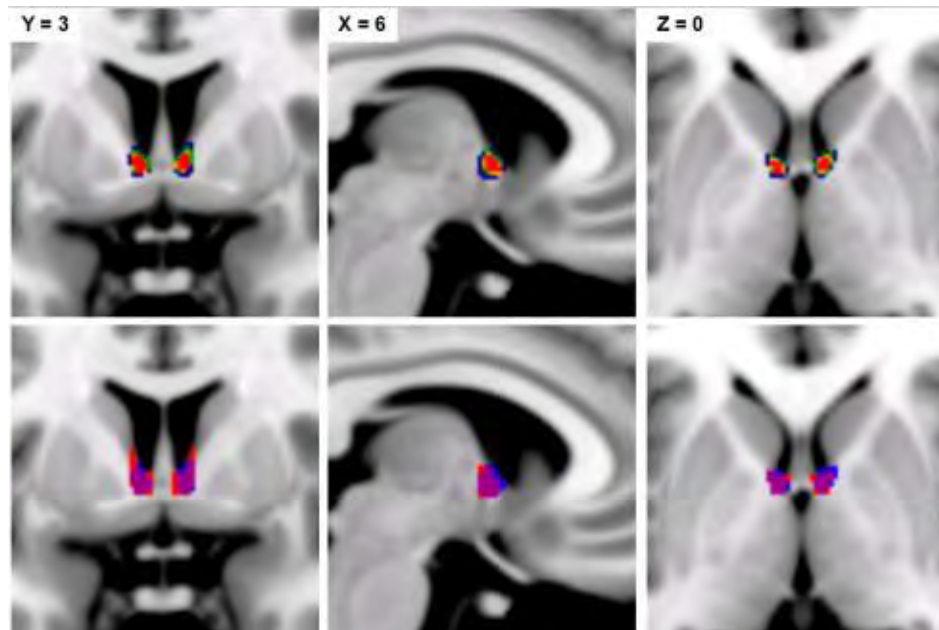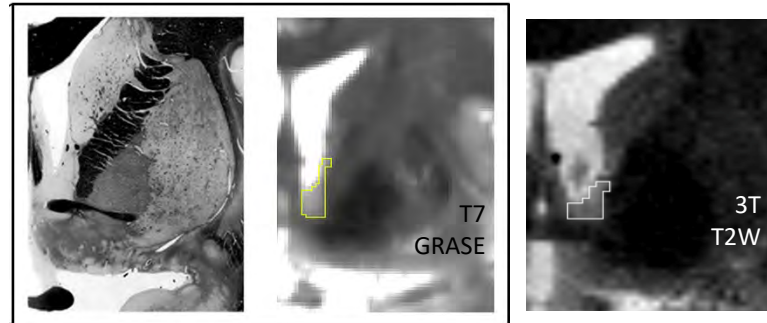
probabilistic
BNST 3T
mask

overlap of
7T + 3T
masks

Justin Theiss

Amygdala and BNST have different triggers and responses

amygdala	BNST
short-lived response	sustained response
"fight or flight"	hypervigilance, avoidance

phobic stimuli	context stimuli
conditioned fear	contextual fear
predictable threat	unpredictable threat

fear   **anxiety**

Davis, LeDoux, Maren, Walker, Fanselow and others

Unpredictable threat as a psychological mechanism

Avery, Clauss & Blackford (2016). Neuropsychopharmacology.
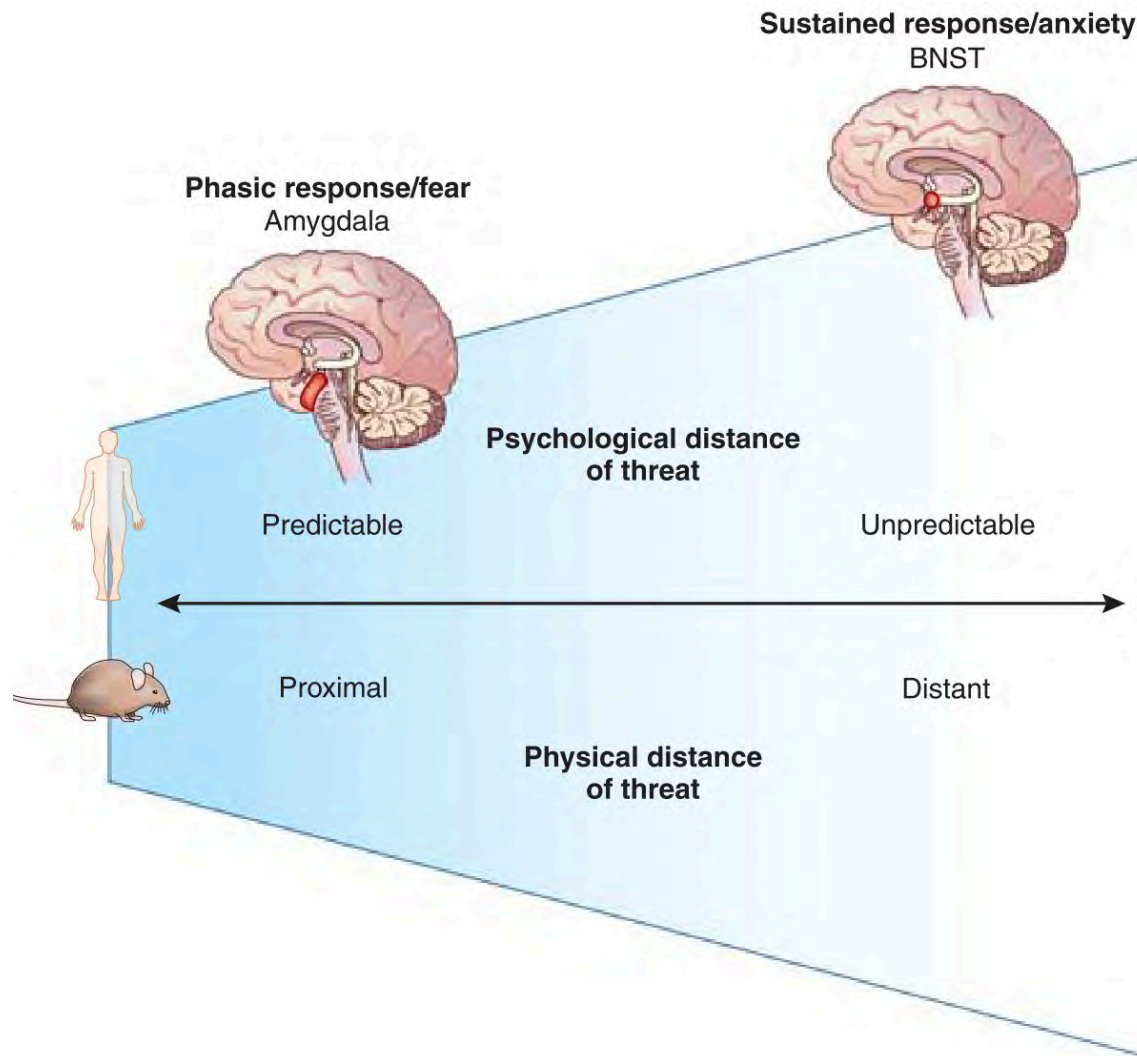
Meta-analysis of fMRI threat anticipation tasks

Avery, Clauss & Blackford (2016). Neuropsychopharmacology.

Unpredictable threat task

Predictable Condition

| 1 sec cue | 5-8 sec | 1 sec stimulus | 5-8 sec | 1 sec cue | 5-8 sec | 1 sec stimulus | 5-8 sec |

predictable fear | predictable neutral

0 sec | 300 sec

Unpredictable Condition

| 1 sec cue | 5-8 sec | 1 sec stimulus | 5-8 sec | 1 sec cue | 5-8 sec | 1 sec stimulus | 5-8 sec |

unpredictable fear | unpredictable neutral

0 sec | 300 sec

Unpredictable threat task

Clauss, Avery, Benningfield, Blackford (2019) Depression and Anxiety.
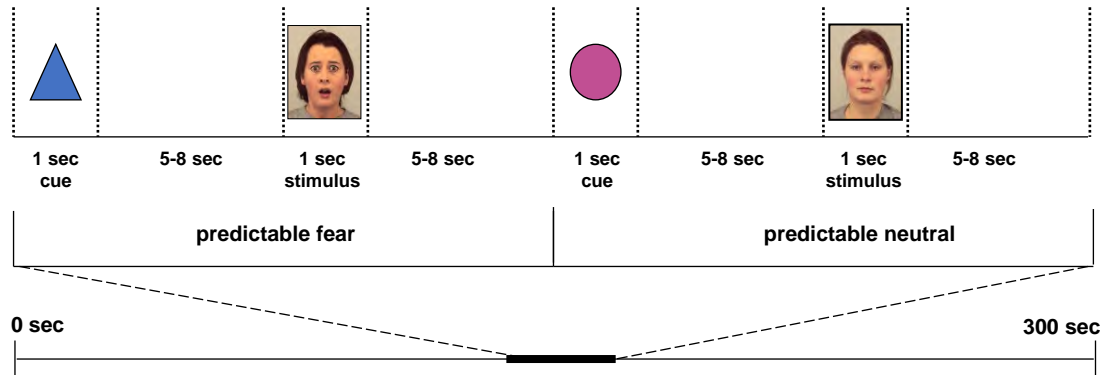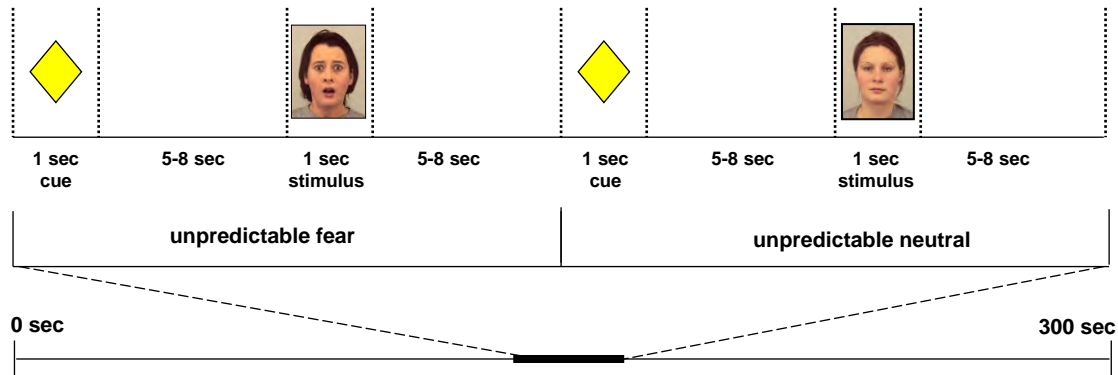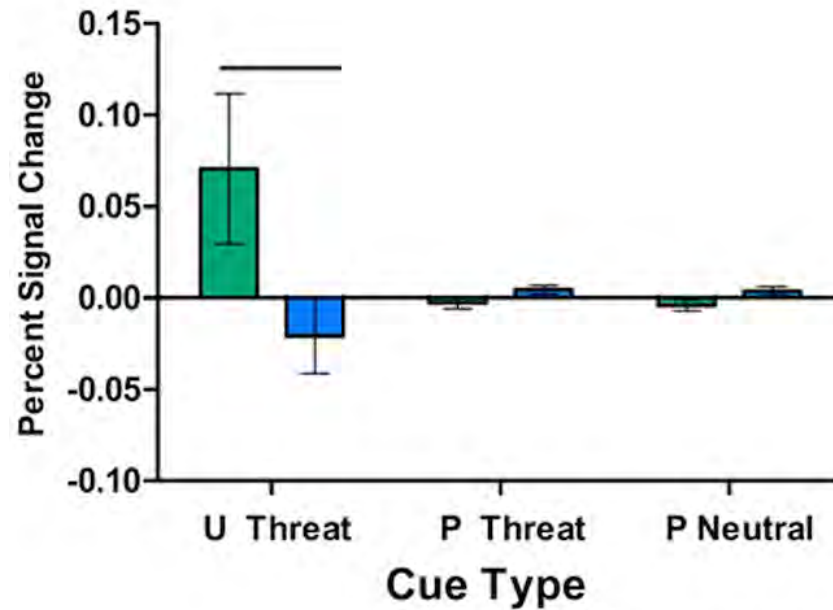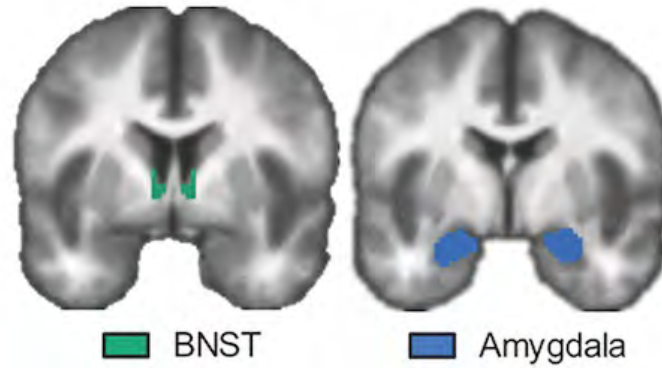
Summary

Animal models identified two brain regions important to fear and anxiety and suggested that the amygdala and BNST may have different roles.

Our lab developed and validated the neuroimaging tools needed for translational studies of fear and anxiety.

There is evidence that threat anticipation tasks can be used to study the BNST.

Caveat: whether the amygdala and BNST have distinct roles in fear and anxiety is a topic of active investigation in the field.

Amygdala and BNST neurocircuity in PTSD

Brandee Feola, PhD   Bunmi Olatunji, PhD   Harry Gwirtzman, MD

National Institute of Mental Health

U.S. Department of Veterans Affairs

Sample characteristics

	PTSD	Trauma-exposed controls
👥	32	13
♂	100% men	85% men
🌍	78% white	92% white
🧠	Current PTSD with combat as the primary trauma	No current or lifetime psychiatric disorders
💊	53% SSRI/SNRI or gabapentin	8%

Study procedures
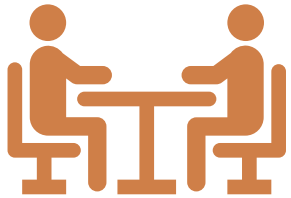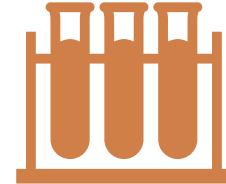
visit 1   visit 2

Unpredictable threat task
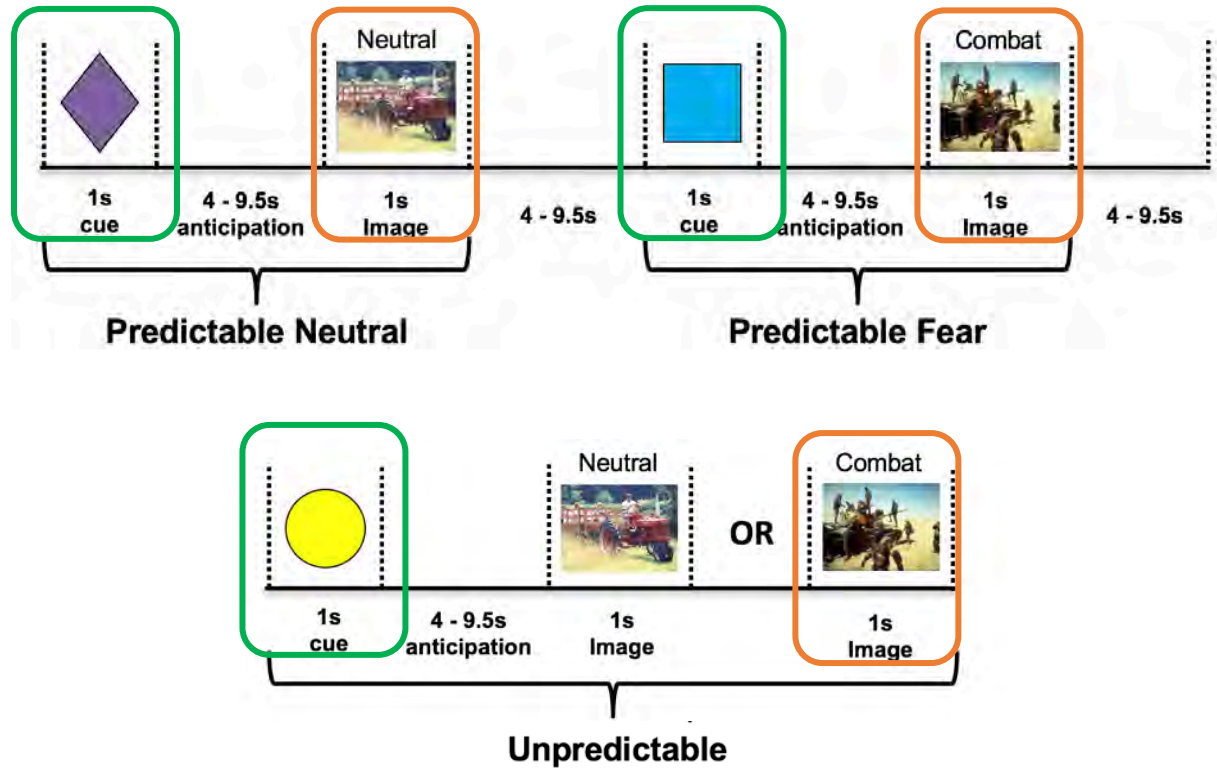
Do combat Veterans with PTSD have heightened BNST or amygdala responses to threat?

Activation

Anticipation Phase

BNST
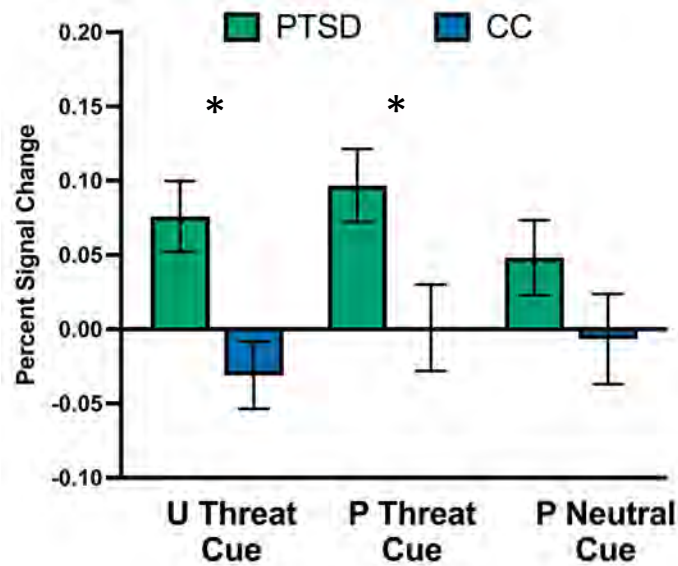
Amygdala
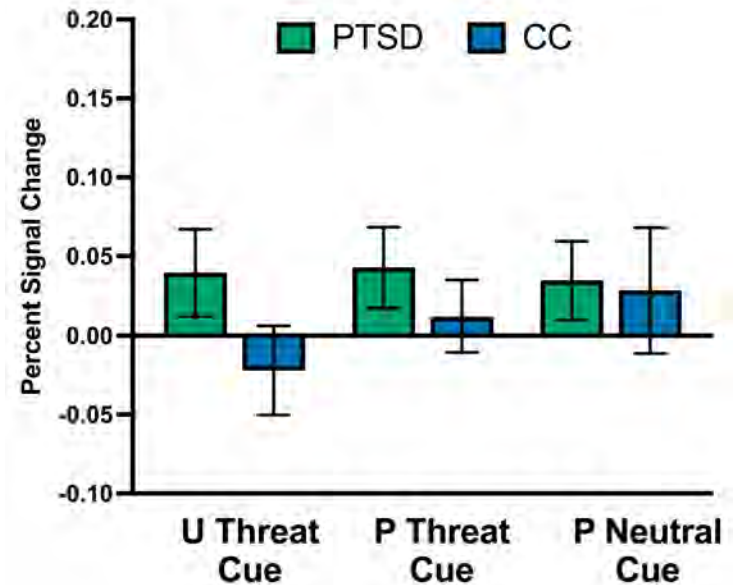
Heightened BNST activation to both unpredictable and predictable threat cues.

Activation

Image Viewing Phase

BNST
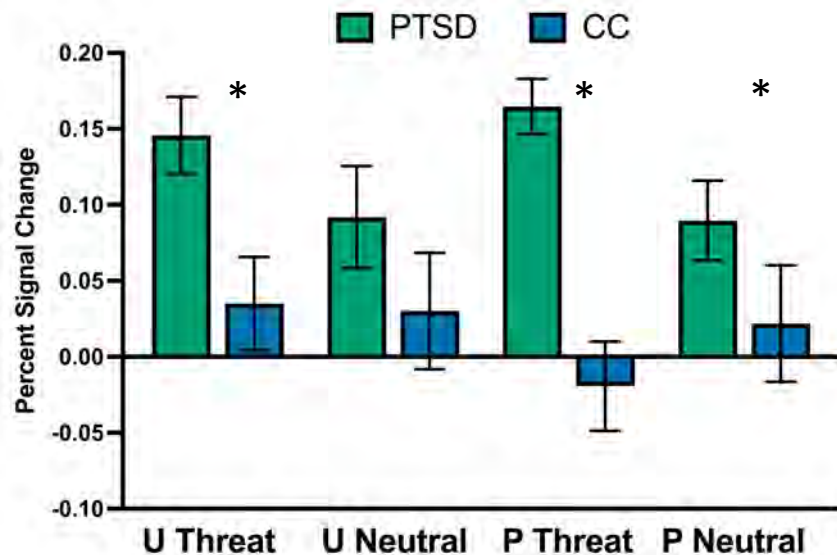
Amygdala
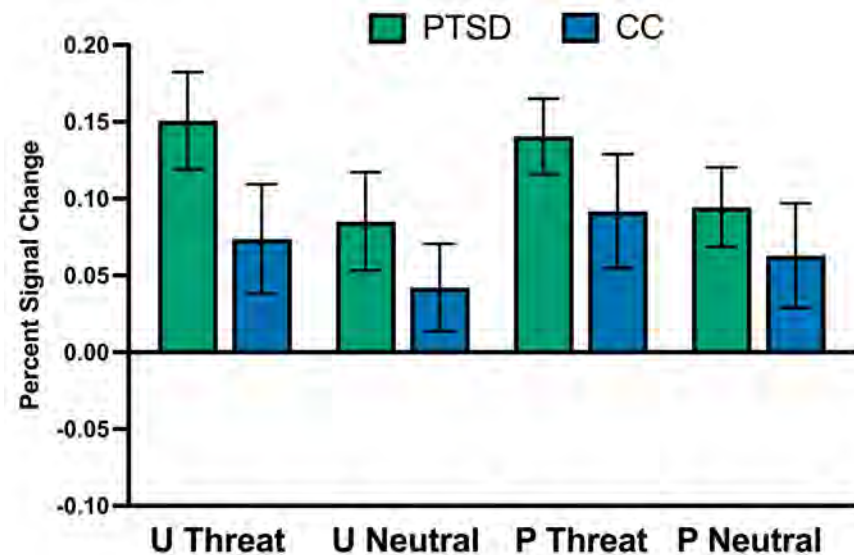
Heightened BNST activation to both unpredictable and predictable threat images and predictable neutral images.

Do combat Veterans with PTSD have disrupted BNST or amygdala connectivity during threat?

BNST network
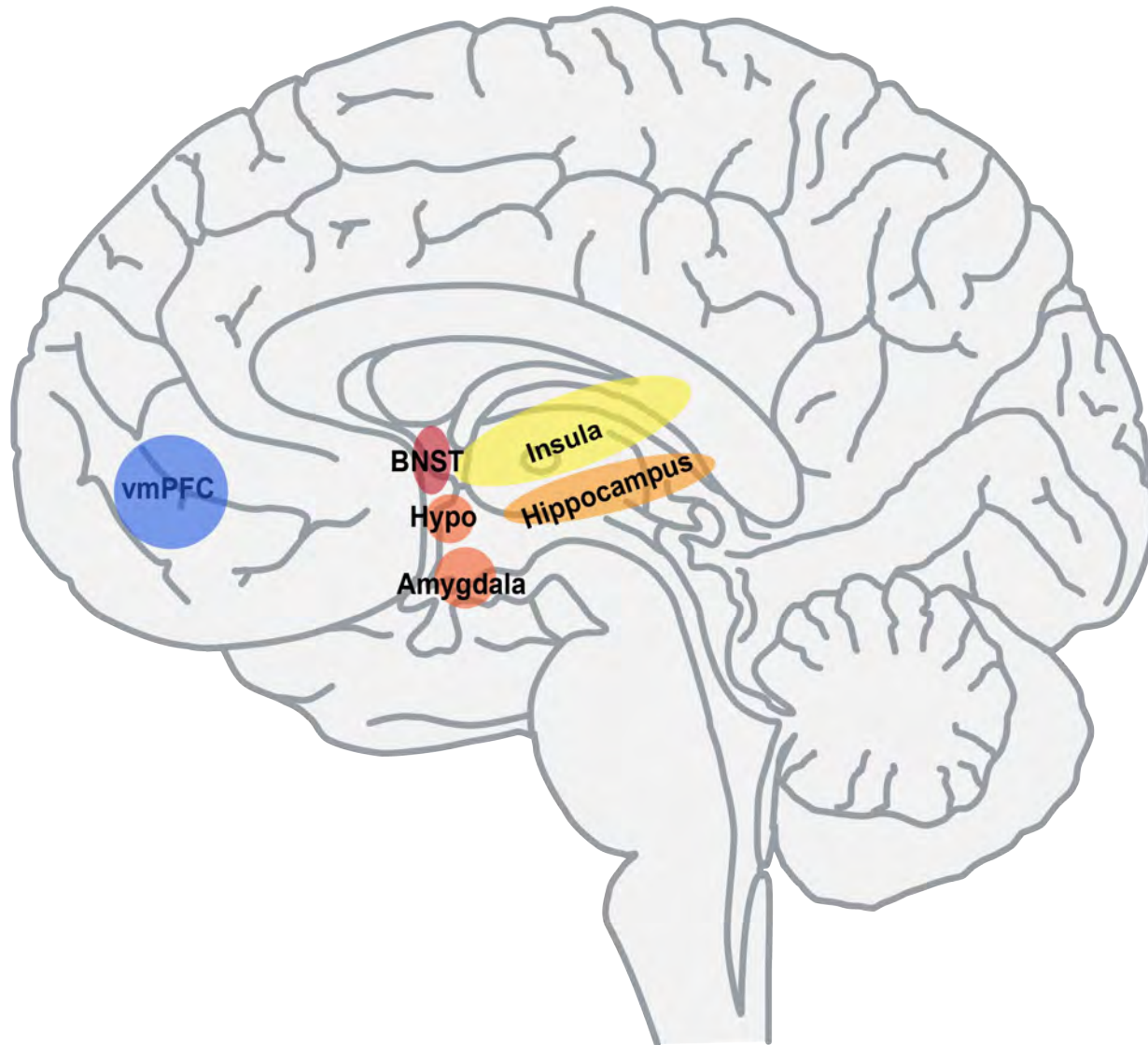
Connectivity during anticipation phase
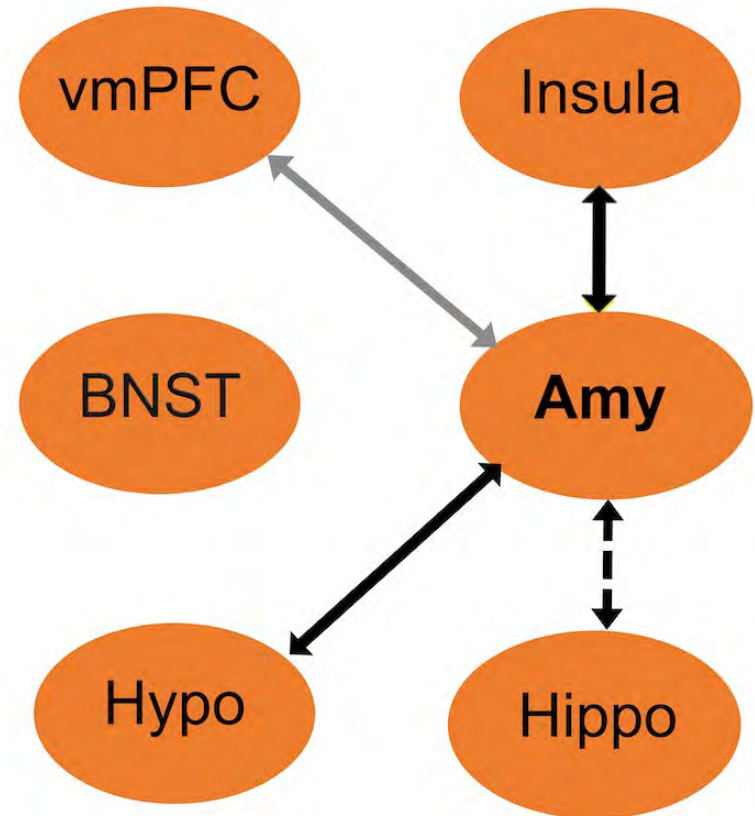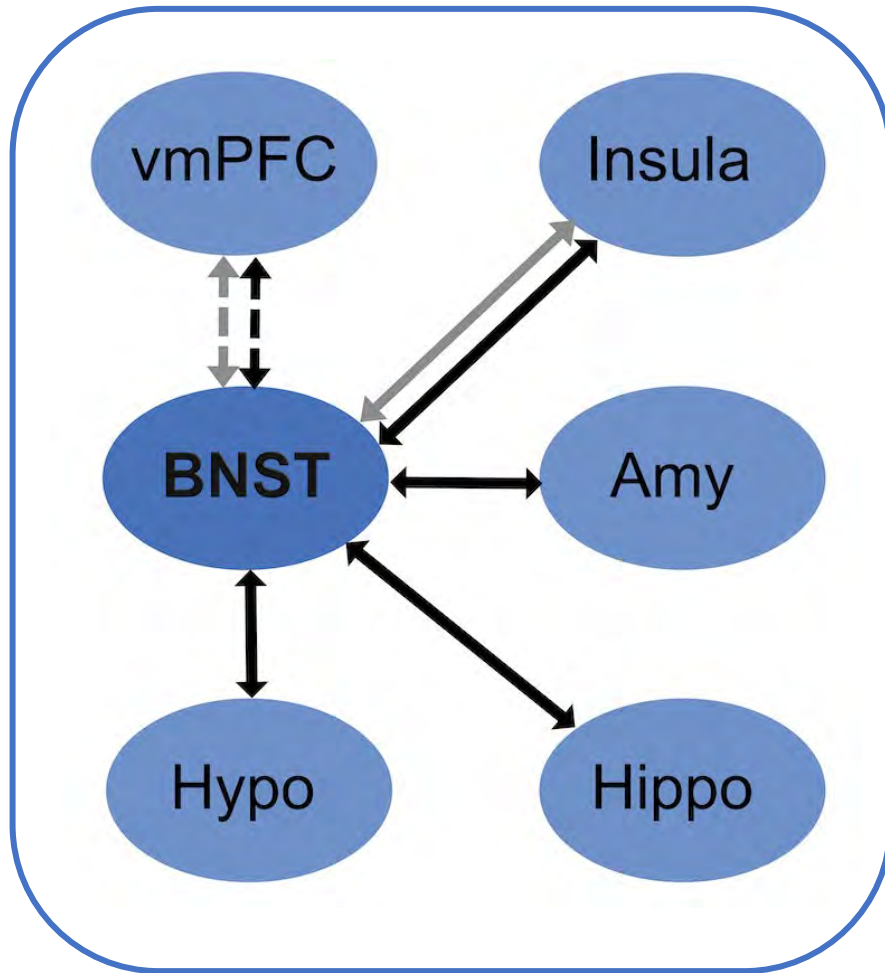
Unpredictable Threat (PTSD Threat > Neutral) Predictable Threat (PTSD Threat > Neutral)
Unpredictable Threat (CC Neutral > Threat) Predictable Threat (CC Neutral > Threat)

Connectivity during image phase
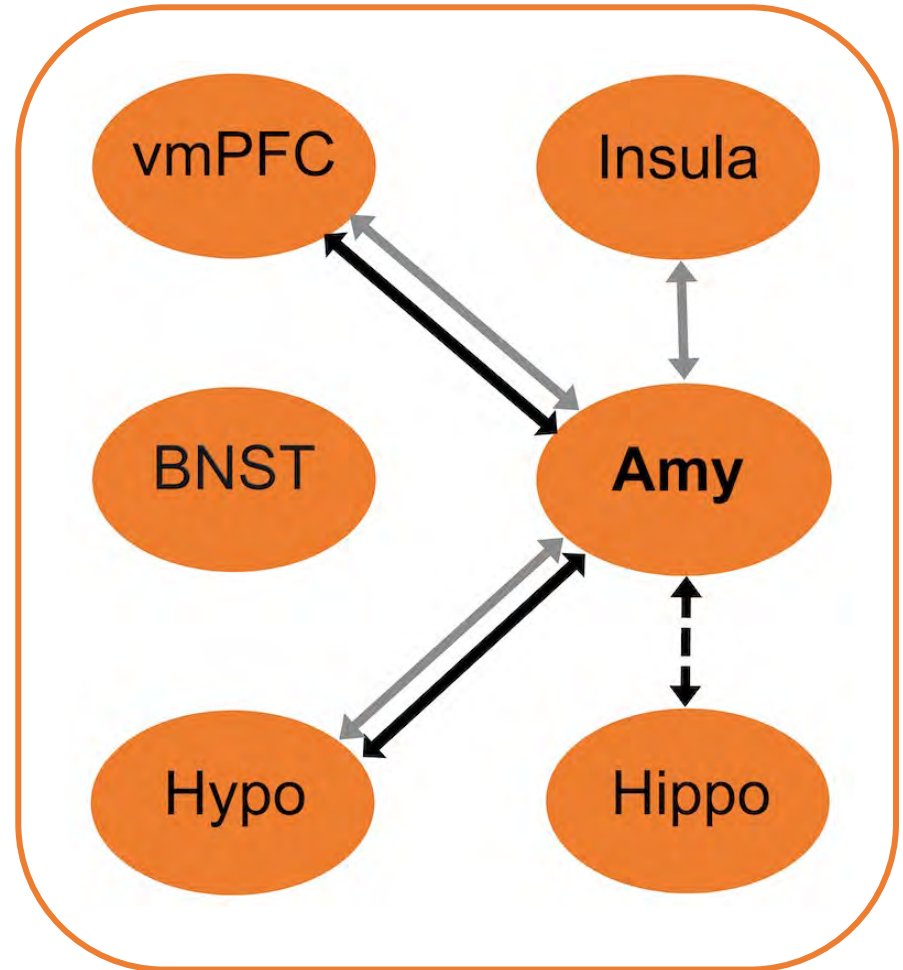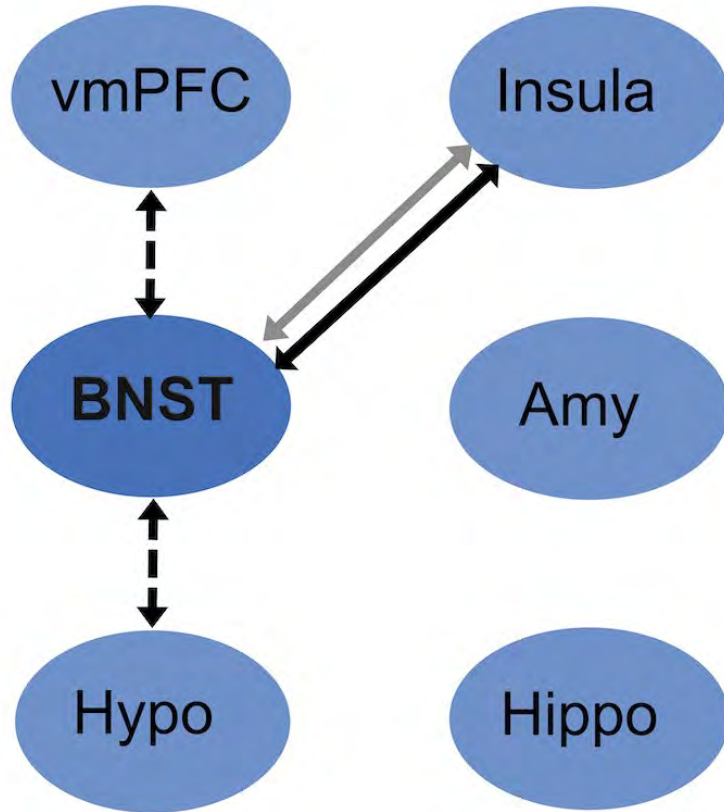
Unpredictable Threat (PTSD Threat > Neutral) ⟷
Predictable Threat (PTSD Threat > Neutral) ⟷
Unpredictable Threat (CC Neutral > Threat) ⟷
Predictable Threat (CC Neutral > Threat) ⟷

Activation and connectivity in PTSD

Stronger BNST activation to unpredictable and predictable threat cues and images

Widespread alterations in BNST and amygdala connectivity

Differences by phase: more BNST disruptions during anticipation more amygdala disruptions during image viewing

What is the role of childhood trauma on brain response to unpredictable threat?

Child maltreatment is a significant risk factor for developing PTSD.
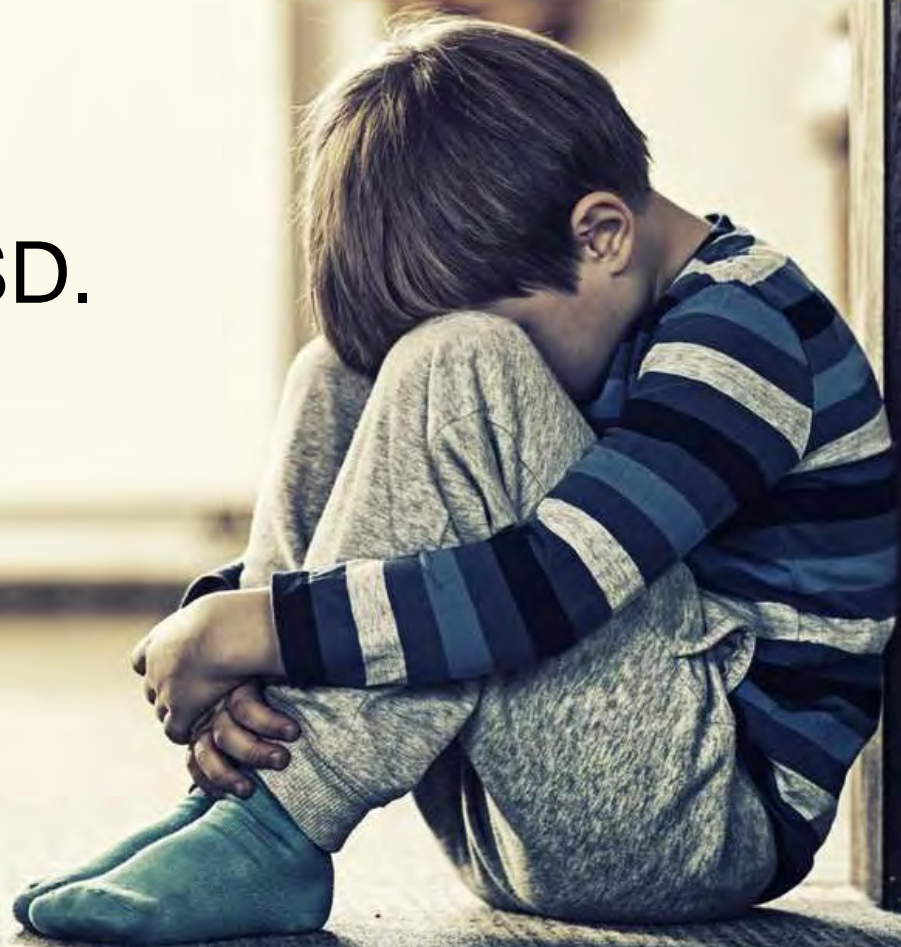
Sample characteristics

	PTSD	Trauma-exposed controls	Healthy controls
👥	46	31	13
♂	96% men	77% men	85% men
🌍	75% white	85% white	85% white
🧠	Current PTSD with combat as the primary trauma	No current or lifetime psychiatric disorders	No current or lifetime psychiatric disorders
💊	37% SSRI/SNRI or gabapentin	10%	0%

Childhood trauma questionnaire

Emotional abuse

Emotional neglect

Physical abuse

Physical neglect

Sexual abuse

Bernstein et al (2003) Child Abuse & Neglect

Childhood trauma scores by group
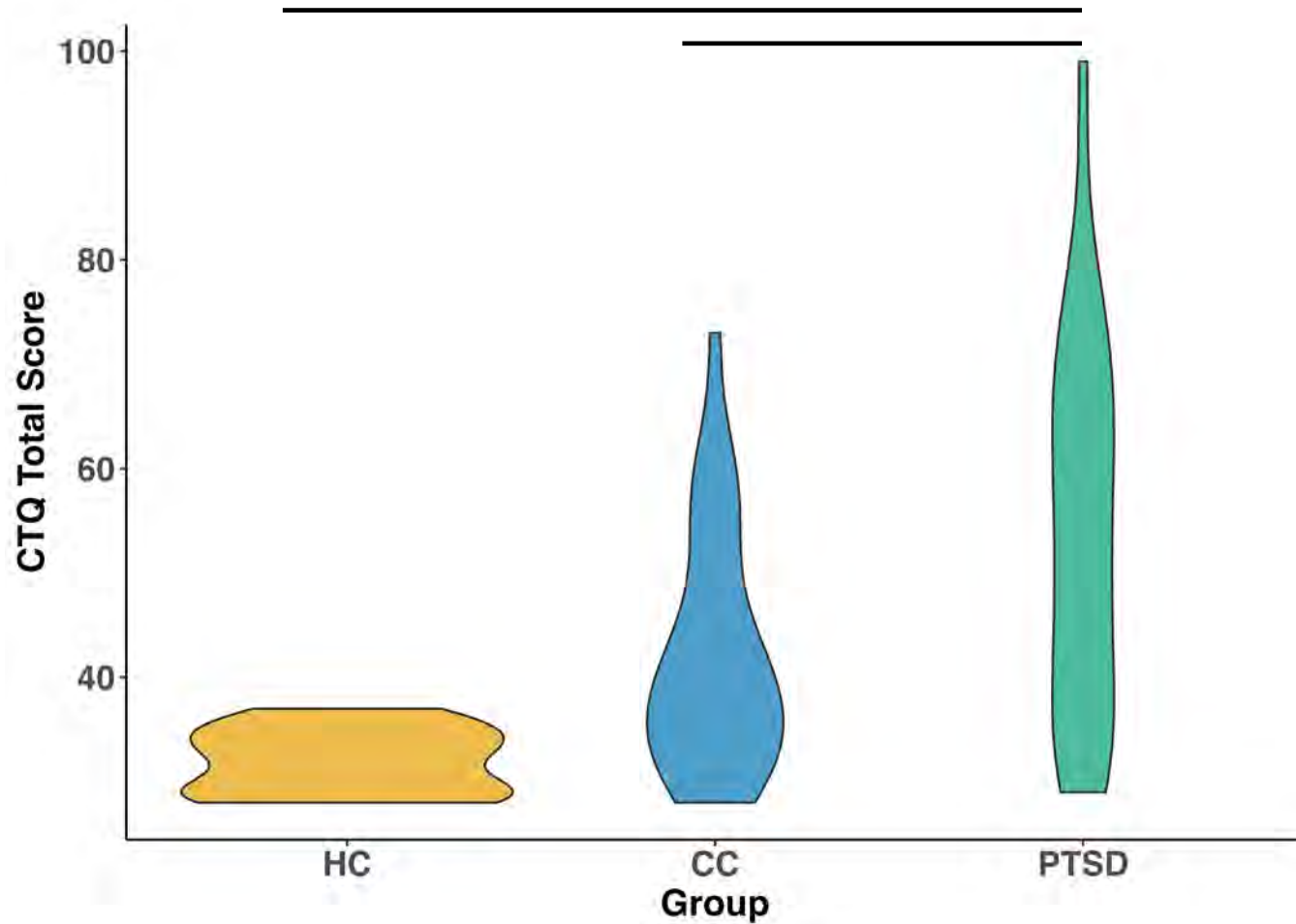
Correlation between childhood trauma and self-reported PTSD symptoms (PCL-5)
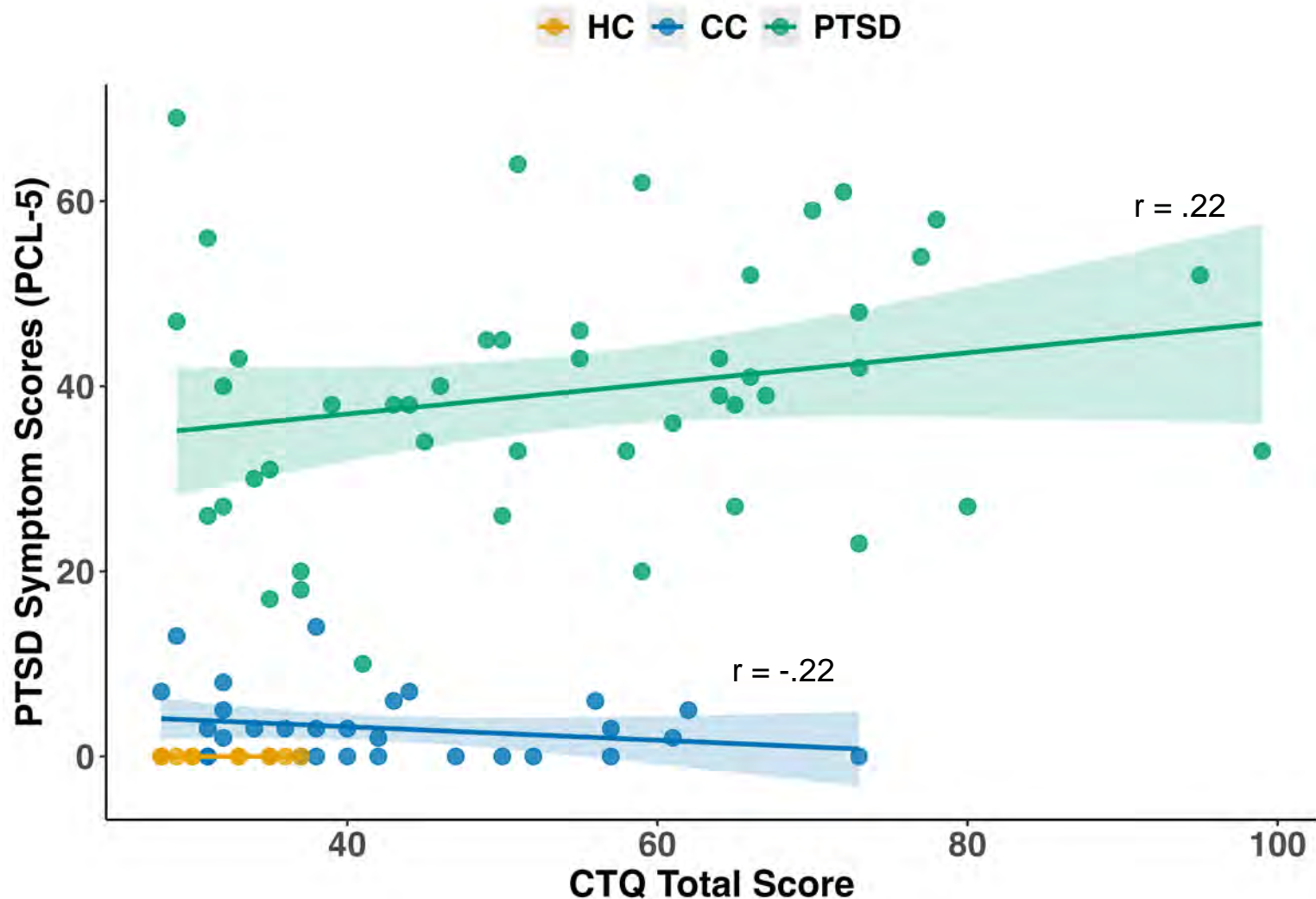
Correlation between CTQ scores and clinician interview symptoms (CAPS-5)
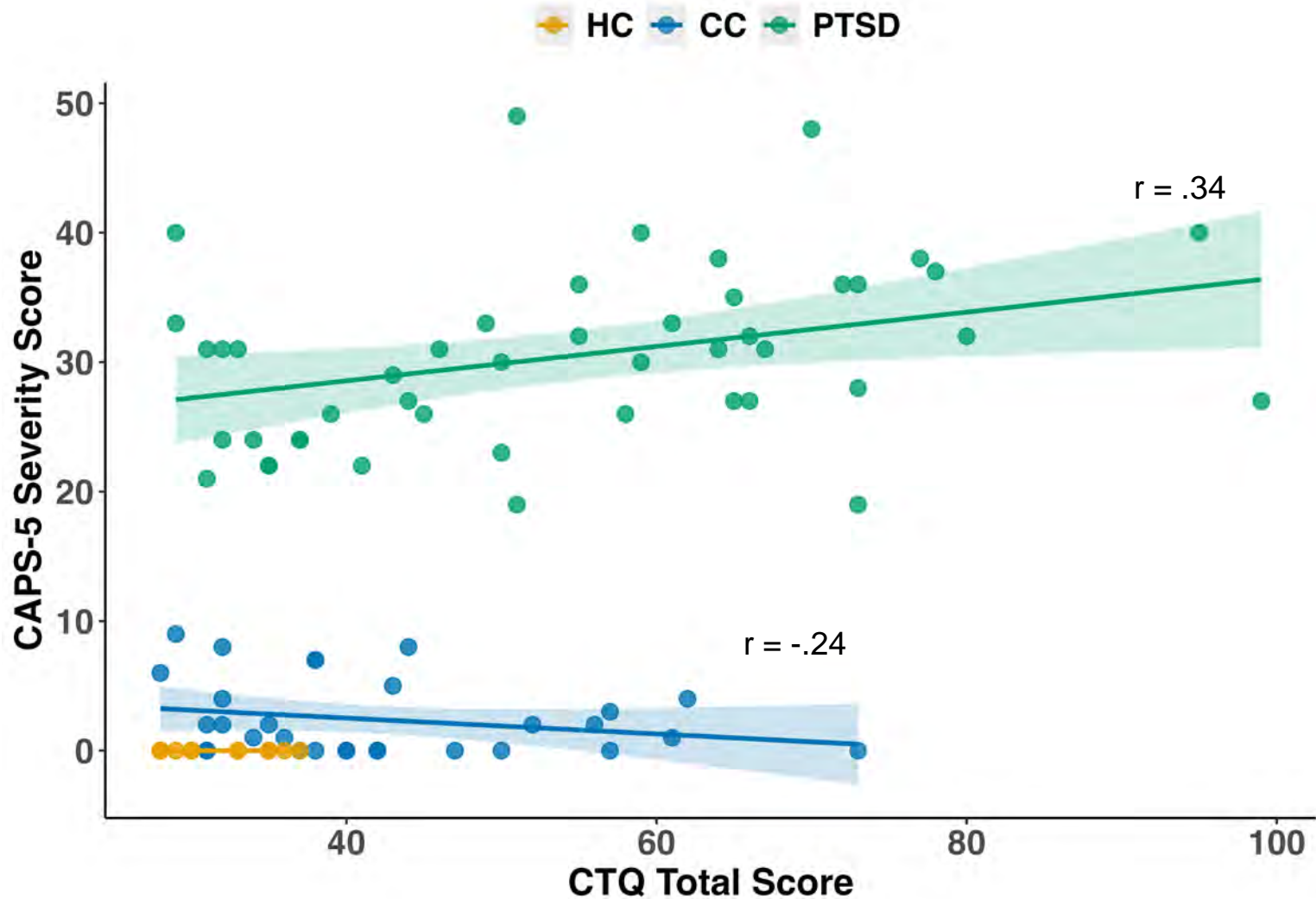
Does childhood trauma predict BNST or amygdala activation during threat anticipation?

Childhood trauma is associated with BNST and amygdala activation to unpredictable threat anticipation
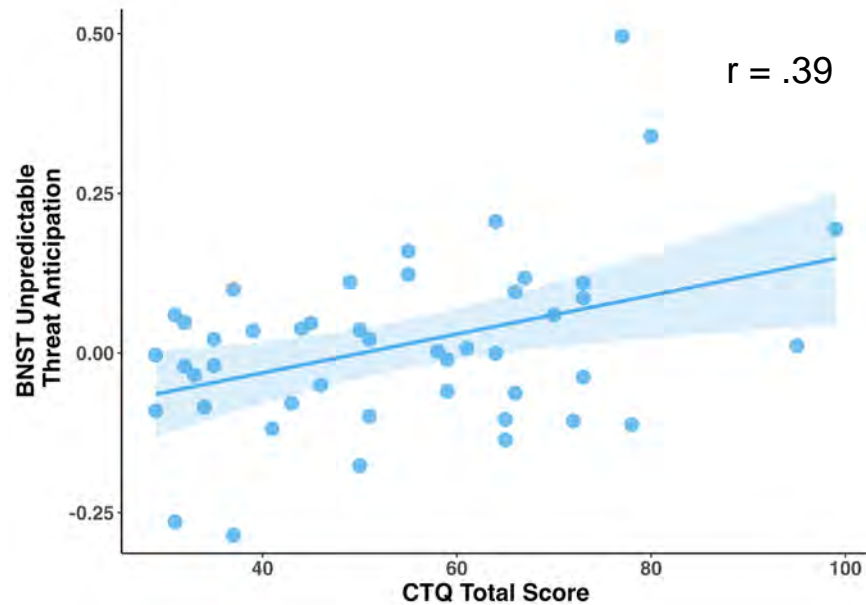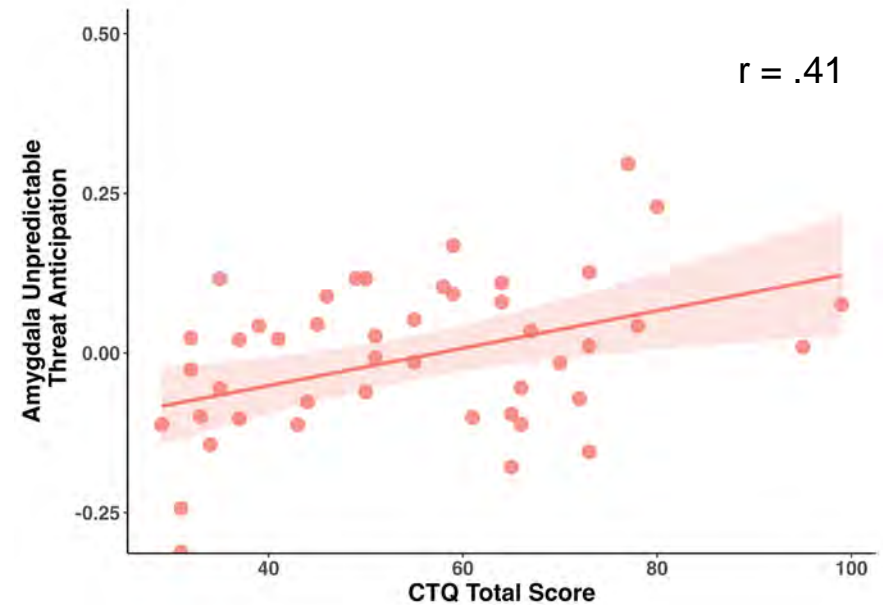
*correlations remain significant after controlling for CAPS severity or PCL-5 scores and are largely driven by response to unpredictable threat

BNST network
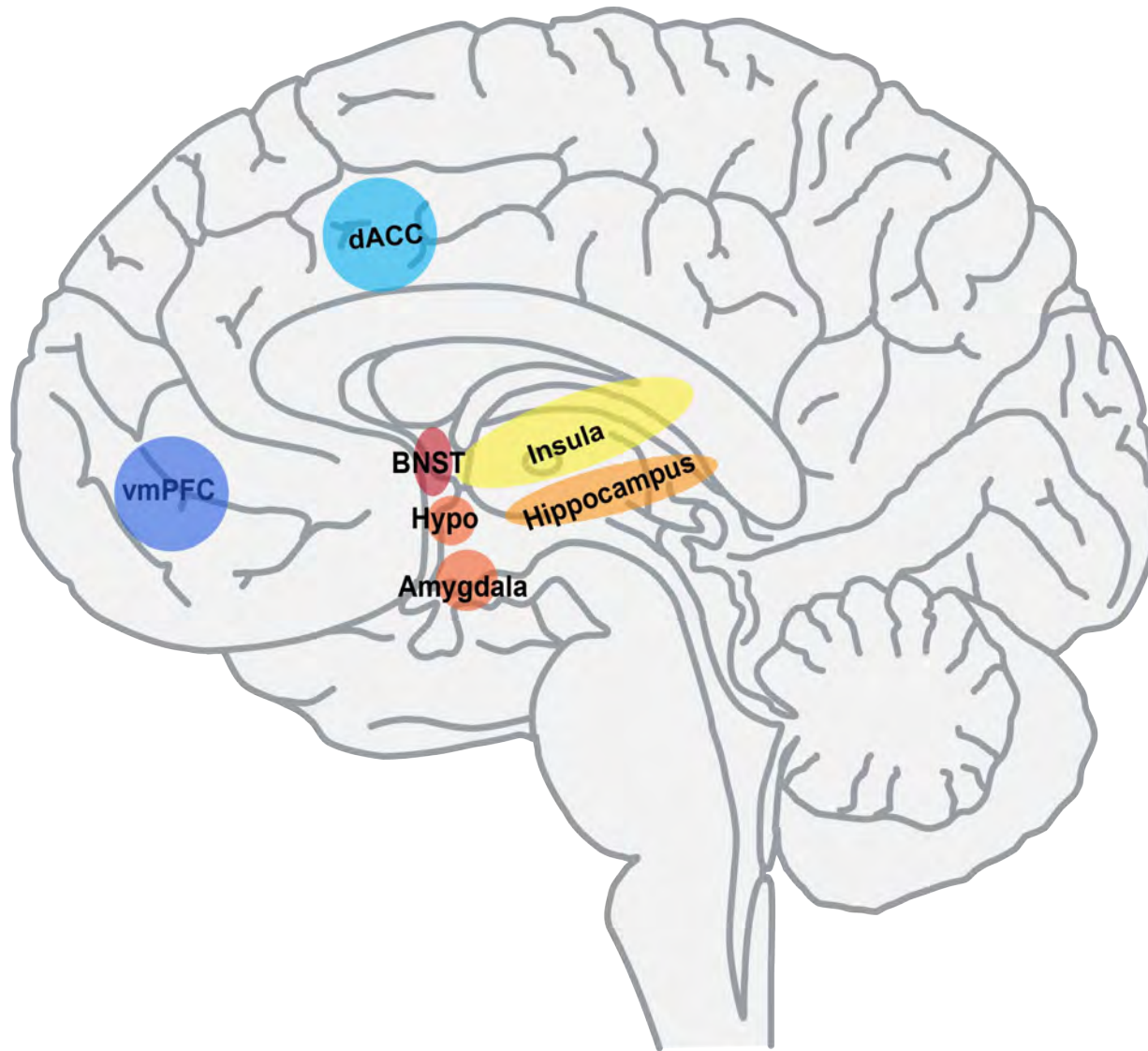
Childhood trauma is associated with unpredictable threat anticipation across the BNST network

Unpredictable Threat Anticipation

	BNST	Amygdala	Hippocampus	Hypothalamus	Insula	dACC	vmPFC
PTSD	☆ 0.39	☆ 0.41	☆ 0.45	☆ 0.4	☆ 0.34	0.25	☆ 0.41
CC	-0.02	0.24	0.27	-0.1	-0.12	-0.12	0.17

Pearson r
0.50
0.25
0.00
-0.25

Predictable Threat Anticipation

	BNST	Amygdala	Hippocampus	Hypothalamus	Insula	dACC	vmPFC
PTSD	0.16	0.26	0.28	0.29	0.08	-0.13	0.06
CC	0.17	0.22	0.27	0.13	0	0.09	0.25

Pearson r
0.50
0.25
0.00
-0.25
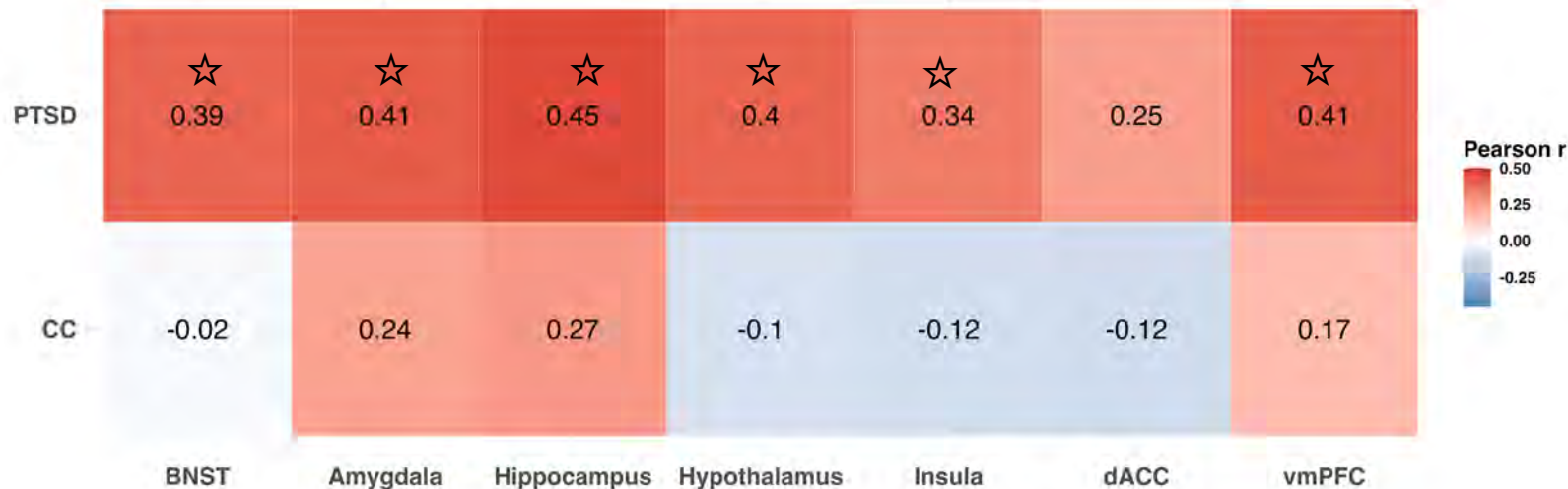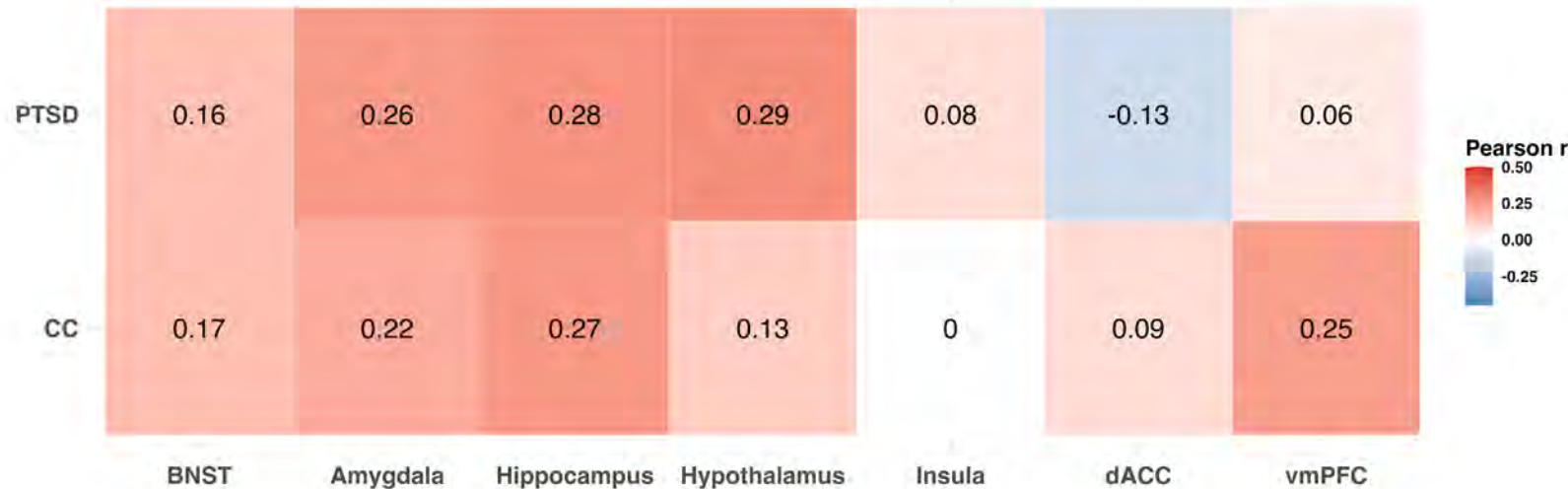
Is the relationship with brain activation specific to a subtype of childhood trauma?

CTQ subscale scores for PTSD group
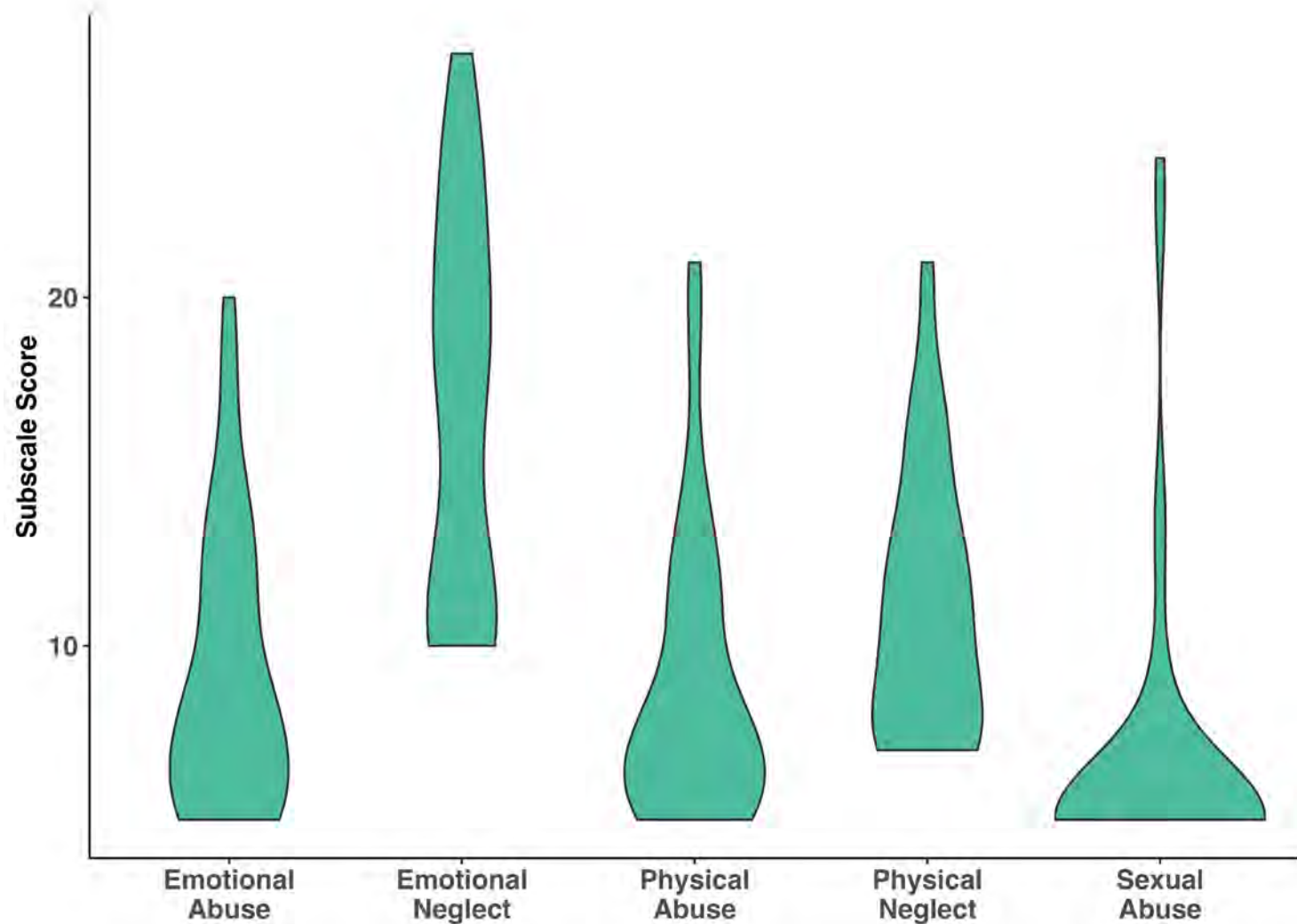
Correlation between activation to unpredictable threat and childhood trauma subscales in PTSD

	BNST	Amygdala	Hippocampus	Hypothalamus	Insula	vmPFC
Emotional Abuse	☆ 0.34	0.27	☆ 0.33	☆ 0.37	0.22	0.22
Emotional Neglect	☆ 0.42	☆ 0.41	☆ 0.45	☆ 0.46	☆ 0.38	☆ 0.44
Physical Abuse	0.09	0.07	0.04	0.24	0.06	-0.04
Physical Neglect	0.28	☆ 0.31	☆ 0.35	0.26	☆ 0.31	0.25
Sexual Abuse	0.16	0.16	0.24	0.01	0.1	☆ 0.4

Pearson r

0.50
0.25
0.00
-0.25
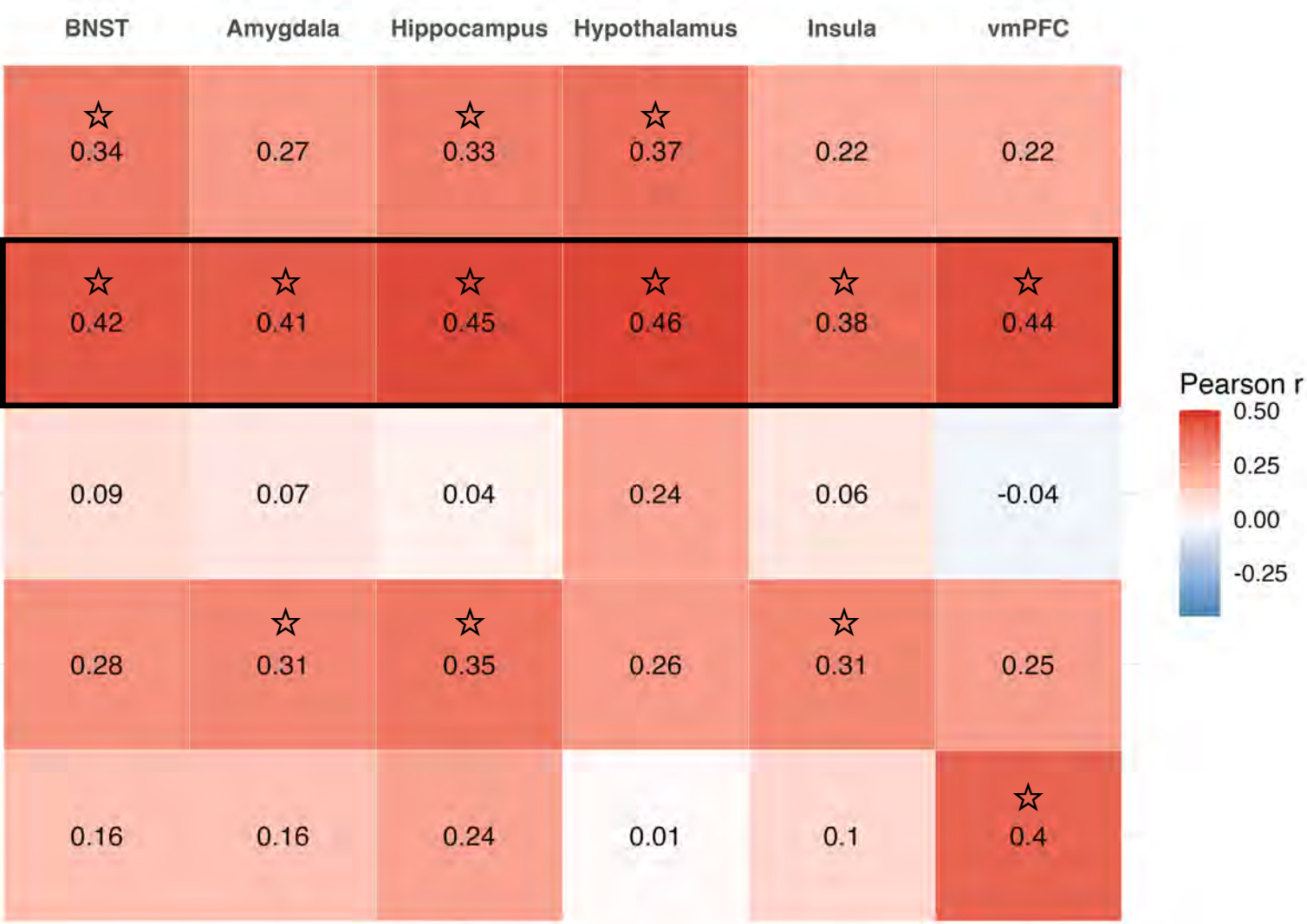
Is childhood trauma associated with cortisol levels?

Cortisol across MRI scan
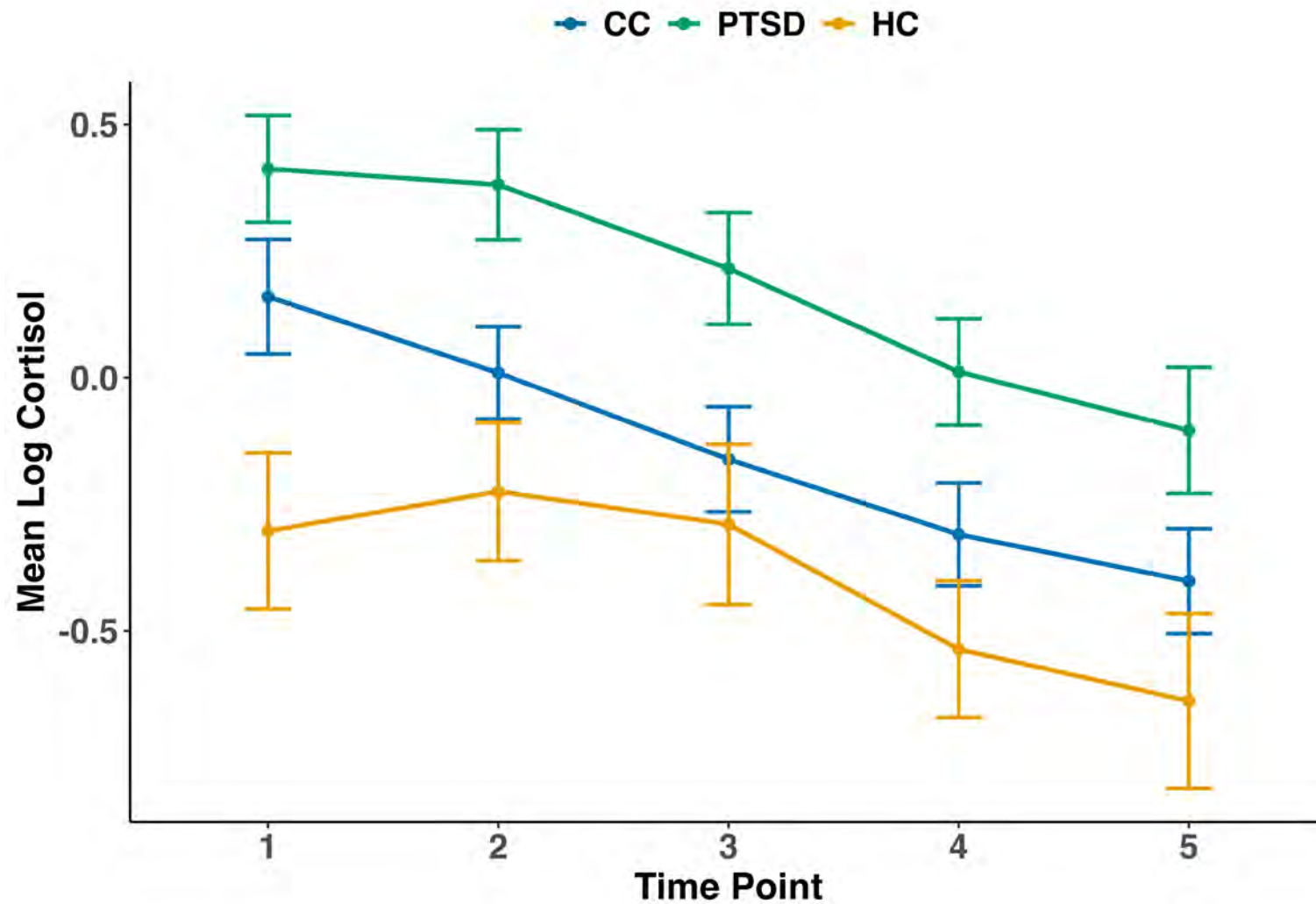
Cortisol area under the curve levels by group
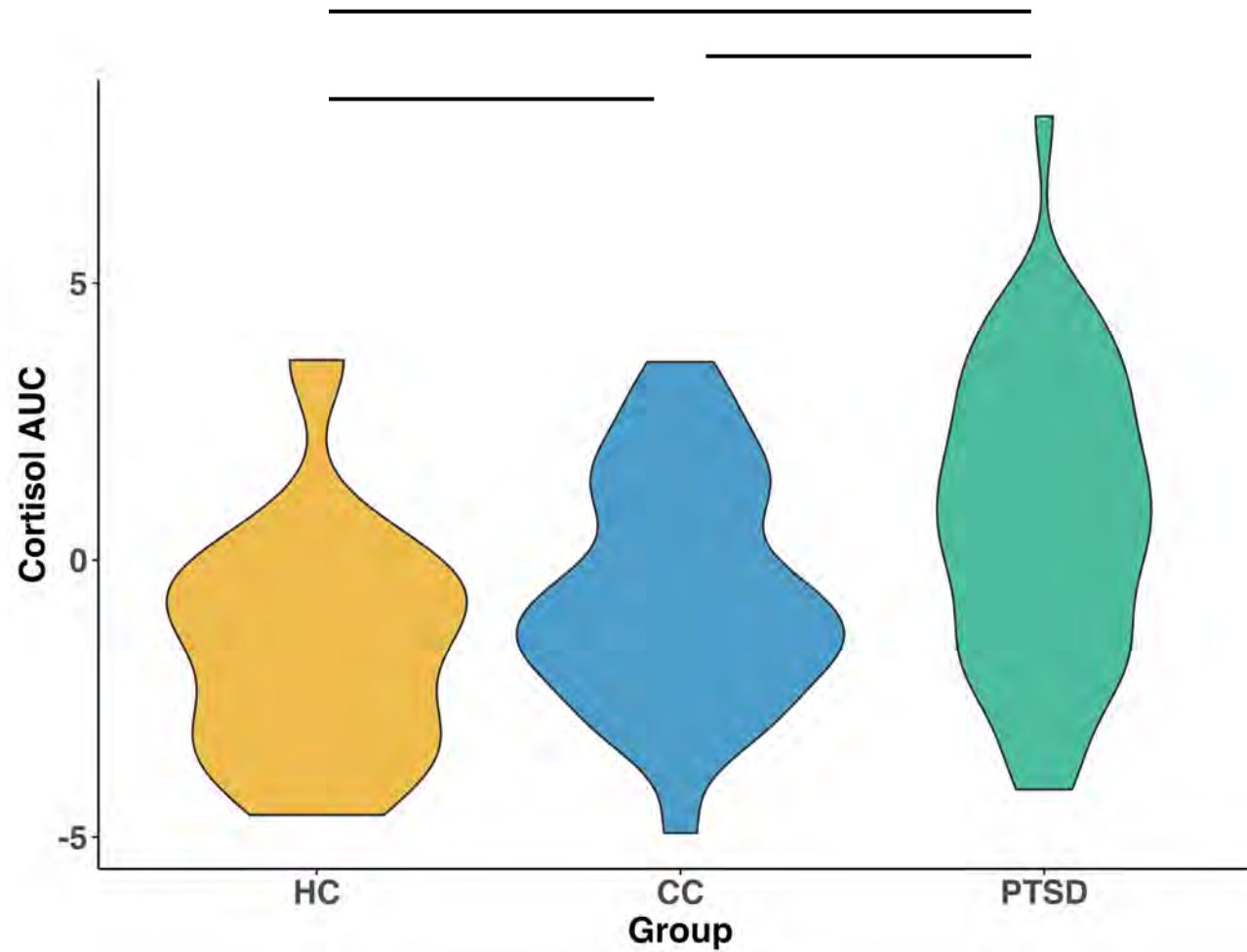
No correlation between childhood trauma and cortisol
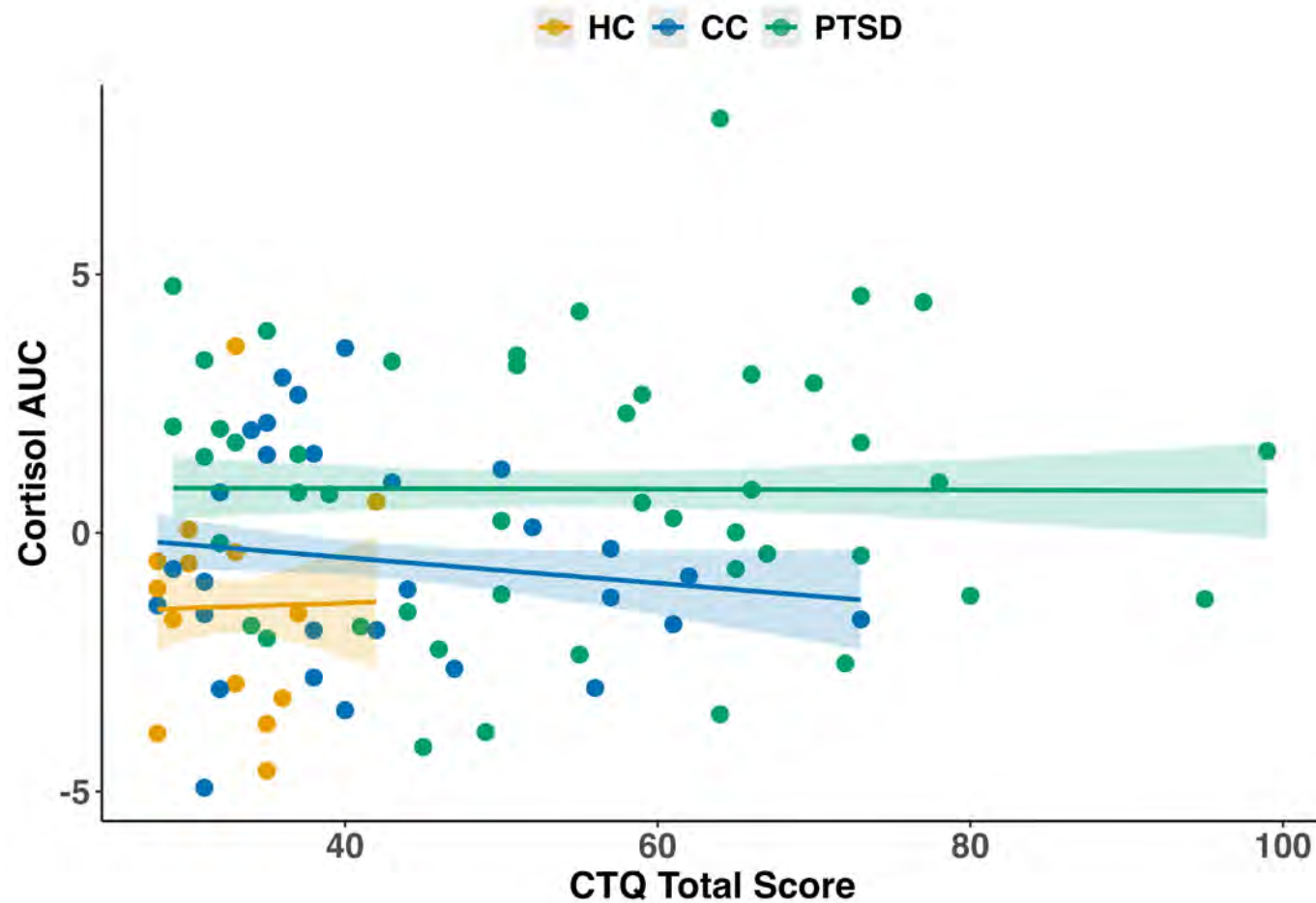
Cortisol is correlated with unpredictable threat anticipation in healthy controls

	BNST	Amygdala	Hippocampus	Hypothalamus	Insula	dACC	vmPFC
HC	0.61	0.5	0.73	0.43	0.51	0.66	0.22
PTSD	0.12	0.01	-0.06	-0.07	0.02	-0.08	0.11
CC	0.09	-0.08	-0.13	-0.15	-0.08	-0.01	-0.22

Pearson r

0.75
0.50
0.25
0.00
-0.25
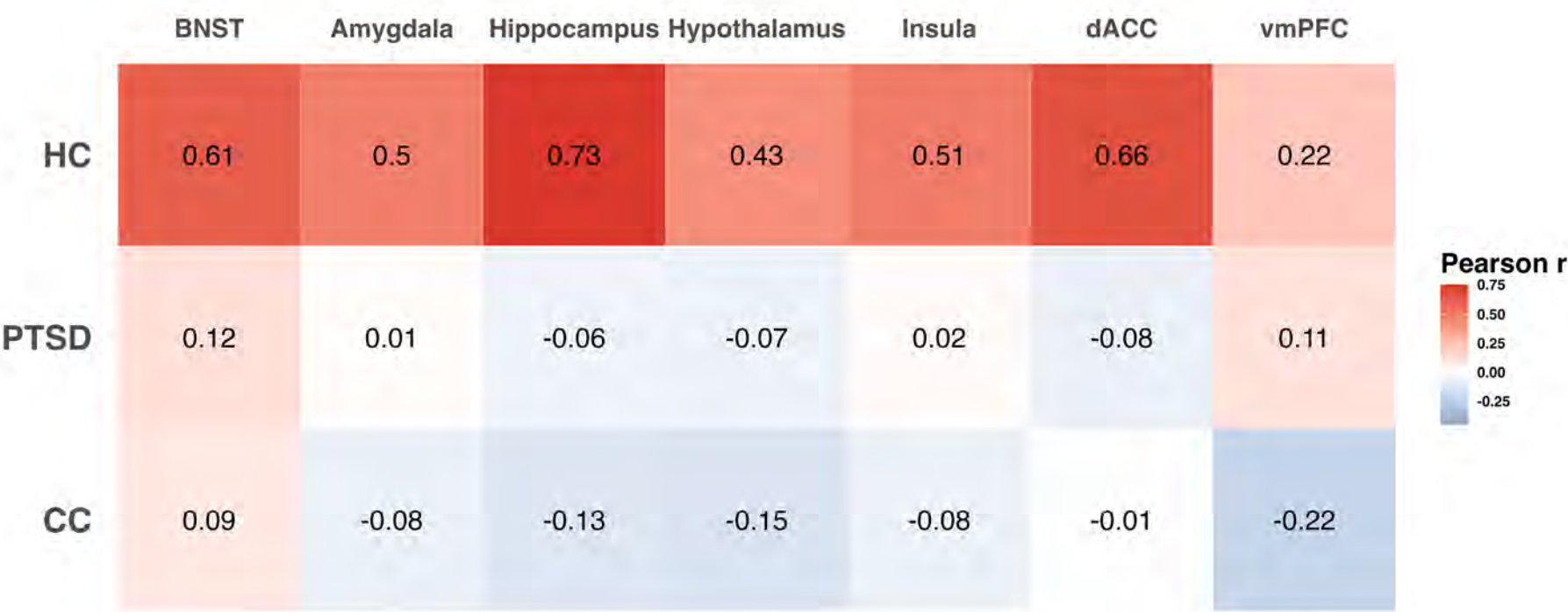
Summary

Childhood trauma was associated with stronger activation in the BNST network regions for unpredictable threat anticipation.

Childhood emotional abuse had the strongest relationships with unpredictable threat anticipation.

Cortisol was not correlated with childhood trauma.

Take home messages

PTSD was associated with BNST hyperactivation to unpredictable AND predictable threat.

PTSD was associated BNST dysconnectivity during anticipation and amygdala dysconnectivity during images.

Childhood trauma is an important predictor of altered BNST responses to unpredictable threat anticipation in PTSD.

Cortisol levels were highest in PTSD but were not associated with unpredictable threat anticipation.

Current Lab Members
Nikki Zabik, PhD
Özgün Özalay, PhD
Katelyn Kelley
Marshall Biven
Samereh Soleimani

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Lizzie Flook, MD, PhD
Kale Edmiston, PhD

Justin Theiss
Cara Bedock
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Alec Seidenberg
Jesse Oler
April Seay, MD

Marina Zaky, MD
Erin Miller
Ariane Huet
Adaora Mgboh
Jessica Stump
Izzy Vargas

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Meg Benningfield, MD
Stephan Heckers, MD
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Baxter Rogers, PhD
David Zald, PhD
Neil Woodward, PhD
Uma Rao, MD
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NIMH
Danny Pine, MD