PTSD: The Brain Basis of Susceptibility

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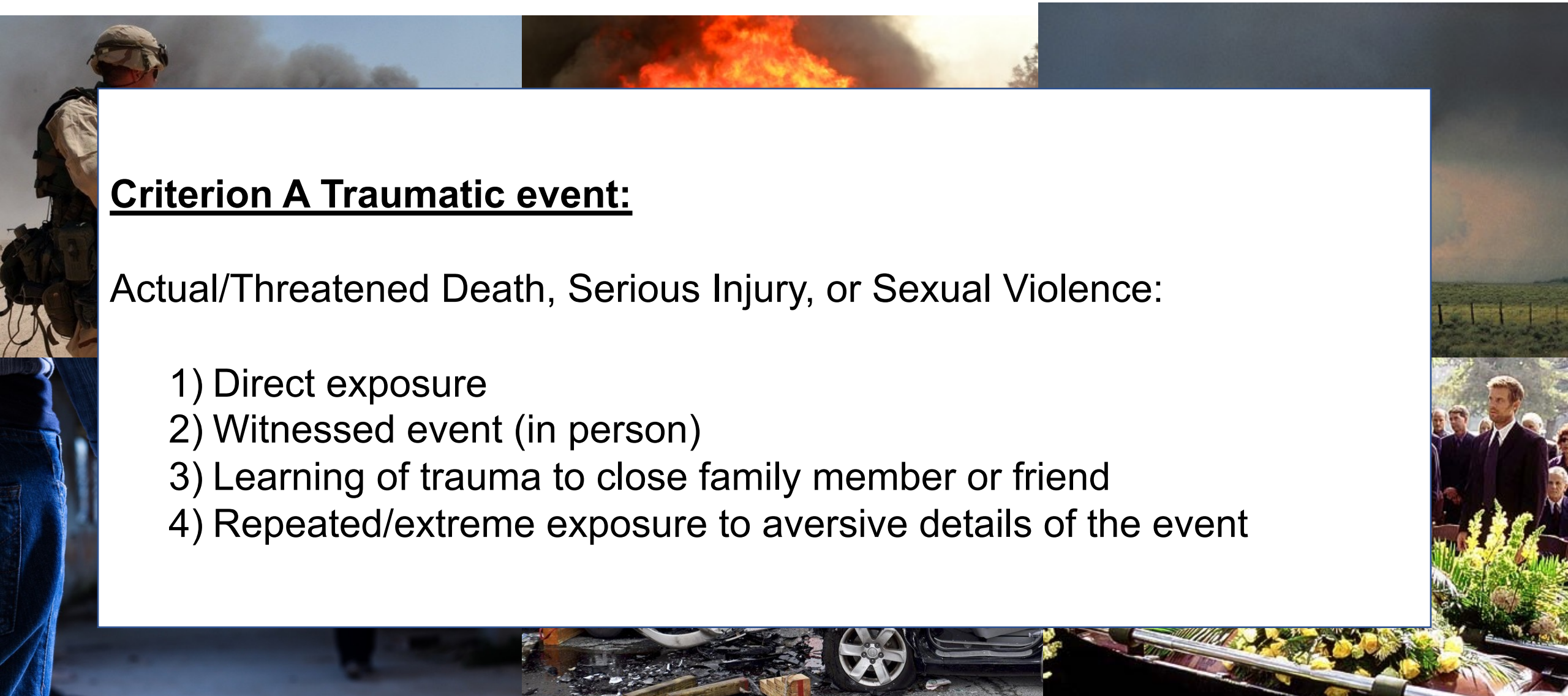
HARVARD MEDICAL SCHOOL
AFFILIATE

Trauma…



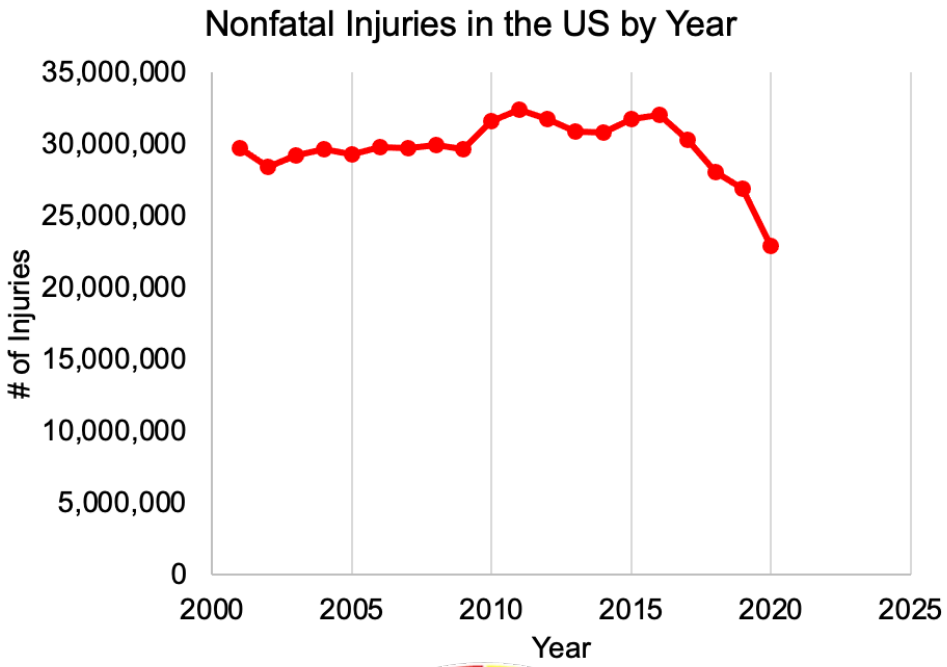
<u>Criterion A Traumatic event:</u>

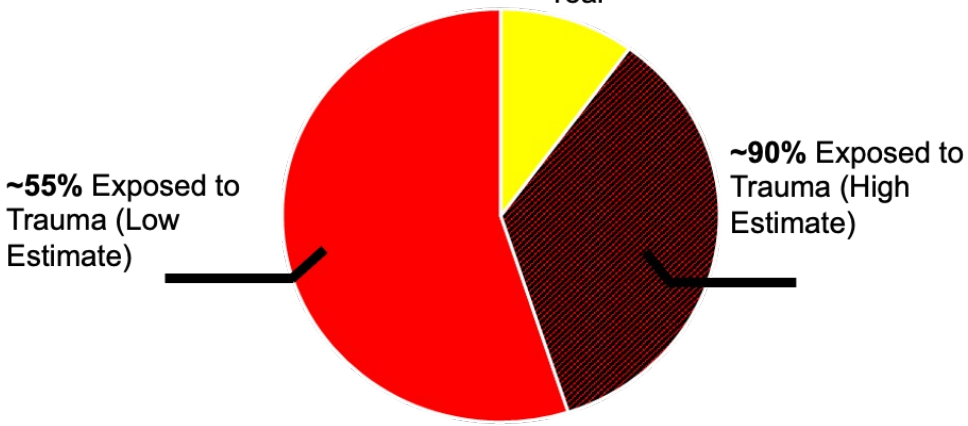
Actual/Threatened Death, Serious Injury, or Sexual Violence:

1) Direct exposure
2) Witnessed event (in person)
3) Learning of trauma to close family member or friend
4) Repeated/extreme exposure to aversive details of the event

Trauma…

…is highly prevalent





… can be highly deleterious

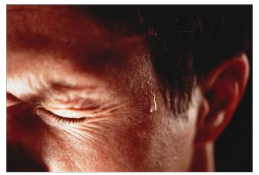
PTSD

Intrusive memories

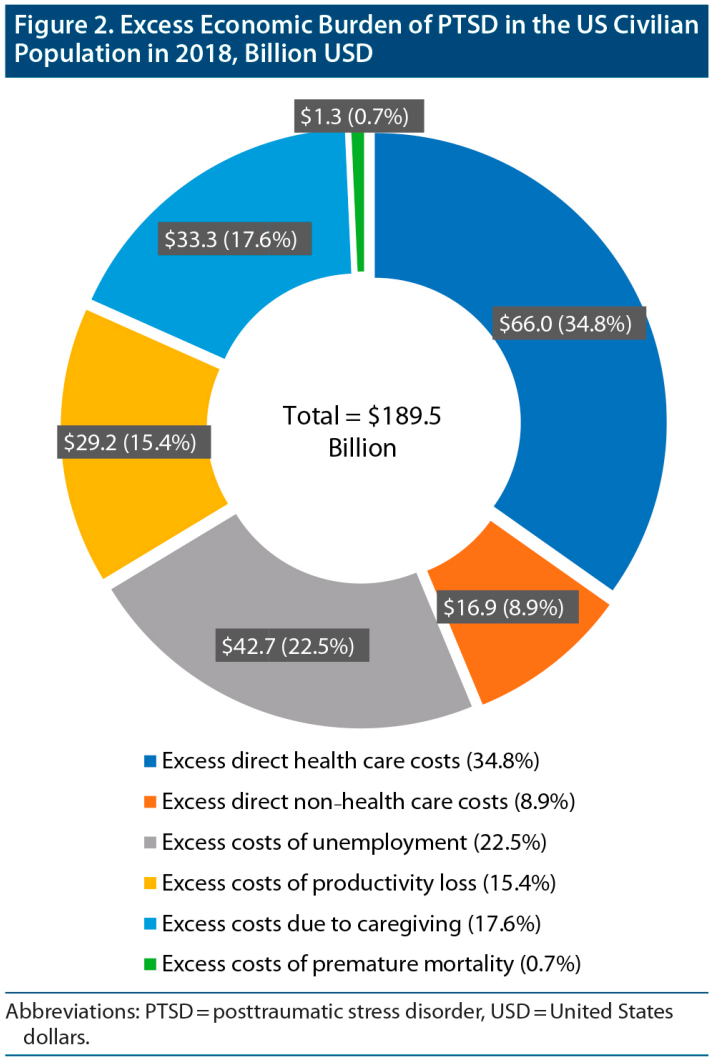
Avoidance

Negative thoughts /beliefs

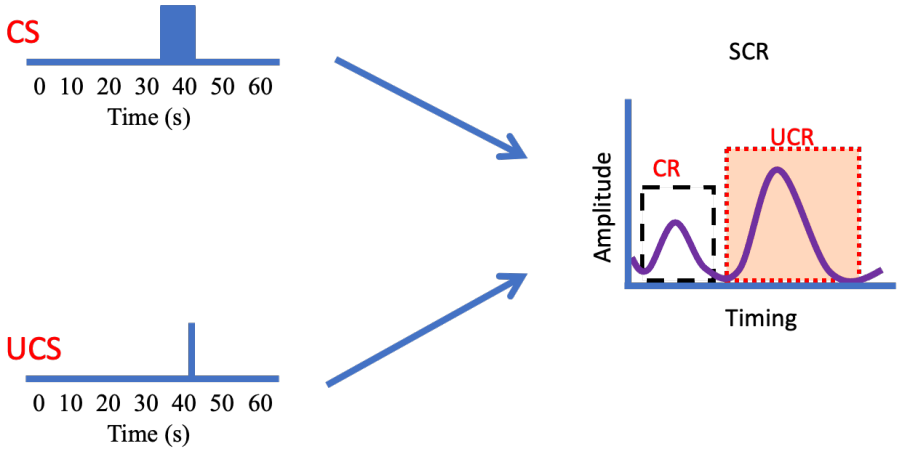
Hyperarousal

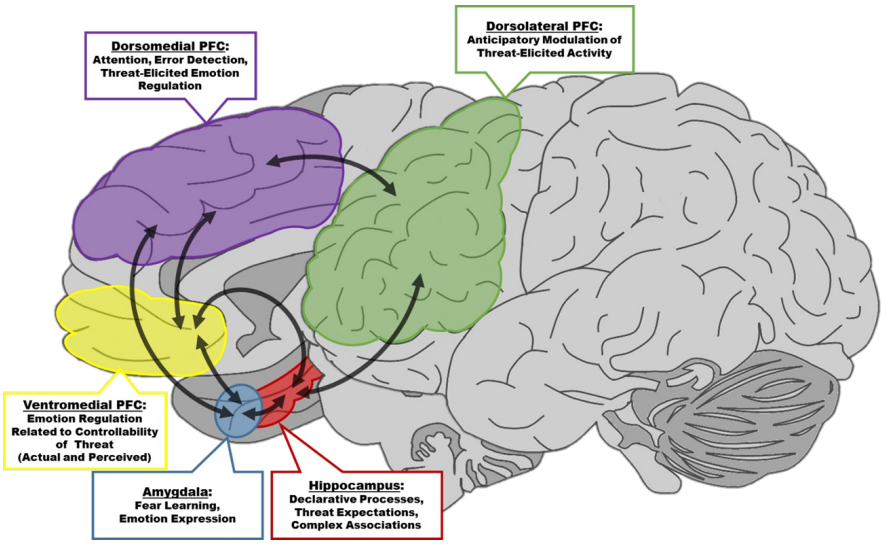


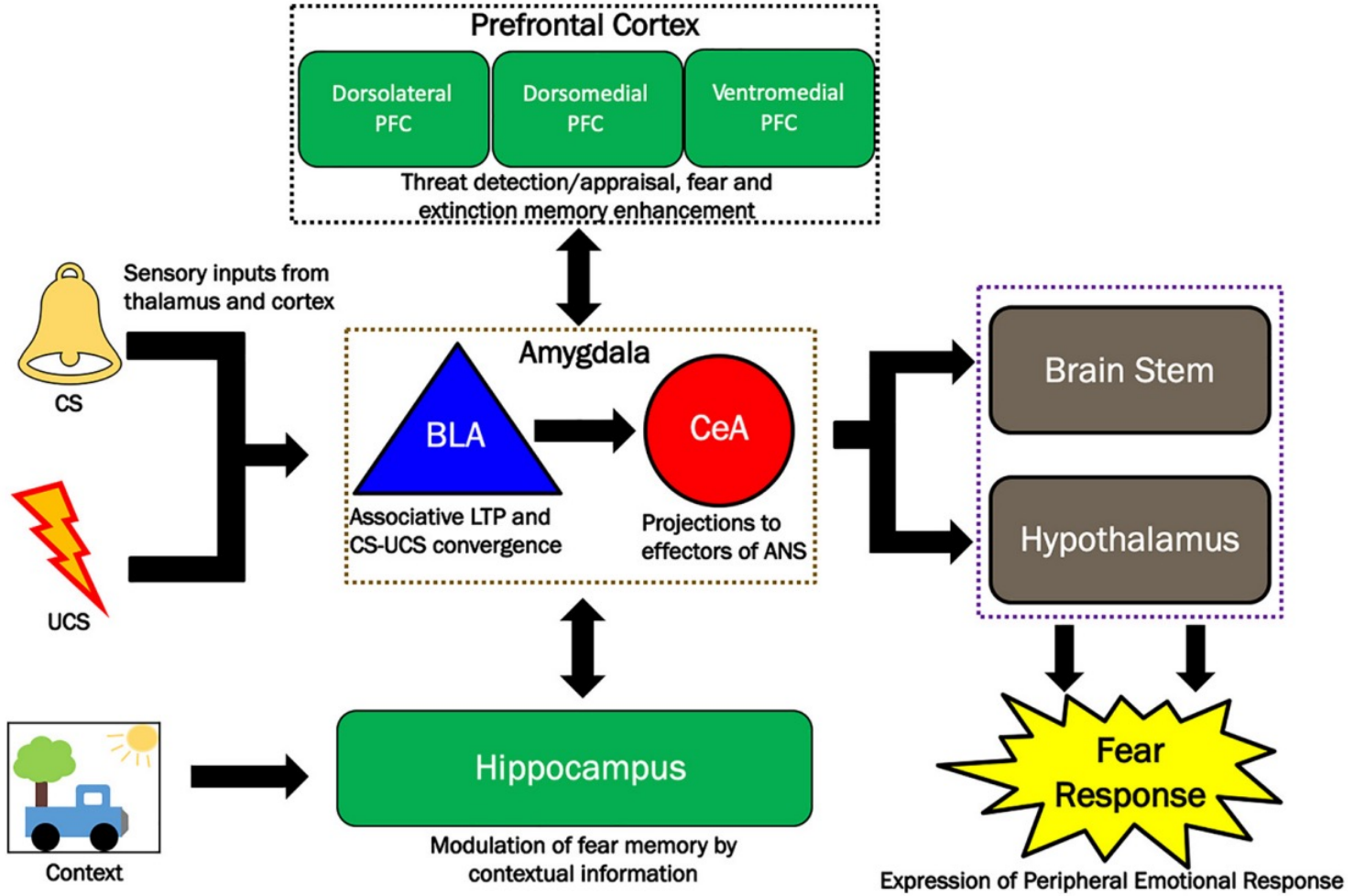
… can be costly



Neural circuitry of threat learning



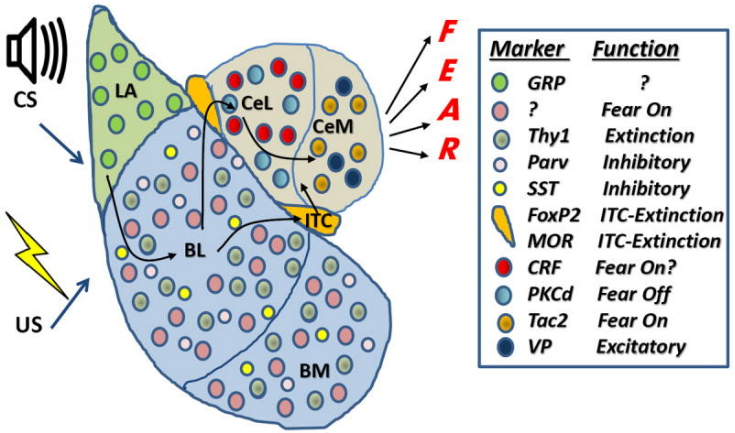




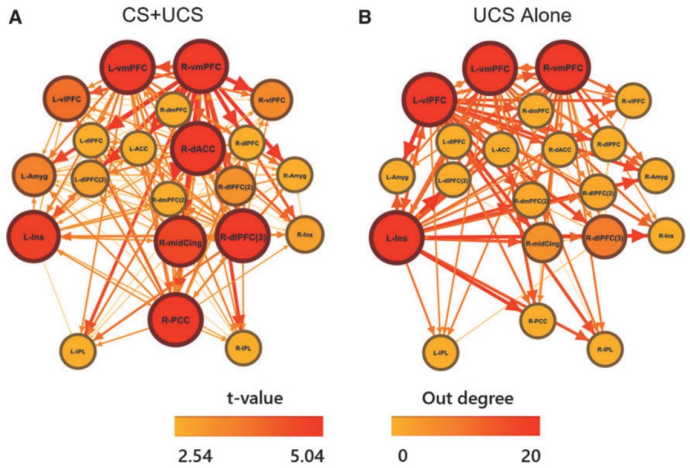
Neural circuitry of threat learning

Animal models

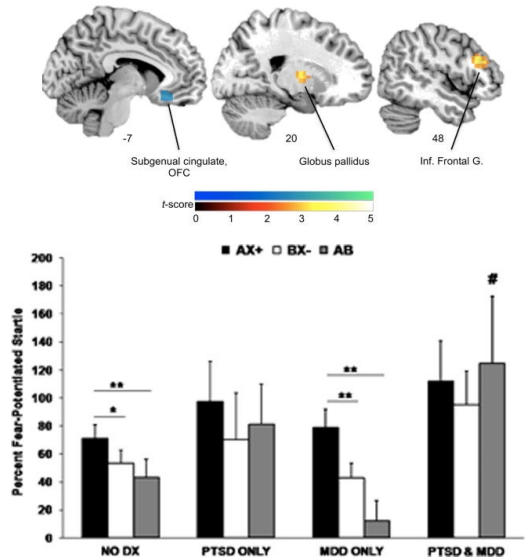
Select Neuronal Populations in Amygdala



Human neuroscience

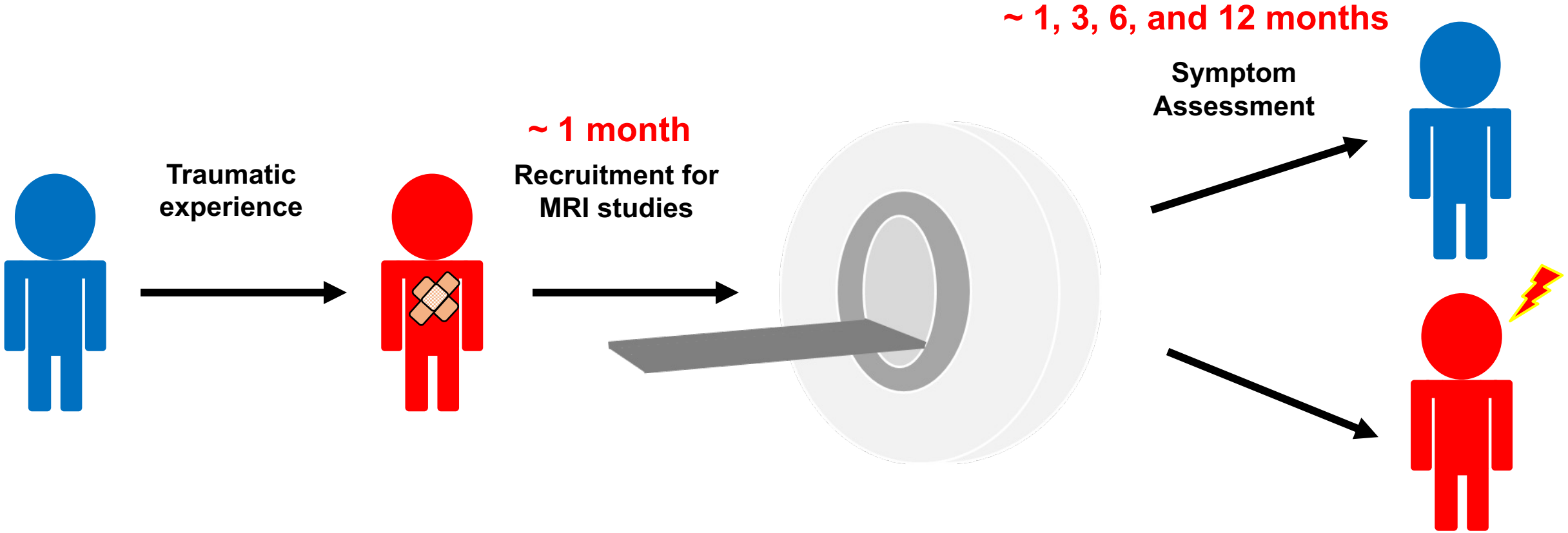


Psychiatric Relevance

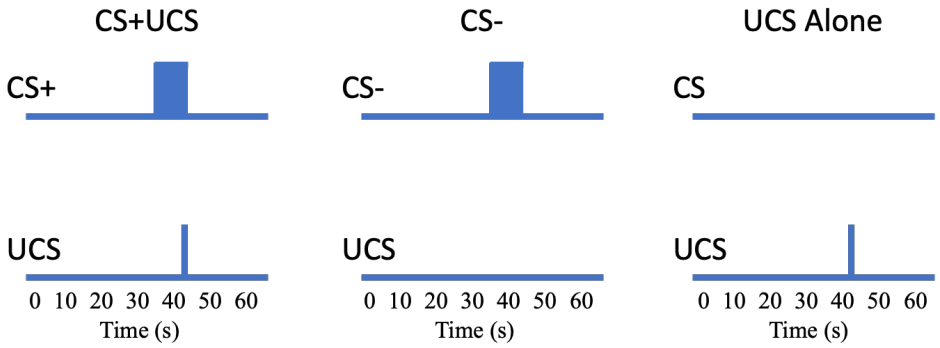


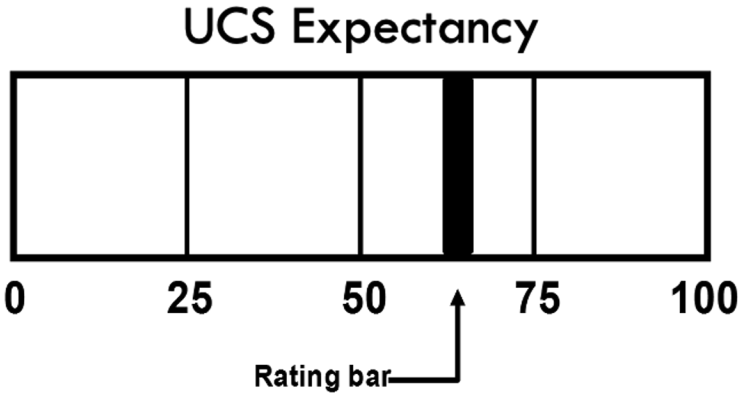
Gafford & Ressler, 2016; Goodman et al., 2021; Jovanovic et al., 2011; Stevens et al., 2013

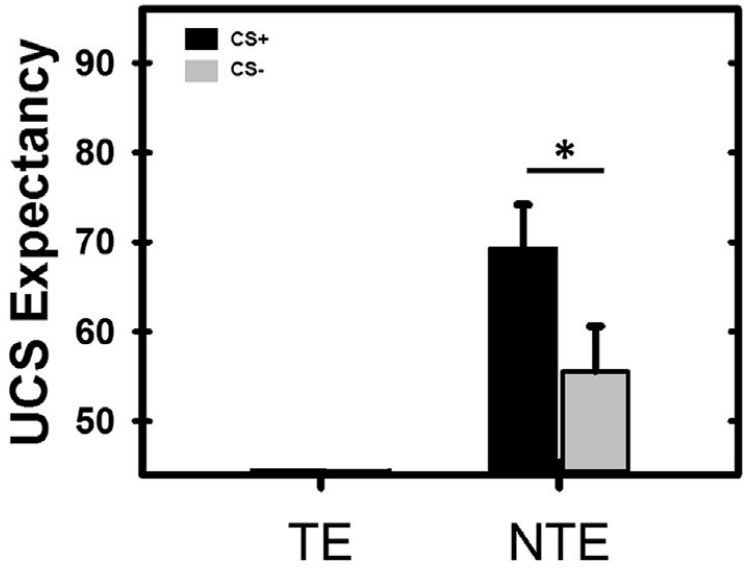
Neuroimaging in the early aftermath of trauma

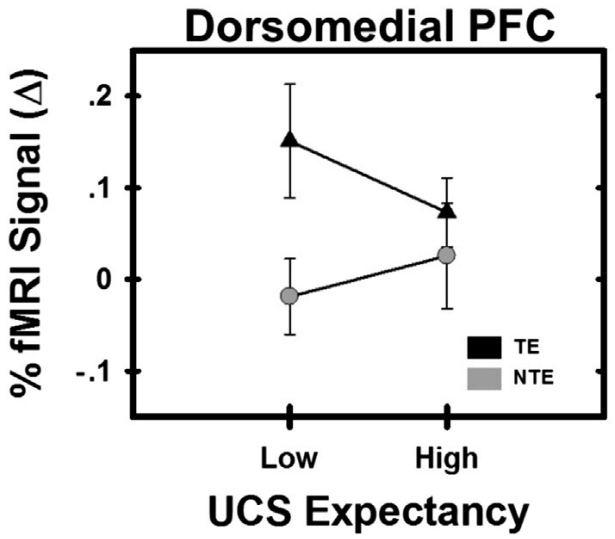


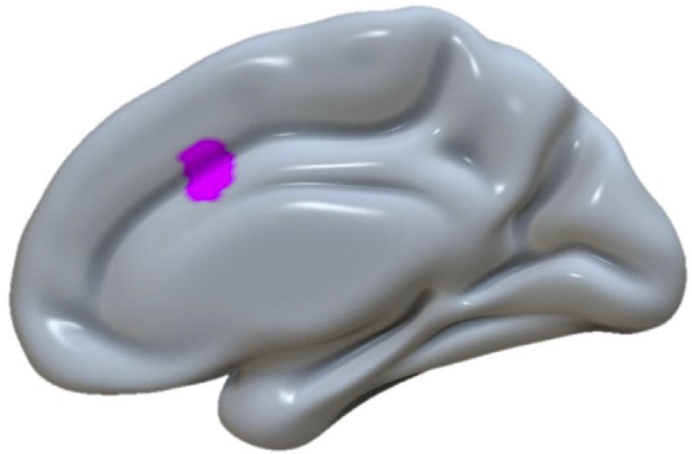
Traumatic stress disrupts threat learning





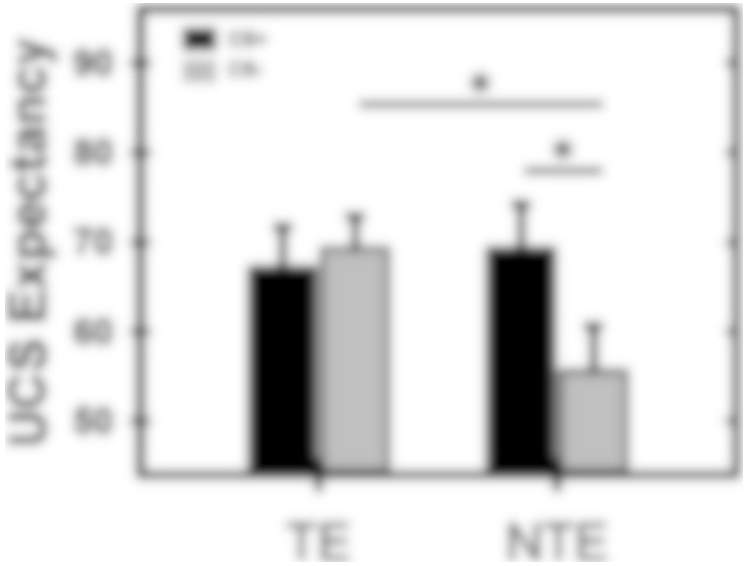


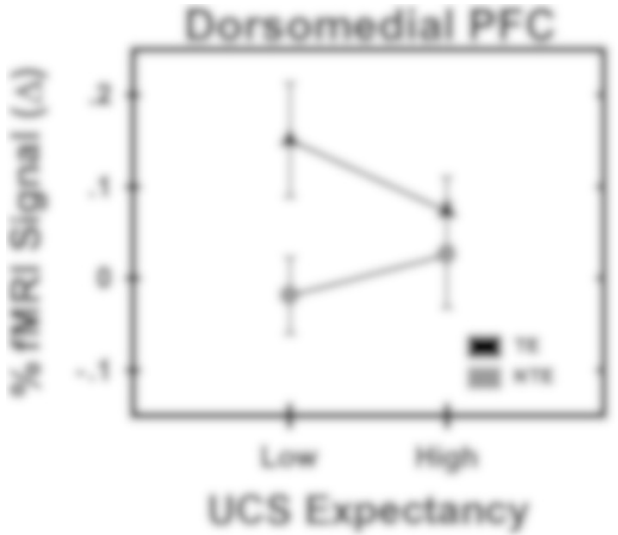


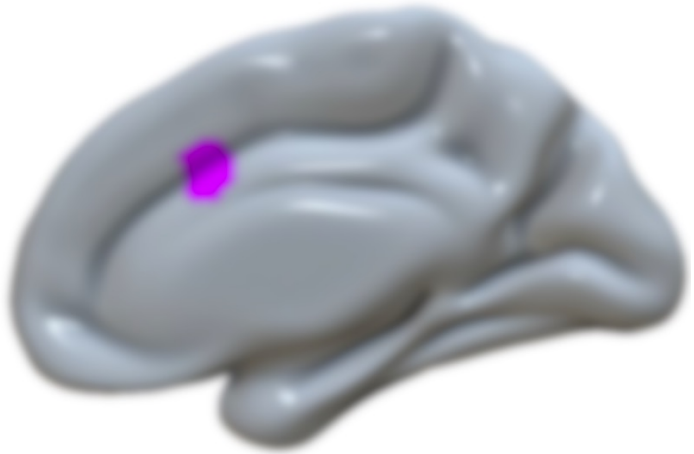


Traumatic stress disrupts threat learning

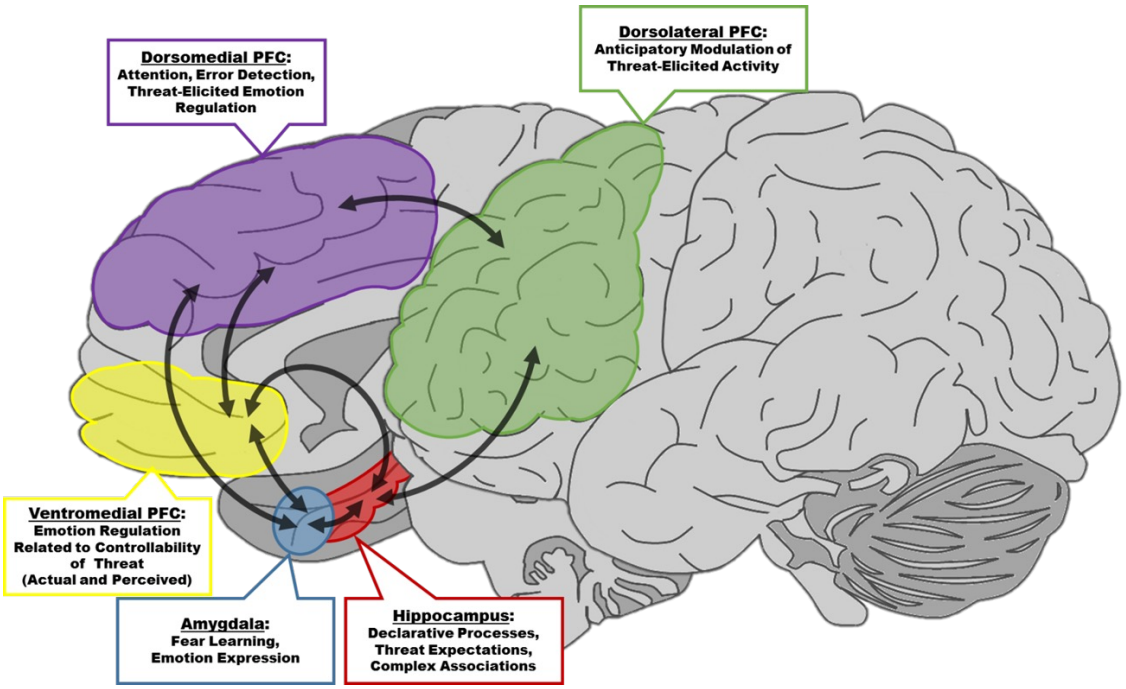
Trauma can lead to altered understanding of safety, potentially driven by disengagement of top-down emotional control regions

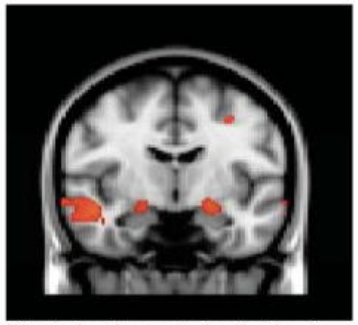




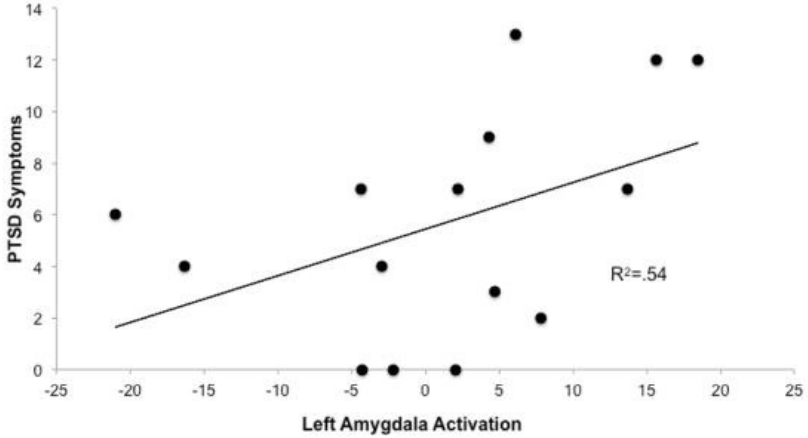


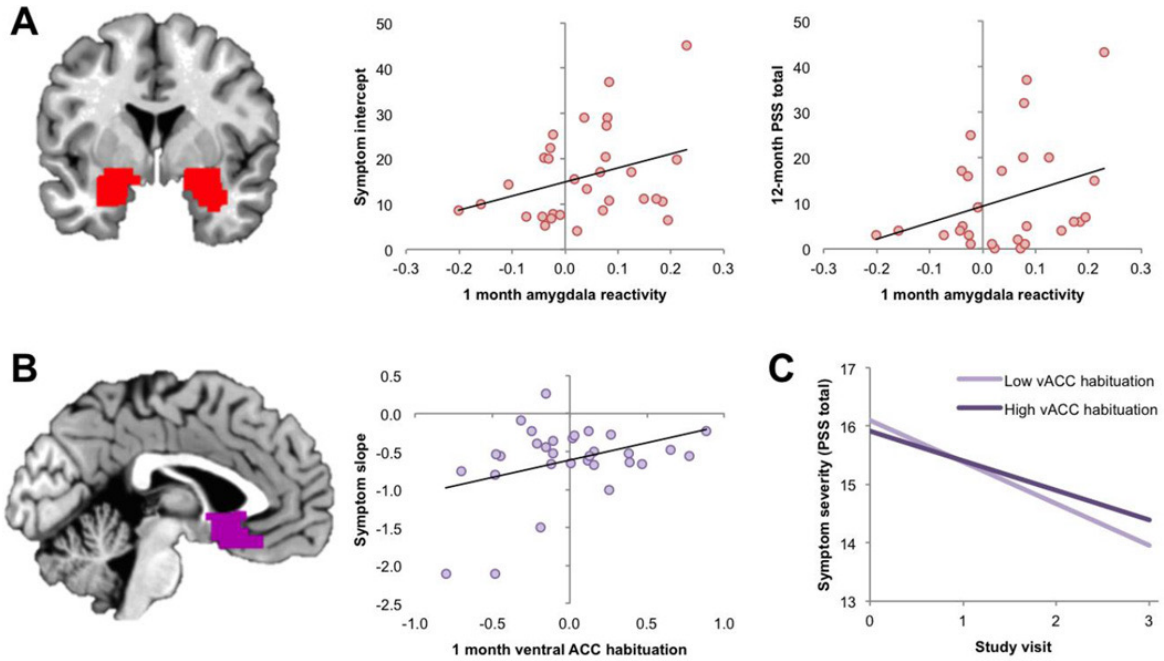
Threat neurobiology predicts future PTSD symptoms





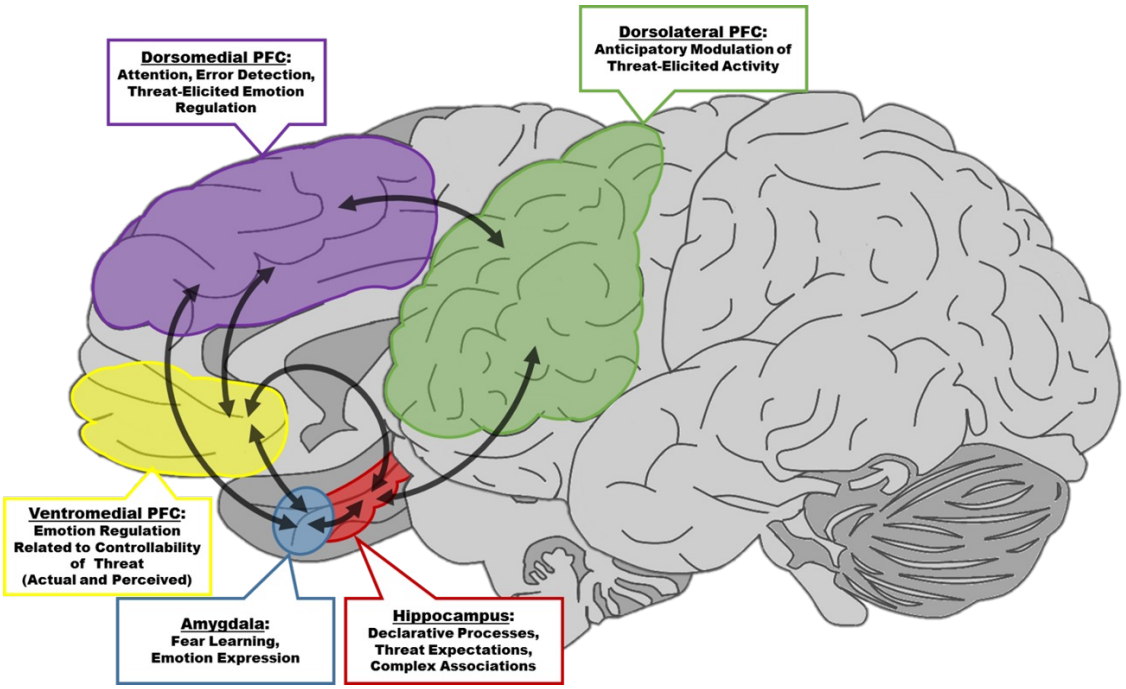
Cluster-level corrected activation for look negative > look neutral contrast. Amygdala activation in the left but not right hemisphere was significantly associated with PTSD symptoms.

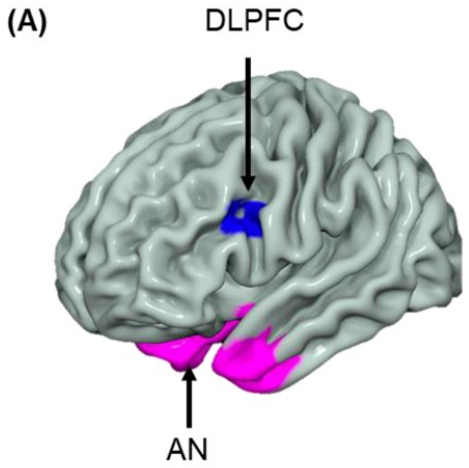


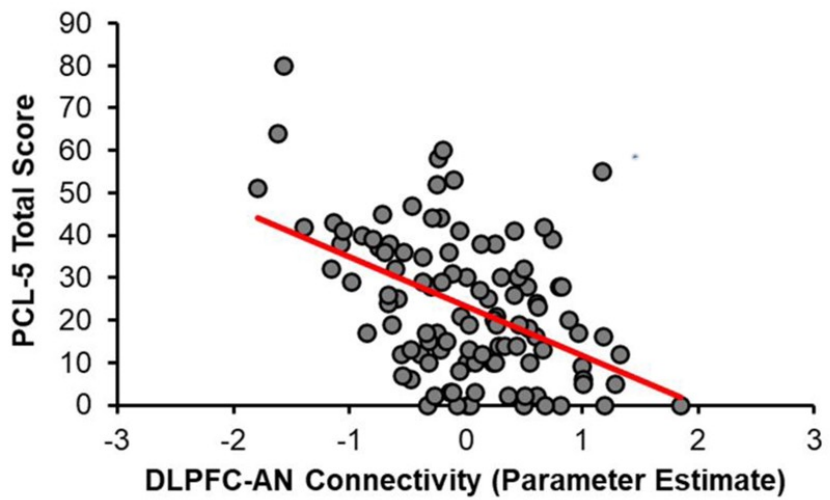


McLaughlin et al., 2014; Stevens et al., 2017

Threat neurobiology predicts future PTSD symptoms

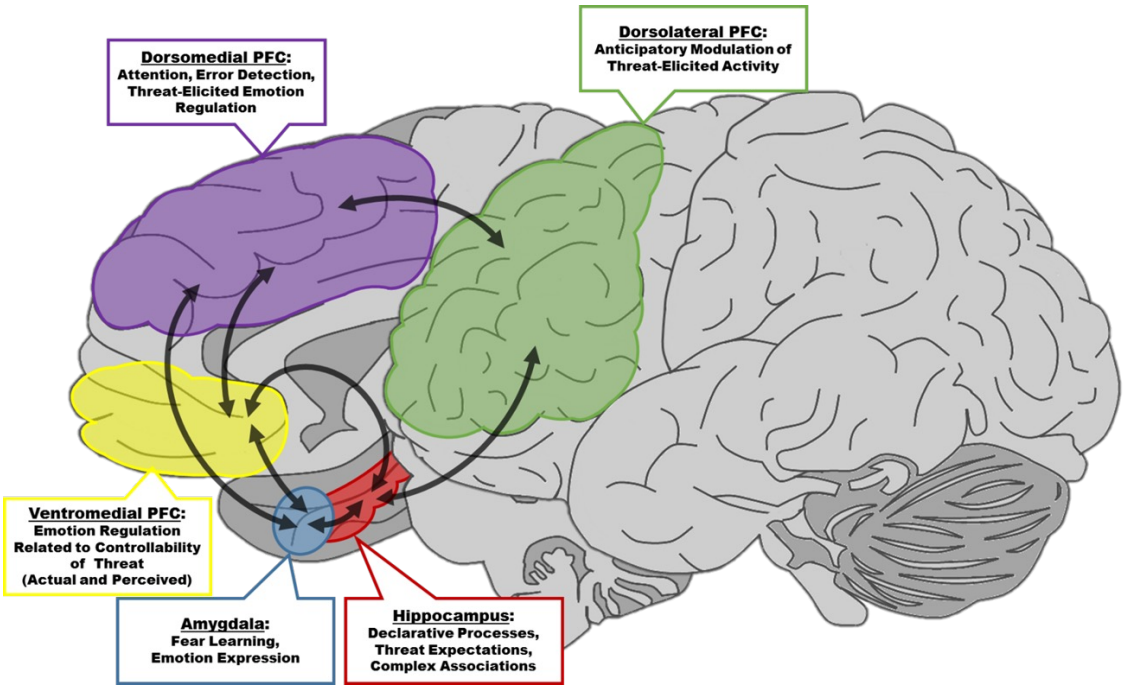


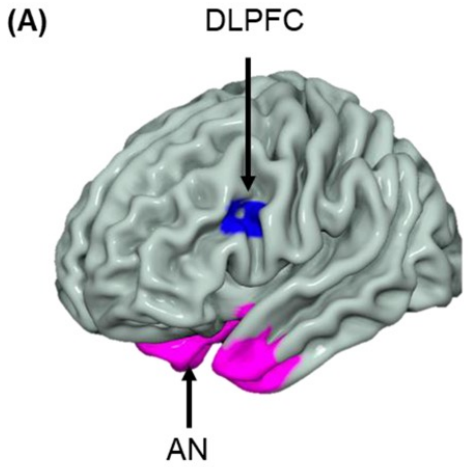


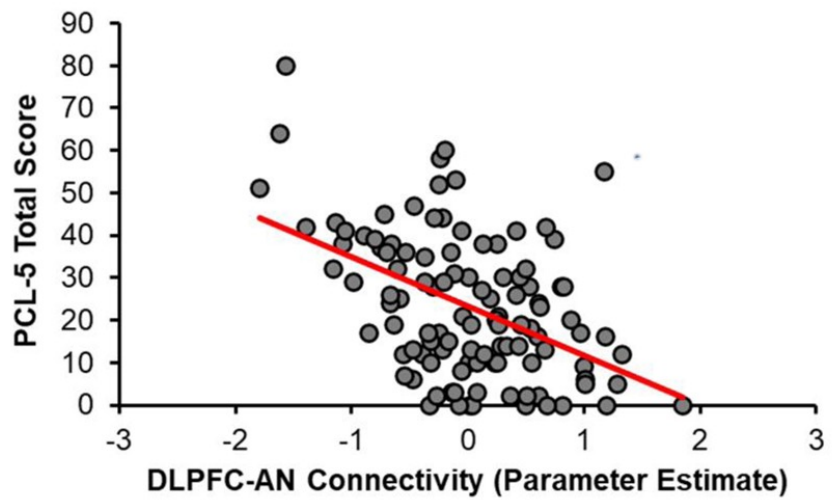


Functional connectivity: Correlation in brain activity over time

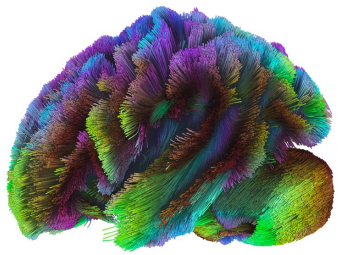
Threat neurobiology predicts future PTSD symptoms

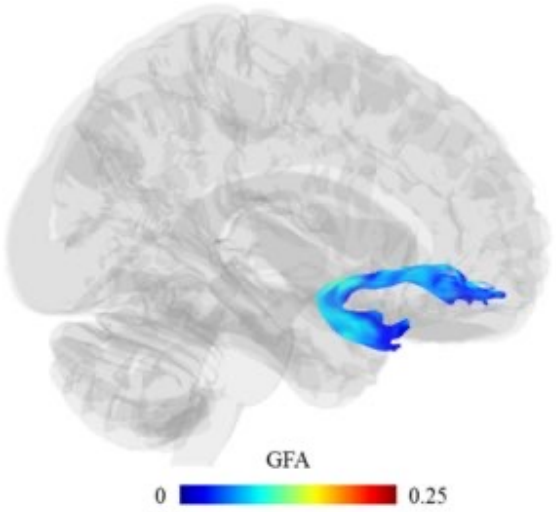


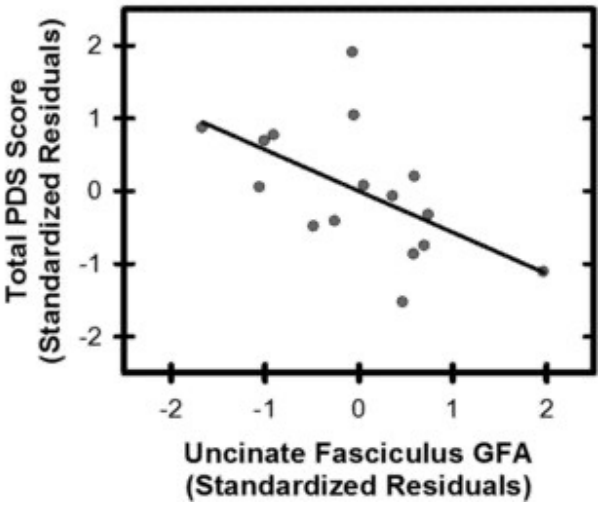




Structural connectivity: Strength of white matter connections







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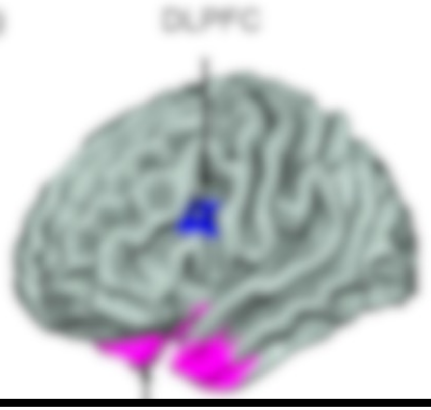
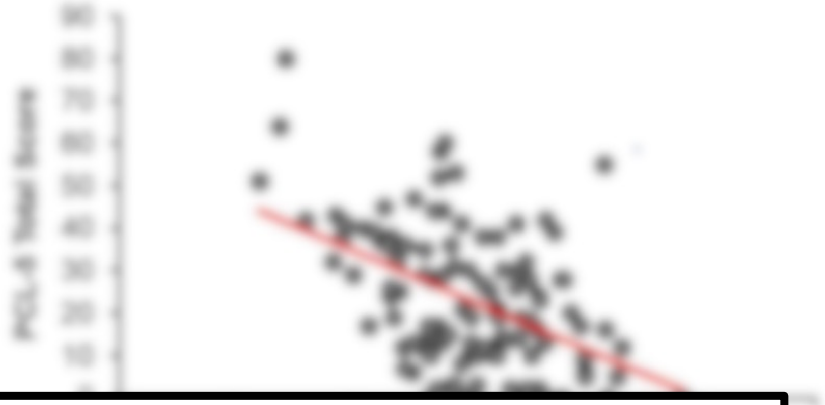
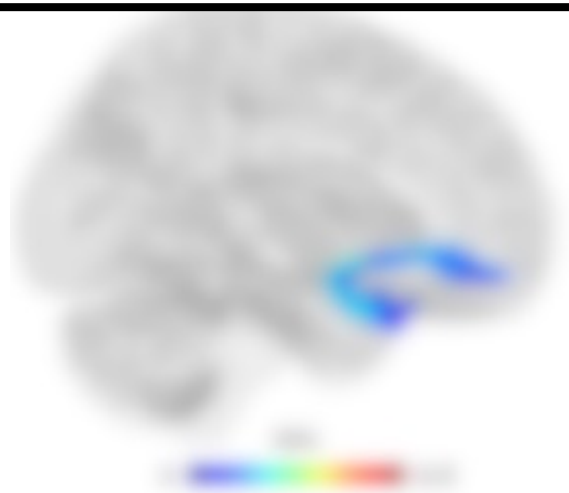
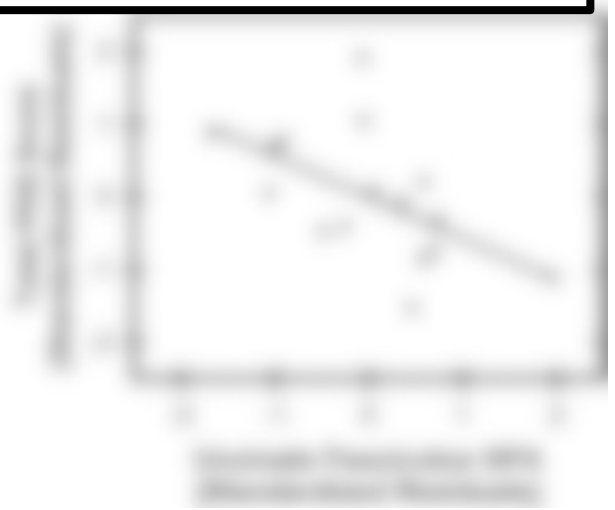


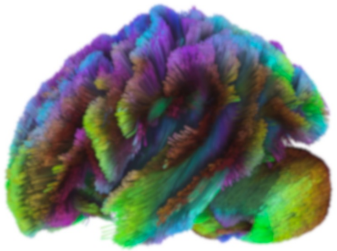


Dysregulation of functional and structural connectivity is associated with greater PTSD symptoms in the future

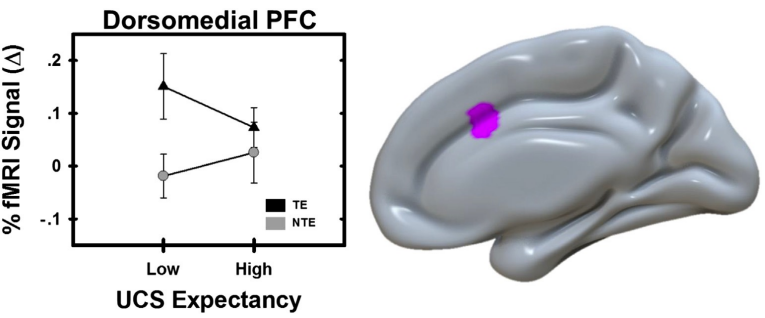


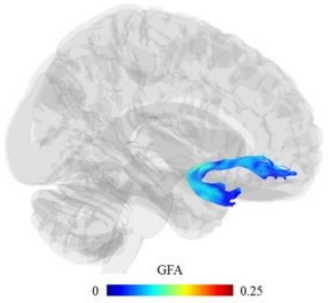


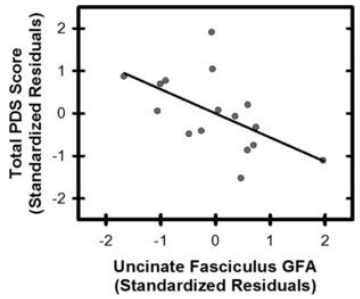
Structural connectivity: Strength of white matter connections

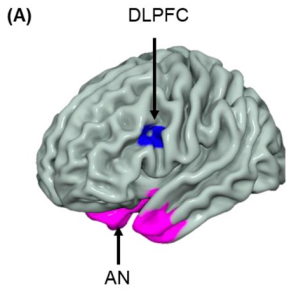


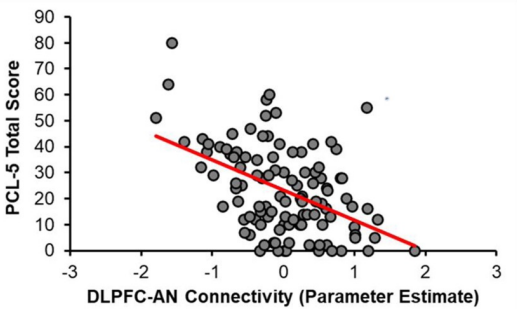
Threat neurocircuitry and PTSD









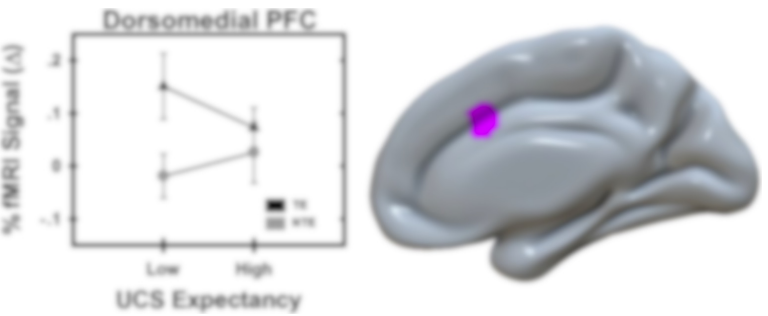


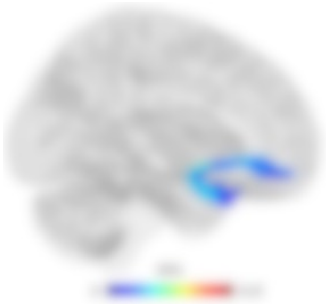
1) Traumatic stress has observable impacts on threat learning and associated neurocircuitry function

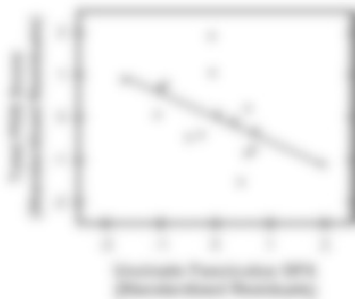
2) Traumatic stress does not *acutely* affect structure, but threat neurocircuitry structure is tied to development of PTSD symptoms

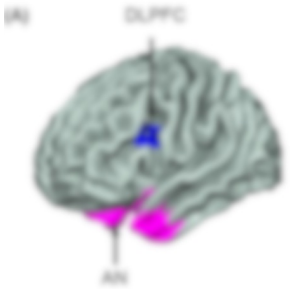
3) Functional interactions between threat neurocircuitry in the early aftermath of trauma contribute to PTSD symptom development

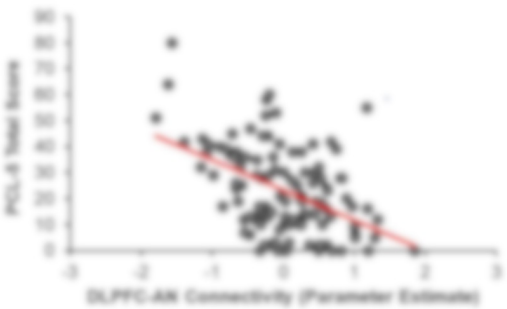
Threat neurocircuitry and PTSD









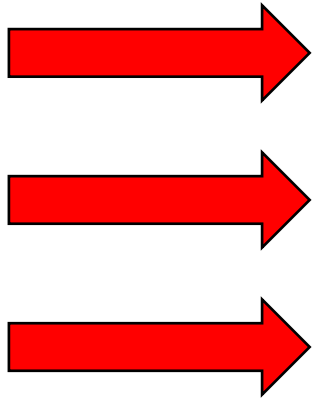


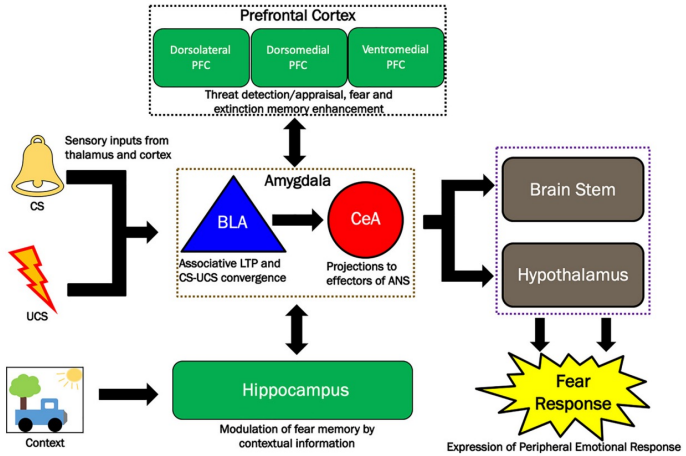
1) Traumatic stress has observable impacts on threat learning an neurocircui

2) Traumatic stress does not *acutely* affect structure, but threat

3) Functional interactions between threat neurocircuitry in the early e to

Threat neurocircuitry appears to be a major contributor to the development of PTSD and predicts future symptoms.





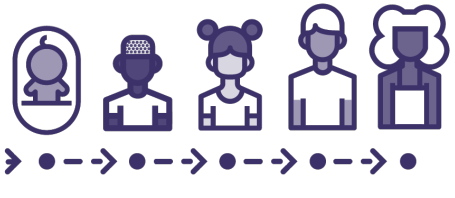
Early life trauma affects later life trauma

What Are Adverse Childhood Experiences?

Adverse childhood experiences, or **ACEs**, mean **potentially traumatic events in childhood (0-17 years)** such as neglect and experiencing or witnessing violence.

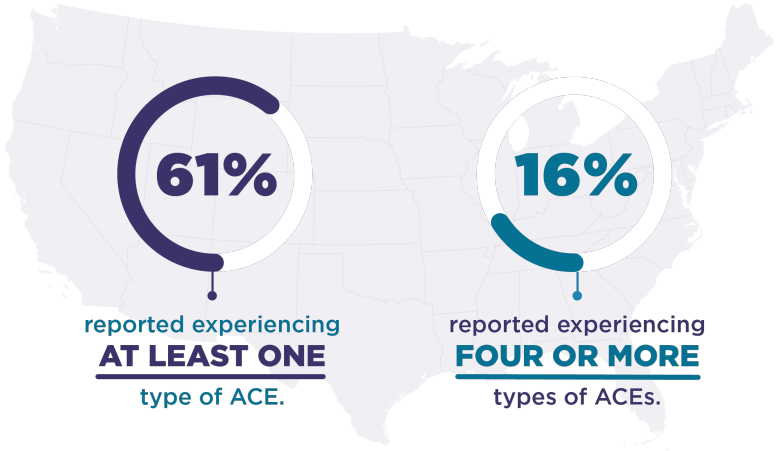
ACEs can negatively impact physical, mental, emotional, and behavioral development.

ACEs can also have lasting effects on health, well-being, and prosperity well into adulthood.



Many People Report ACEs

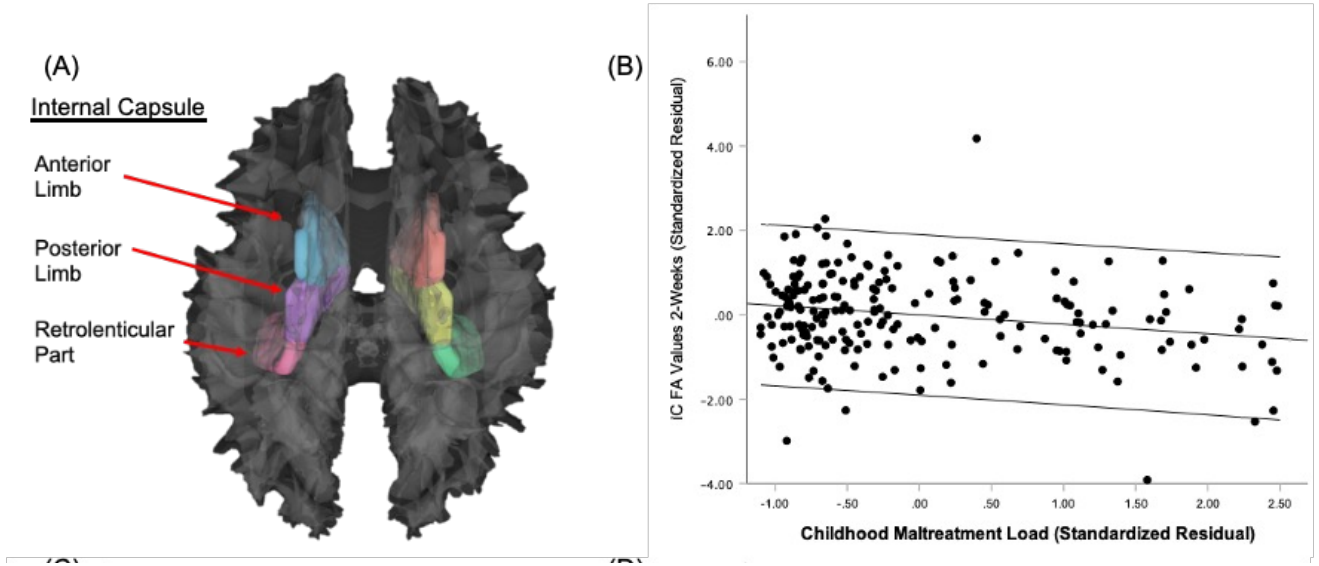
According to data collected from **more than 144,000 adults across 25 states** between 2015 and 2017:

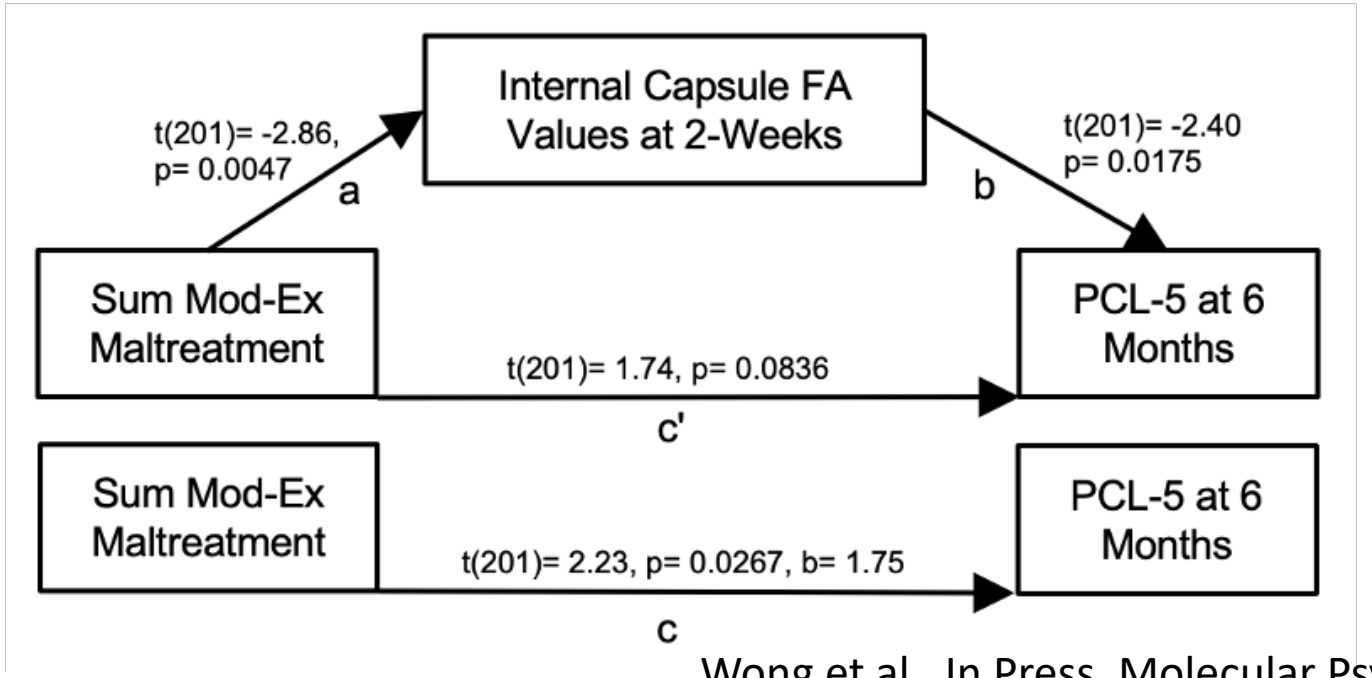


ACEs can include:

-Abuse/neglect
-Witnessing community violence
-Lack of resources
-Growing up around substance abuse

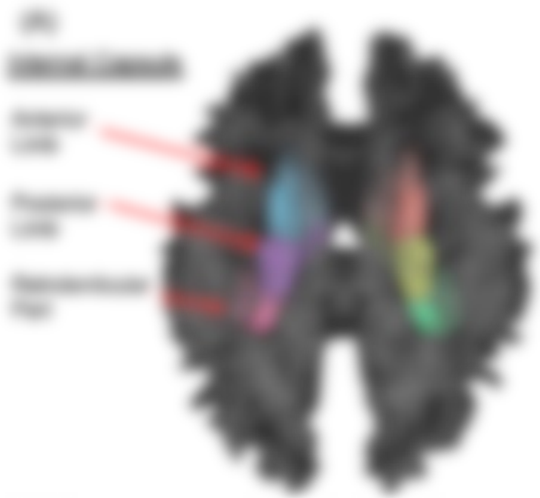
Childhood maltreatment and PTSD susceptibility





Wong et al., In Press, Molecular Psychiatry

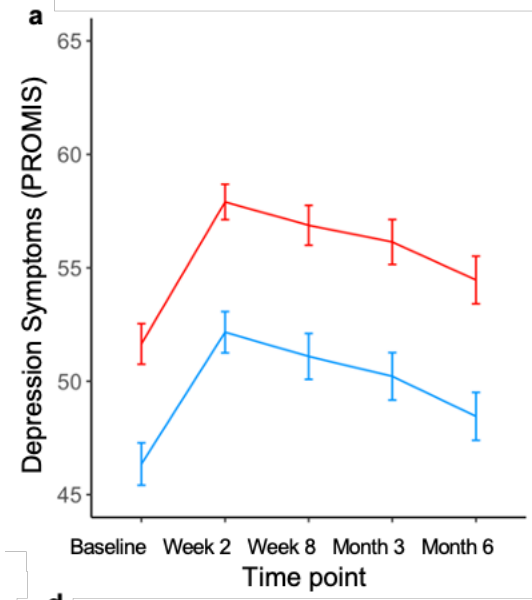
Childhood maltreatment and PTSD susceptibility

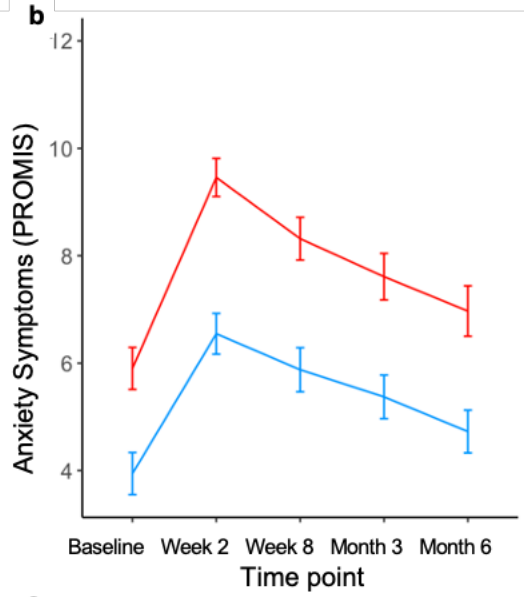


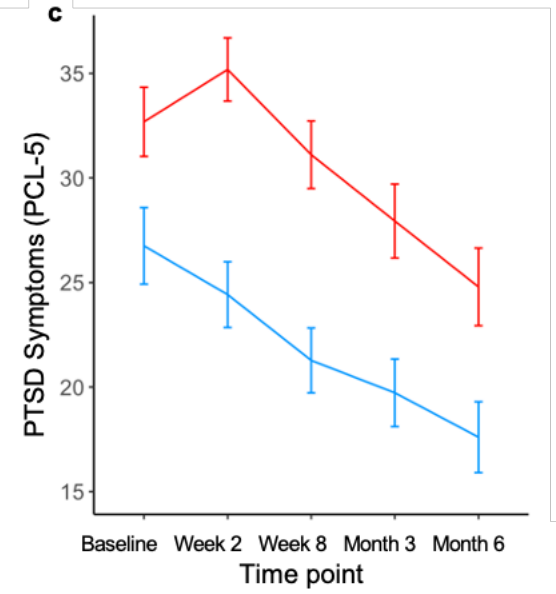
Childhood trauma modifies neural circuits that carry sensory information to contribute to future PTSD susceptibility

Wong et al., In Press, Molecular Psychiatry

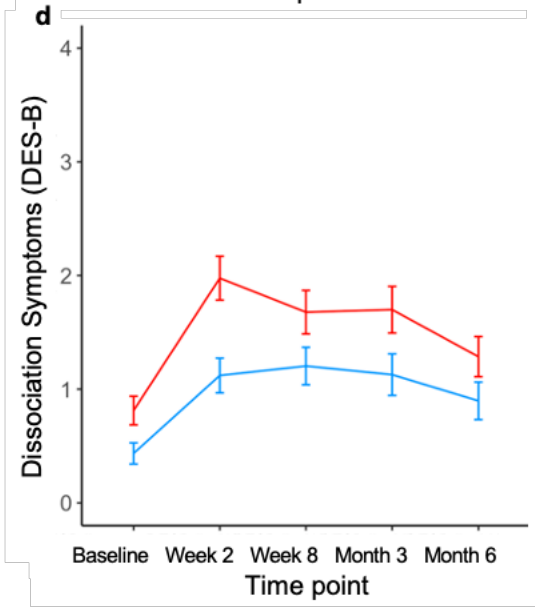
Prior sexual trauma and PTSD susceptibility

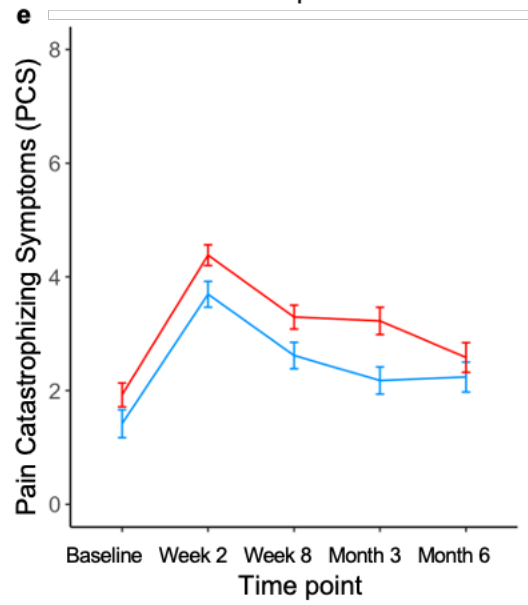


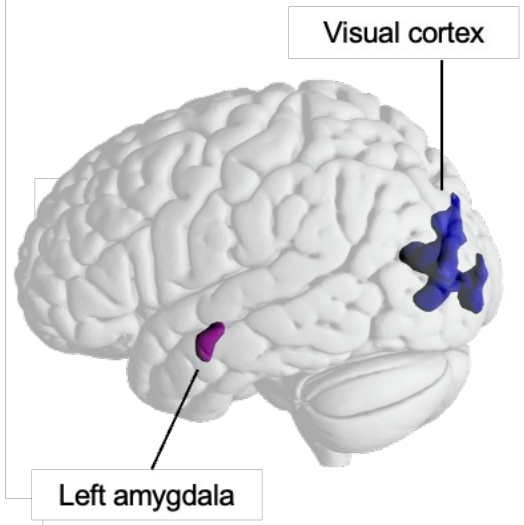


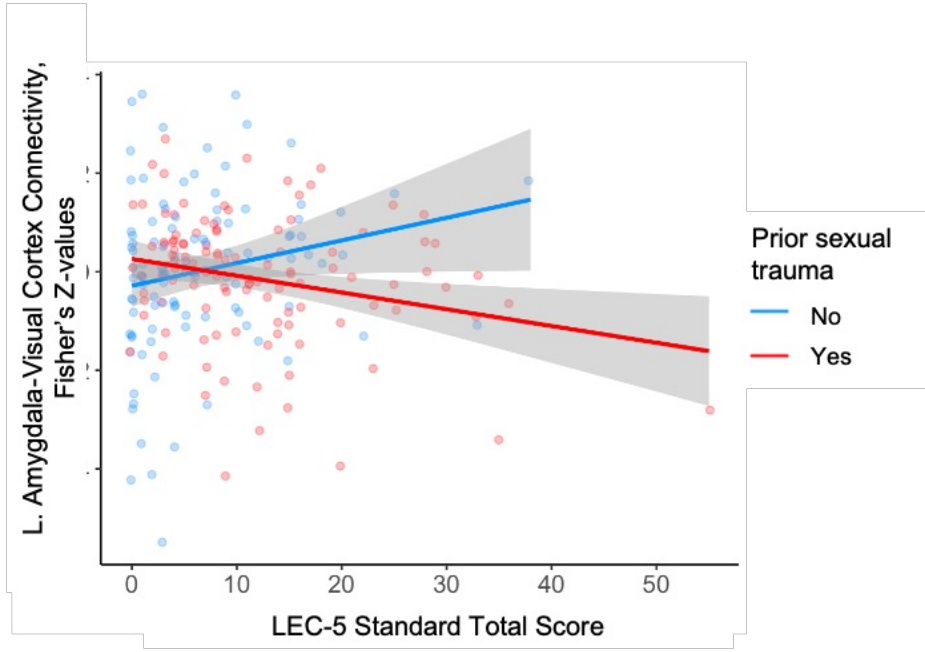


Rowland et al., In Press, *BP:GOS*

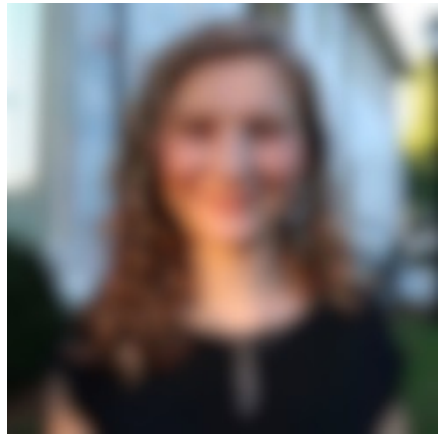








Prior sexual trauma and PTSD susceptibility

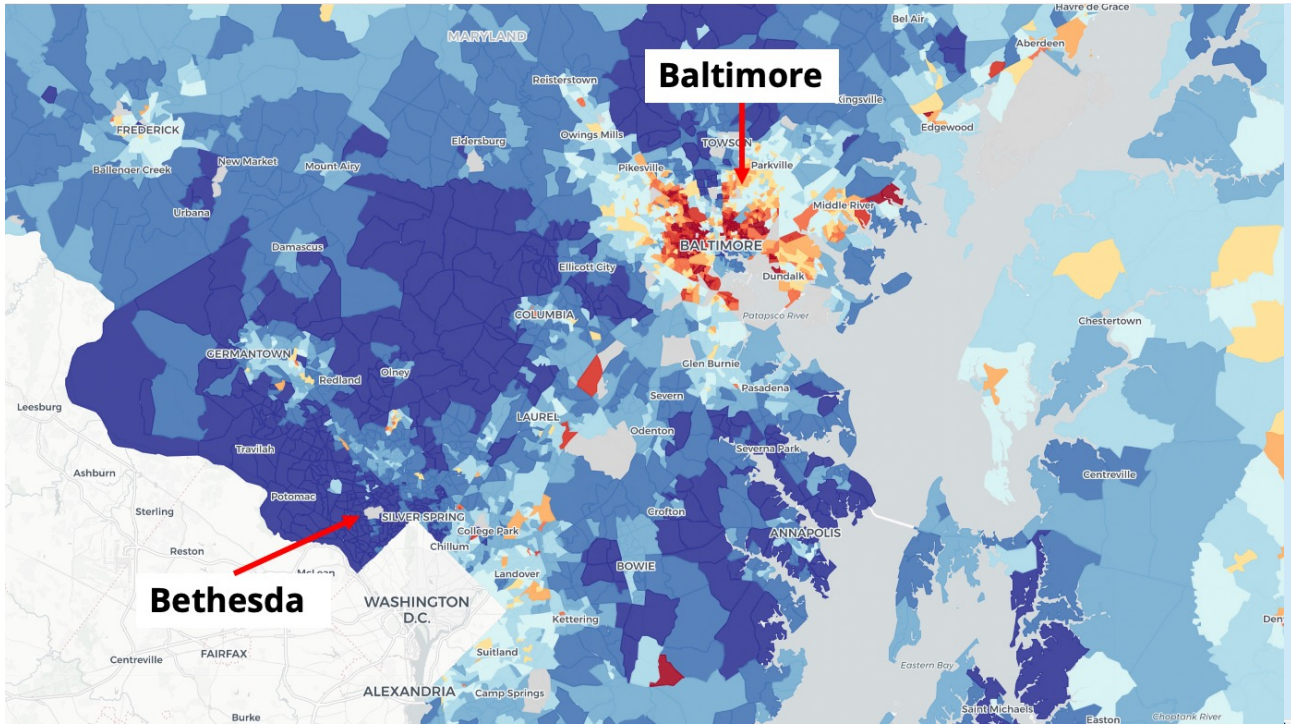


Rowland et al., In Press,

Highly adverse pretraumatic events heighten later symptoms and modify functional connectivity of threat and sensory regions.

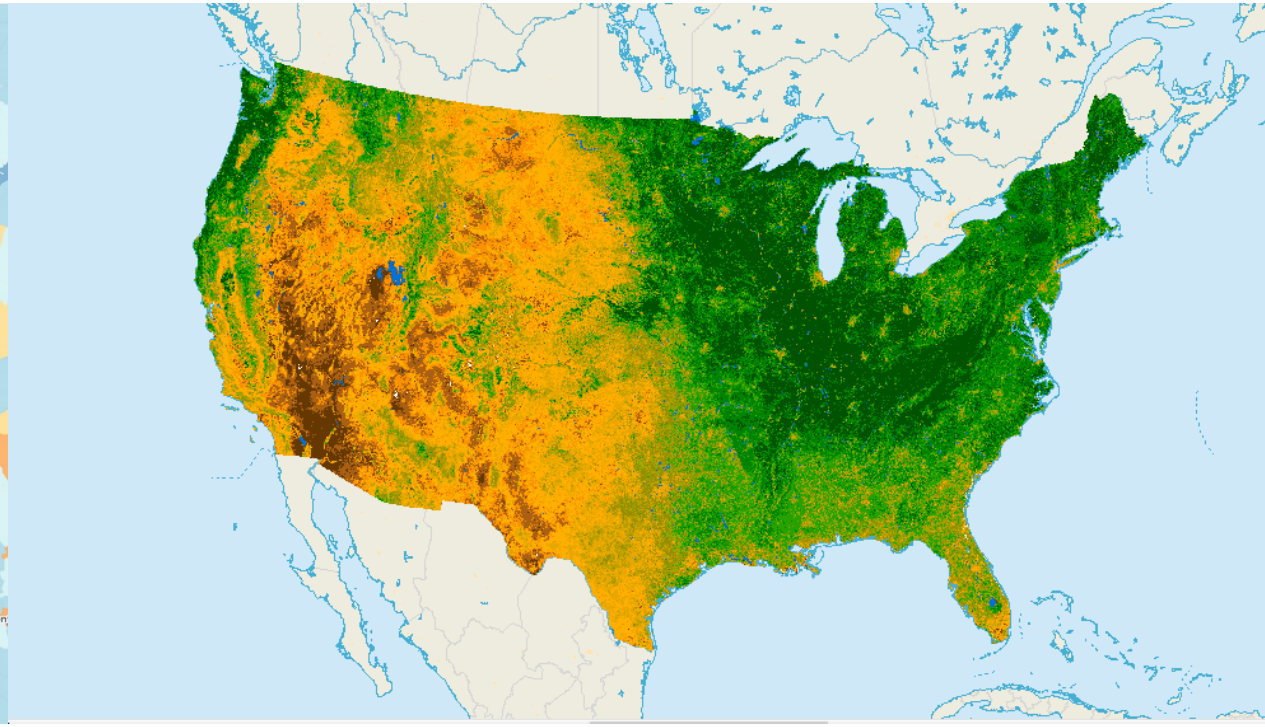
Context shapes responses to trauma

Neighborhood disadvantage



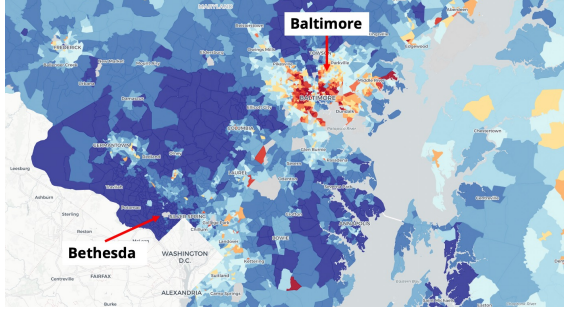
Area Deprivation Index
(Kind & Buckingham, 2018, *NEJM*)

Residential Greenspace

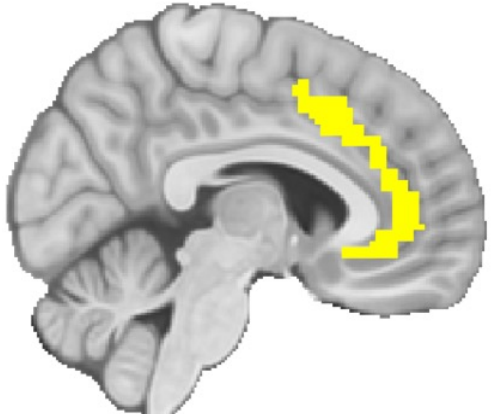


National Vegetation Index

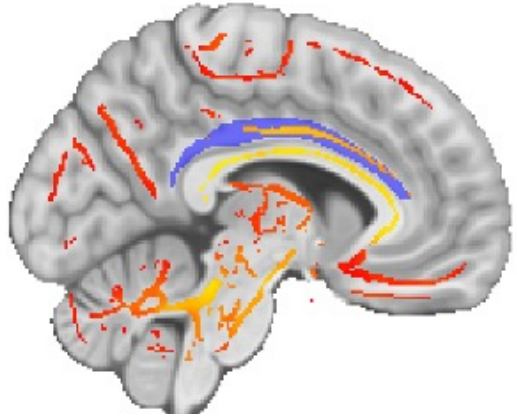
Context shapes responses to trauma



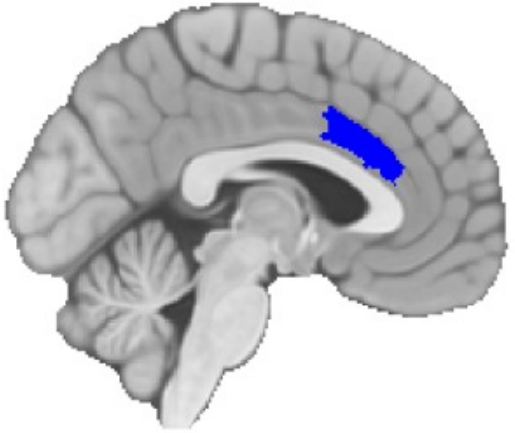
Function

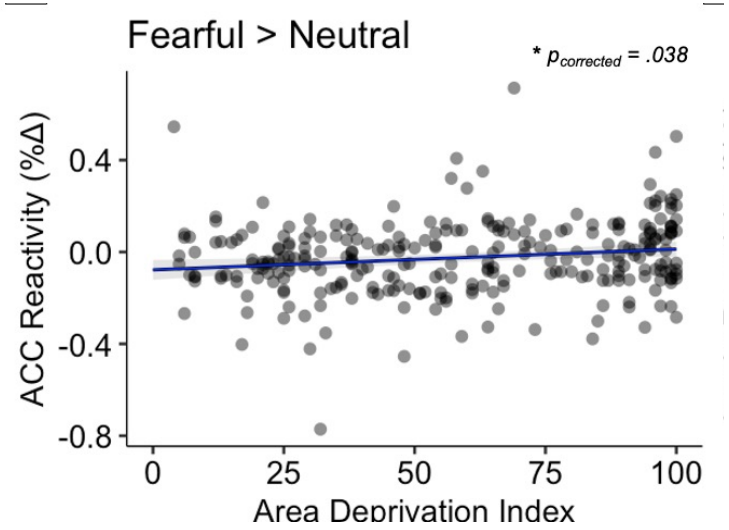


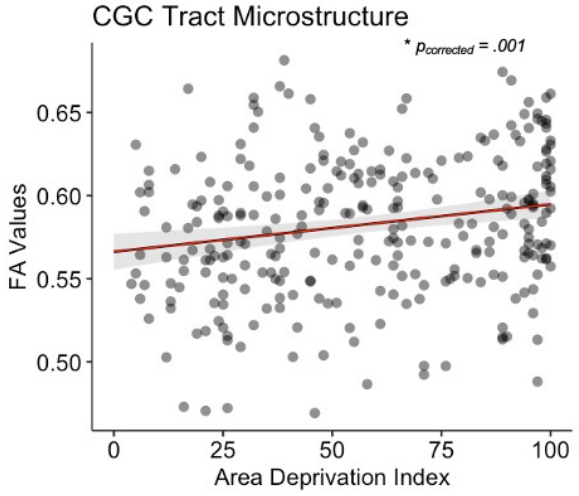
White matter

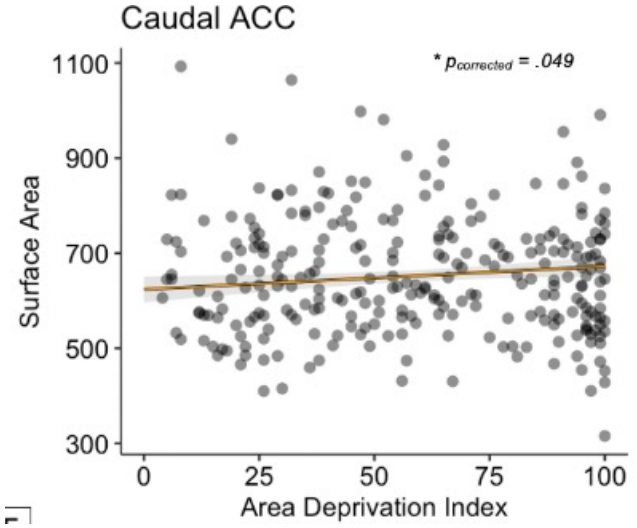


Gray matter



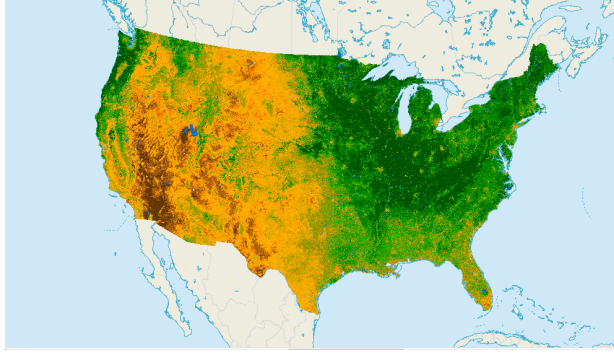




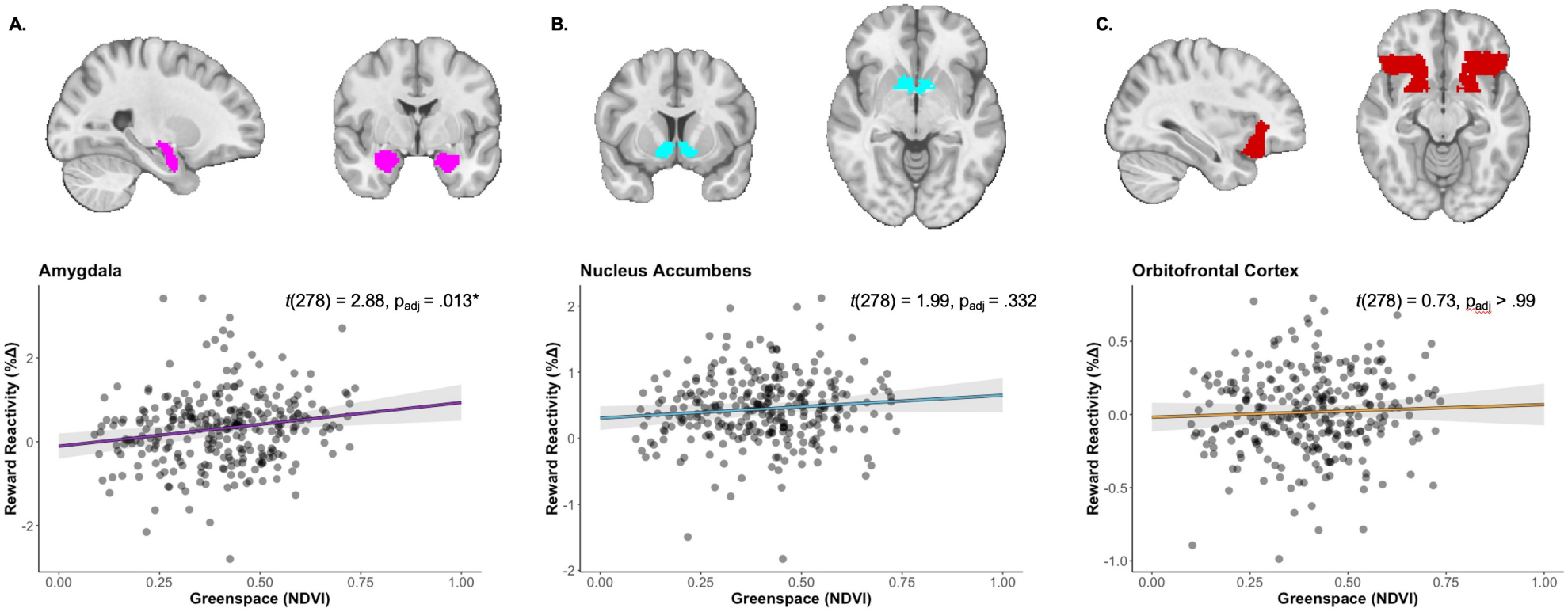


Webb et al., In Press, JAMA Network Open

Context shapes responses to trauma

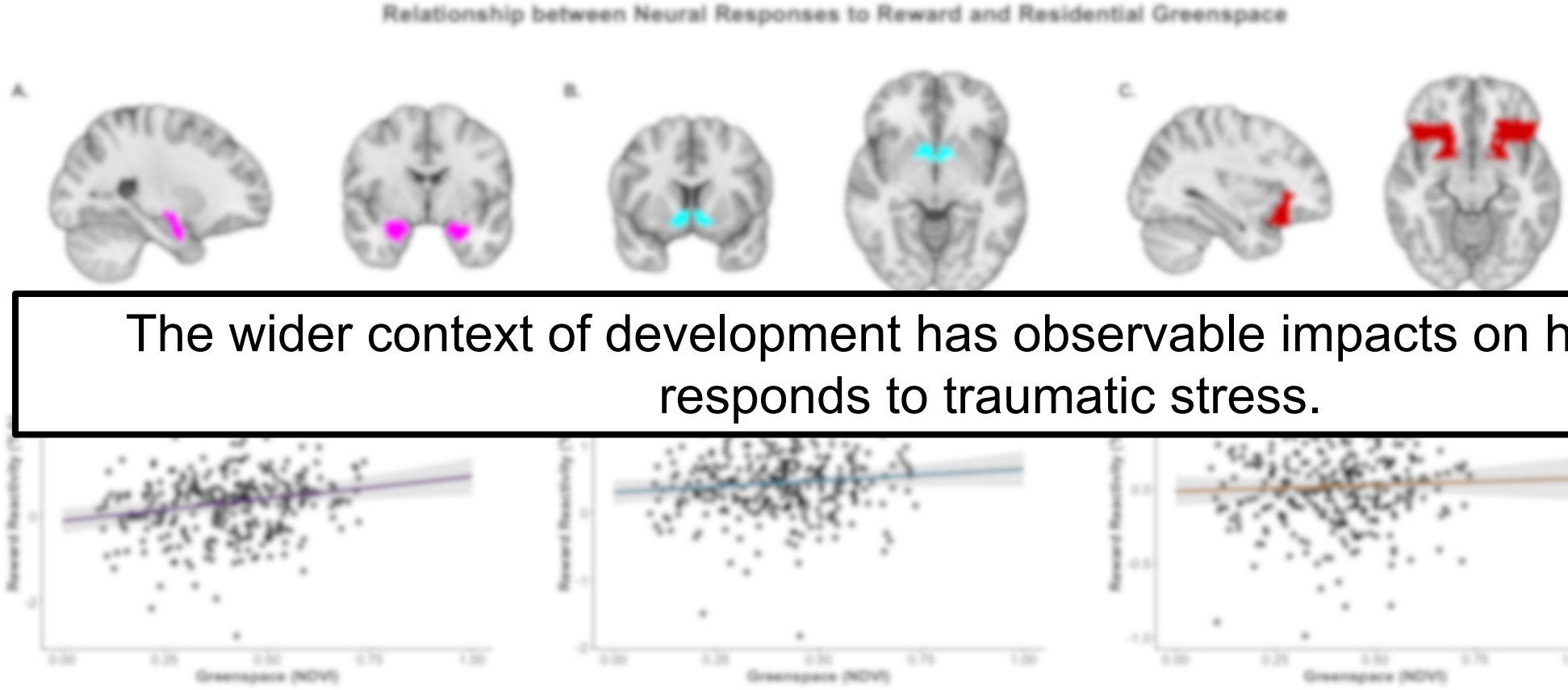


Relationship between Neural Responses to Reward and Residential Greenspace

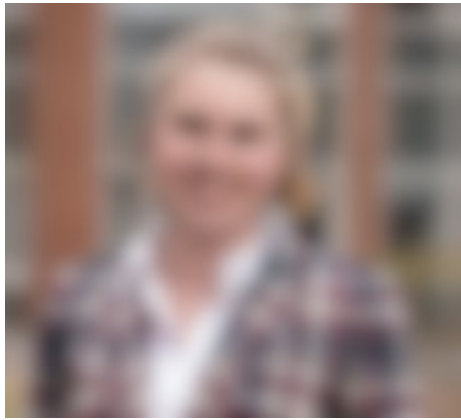


Webb et al., Under Review

Context shapes responses to trauma



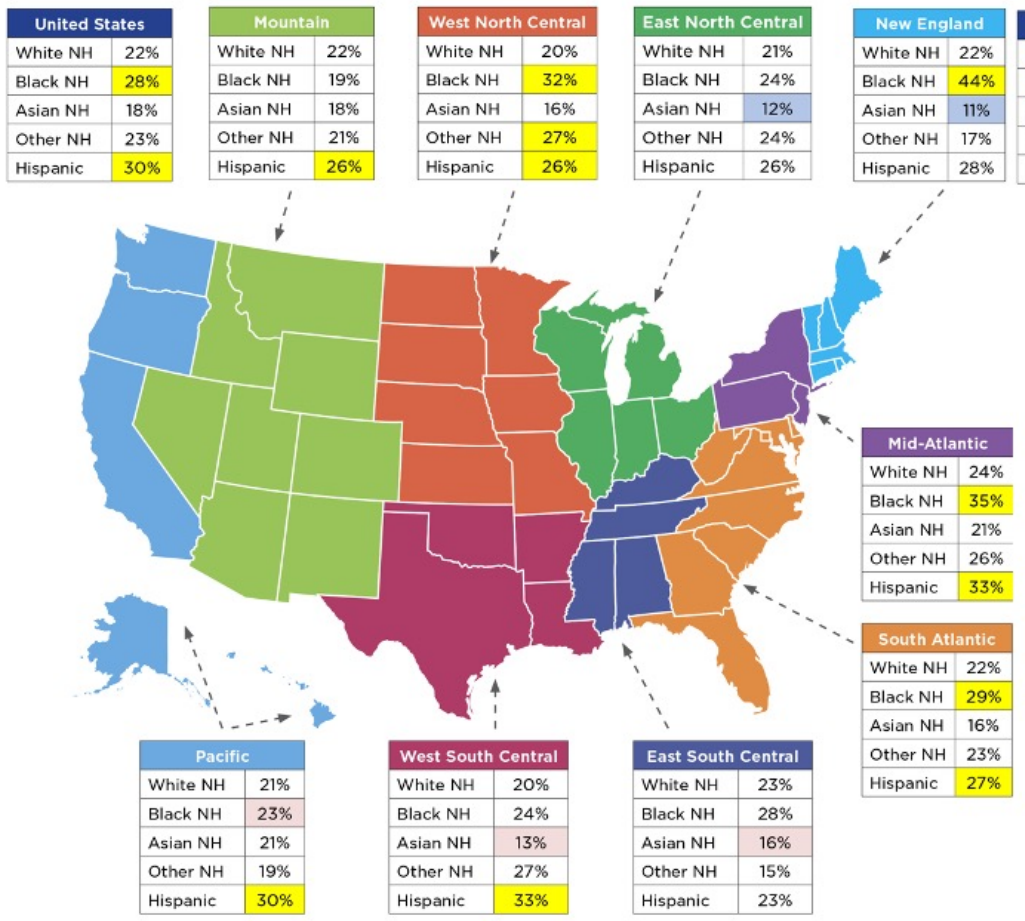
The wider context of development has observable impacts on how the brain responds to traumatic stress.



Webb et al., Under Review

Early exposures are highly racialized

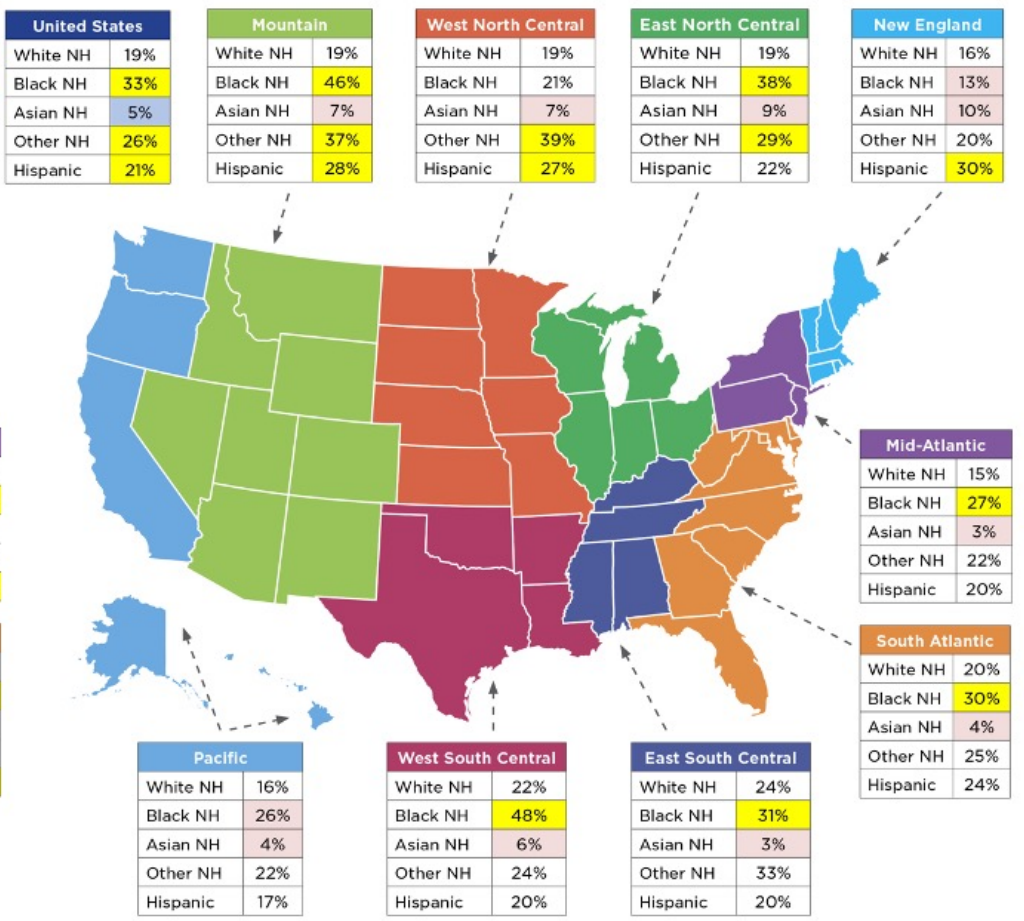
Percentage of children with 1 ACE



NH=Non-Hispanic

Yellow shading = Percentage is higher than white non-Hispanic children at a statistically significant level.
Blue shading = Percentage is lower than white non-Hispanic children at a statistically significant level.
Red shading = Estimate should be interpreted with caution, because the relative confidence interval is greater than 120 percent. See the "About the data used in this report" section for more information.

Percentage of children with 2 or more ACEs



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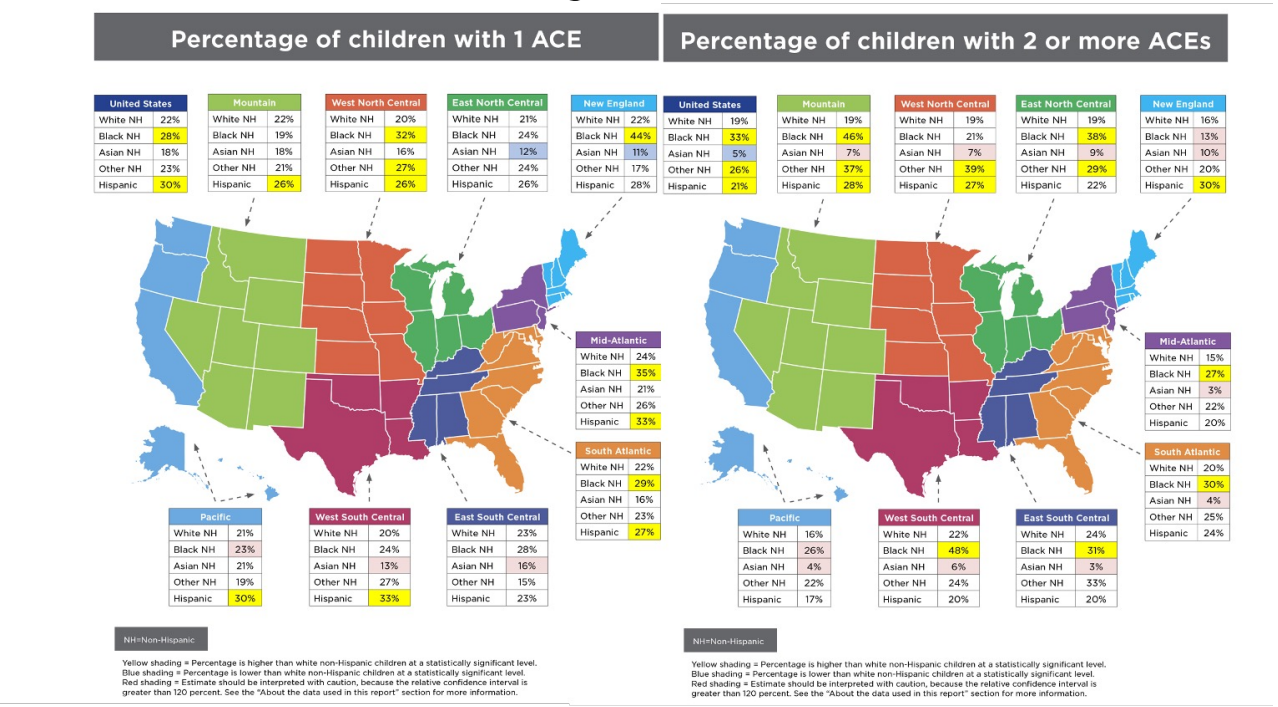
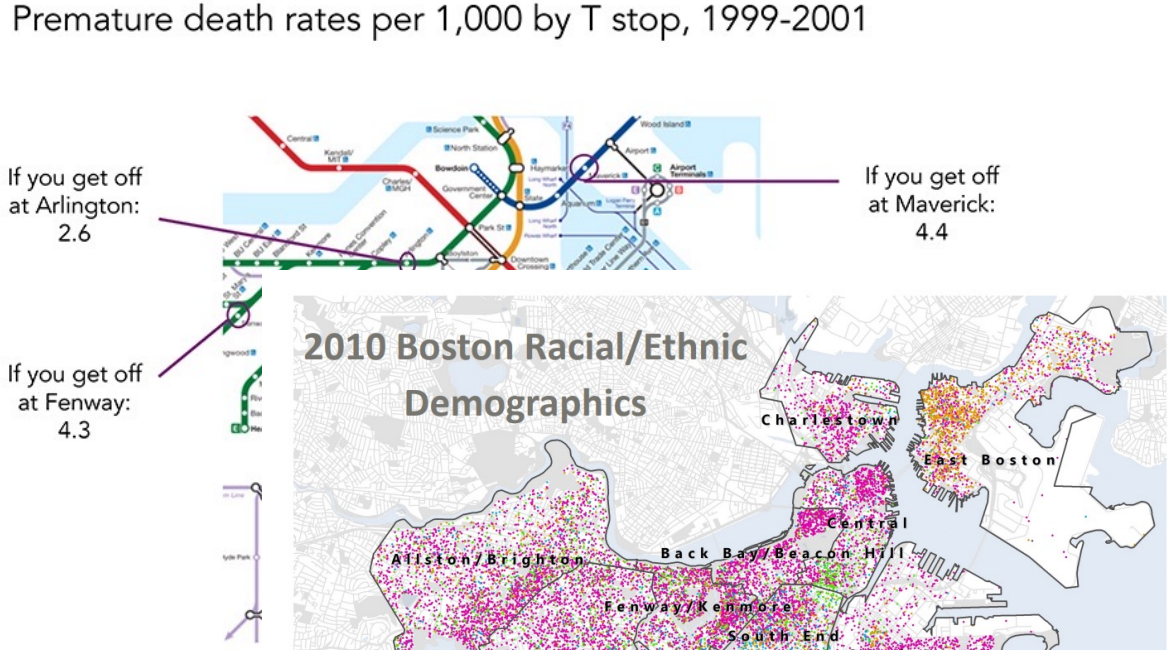
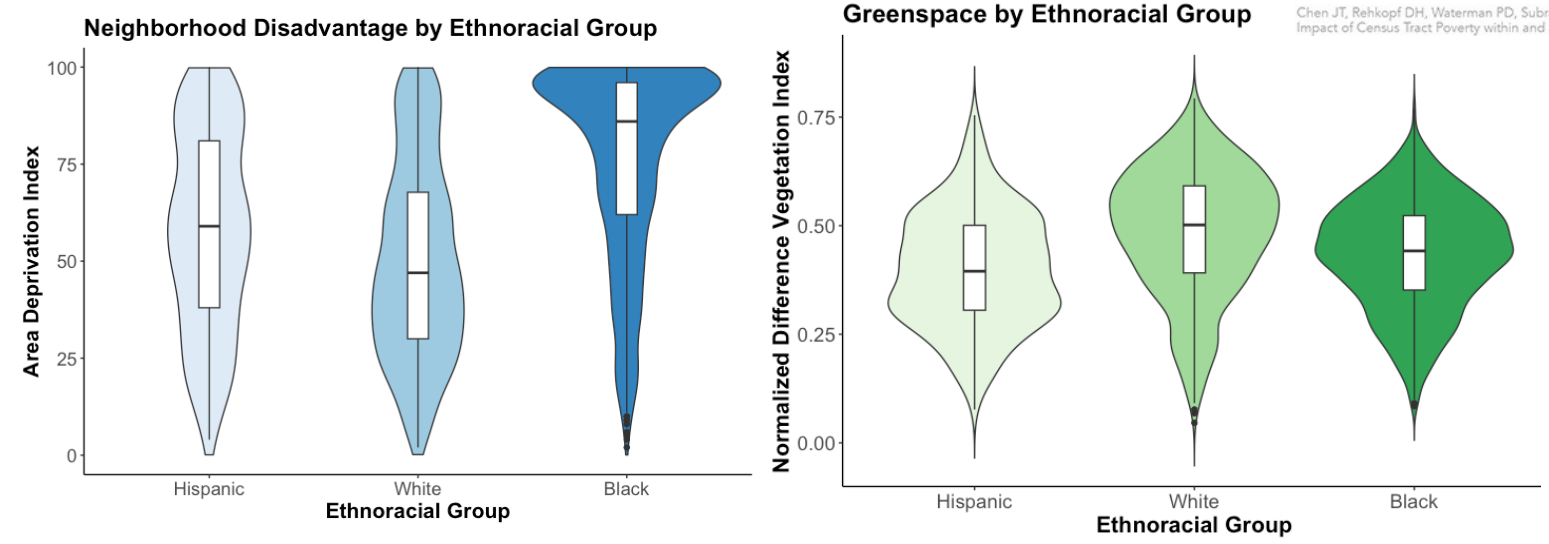
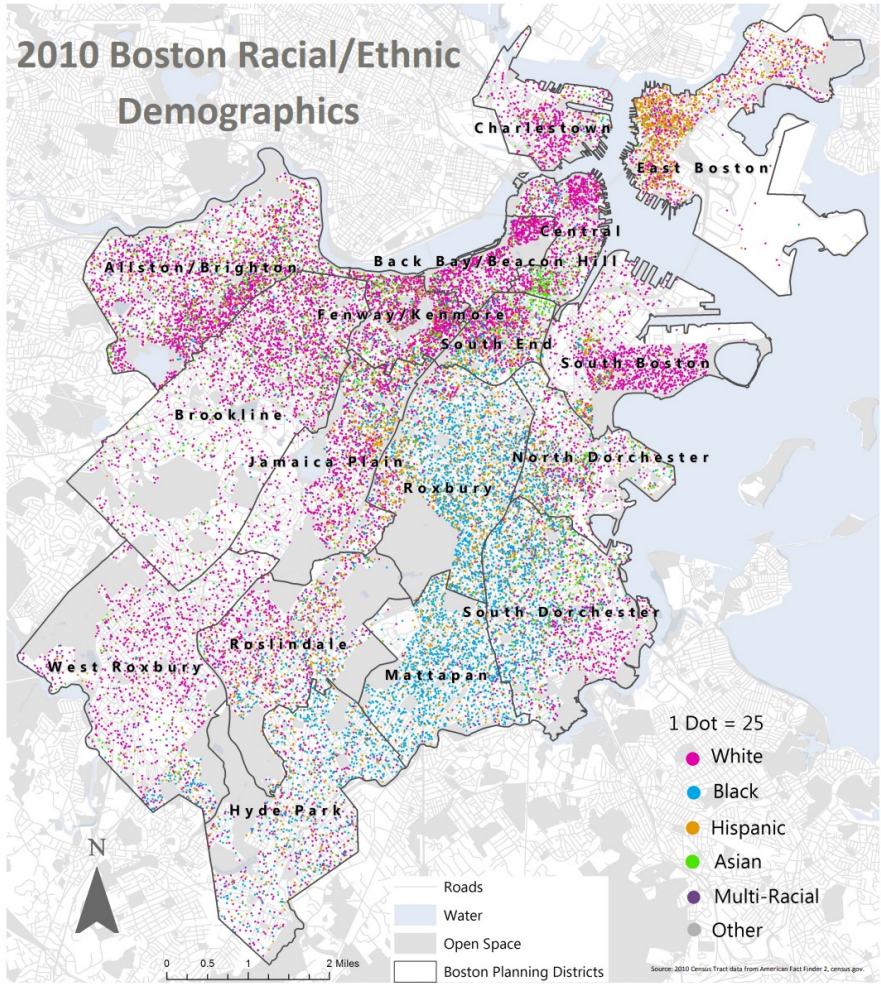
Early exposures are highly racialized





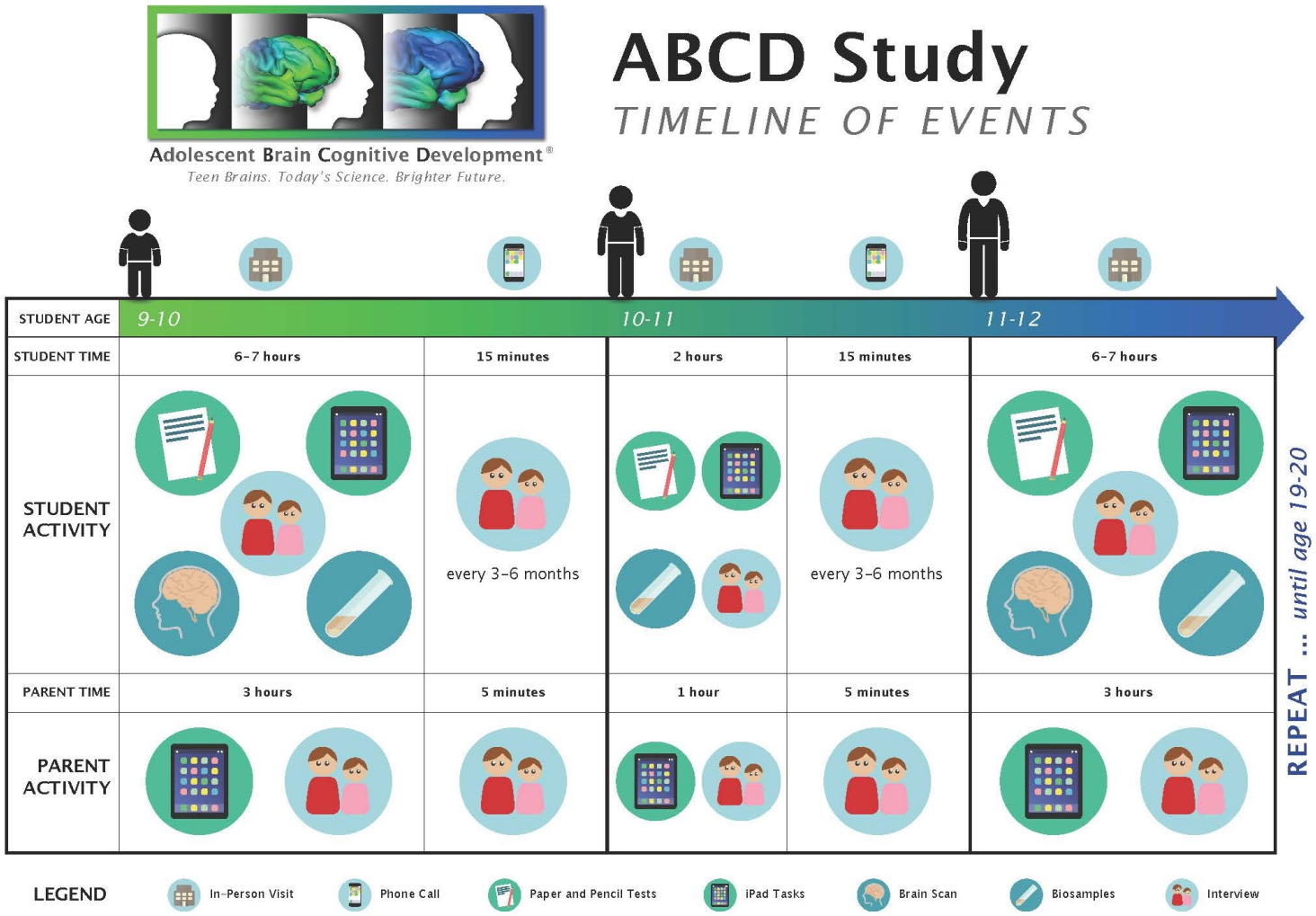


Chen JT, Rehkopf DH, Waterman PD, Subram
Impact of Census Tract Poverty within and acr



Structural inequities and the brain (child)

Dumornay et al., 2023, *American Journal of Psychiatry*



Demographics:

- Parent reported race and SAAB
  - Black/White, Male/Female

Experiences and context:

- Family conflict
- Family hardship
- Trauma load
- Family income
- Parent education
- Parent employment
- Neighborhood disadvantage

Neuroimaging:

- Gray matter volume

Structural inequities and the brain (child)

Dumornay et al., 2023, *American Journal of Psychiatry*

Variable	Total *N*	White American % or *M* (*SD*)	Black American % or *M* (*SD*)	Statistics $\chi 2$ or *t*(df)	*p-value*
Age*	9382	119.03 (7.50)	118.82 (7.26)	*t*(9380) = 1.09	0.28
Sex	9382			$\chi 2$ = 5.86	0.02
Male		53.1%	50.1%		
Female		46.9%	49.9%		
Parent education	9373			*t*(2802) = 33.15§	< 0.001
Grade school		3.8%	11.9%		
High school diploma or equiv.		6.9%	24.1%		
Some college		14.0%	23.4%		
Associate degree		12.1%	16.9%		
Bachelor's degree		33.1%	12.7%		
Master's degree		22.9%	9.6%		
Doctoral or professional deg.		7.1%	1.3%		
Parent employment	9121			$\chi 2$ = 344.90	< 0.001
Not currently employed		5.6%	19.0%		
Currently employed		94.4%	81.0%		
Family income	8654			*t*(1985) = 40.30§	< 0.001
Less than $5,000		1.2%	14.2%		
$5,000 through $11,999		1.8%	11.2%		
$12,000 through $15,999		1.4%	5.9%		
$16,000 through $24,999		3.2%	9.8%		
$25,000 through $34,999		4.3%	12.2%		
$35,000 through $49,999		6.5%	13.3%		
$50,000 through $74,999		14.0%	13.9%		
$75,000 through $99,999		16.5%	7.7%		
$100,000 through $199,999		36.9%	9.7%		
$200,000 and greater		14.2%	2.1%		
Neighborhood disadvantage	8840	90.30 (23.91)	105.94 (22.25)	*t*(2706) = -25.66§	< 0.001
Family conflict	9363	1.96 (1.94)	2.43 (2.01)	*t*(2786) = -9.17§	< 0.001
Financial hardship	9296	0.30 (0.89)	1.01 (1.49)	*t*(2166) = -19.63§	< 0.001
Trauma history	9043	0.48 (1.10)	0.67 (1.02)	*t*(2965) = -7.26§	< 0.001

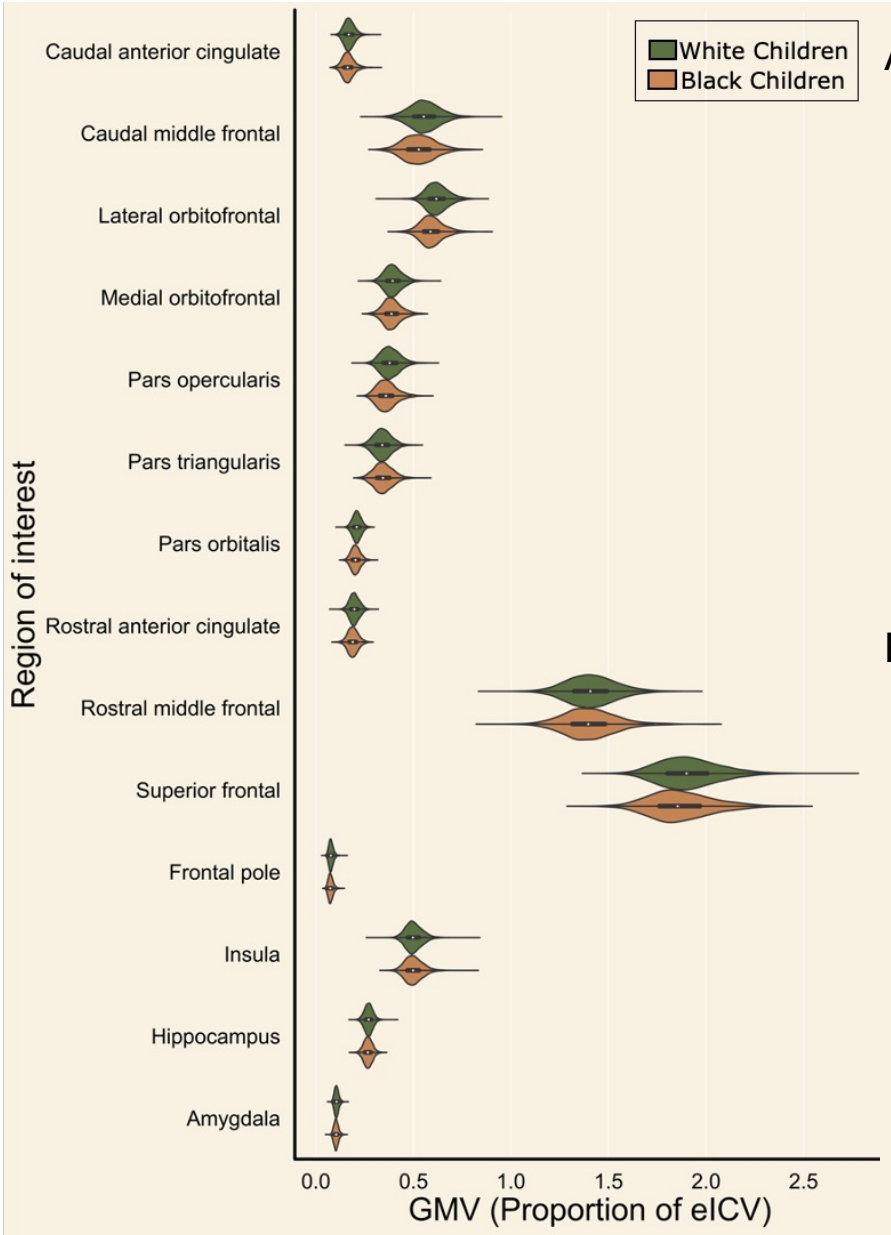
Note. *Age presented in months. WA and BA participants statistically differed in all demographic variables except age. §Symbol indicates that the test was corrected for unequal variances due to violation of Levene's test for homogeneity of variance.

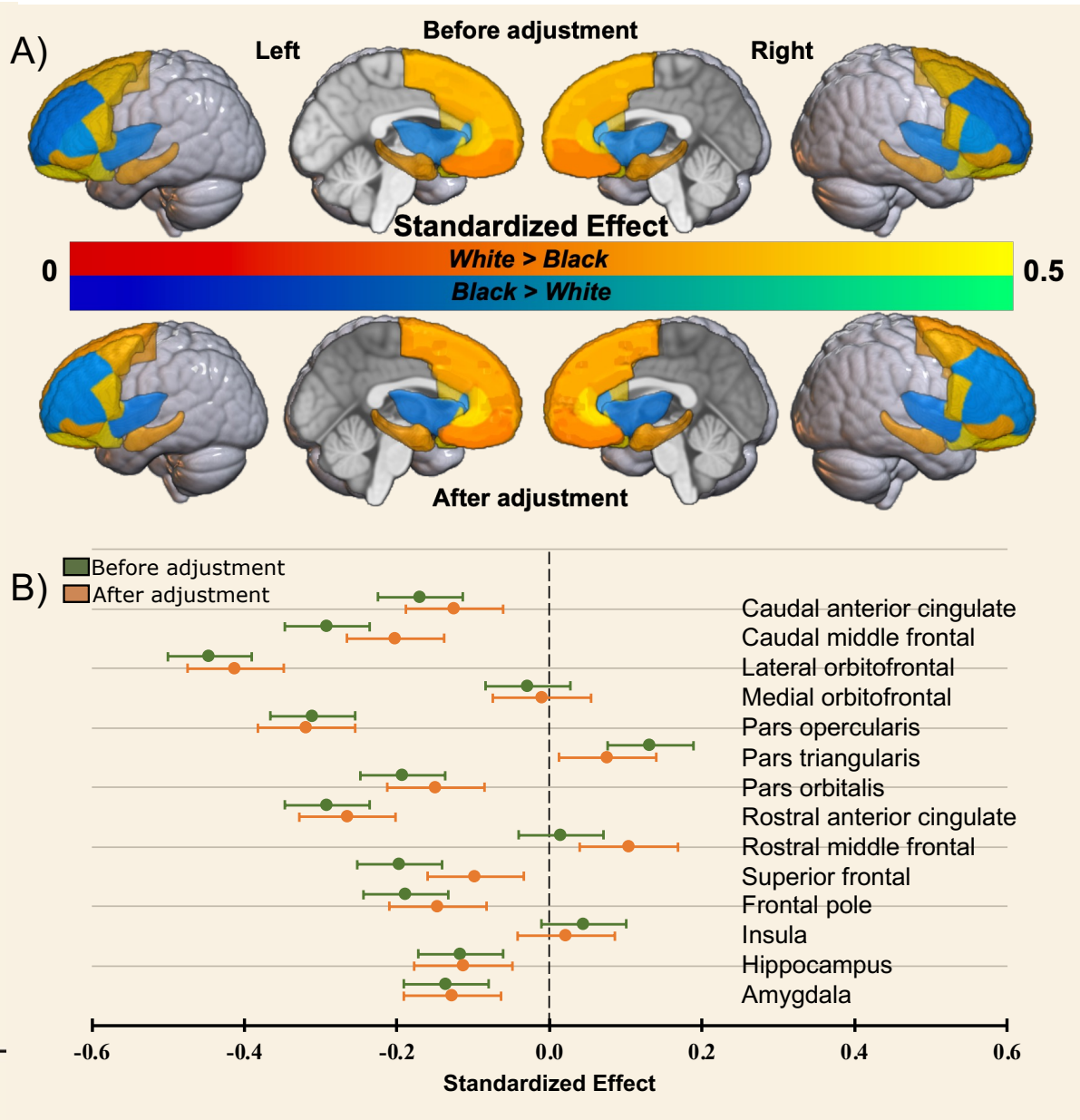
Compared to White children, Black children in the ABCD study:

- Have caregivers with less education
- Have more unemployed parents
- Have lower family income
- Come from more disadvantaged neighborhoods
- Experience more family conflict
- Experience more financial hardship
- Have greater endorsement of traumatic events

Structural inequities and the brain (child)

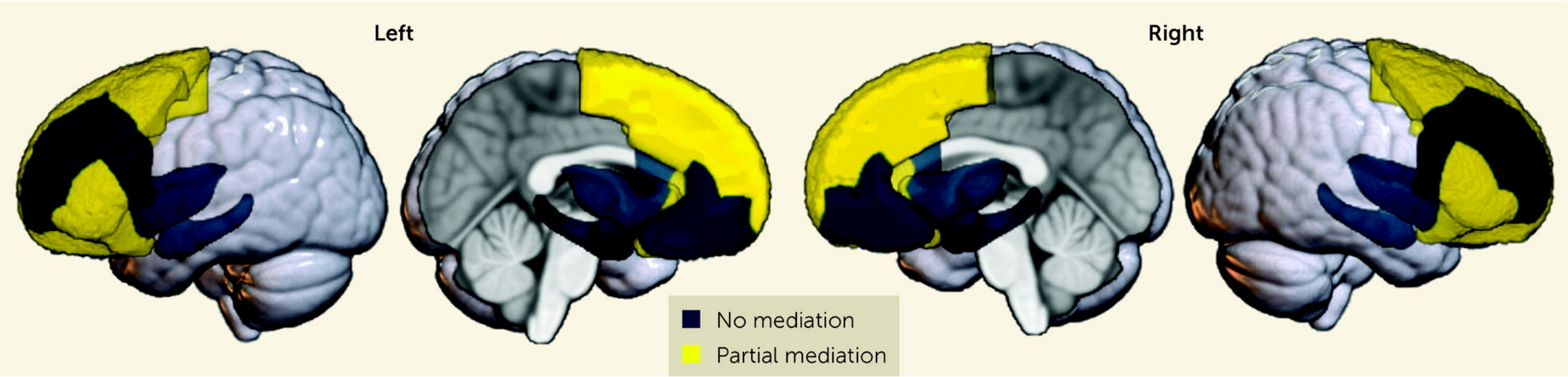
Dumornay et al., 2023, *American Journal of Psychiatry*





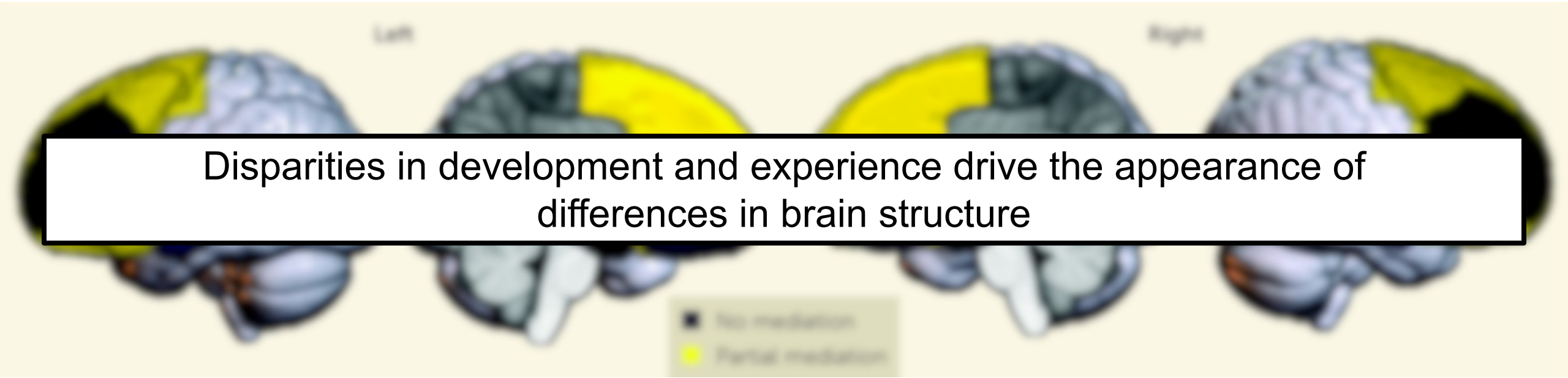
Structural inequities and the brain (child)

Dumornay et al., 2023, *American Journal of Psychiatry*

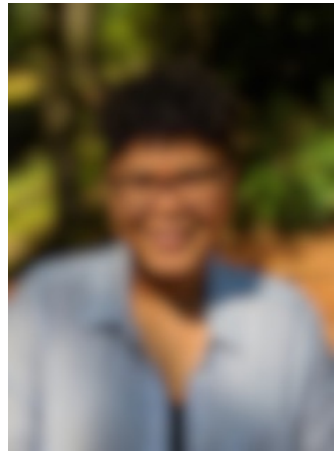


Structural inequities and the brain (child)

Dumornay et al., 2023, *American Journal of Psychiatry*

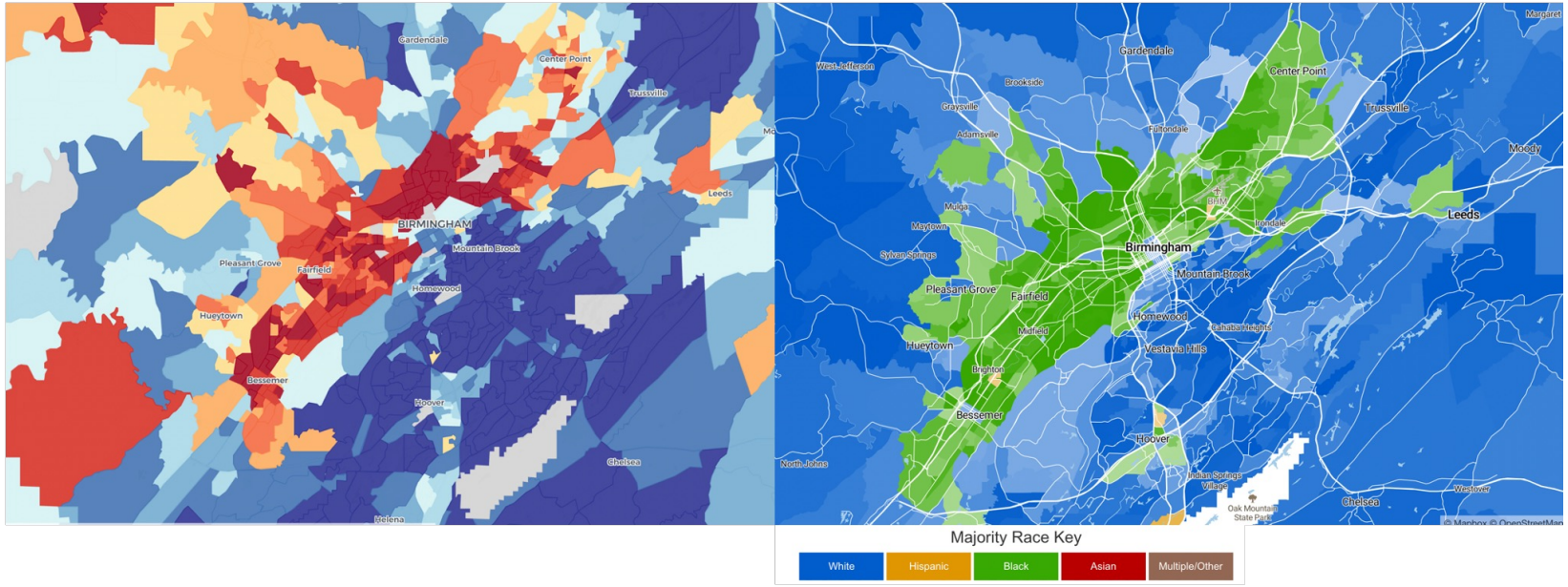


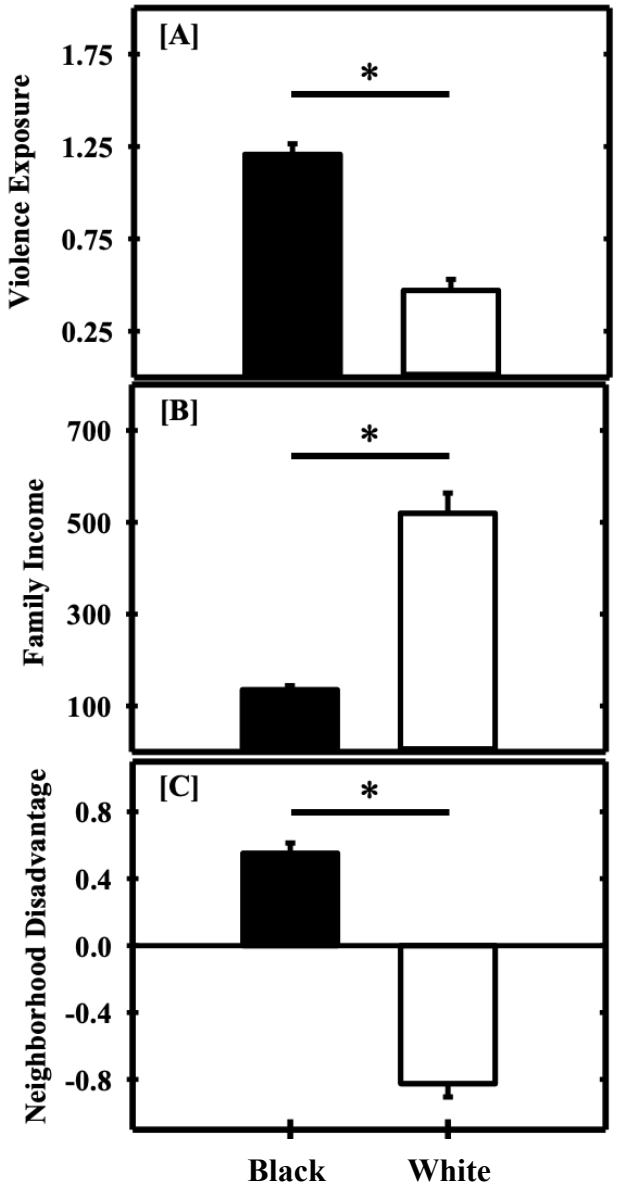
Disparities in development and experience drive the appearance of differences in brain structure



Structural inequities and the brain (adult)

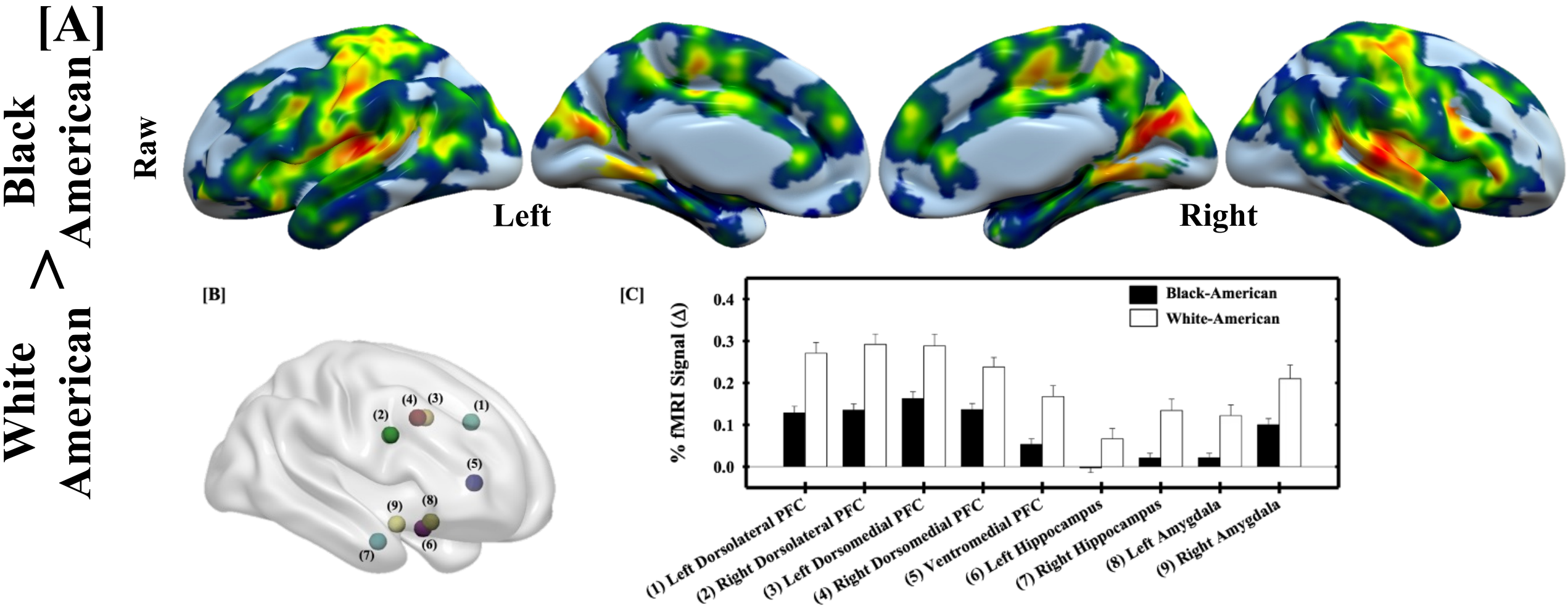
- 198 Young Adults from Birmingham, Alabama
  - 143 Black-American (BA)
  - 55 White-American (WA)
  - Prior data collected on violence exposure, family income levels, and neighborhood disadvantage





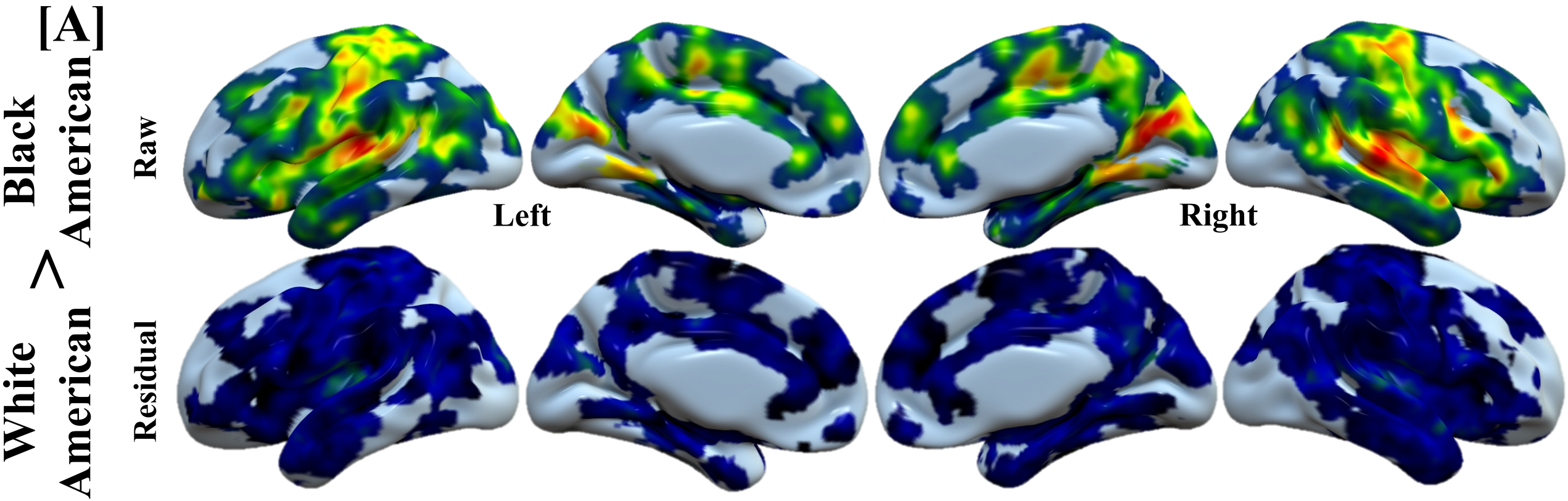
Harnett et al., 2019, *NeuroImage*

Structural inequities and the brain (adult)



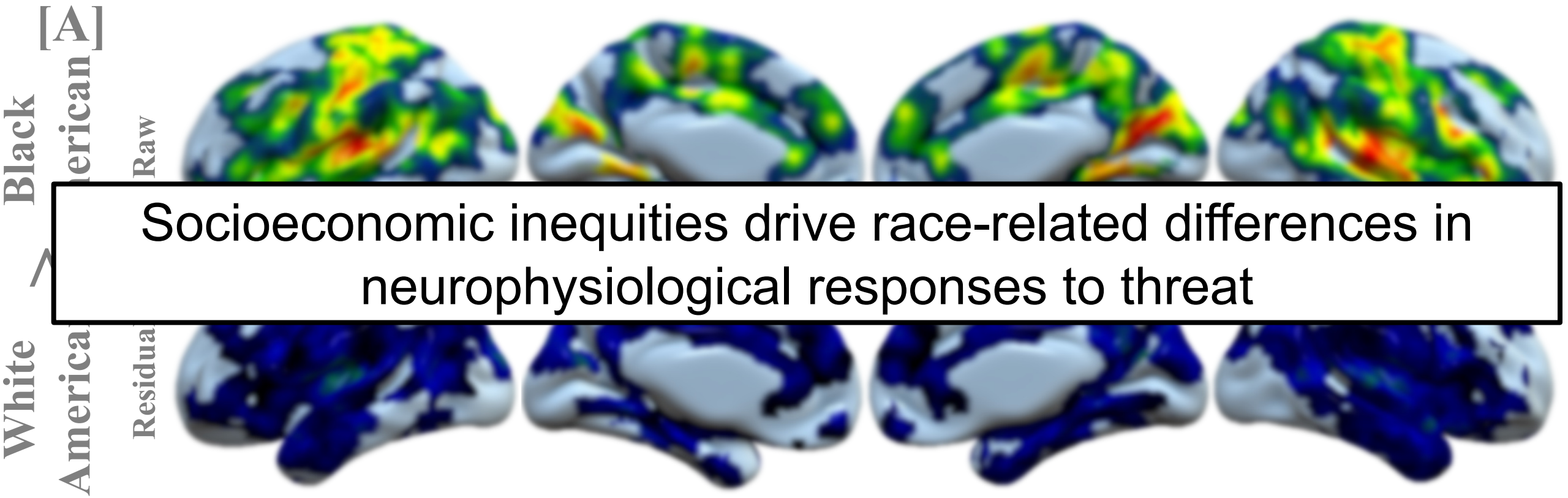
Harnett et al., 2019, *NeuroImage*

Structural inequities and the brain (adult)



Harnett et al., 2019, *NeuroImage*

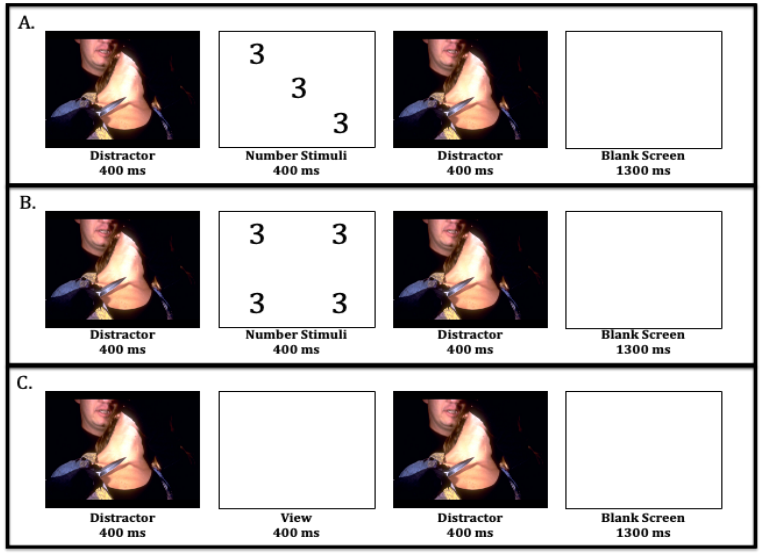
Structural inequities and the brain (adult)



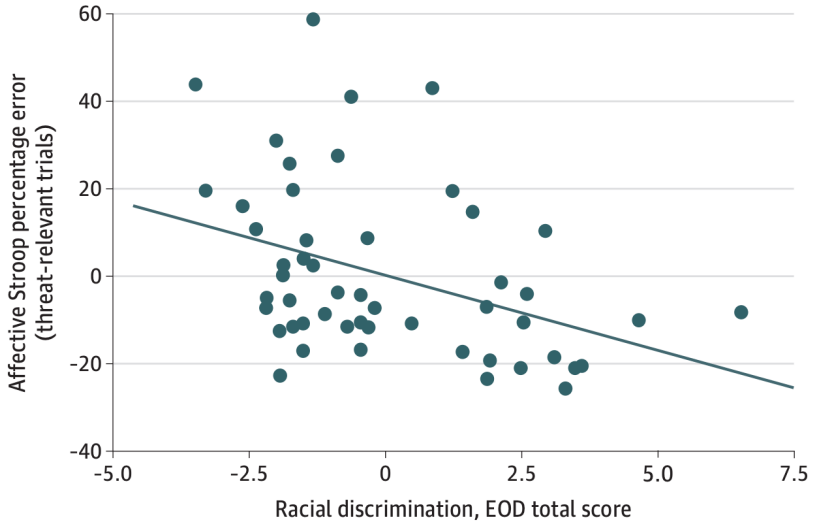
Socioeconomic inequities drive race-related differences in neurophysiological responses to threat

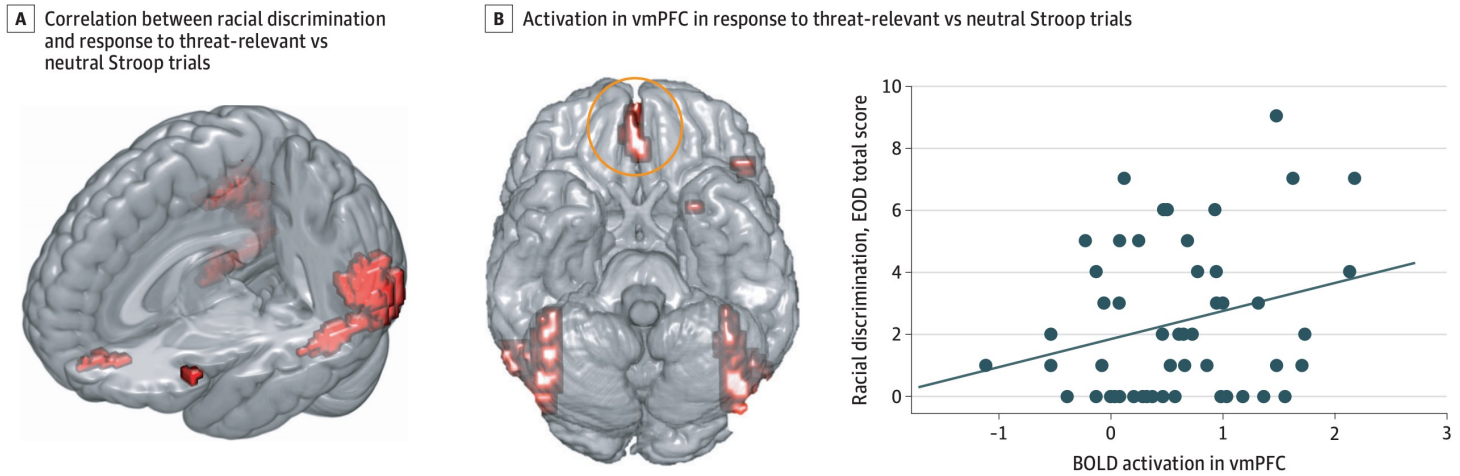
Harnett et al., 2019, *NeuroImage*

Racial discrimination and threat circuitry



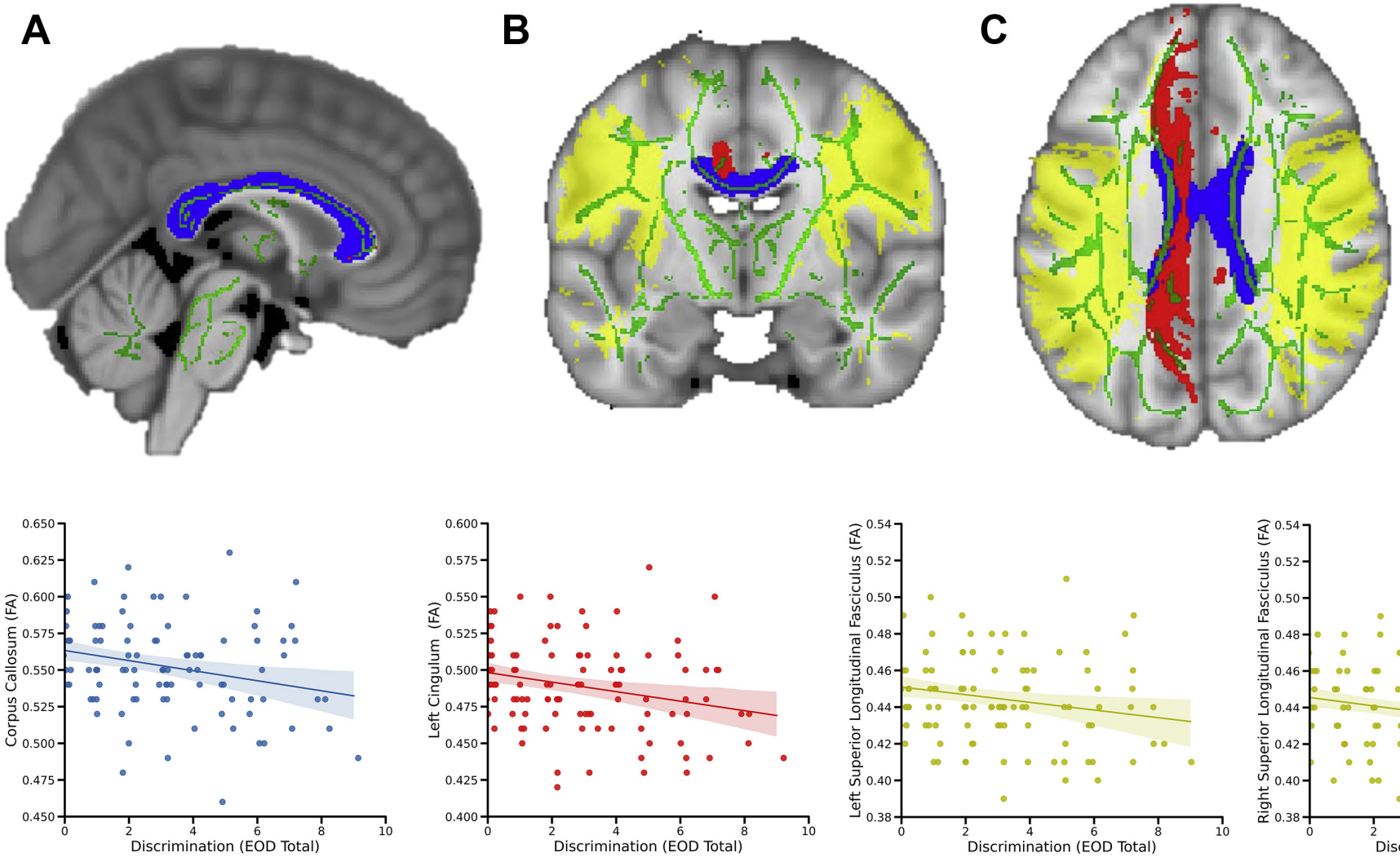
Supplemental Figure 1. Schematic Representation of Affective Number Stroop. A) number congruent, B) number incongruent and C) view only trials.





Fani et al., 2021; Fani et al., 2022; Okeke et al., 2022

Racial discrimination and threat circuitry



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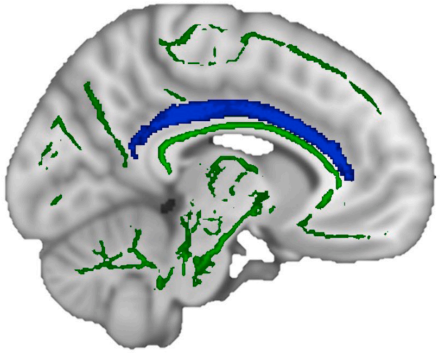
Racial discrimination and threat circuitry



Left Anterior Cingulum

a = -.003*

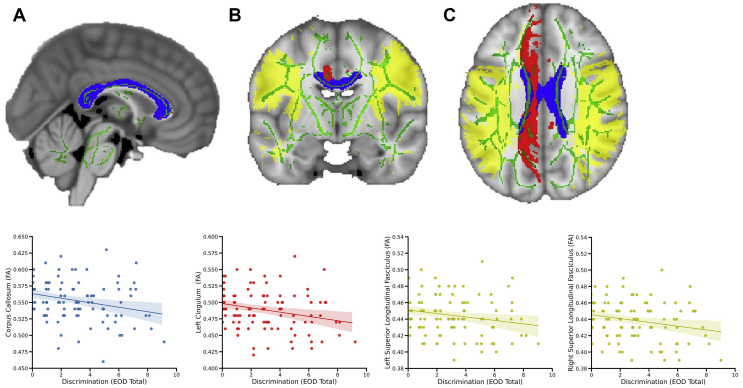
b = -20.65*

Racial Discrimination

c = .28*

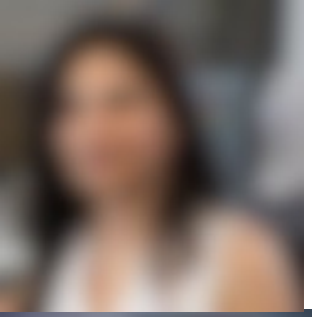
c' = .22*

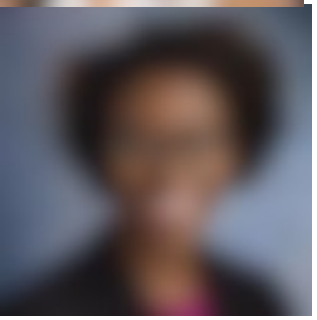
Health Problems



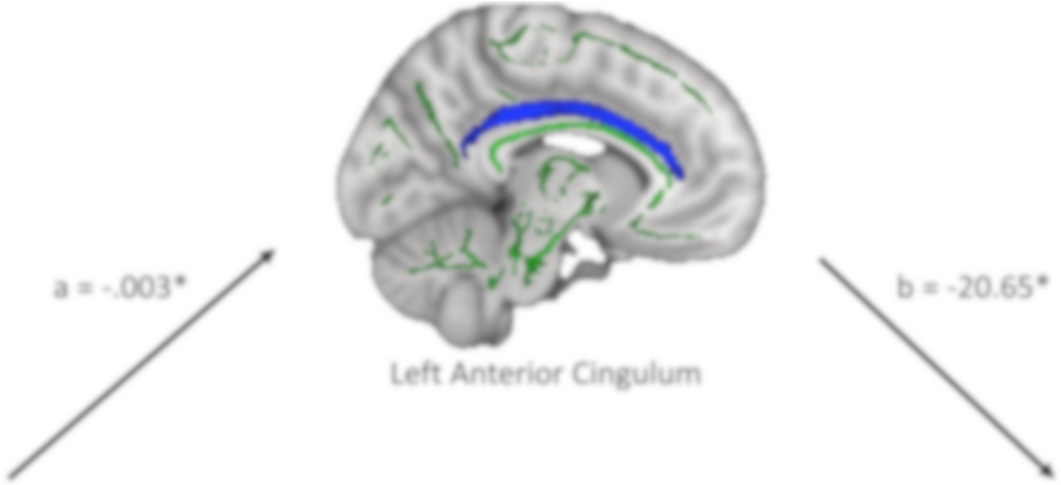
Even though individuals *performed* better, the greater exposure to racism *worsened* brain structure *and contributed to more health problems.*

Fani et al., 2021; Fani et al., 2022; Okeke et al., 2022

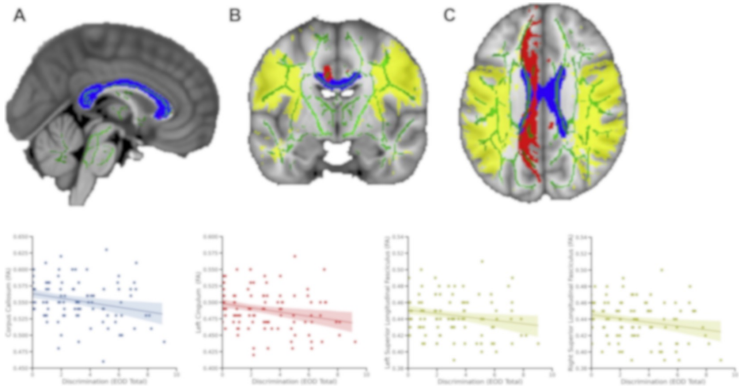




Racial discrimination and threat circuitry



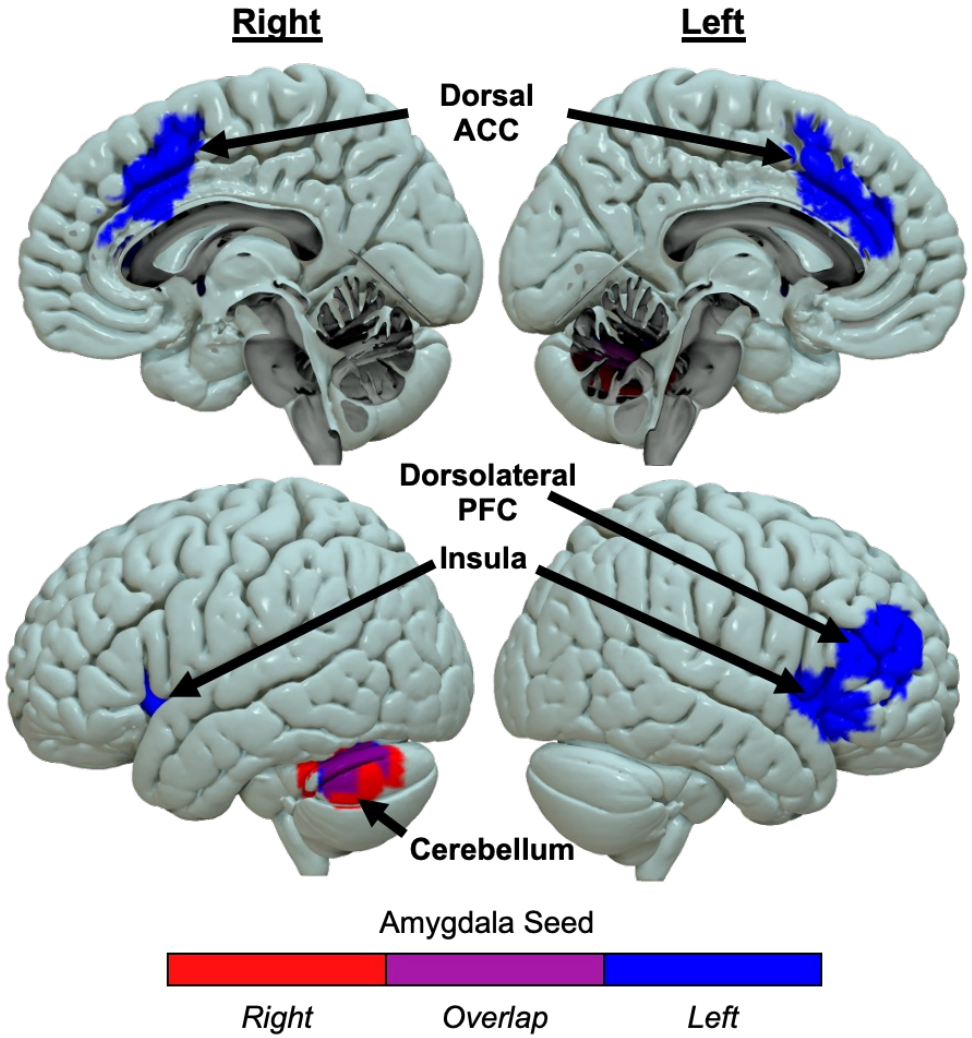
Individuals develop adaptive brain coping mechanisms to deal with stress, but these can have a major cost and contribute to downstream health problems

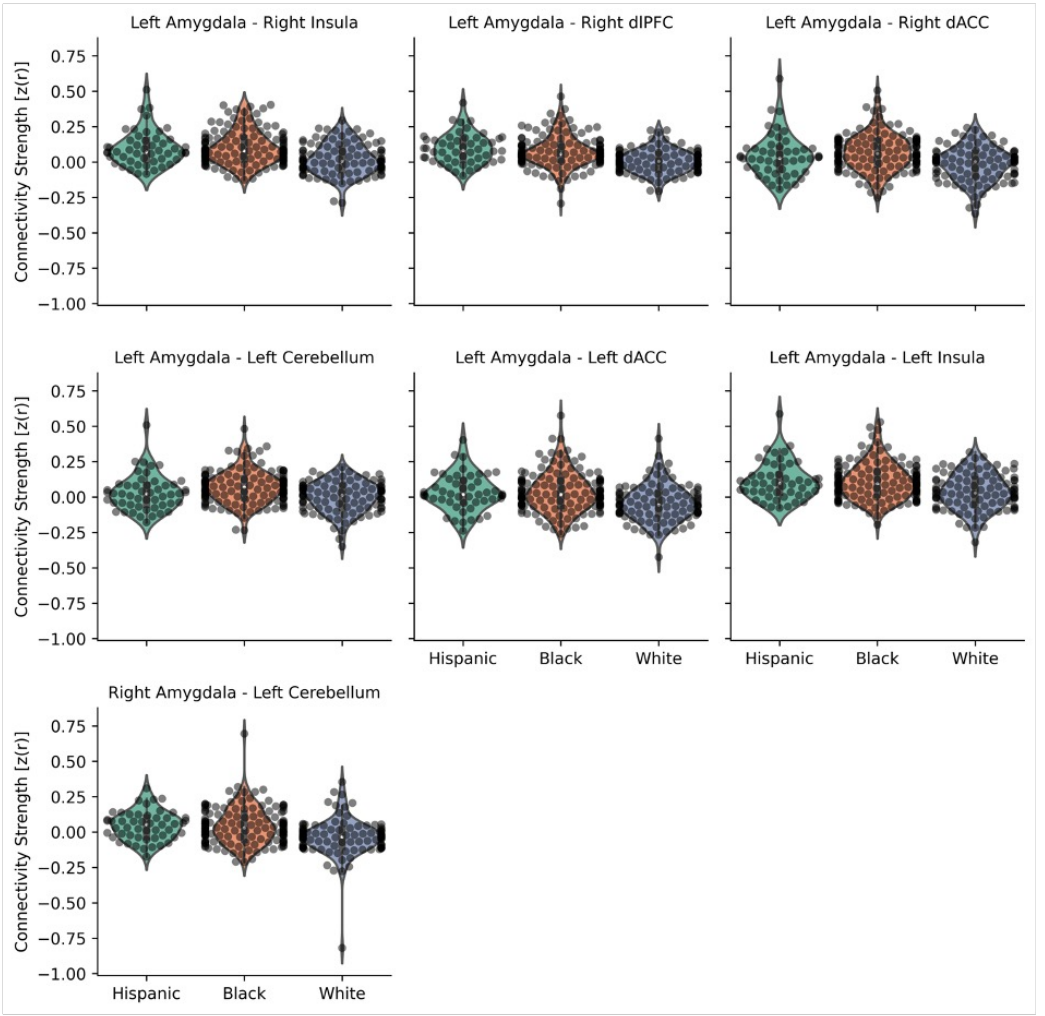


Even though individuals *performed* better, the greater exposure to racism *worsened* brain structure *and contributed to more health problems.*

Fani et al., 2021; Fani et al., 2022; Okeke et al., 2022

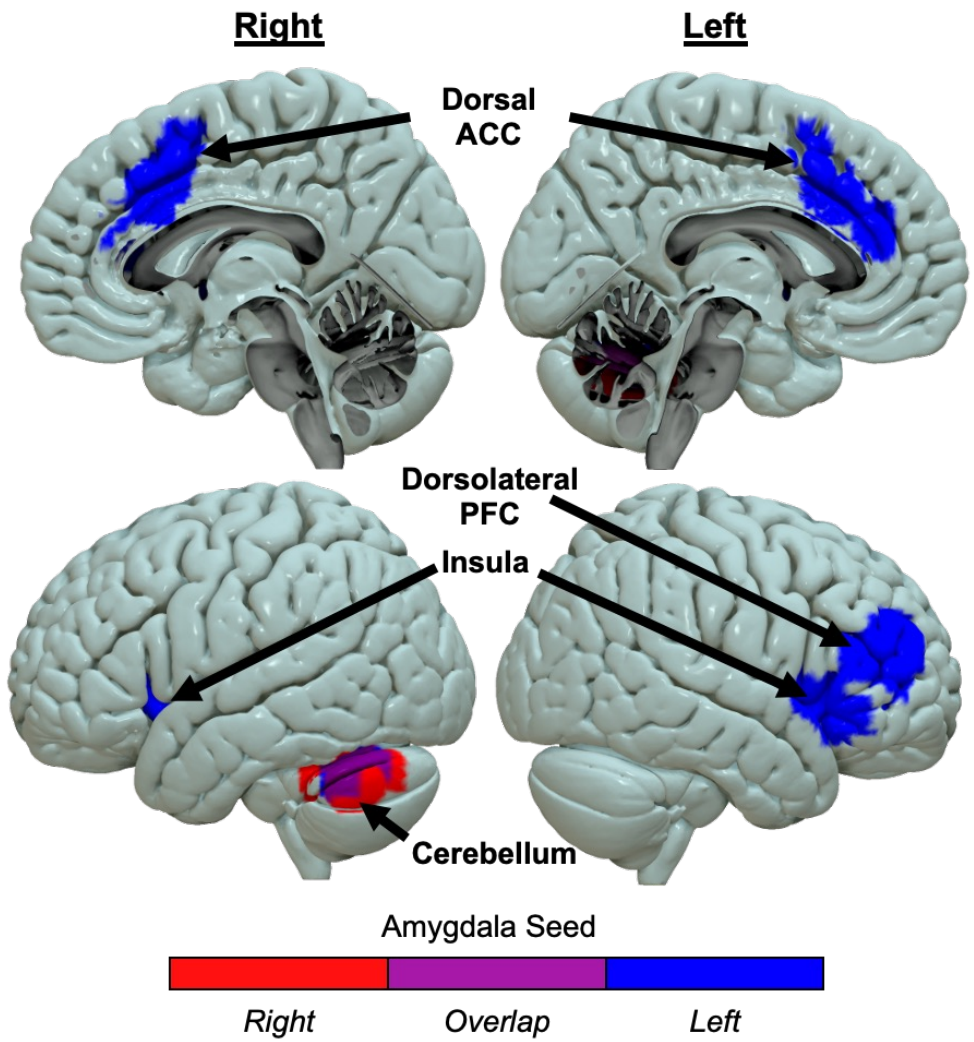
Racial inequity affects brain-based biomarkers

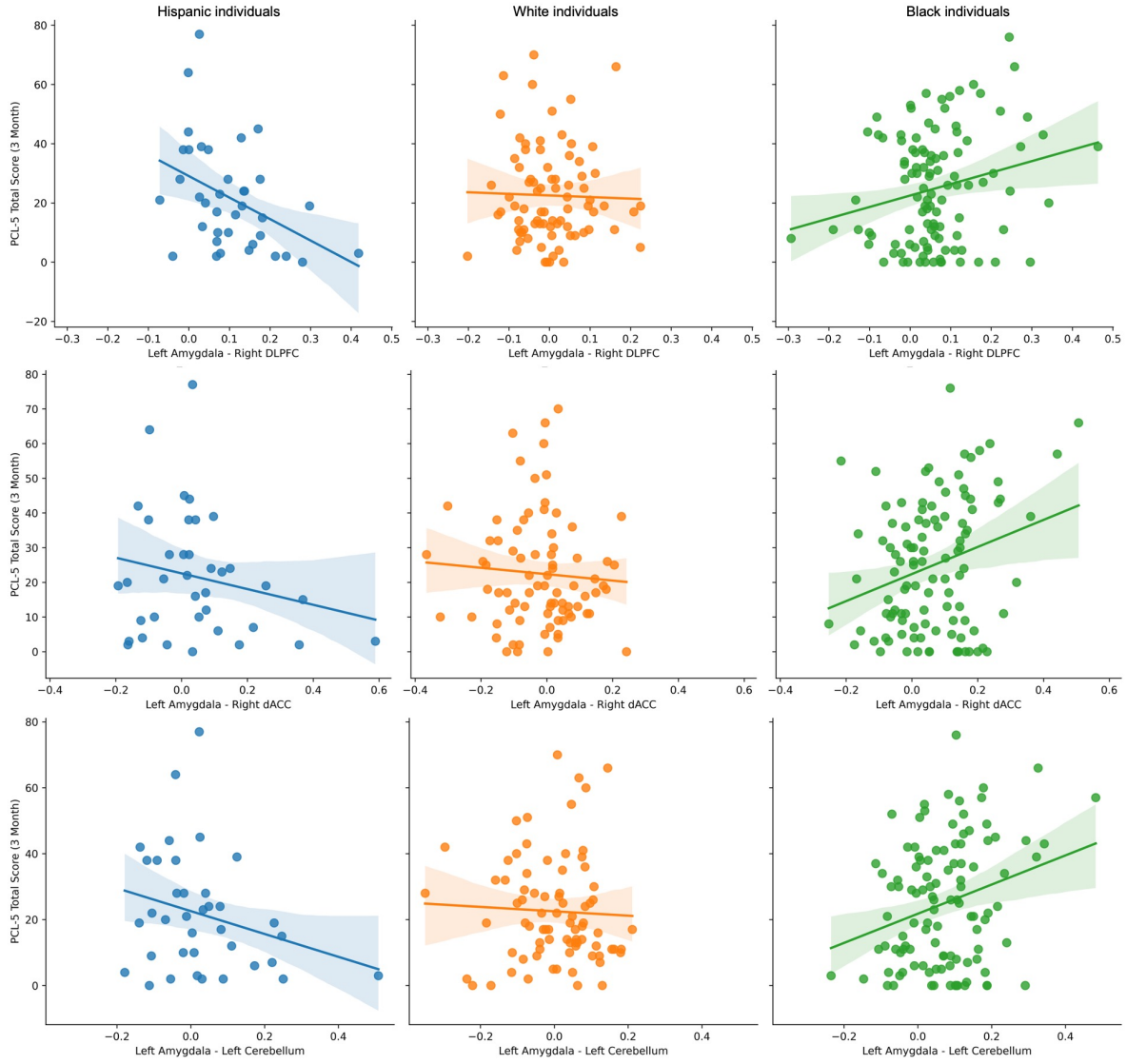




Harnett et al., 2023, *Molecular Psychiatry*

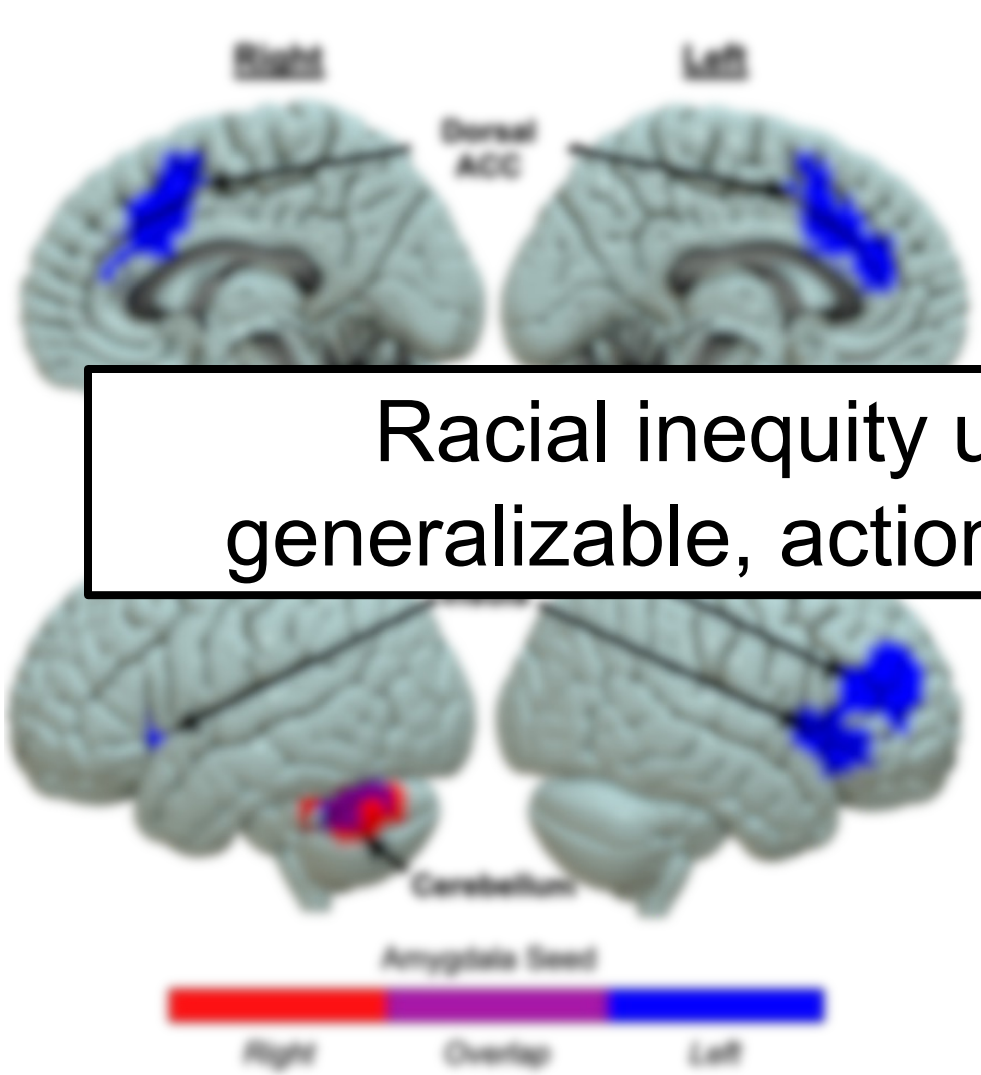
Racial inequity affects brain-based biomarkers

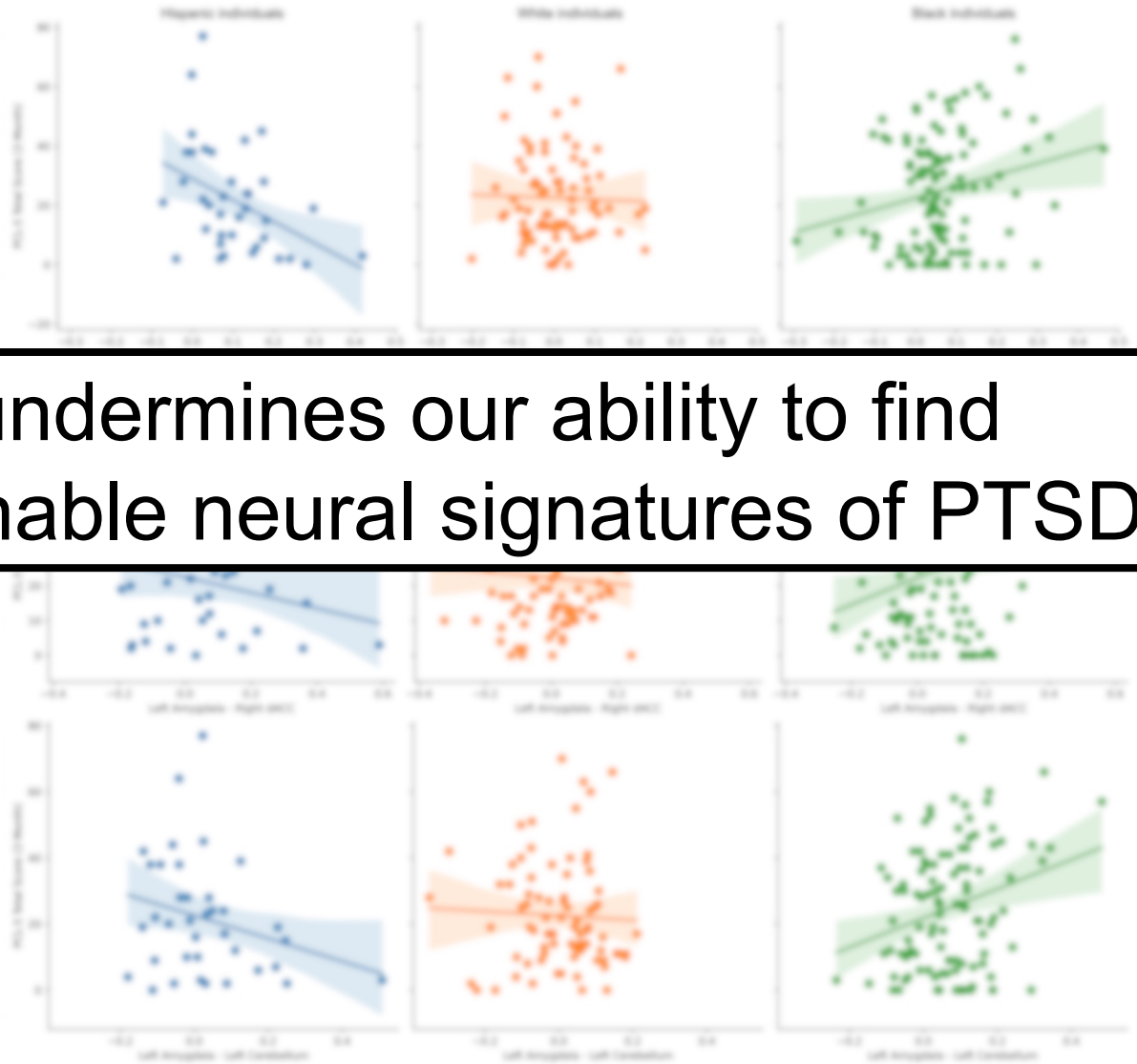




Harnett et al., 2023, *Molecular Psychiatry*

Racial inequity affects brain-based biomarkers

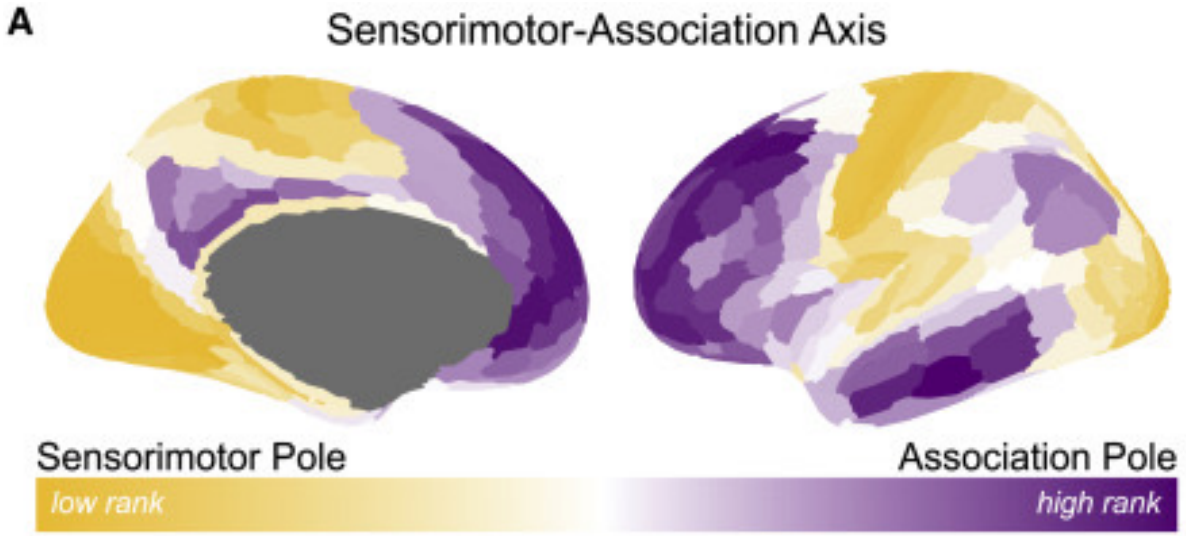


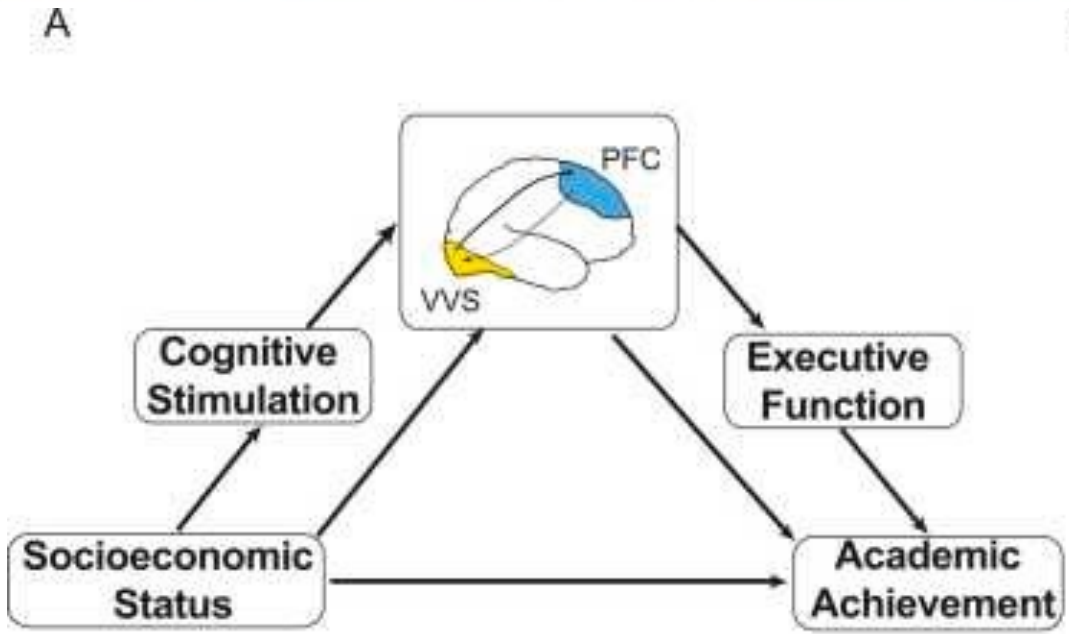


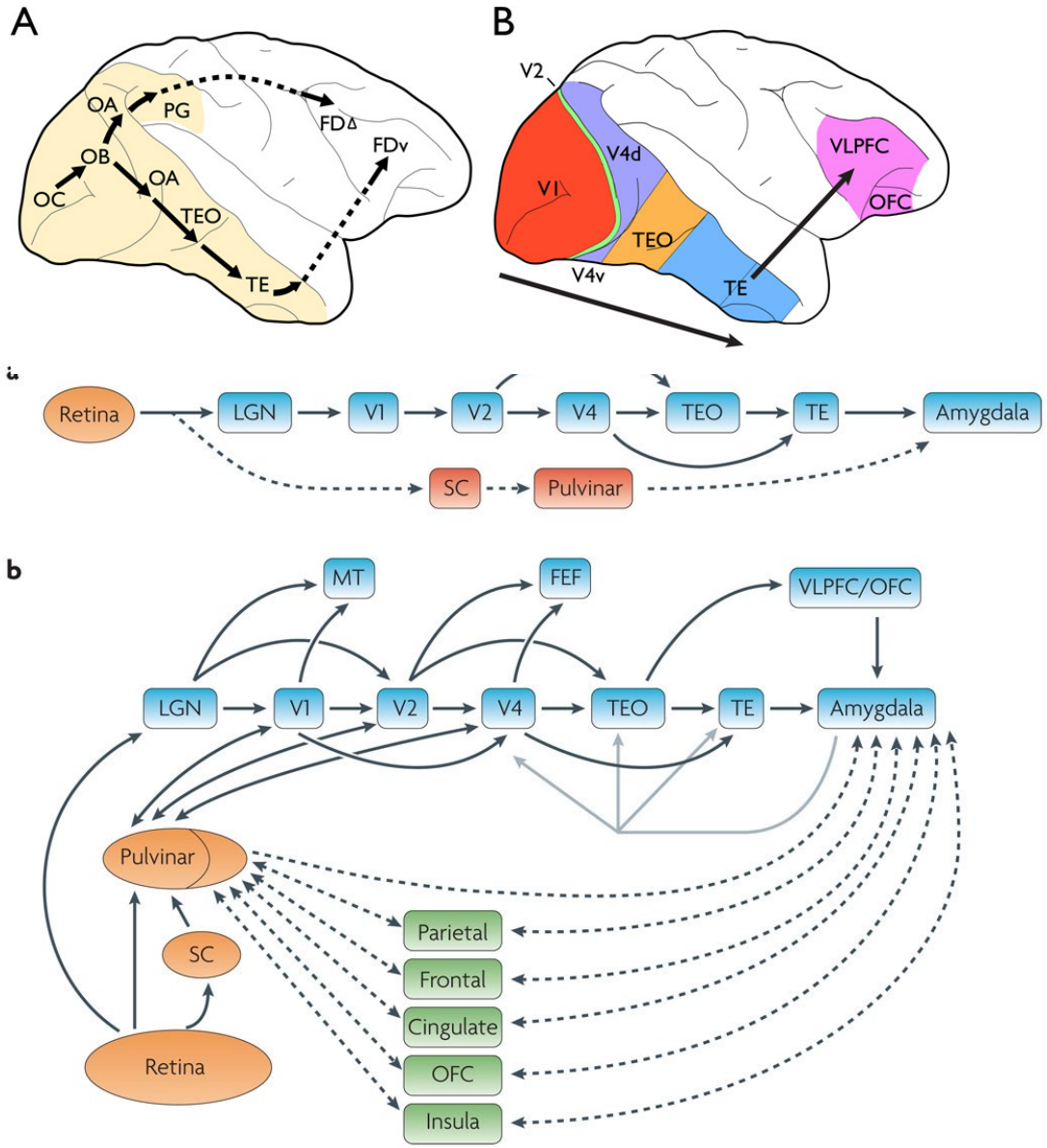
Racial inequity undermines our ability to find generalizable, actionable neural signatures of PTSD

Harnett et al., 2023, *Molecular Psychiatry*

Sensory circuitry and PTSD susceptibility

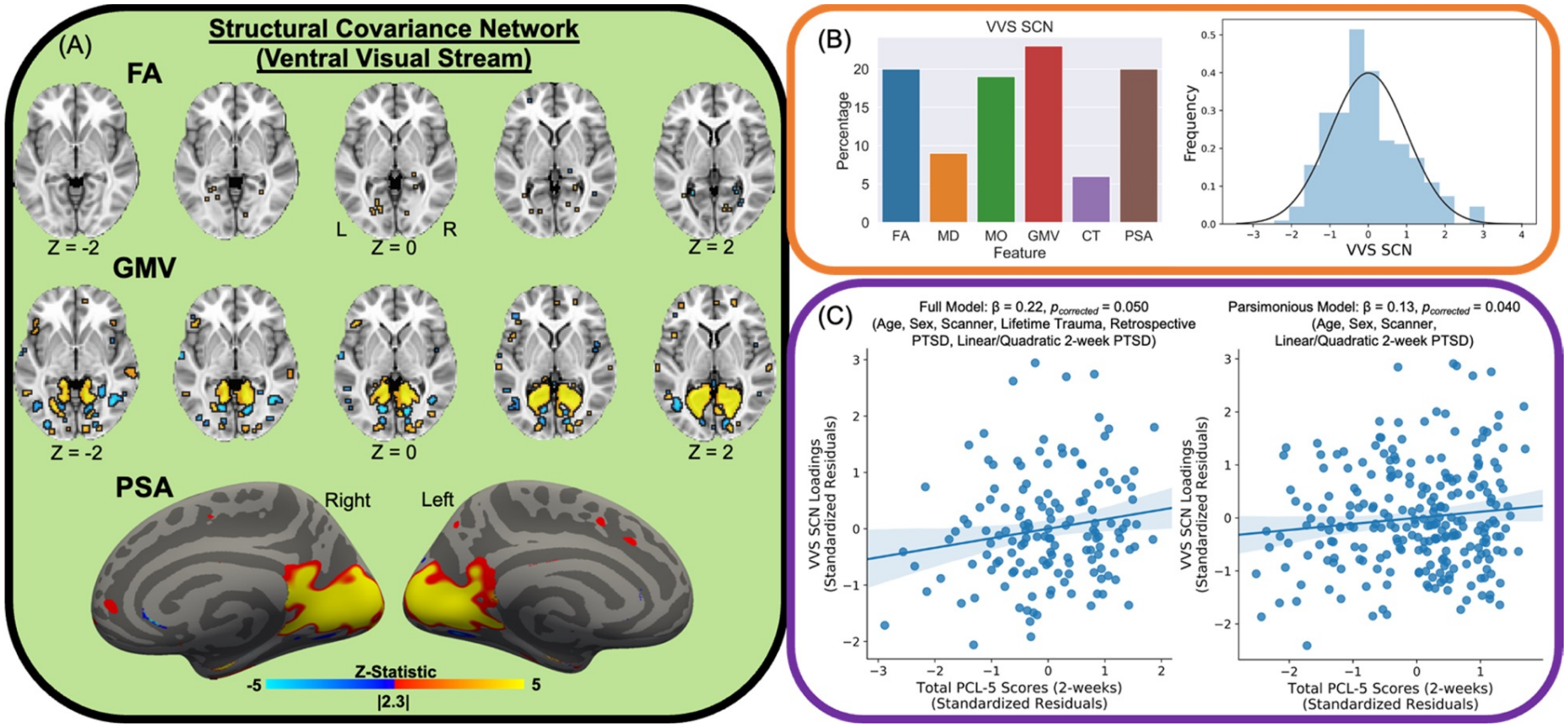






Sydnor et al., 2021; Rosen et al., 2021 Pessoa & Adolphs, 2010; Kravitz et al., 2013

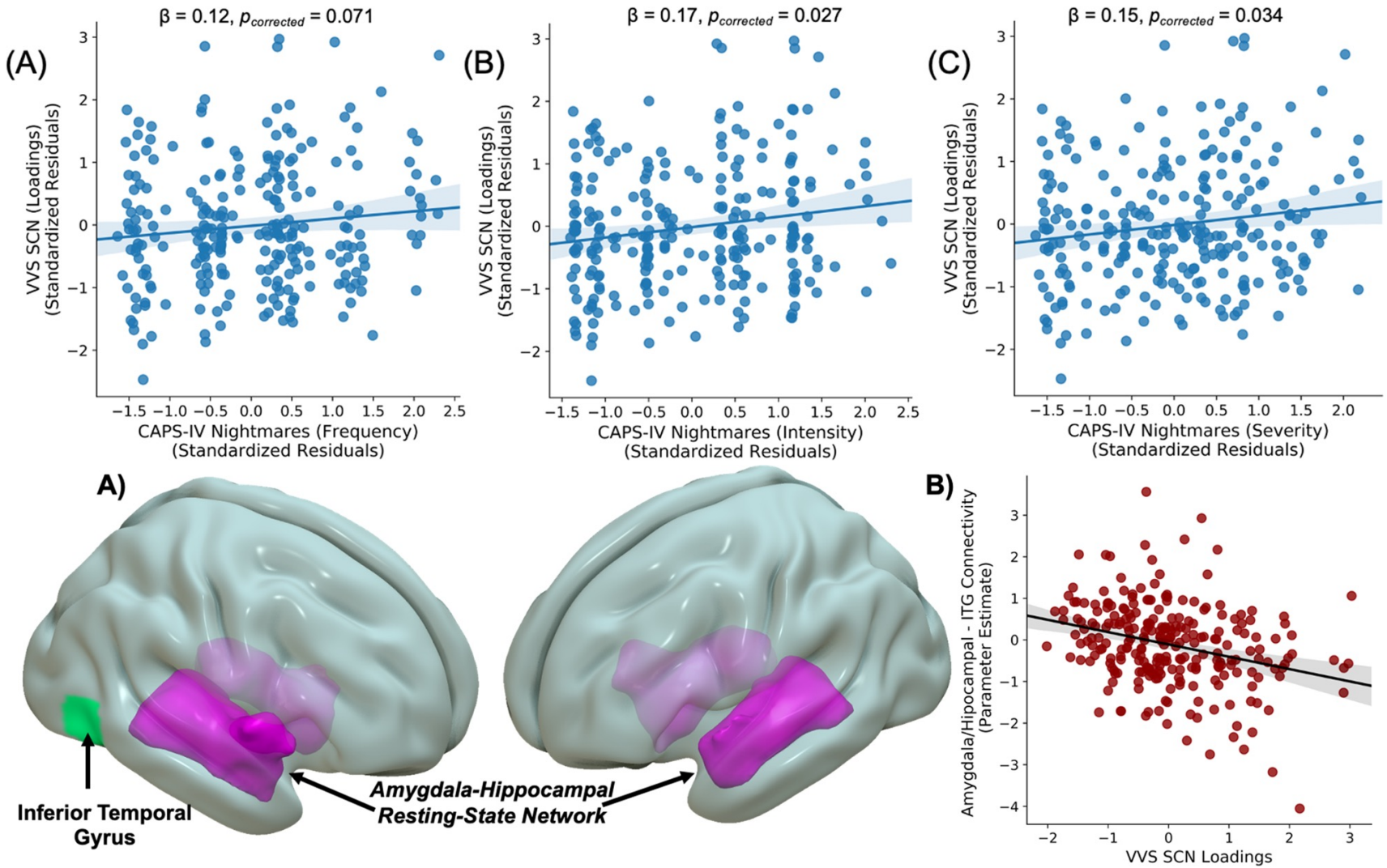
Affective visual circuitry and PTSD susceptibility



Ventral visual stream analog is reliably associated with PTSD symptoms in the early aftermath of trauma, and the change in symptoms, in two separate datasets.

Harnett et al., 2022, *Trans. Psych.*

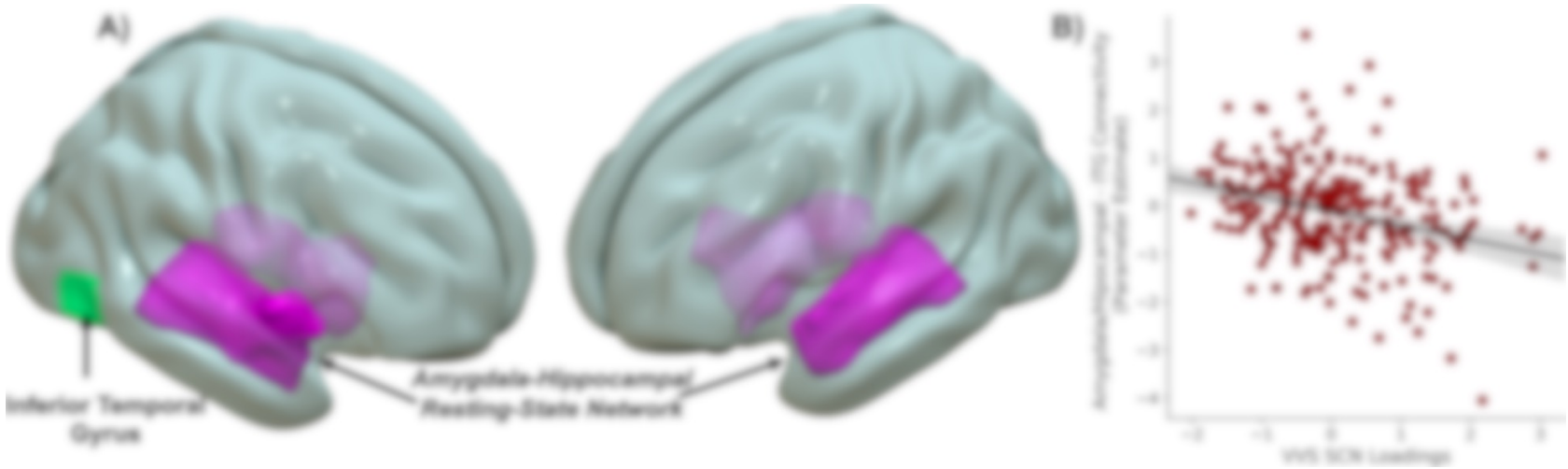
Affective visual circuitry and PTSD susceptibility



Harnett et al., 2022, *Trans. Psych.*

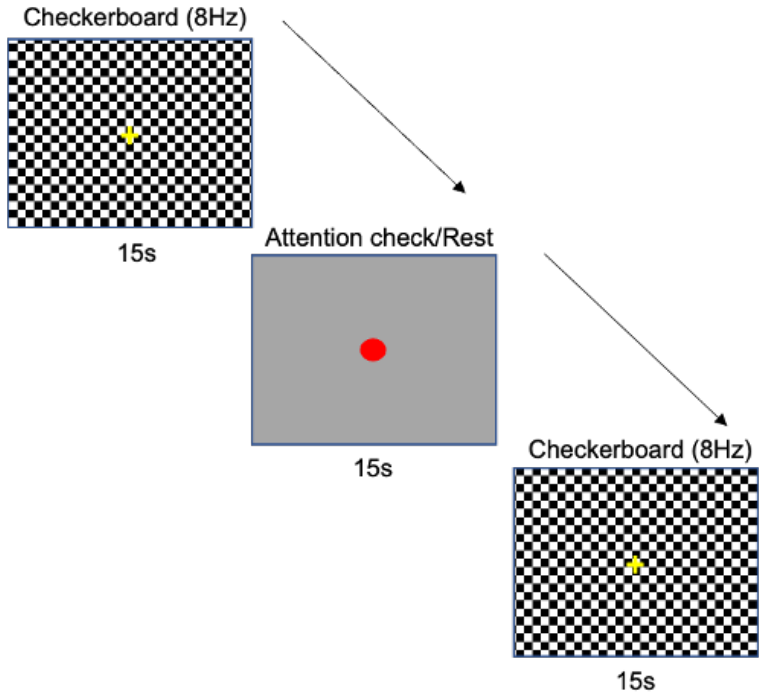
Affective visual circuitry and PTSD susceptibility

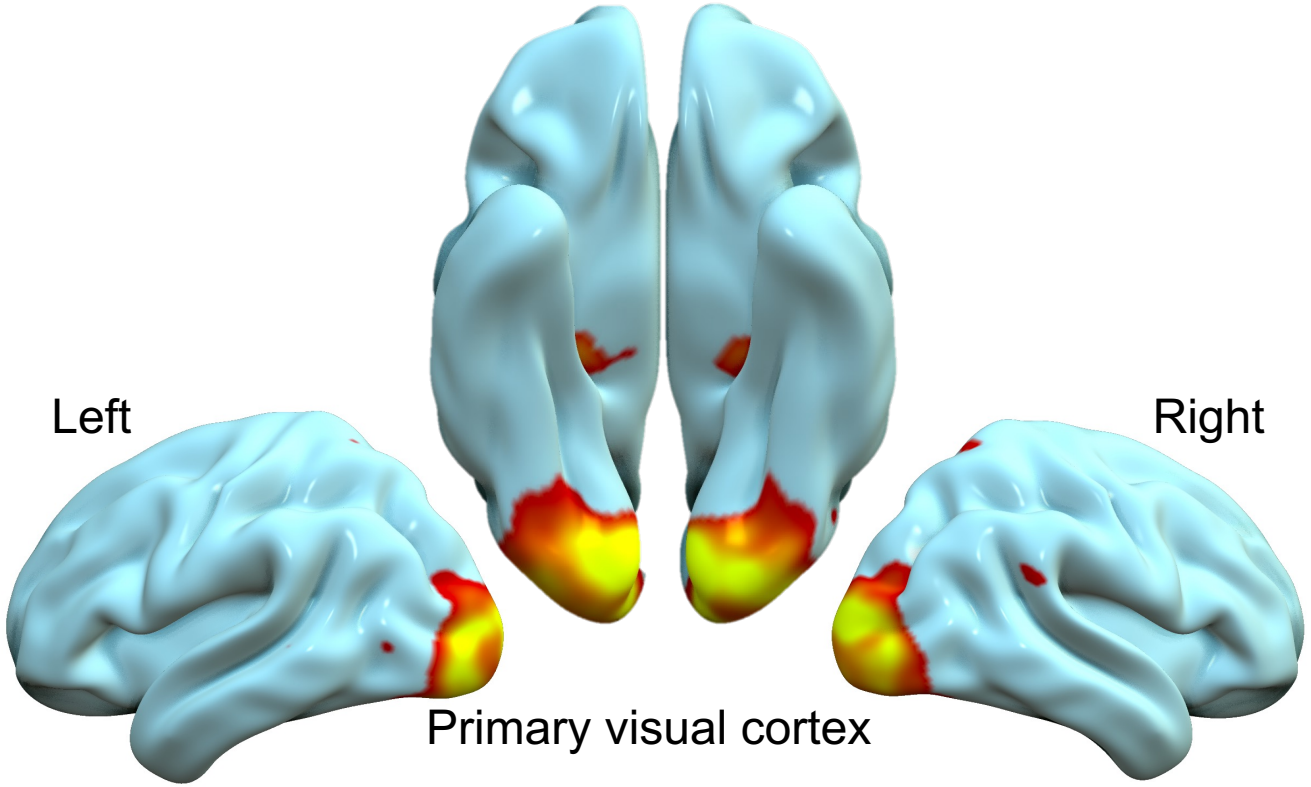
PTSD susceptibility is reliably and robustly associated with function and structure of sensory/threat circuitry



Harnett et al., 2022, *Trans. Psych.*

Affective visual circuitry and PTSD susceptibility

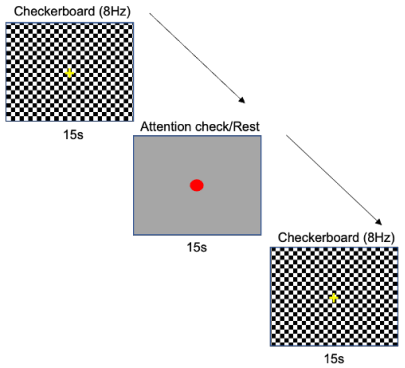


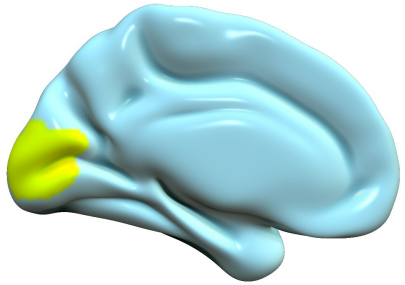


Ongoing research using a visual stimulation procedure (flickering checkerboard, on/off) to index neural reactivity to non-affective visual stimuli

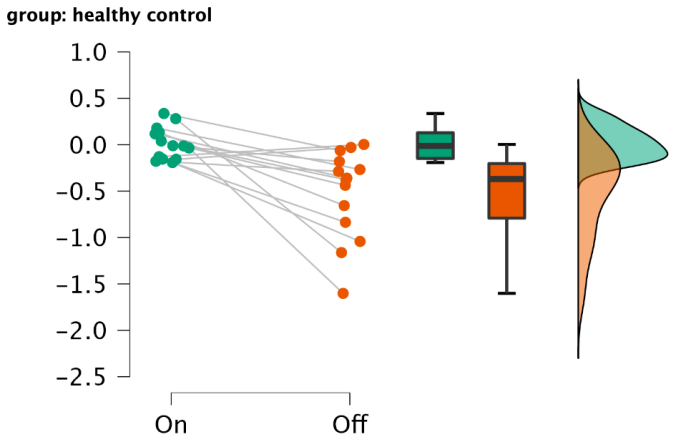
Harnett et al., In Progress

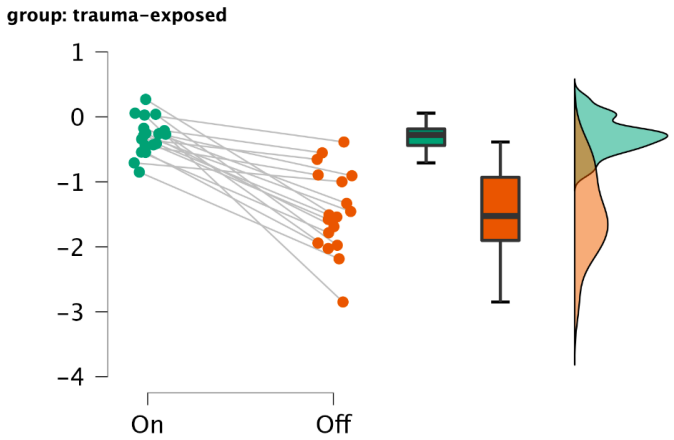
Affective visual circuitry and PTSD susceptibility

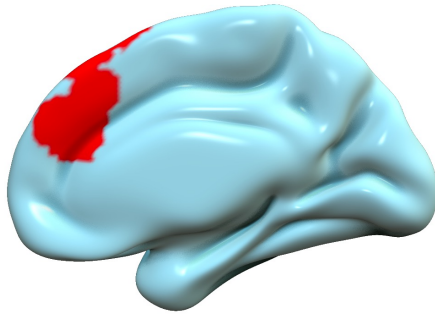




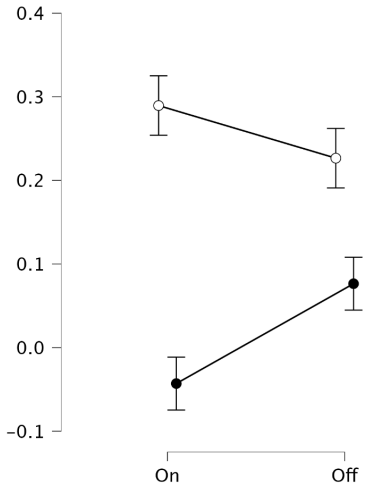
Primary visual cortex

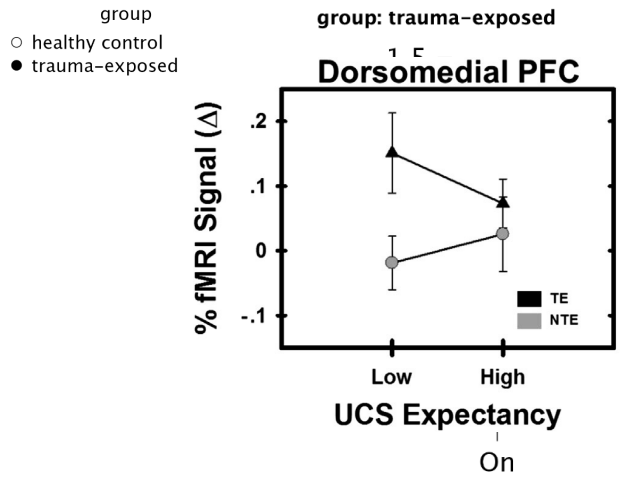


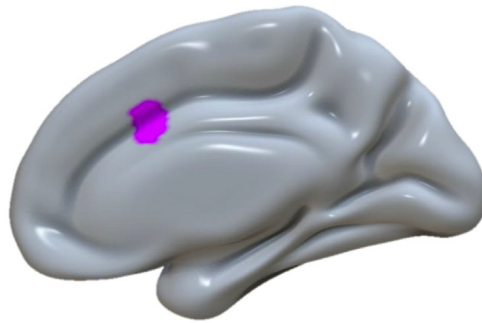




Dorsomedial PFC



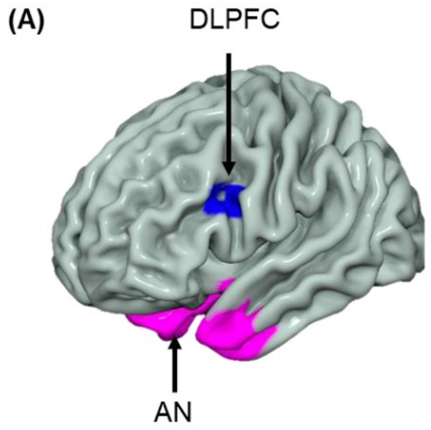


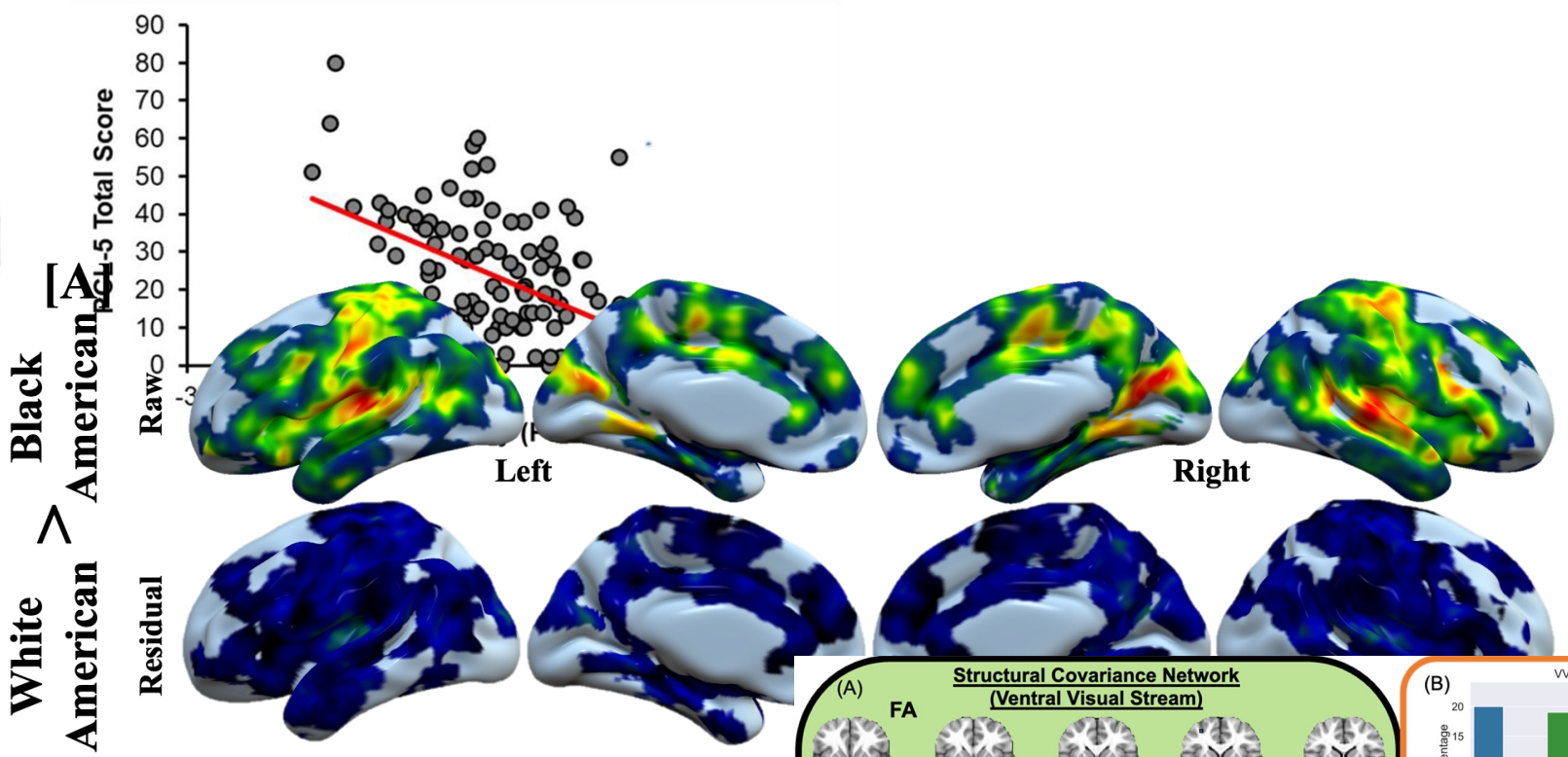


Recent trauma survivors show greater deactivation once the stimulation ends, and are showing altered patterns within the dorsomedial PFC reflecting earlier affective studies

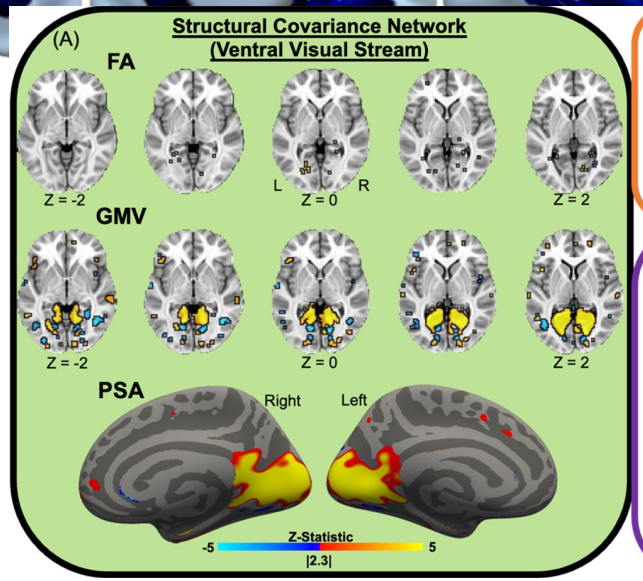
Harnett et al., In Progress

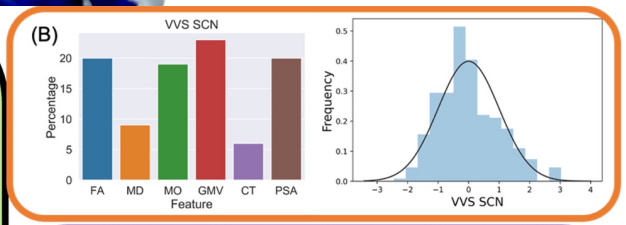
Summary

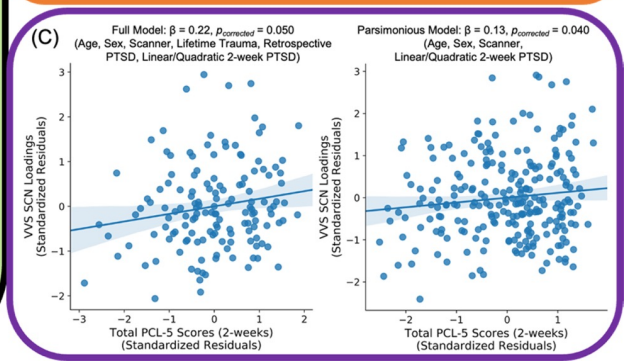




Harnett et al., 2019, *NeuroImage*







What does this mean for MRI-markers of PTSD?

- Neuroimaging in early aftermath of trauma may provide important information about neurobiology related to the development of posttraumatic dysfunction.

- We need to consider prior life events that may shape our brains in the early aftermath of a later trauma.
  - Particularly important we begin to think about how race-related disparities may impact our predictive models if we want to develop generalizable markers of PTSD.

What does this mean for MRI-markers of PTSD?

Core threat circuitry is integral to understanding expression and maintenance of PTSD symptoms from acute to long-term phases.

Structural covariance of the ventral visual stream is a cross-modality marker of early PTSD symptom development and prognosis.

New work is needed to better understand the interaction across neural circuits related to the pathophysiology of PTSD.

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