Mindfulness Training for Resilience in Early Life: A Neurobiological Perspective

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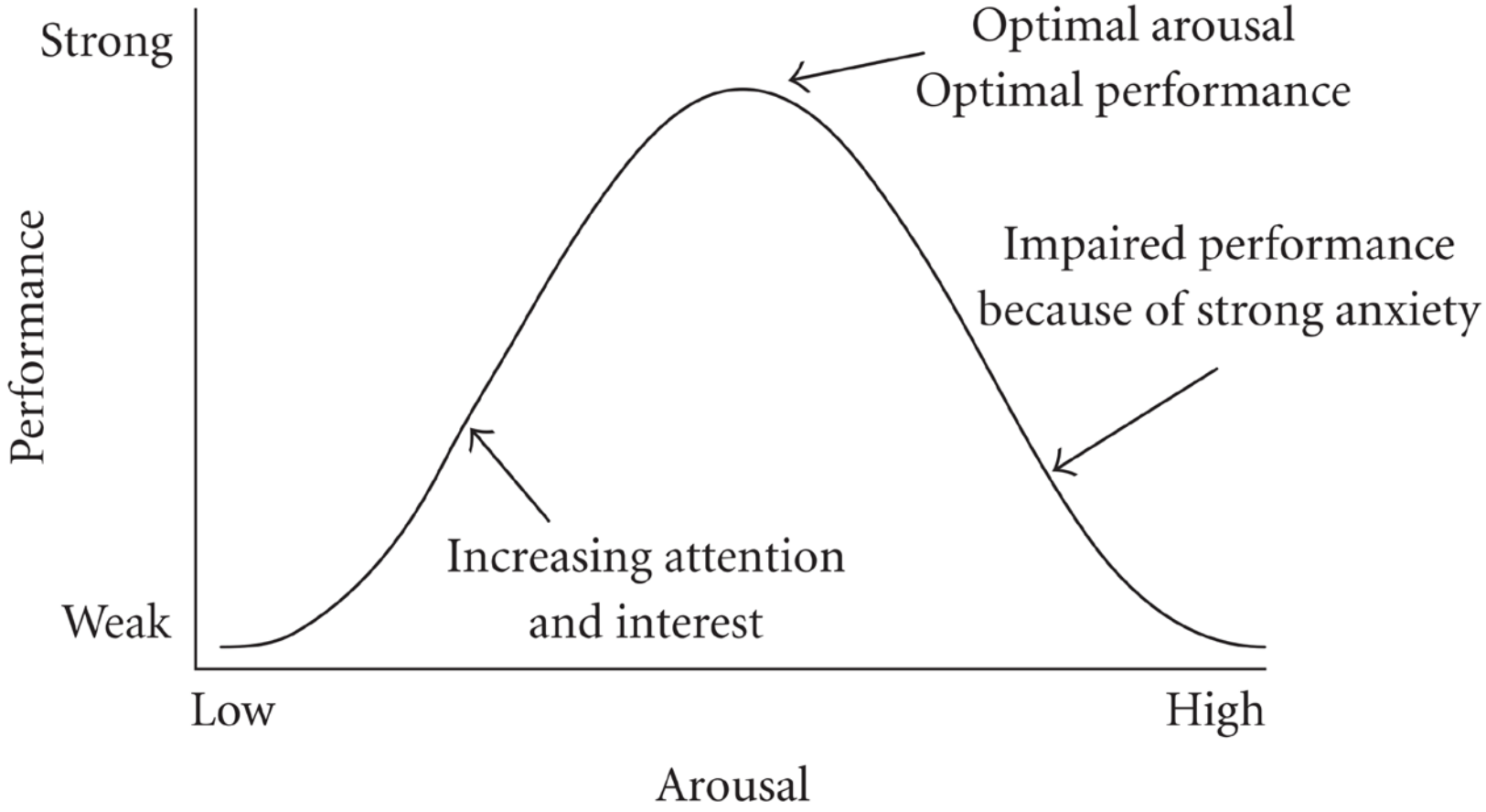
STRESS

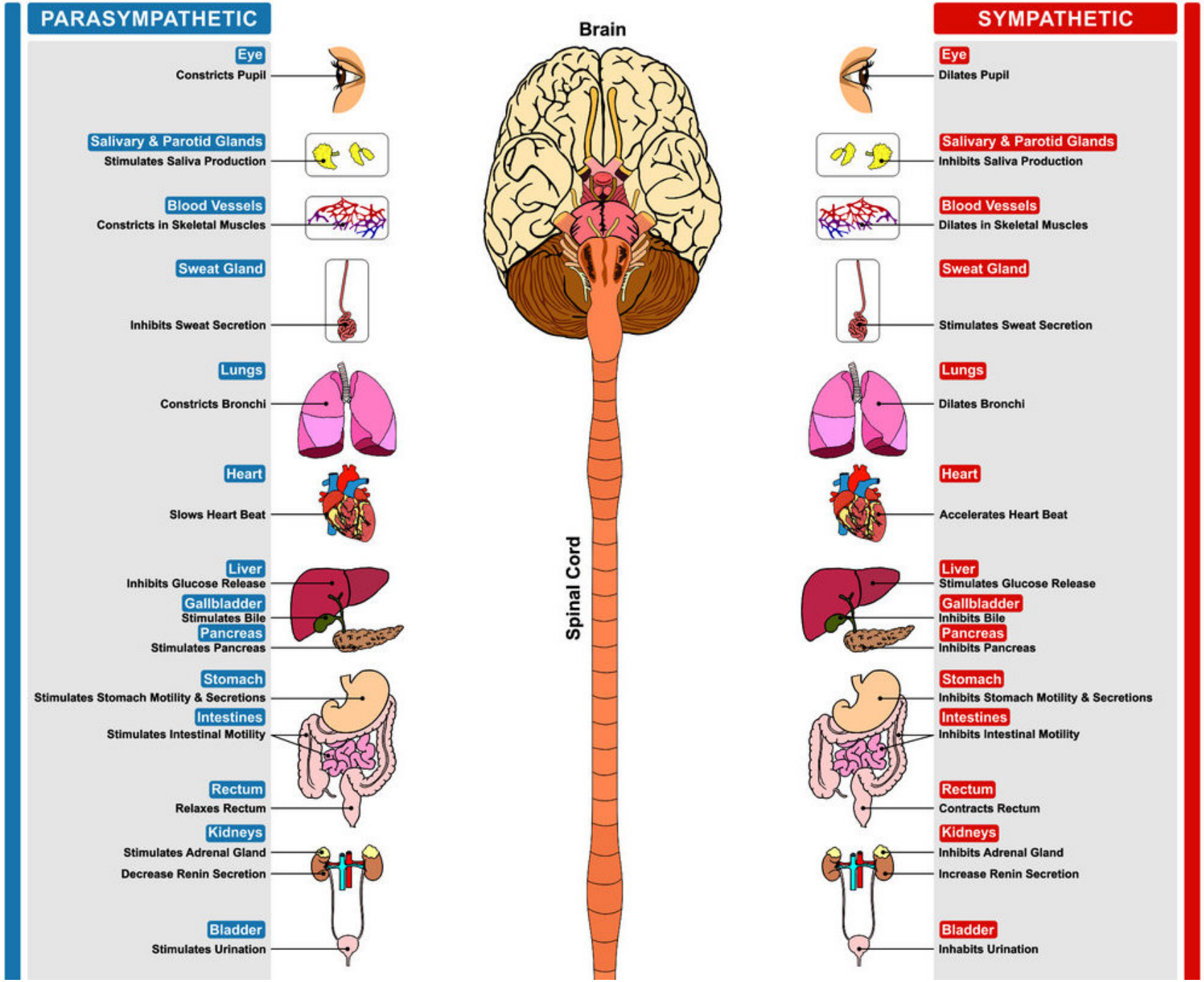
pressure or tension exerted on a material object

a state of mental or emotional strain or tension resulting from adverse or very demanding circumstances

What happens when you face a stressor



Rabe et al., 2013; Marketon et al., 2010



Rabe et al., 2013;
Marketon et al., 2010

Hypothalamic-pituitary-adrenal (HPA) system

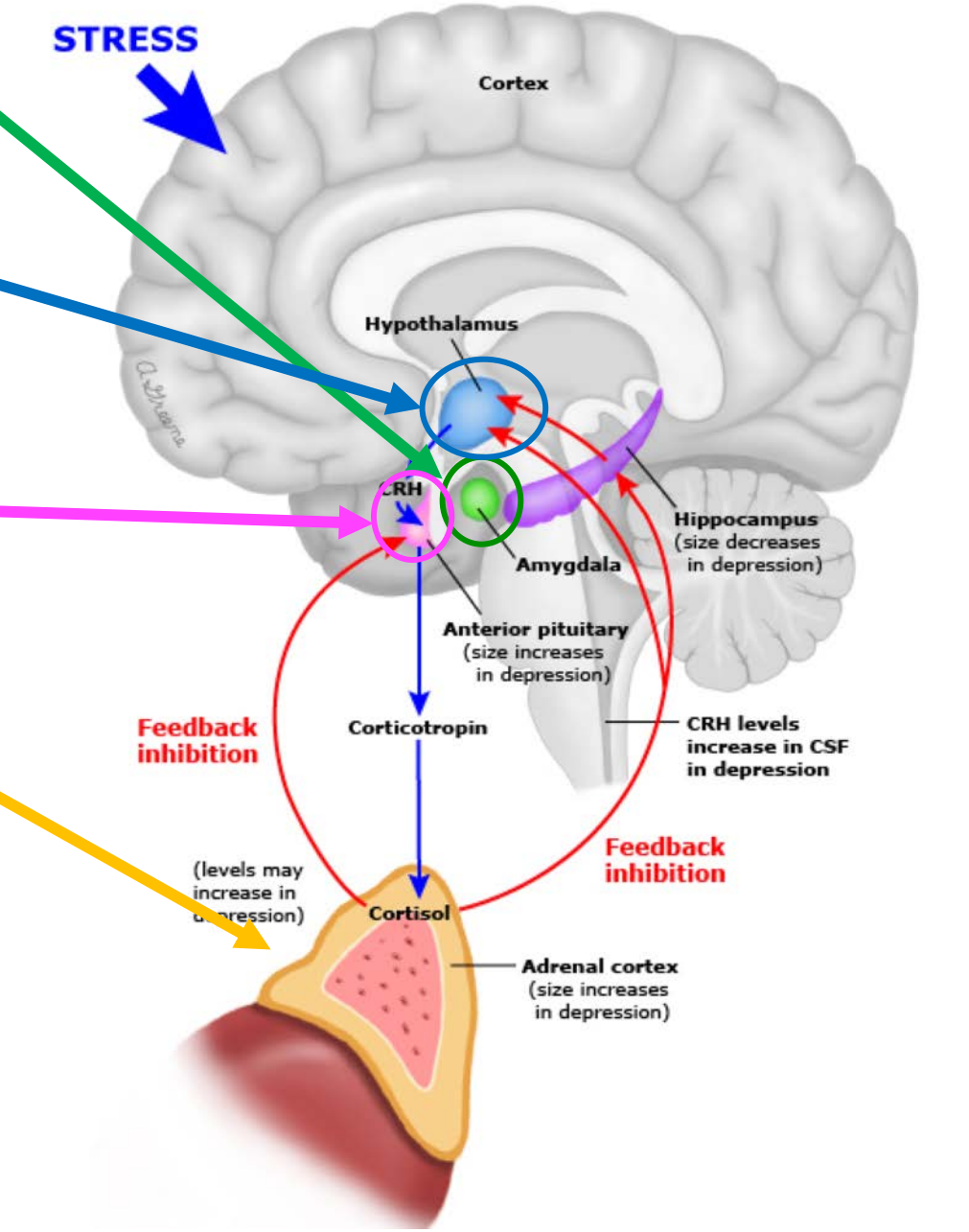
Amygdala – detects salient information in our environment.

Hypothalamus – releases hormones that in turn stimulates the pituitary gland.

Pituitary Gland – releases hormones that in turn stimulates the adrenal gland.

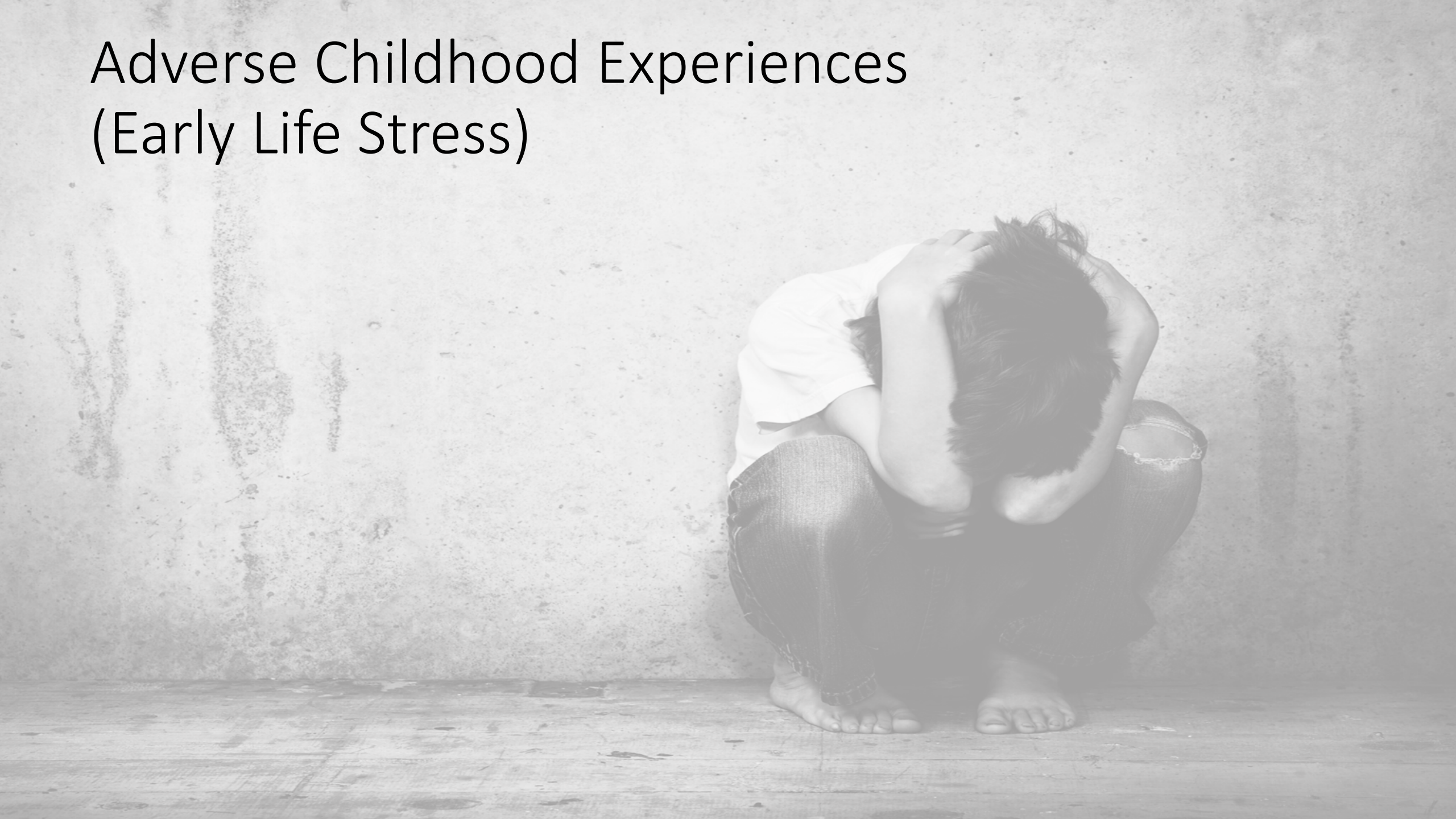
Adrenal Glands – endocrine glands above the kidneys that release cortisol

Cortisol– glucocorticoid; increases blood pressure, blood glucose, and suppresses immune system.



Heim et al. (2008).

Adverse Childhood Experiences (Early Life Stress)



Early Life Stress

- ACEs categories
  - Physical abuse and neglect
  - Emotional abuse
  - Sexual abuse
  - Interpersonal violence
  - Household psychopathology and substance abuse
  - Parental separation or divorce

- Other measures ELS
  - Childhood Trauma Questionnaire (28 items)
    - 5 subscales: physical abuse, physical neglect, emotional abuse, emotional neglect, sexual abuse. Also: denial score
    - Adds: severity of exposure (never true, rarely true, sometimes true, often true, and very often true)
  - Maltreatment and Abuse Chronology of Exposure (MACEs) scale
    - 10 subscales: emotional neglect, non-verbal emotional abuse, parental physical maltreatment, parental verbal abuse, peer emotional abuse, peer physical bullying, physical neglect, sexual abuse, witnessing interparental violence and witnessing violence to siblings
    - Adds: timelines

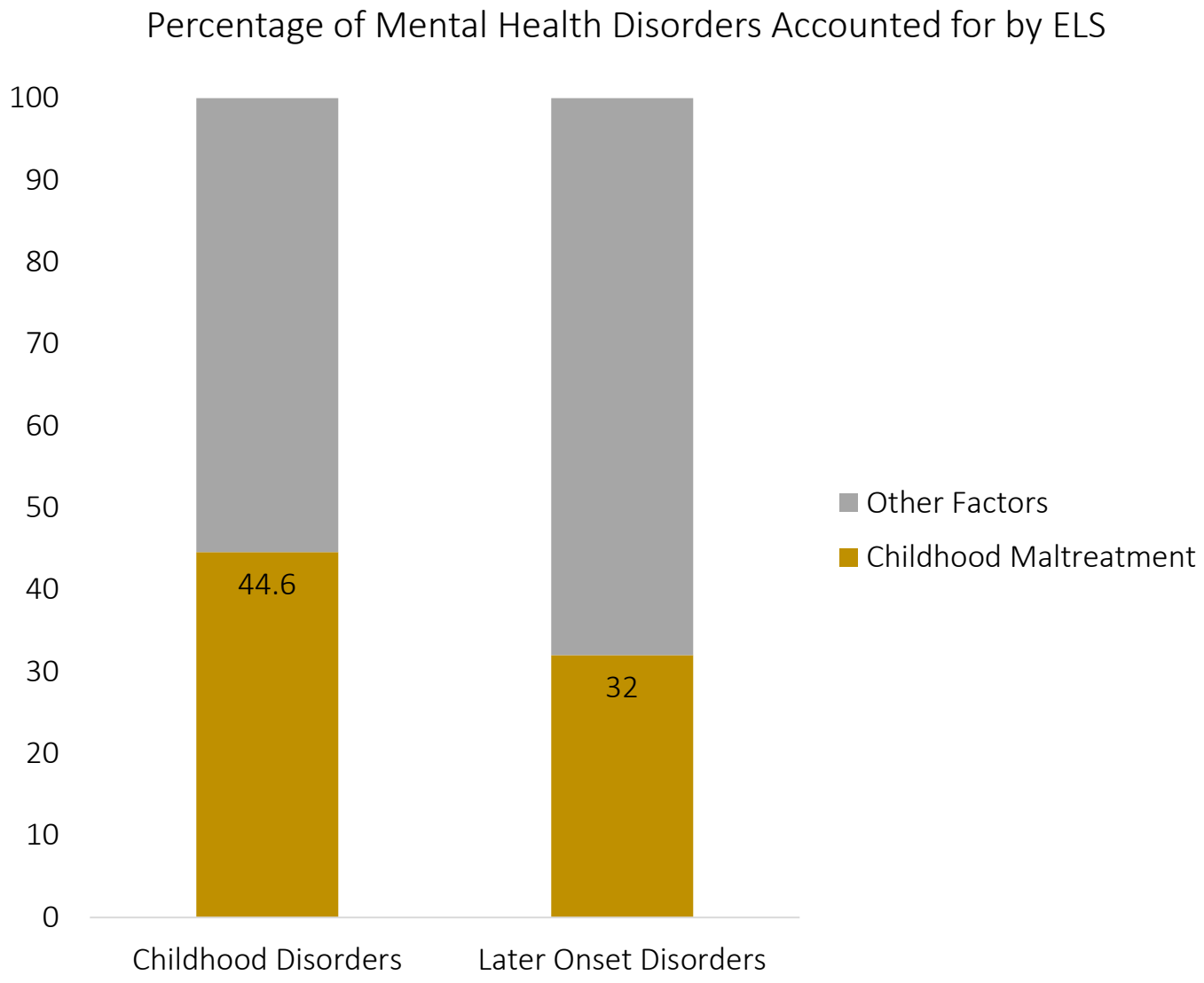
Early Life Stress

- Early Life Adversity (ELS) is a major public health crisis
  - More than 670,000 substantiated children and adolescents in the US
  - 1750 abuse and neglect related deaths in 2016
  - $120+ billion in yearly cumulative costs

- Highly prevalent in Oklahoma
  - 30% - economic hardship (45th)
  - 30% - divorce (50th)
  - 17% - parental alcohol/drug abuse (49th)
  - 11% - domestic violence (50th)
  - 12% - parent with mental illness (43rd)
  - 10% - incarcerated parent (48th)
  - 13% - victims of / witnessed neighborhood violence (49th)
  - 24% - 4 or more ACEs (50th)

US Department of Healthy and Human Services, 2014; Geles et al., 2012; Anda et al., 2006; CDC; Child Trends, 2014; 2016

Psychiatric consequences of ELS

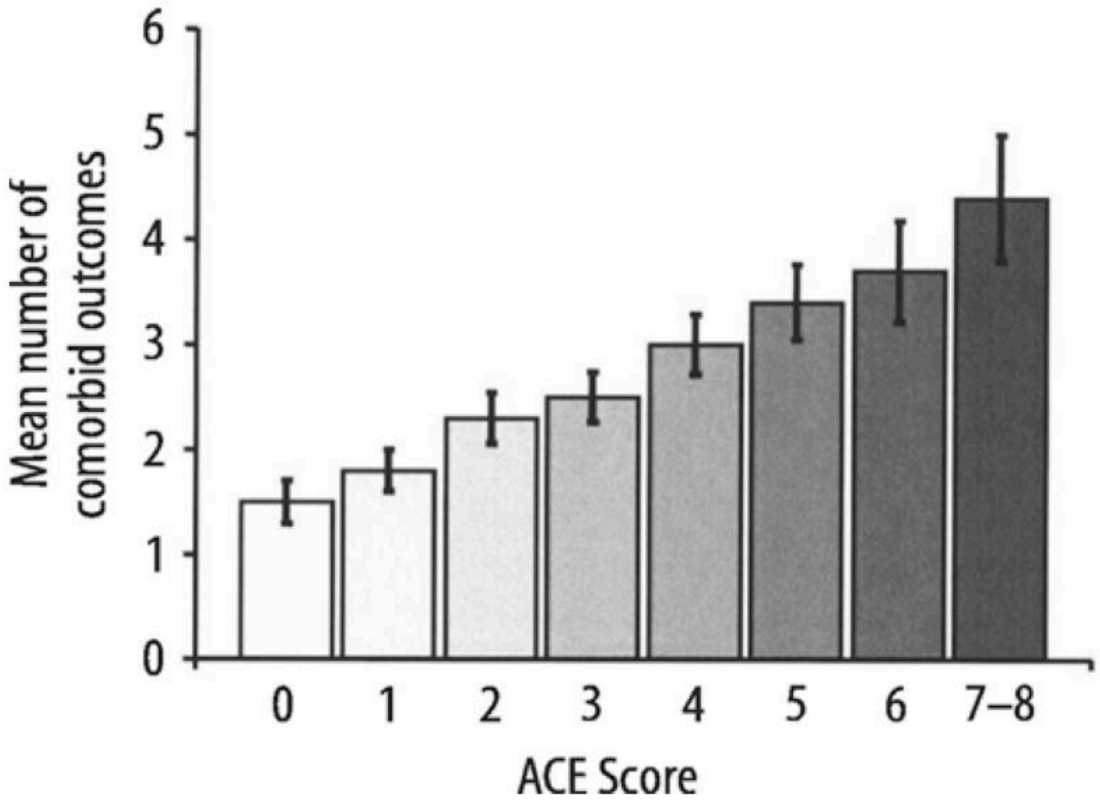


Green et al., 2010

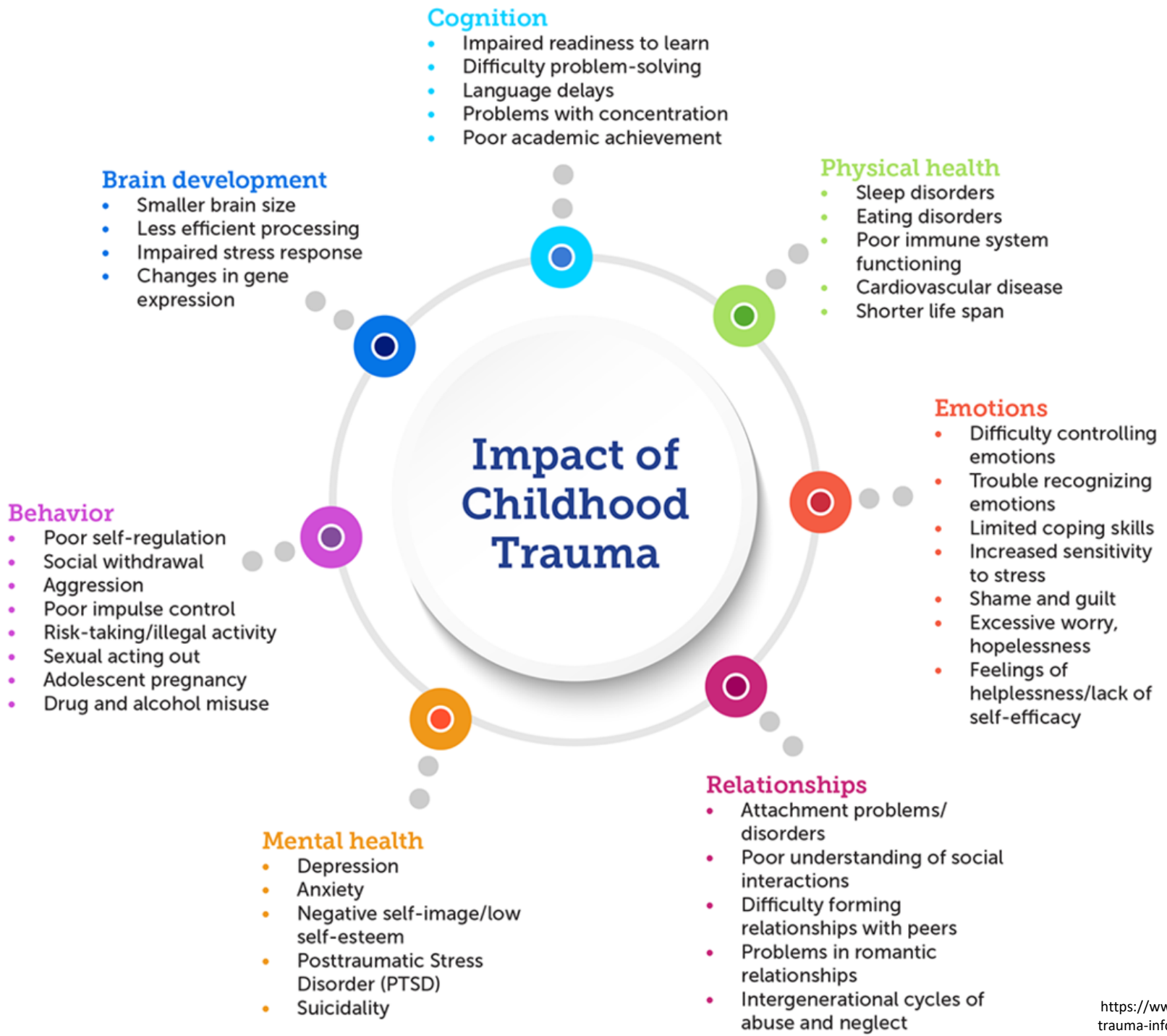
Psychiatric consequences of ELS

Table 1
Prevalence of each category of adverse childhood experience and reporting of additional ACEs

ACE category	*N*	Prevalence (%)	Additional ACEs (%)						
			0	≥1	≥2	≥3	≥4	≥5	≥6
Abuse									
Emotional	878	10.2	2	98	90	77	62	42	25
Physical	2,275	26.4	17	83	64	46	32	20	12
Sexual	1,812	21.0	22	78	58	42	29	19	12
Neglect									
Emotional	1,274	14.8	7	93	79	63	47	32	19
Physical	855	9.9	11	89	75	61	50	37	24
Household dysfunction									
Parental separation or divorce	1,125	13.0	18	82	61	43	30	19	12
Household substance abuse	2,435	28.2	19	81	60	41	29	18	11
Household mental illness	1,749	20.3	16	84	65	48	34	21	13
Domestic violence	2,081	24.1	5	95	82	64	48	32	20
Crime	516	6.0	10	90	74	56	43	30	23
Median			13.5	86.5	69.5	52.0	38.5	25.0	16.0
Range			2–22	78–98	58–90	41–77	29–62	18–42	11–25

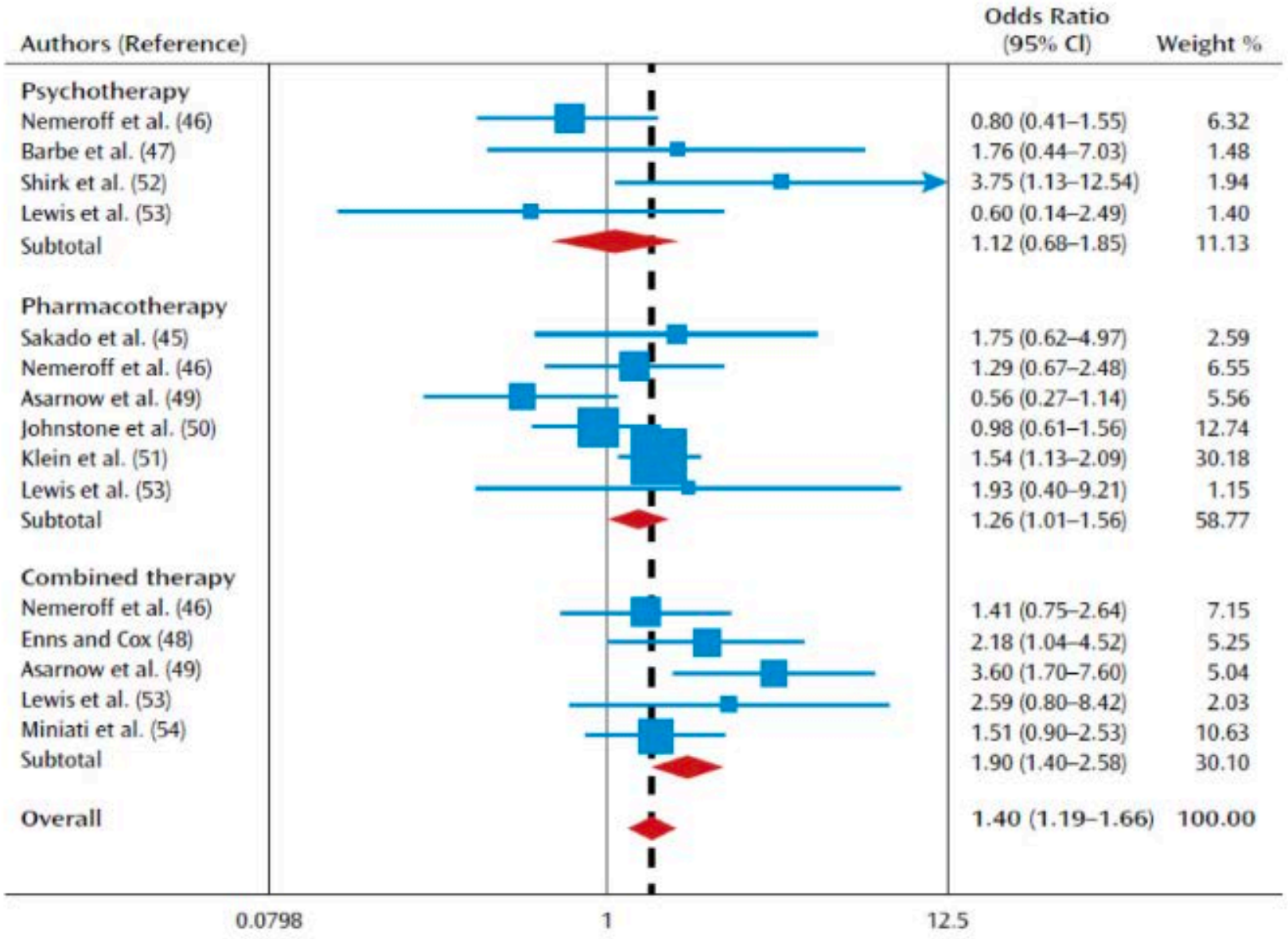


Anda et al., 2011; Dong et al., 2004



https://www.childtrends.org/publications/how-to-implement-trauma-informed-care-to-build-resilience-to-childhood-trauma

ELS and treatment outcomes



Nanni et al. (2012)

The gap in treatment of ELS-related psychopathology

Neuroscience-based preventive intervention that target the disrupted neurobiological and psychosocial mechanisms, thereby reversing the long-term consequences of ELS and improving outcomes.

PREVENTION

ELS

HPA activity
Altered cortisol stress response

Brain development
Altered brain structure and function

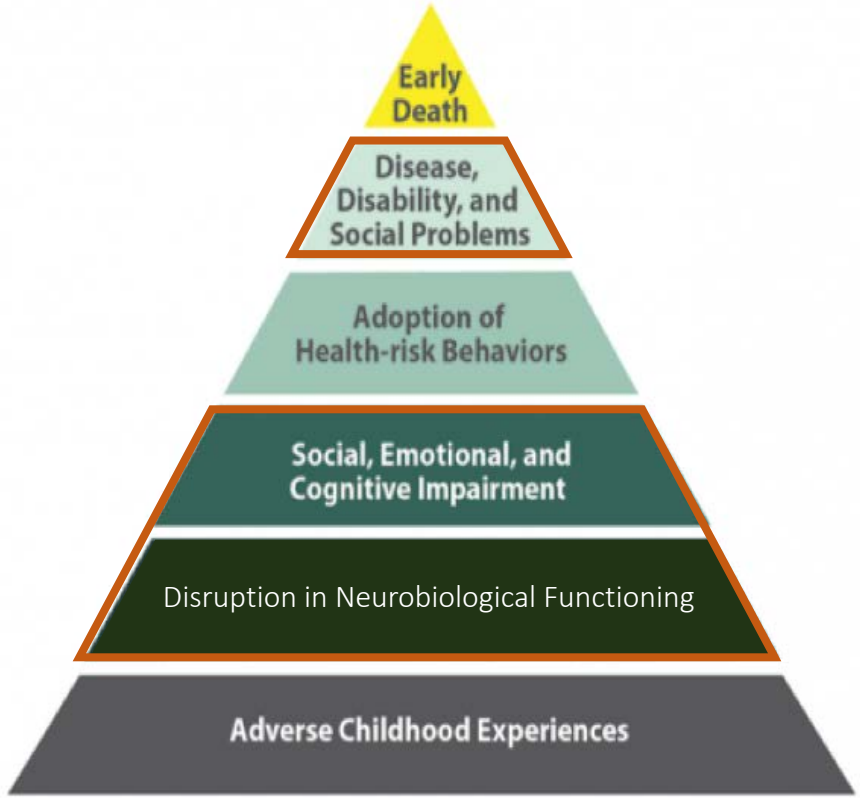
Epigenetics
DNA Methylation
(FKBP5, NR3C1, NR3C2)

Immune Function
Alterations in inflammatory responses

Outcomes

Cardiovascular disease
Pulmonary disease
Obesity
Diabetes
Chronic pain
Psychiatric disorders
Substance abuse

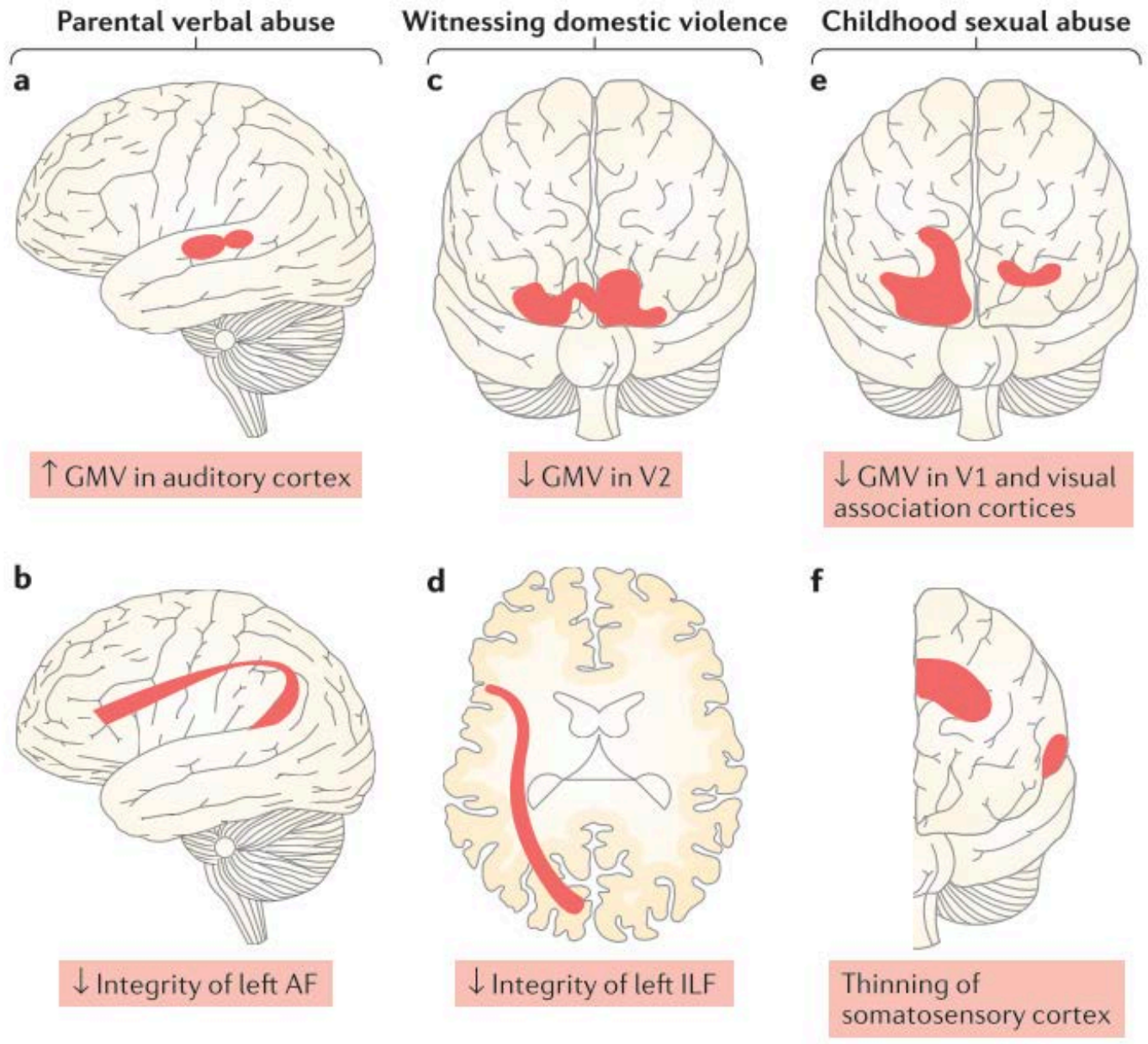
Intervention



Mechanism by Which Adverse Childhood Experiences Influence Health and Well-being Throughout the Lifespan

CDC; Klenge et al, 2013; Danese et al, 2011; Slopen et al, 2013; Teicher et al, 2016, 2014; Jaffee et al, 2014; Susman et al, 2006; Pace et al, 2006; Danese et al, 2007

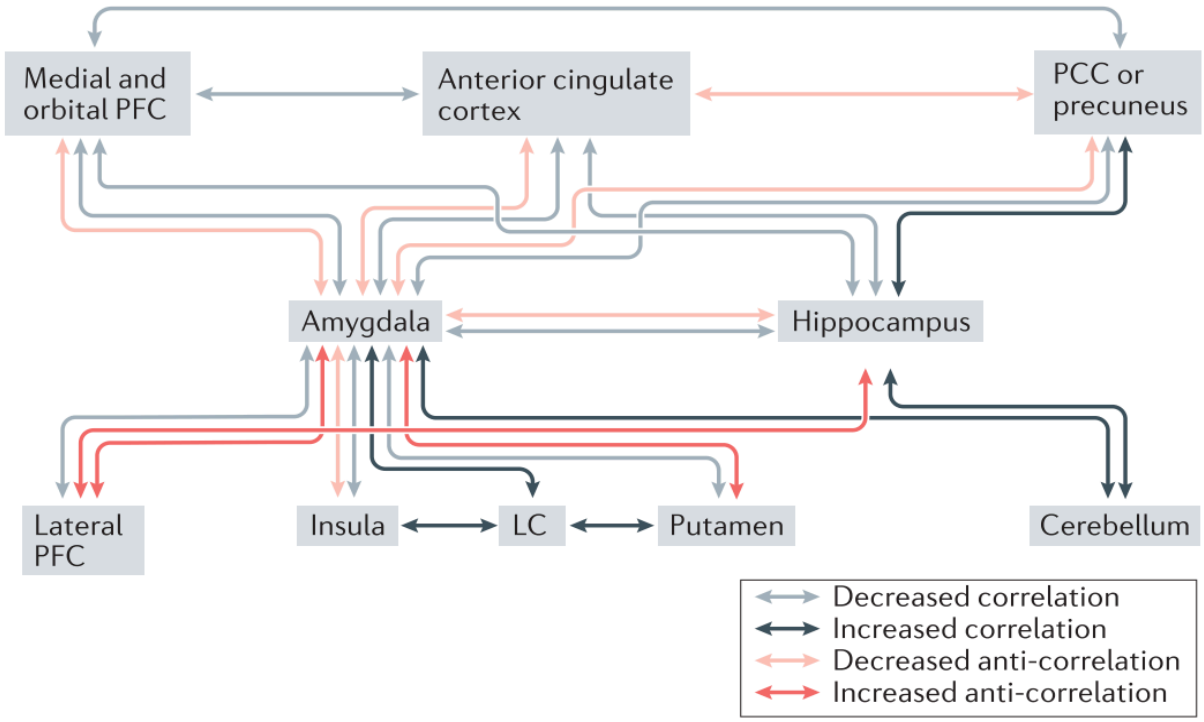
The effect of ELS on the developing brain



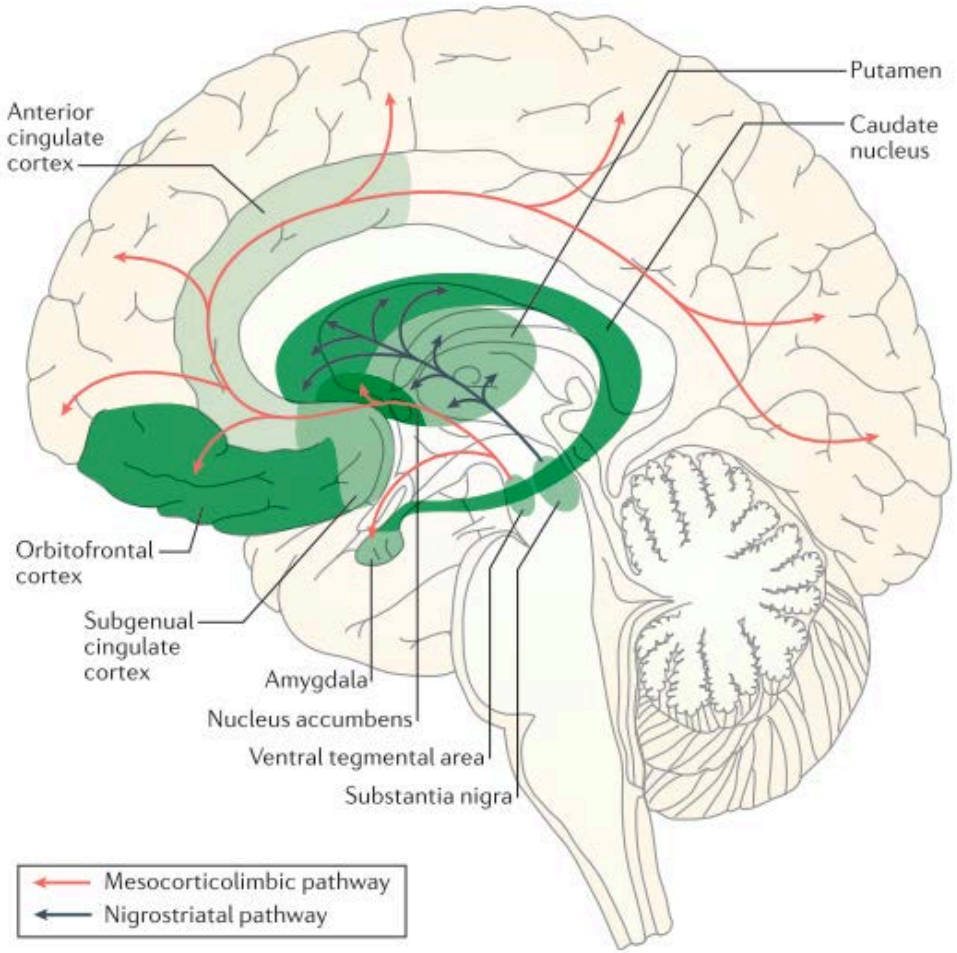
Teicher et al., 2016

Brain correlates of ELS

Emotion dysregulation

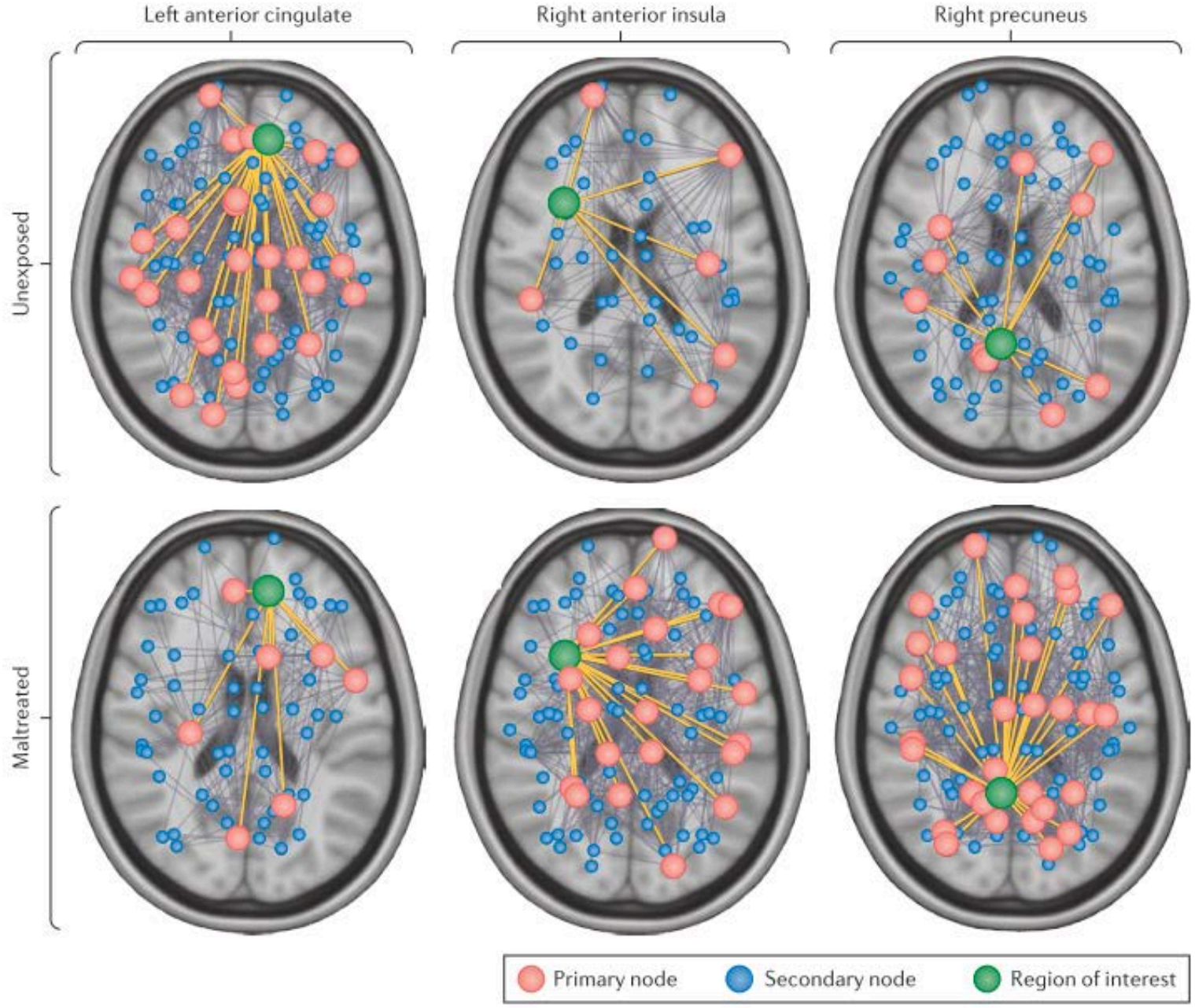


Reward Processing



Teicher et al., 2016

Brain correlates of ELS



Teicher et al., 2016

R E S I L I E N C E

pressure or tension exerted on a material object

(of a substance or object) able to recoil or spring back into shape after bending, stretching, or being compressed.

a state of mental or emotional strain or tension resulting from adverse or very demanding circumstances

(of a person or animal) able to withstand or recover quickly from difficult conditions.

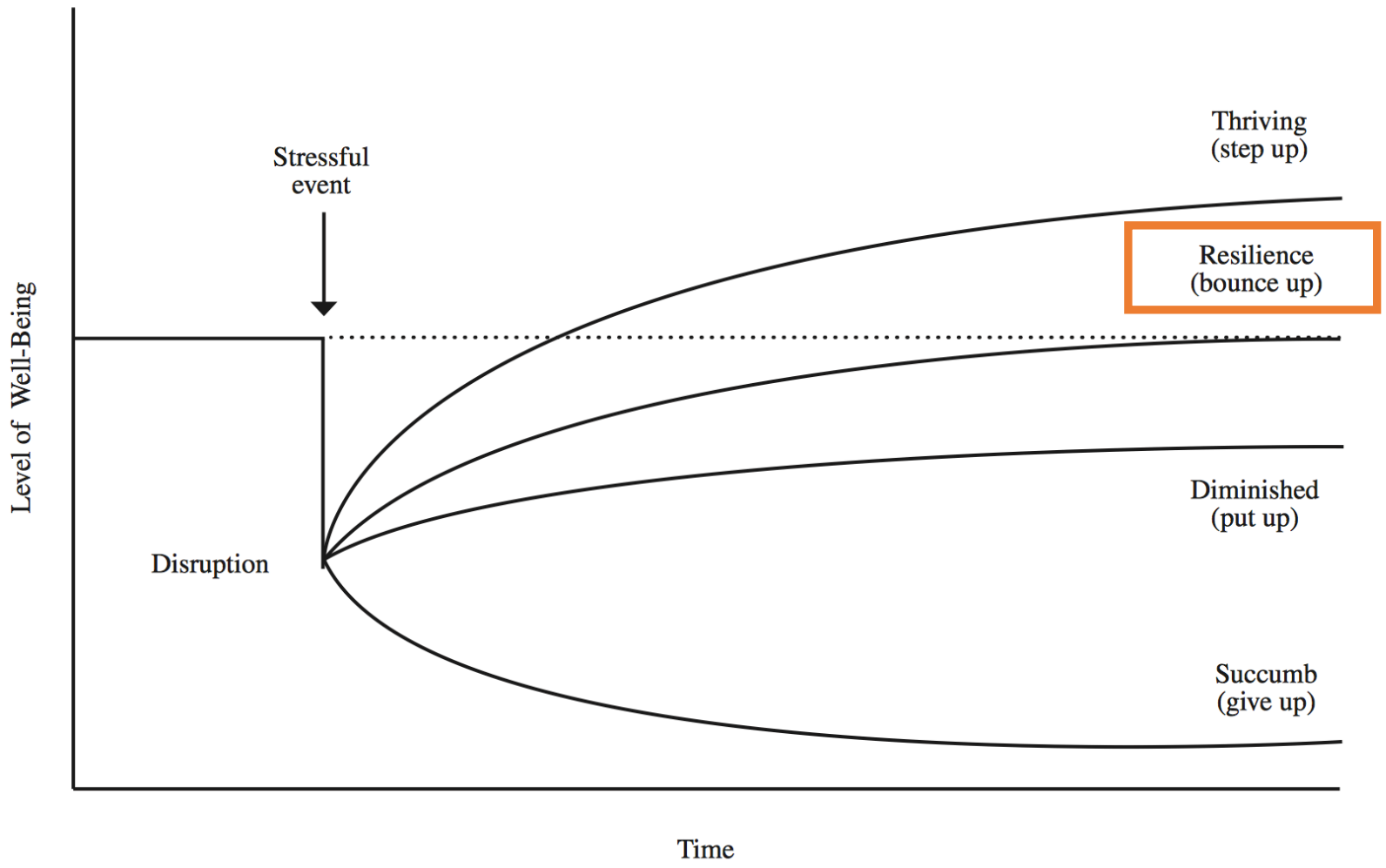
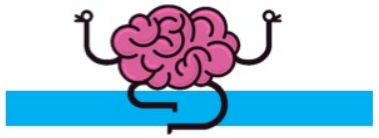


FIGURE 1. The resilience model taught in the curriculum, *Transforming Lives Through Resilience Education*, based on the work of Carver[5] and O'Leary and Ickovics.[6]



REaL

Resilience in Early Life

Laureate Institute for
Brain Research

M I N D F U L N E S S

is

awareness of your thoughts, feelings, and physical sensations,

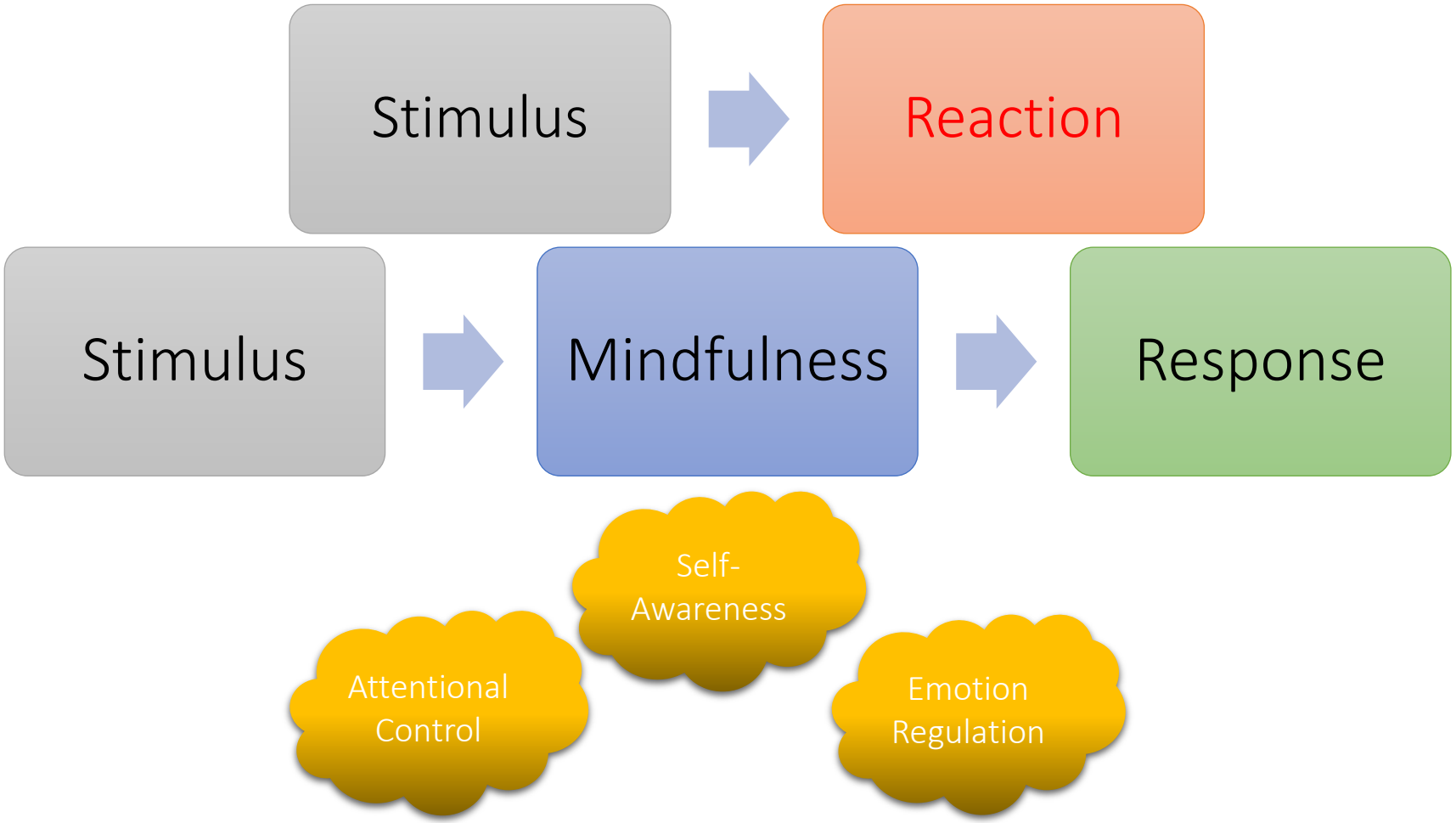
in the present moment,

and without any judgment

Mindfulness practice

Promotes regulation and inhibition by teaching attentional control over actions/behaviors, emotional responses, and cognitions.

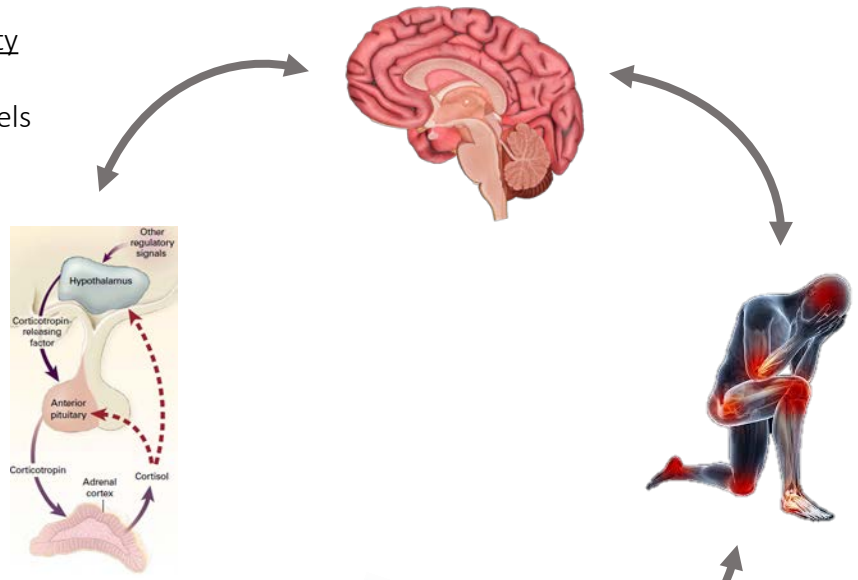
Fosters inhibition of emotional impulses, modulation of emotional behavior, and engagement in goal-directed behavior.



Creswell, 2017

Mindfulness – what we know

MINDFULNESS PRACTICE



HPA activity

↓ Cortisol levels

Brain function

dlPFC
mPFC
ACC
insula
PCC
precuneus
↑

Outcomes

Depression
Anxiety
Pain
Cravings
↓

Cognitive function
Relational outcomes
Extinction learning
↑

Immune Function

CRP ↓

Epigenetics

↓ Expression of pro-inflammatory genes

Creswell, 2017; Zenner et al, 2014; Zack et al, 2014; Black & Slavich, 2016; Creswell et al, 2014; Kaliman et al, 2014; Holzel et al, 2007; Tomasino et al, 2016; Zeidan et al, 2015; Garland et al, 2016

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Mindfulness Training for Resilience in Early Life (MindREaL)

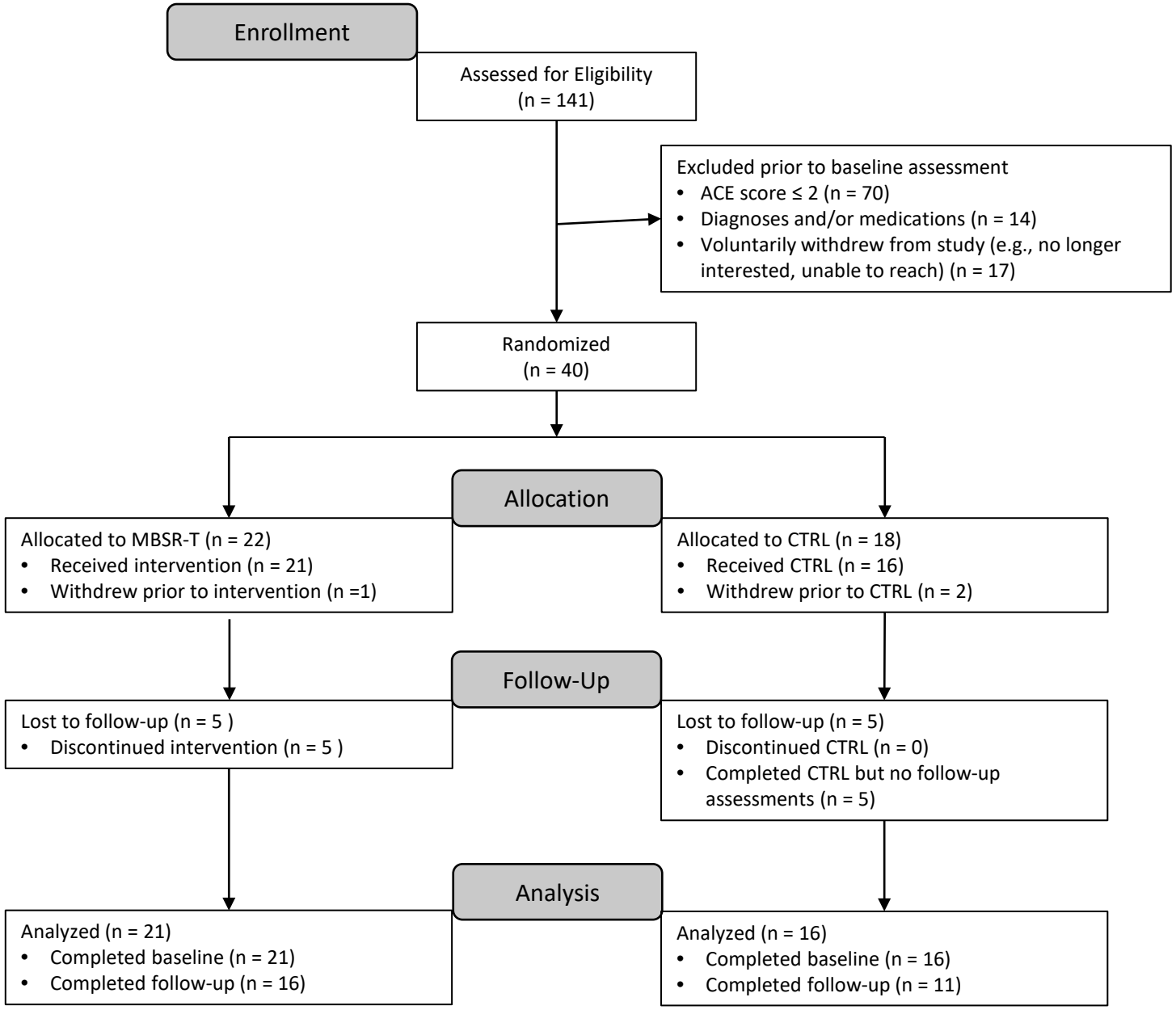
FUNDING:
Oklahoma State University Center for Health Sciences
Center for Integrative Research on Childhood Adversity (CIRCA) CoBRE Pilot Project
(5P20GM109097-04; completed)

Aims:

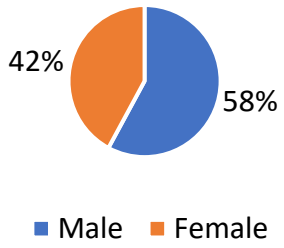
Identify how ELS exposure impacts affective symptoms and biological processes

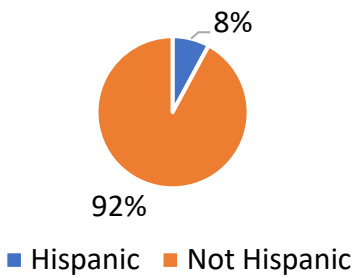
Identify how mindfulness practice impacts affective symptoms and biological processes dysregulated by ELS

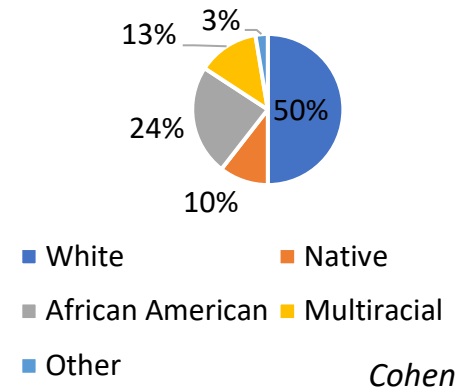
MindREal: Study Design and Sample



Age: 14.28 (.76)







Cohen et al., 2021a

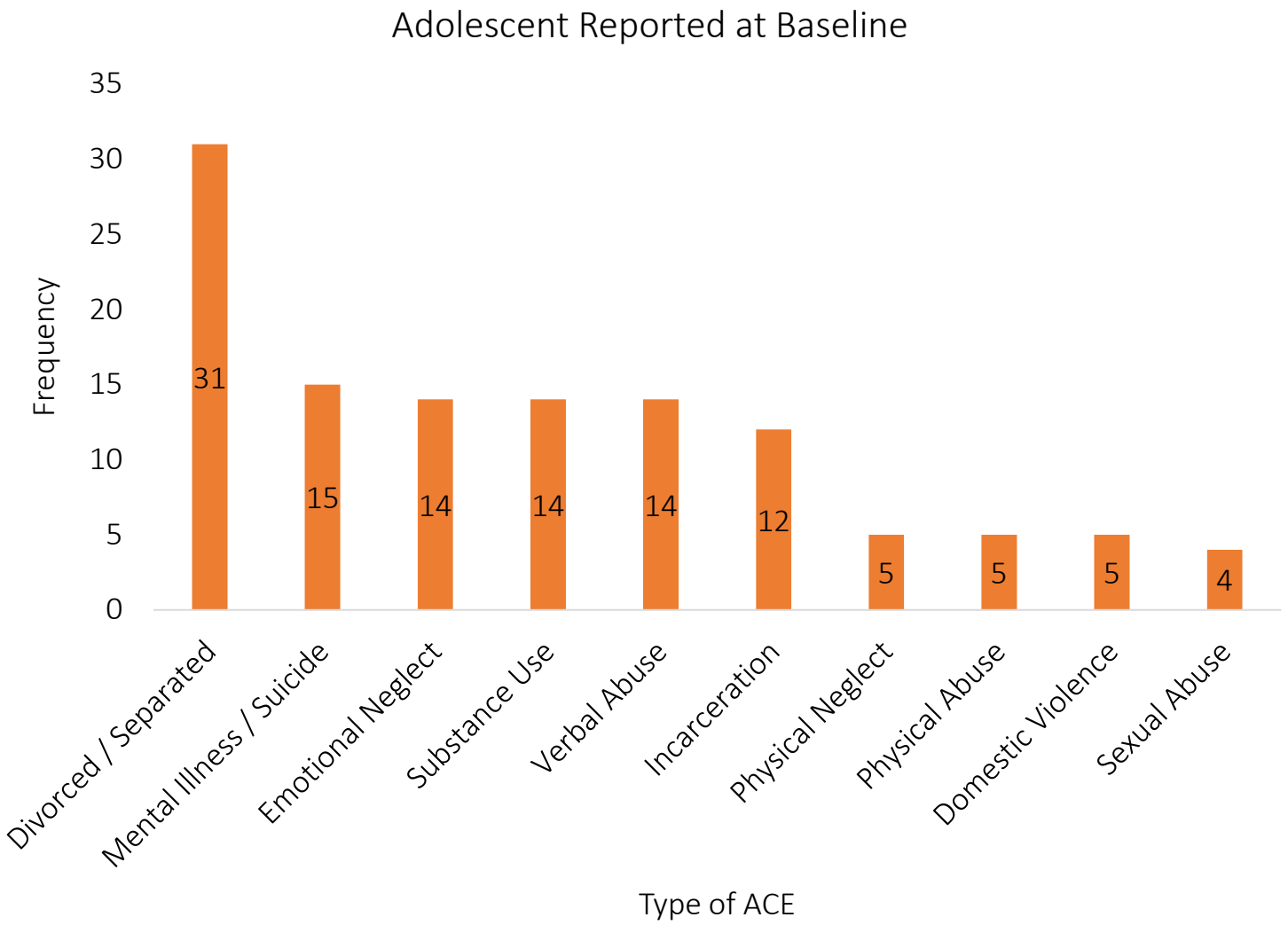
MindREal: Study Design

Measures	Baseline	Online Assess 1	Online Assess 2	Sessions 1 – 8	Follow-Up
Questionnaires: ELA Exposure (ACEs and CTQ), Alcohol and Drug Involvement, Resilience, Difficulties in Emotion Regulation, Mindfulness Attention and Awareness					
Symptom and Treatment Questionnaires: Mood and Feelings Questionnaire, Suicide Behaviors Questionnaire - Revised, Homework Rating Scale, Working Alliance Inventory					
Trier Social Stress Task Salivary Cortisol Collection Blood Collection [IL-6, CRP, TNF-alpha, FKBP5, NR3C1]					
Treatment Allocation: MBSR-T or CTRL					

Averaged for Baseline Score

Cohen et al., 2021a

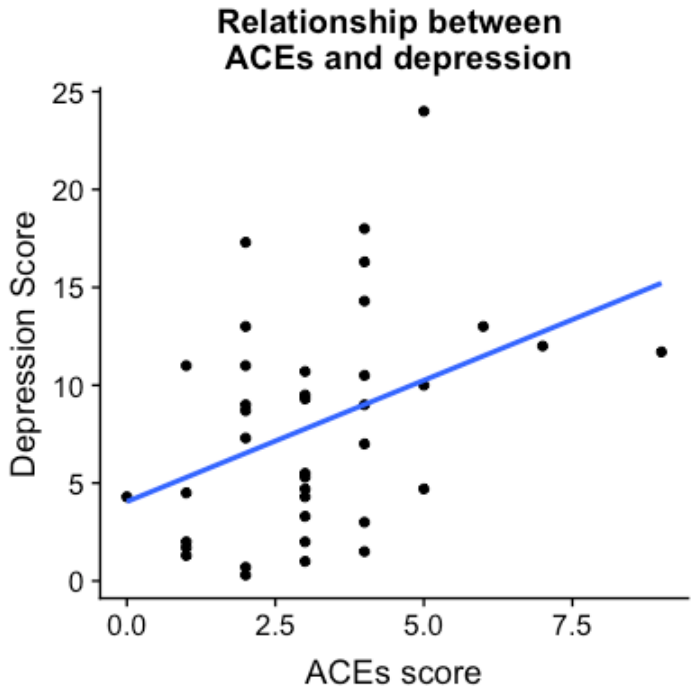
MindREaL: Results



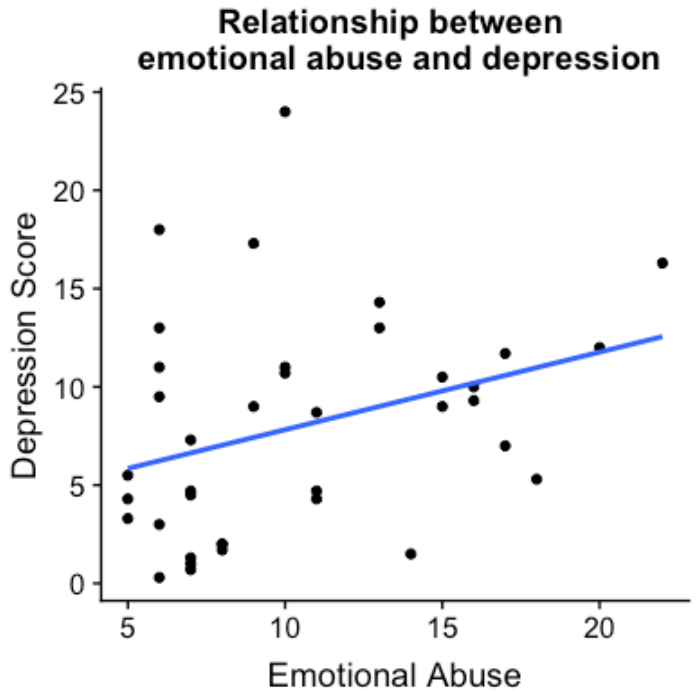
n = 41

Cohen et al., 2021a

MindREaL: Results



$r_{s(36)} = .41$, $p < .01$



$r_{s(36)} = .34$, $p < .05$

Cohen et al., 2021a

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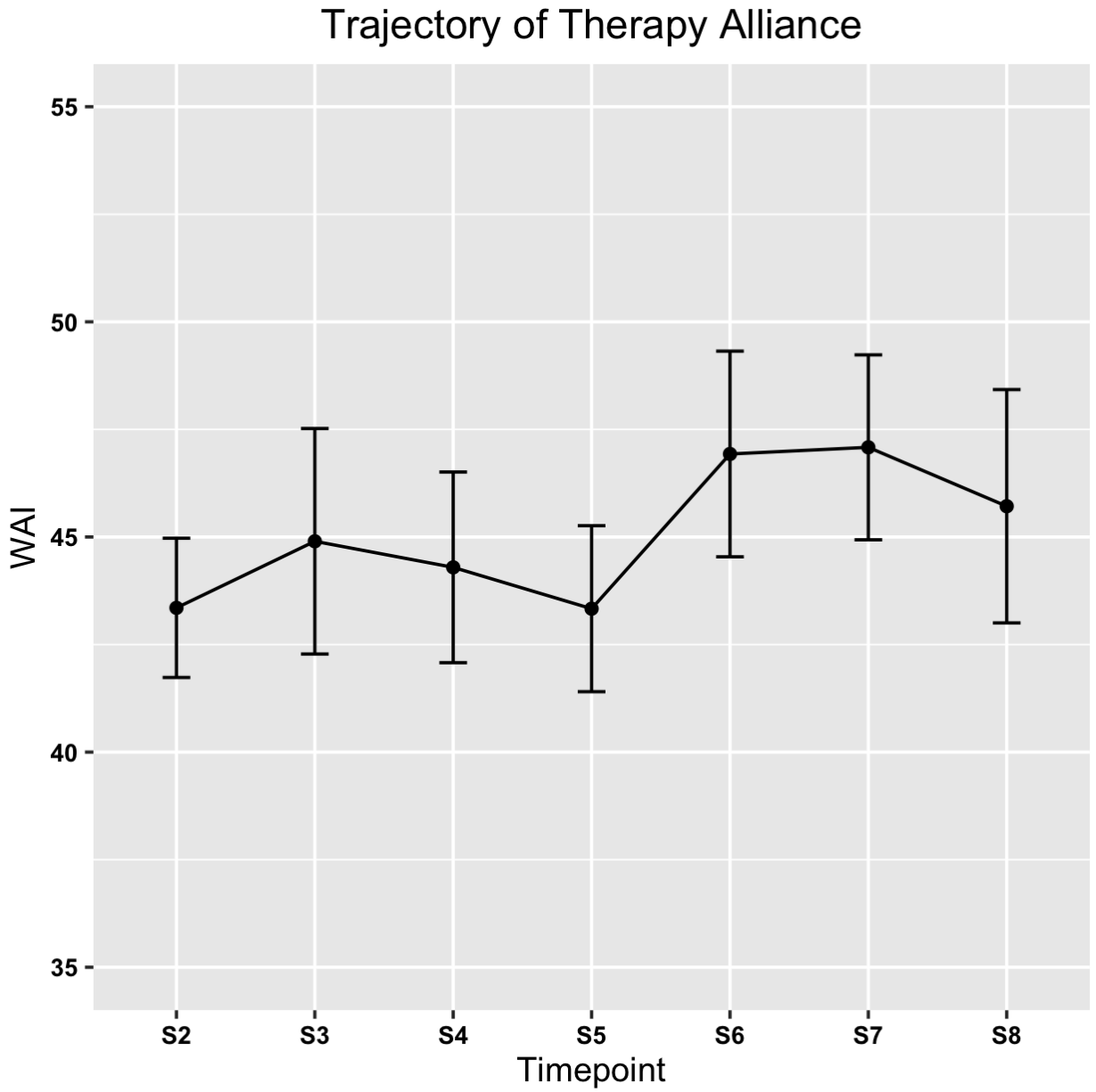
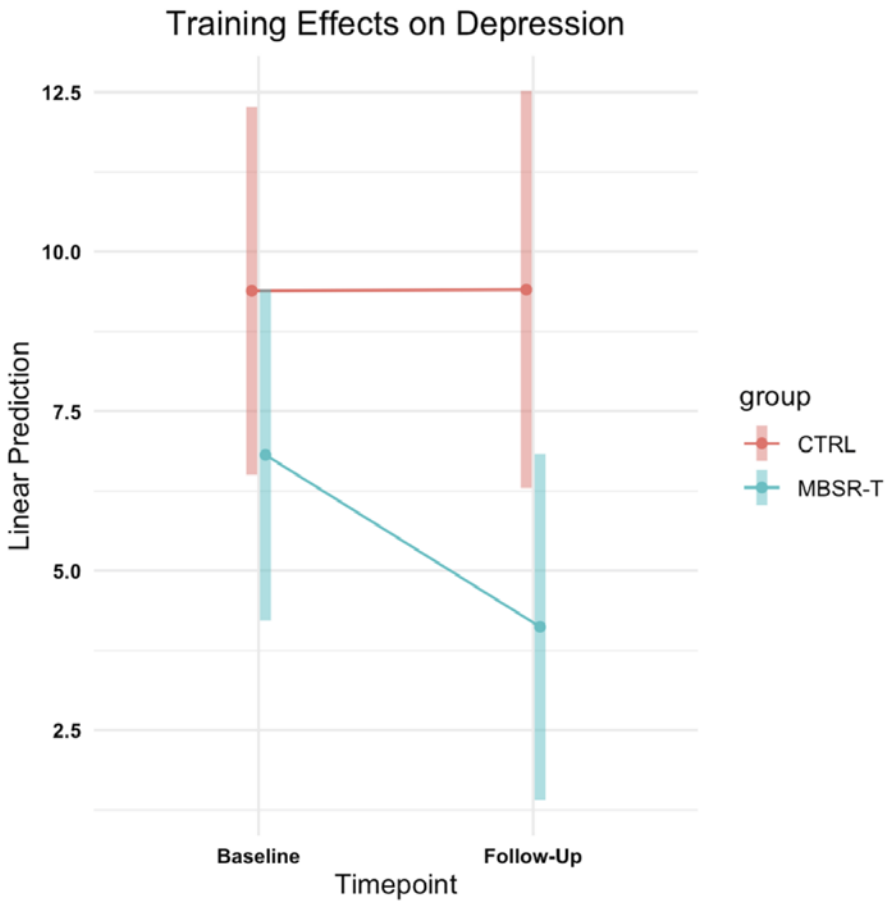
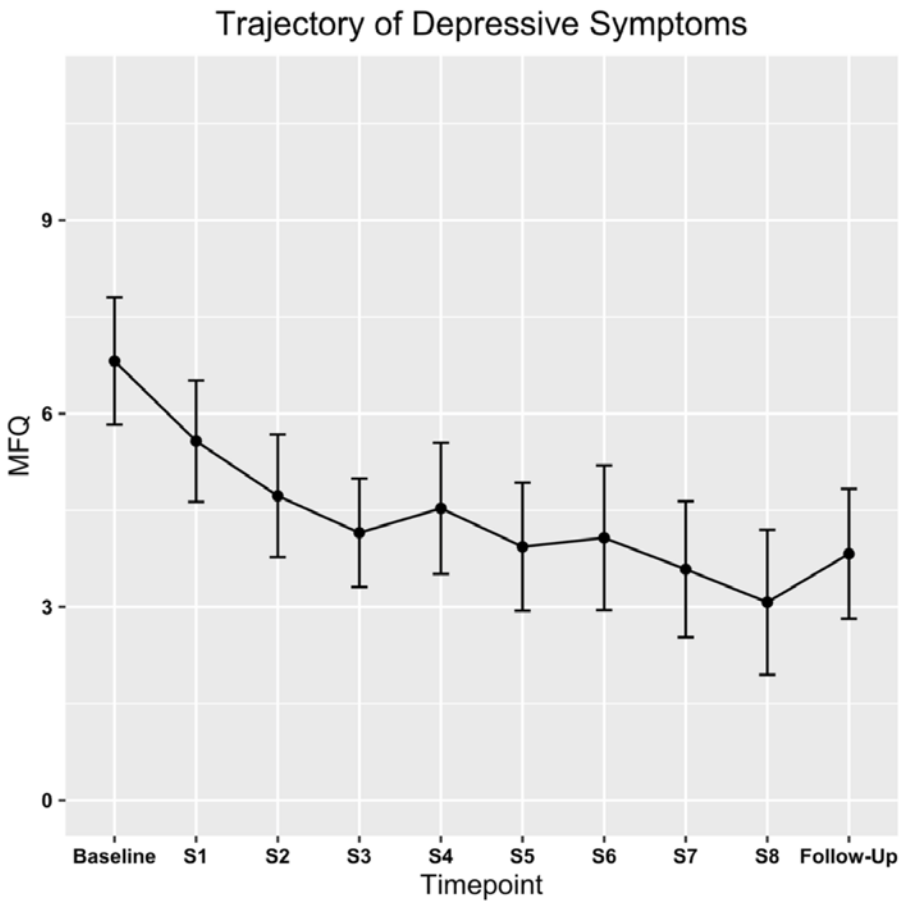
MindREaL: Increase in working alliance during the course of intervention



Cohen et al., 2021a

MindREaL: Change in symptoms of depression



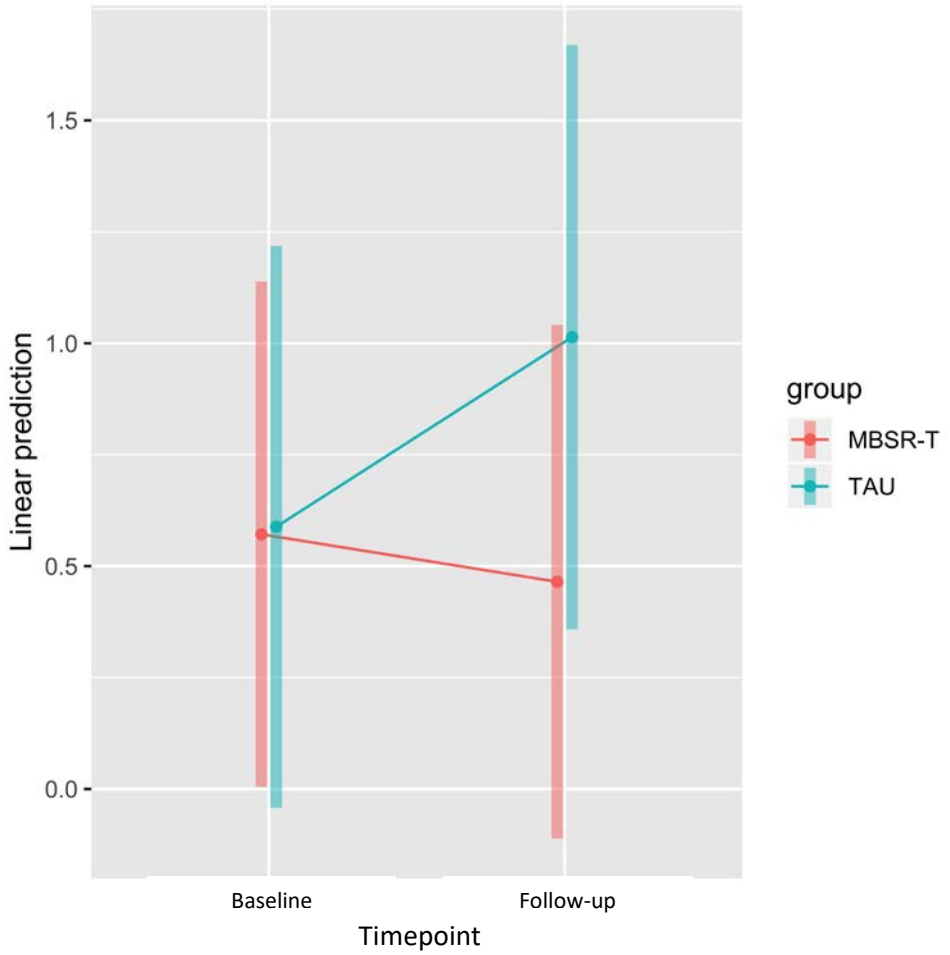


[$F_{(1,28)}$ = 3.31, p = .079, d = .69]
MBSRT: [$t_{(28.2)}$ = -2.972, p < .01, d = 398 1.40]
CTRL: [$t_{(29)}$ = -.016, p = .988, d = .01]

MBSR-T group showed a significant decrease in depressive symptoms from baseline to follow-up, with a decreasing trend was observed over the course of treatment [$F_{(9,139)}$ = 5.27, p <.001, d = .51].

Cohen et al., 2021a

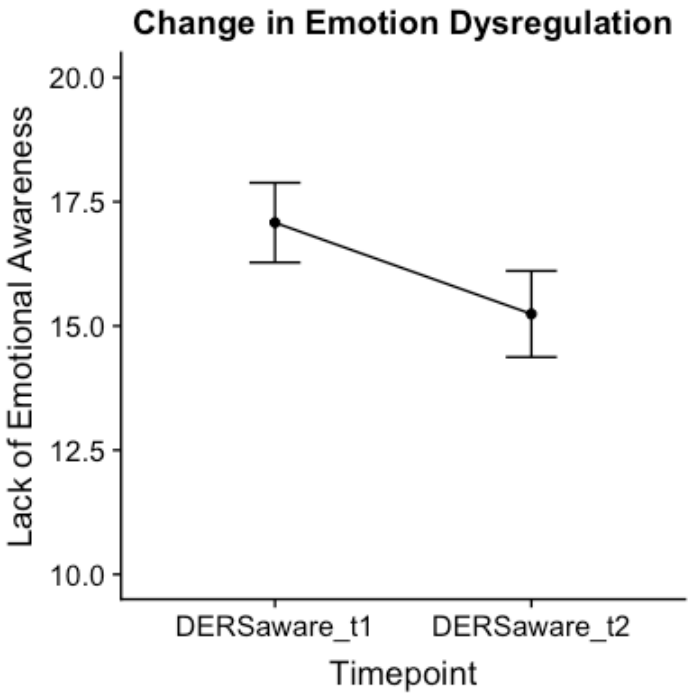
MindREaL: Marijuana use



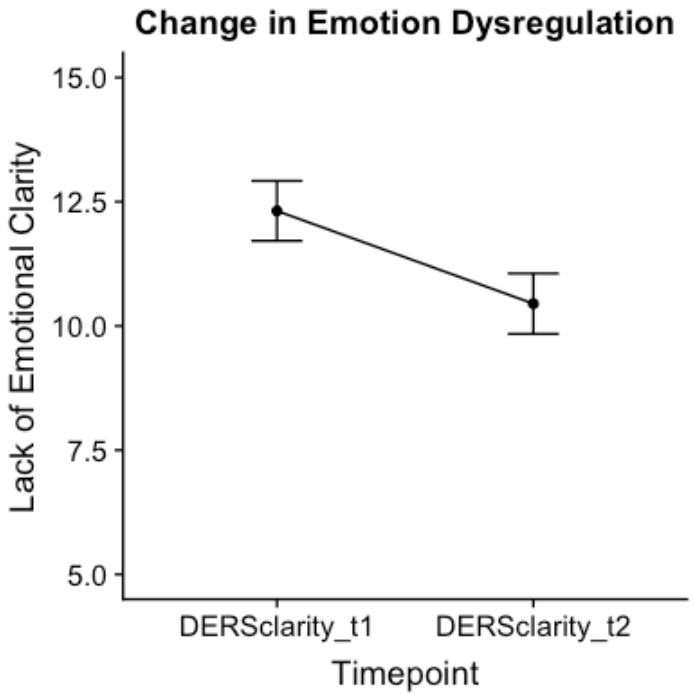
[$F_{(1,29)}$ = 5.47, p = .03, d = .86]
MBSRT: [$t_{(29)}$ = -.74, p = .47, d = .24]
CTRL: [$t_{(29)}$ = 2.414 p = .02, d = 1.40]

Cohen et al., 2021a

MindREaL: change in emotion regulation



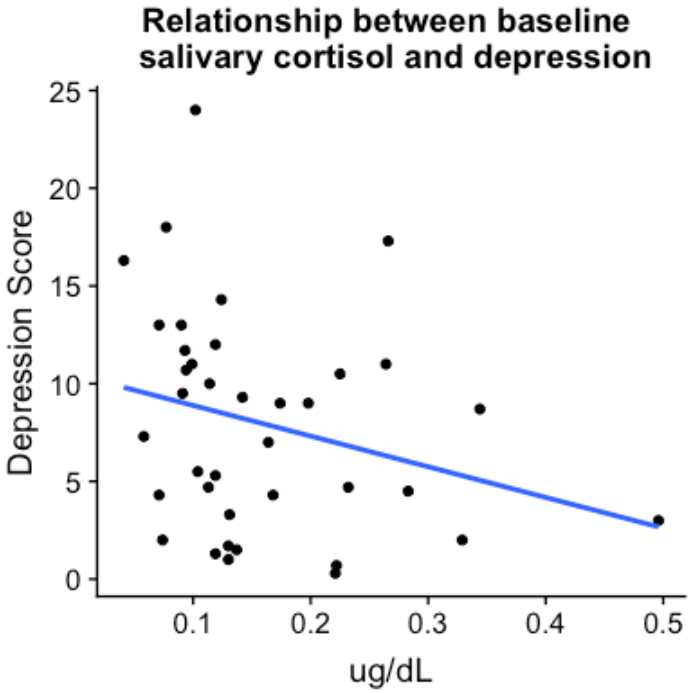
95%CI: .23 to 4.59; $p < .05$, *Cohen's d* = .39



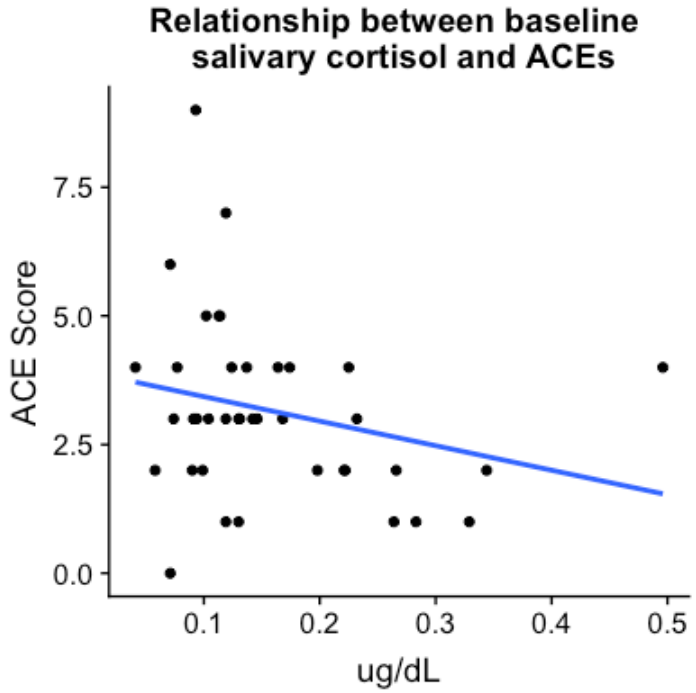
95%CI: 1.12 to 4.53; $p < .05$, *Cohen's d* = .62

Cohen et al., 2021a

MindREaL: cortisol levels



$r_{s(36)} = -.35, p < .05$

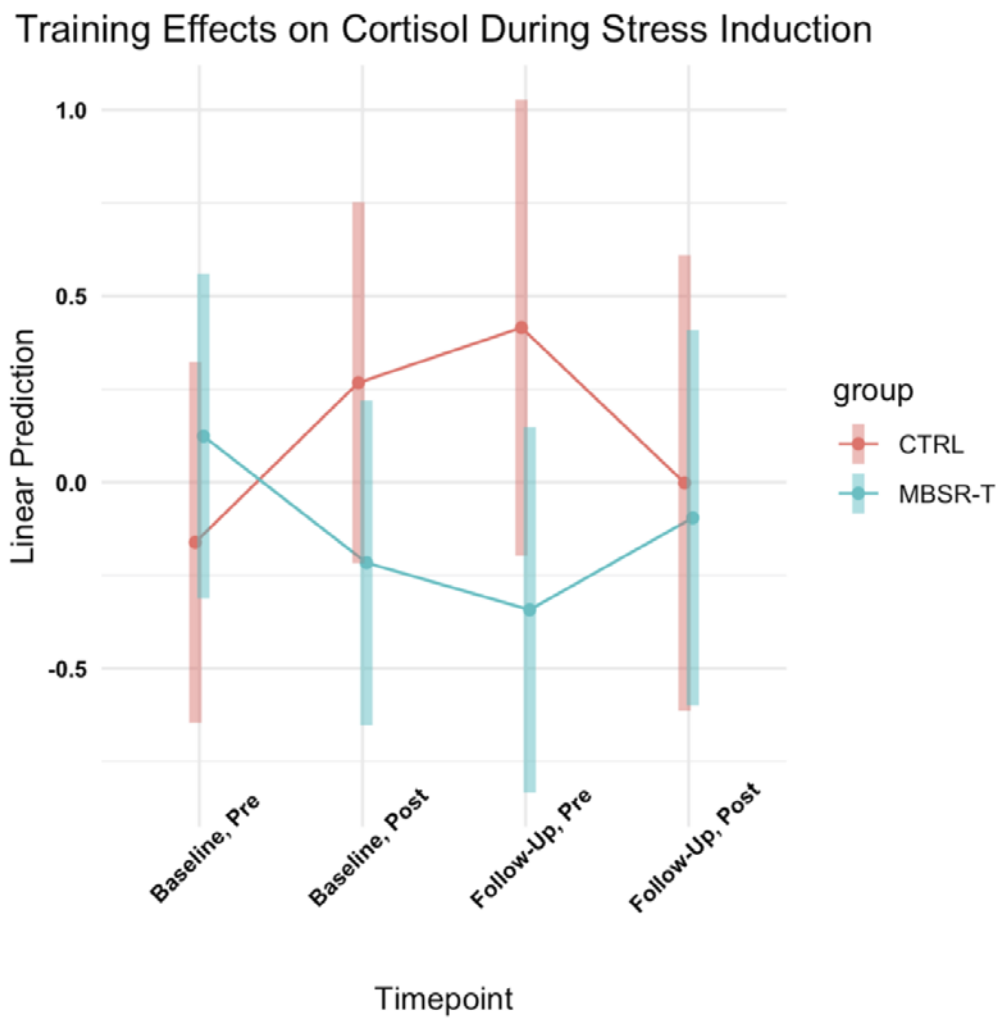


$r_{s(36)} = -.27, p = .09$

Cohen et al., 2021a

MindREaL: change in cortisol levels and self-reported arousal during stress

(A)



[$F_{(3,86)}$ = 2.36, p = .077, d = .60]
[$t_{(111)}$) = 1.92, p = .058, d = -0.56]

(B)

[$F_{(3,86)}$ = 4.49. p = .006, d = .83]
[$t_{(108)}$, = 2.19, p = .031, d = -.74]

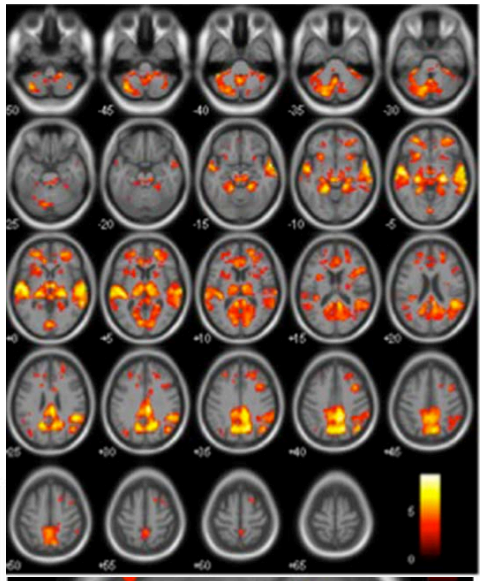
Cohen et al., 2021a

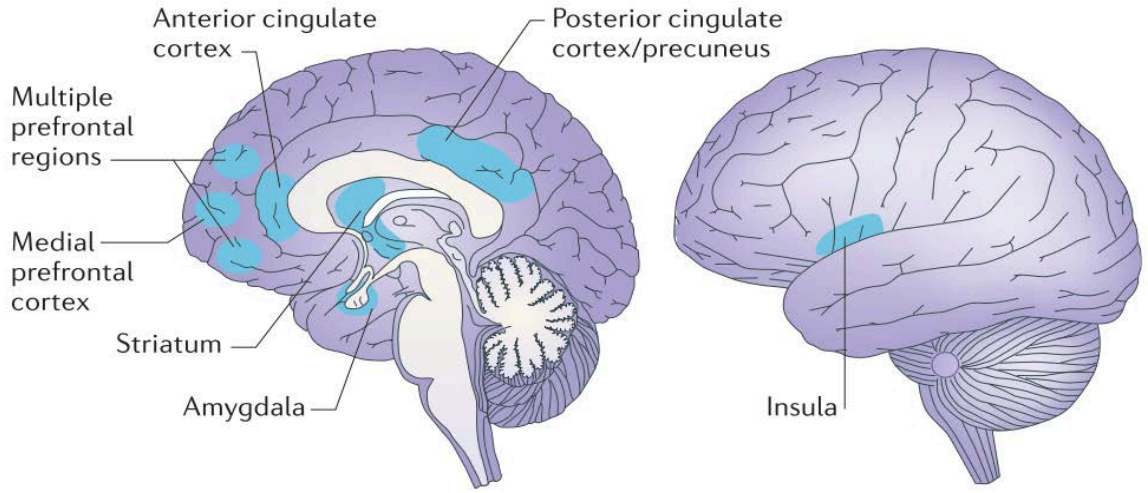
Augmented Mindfulness Training for Resilience in Early Life (A-MindREaL)

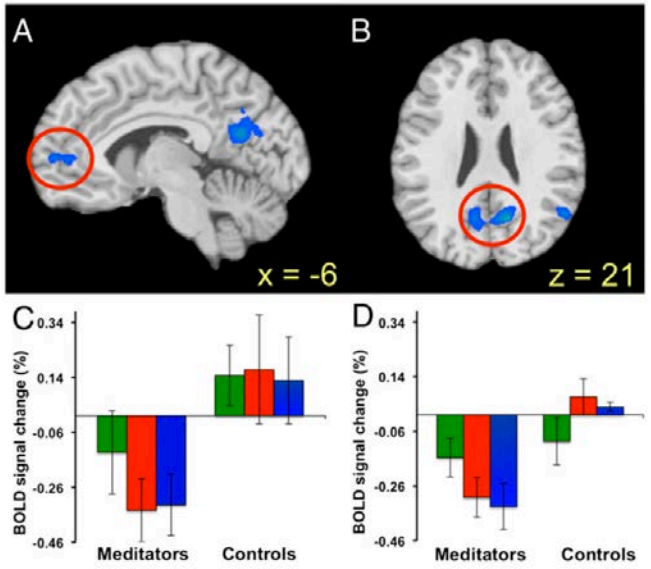
FUNDING:
Laureate Institute for Brain Research
Neuroscience-based Mental Health Assessment and Prediction
(5P20GM121312-02) CoBRE Project

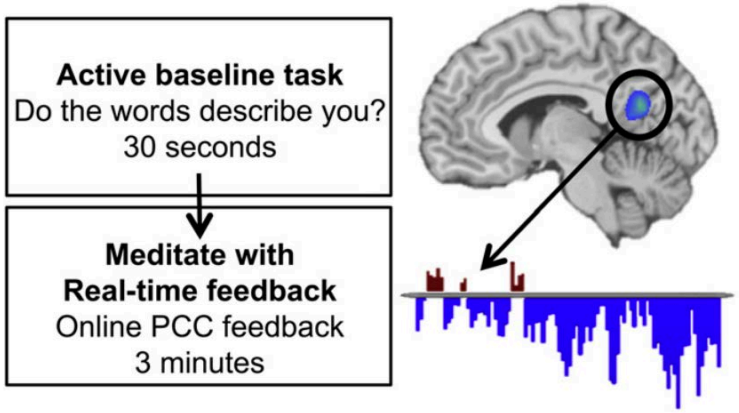
Overarching Aim:
use *augmented mindfulness*, i.e., combined standard mindfulness training with rtfMRI neurofeedback, to influence and increase plasticity of brain areas affected by ELA, and, in turn, affect state changes in symptoms the affected youth.

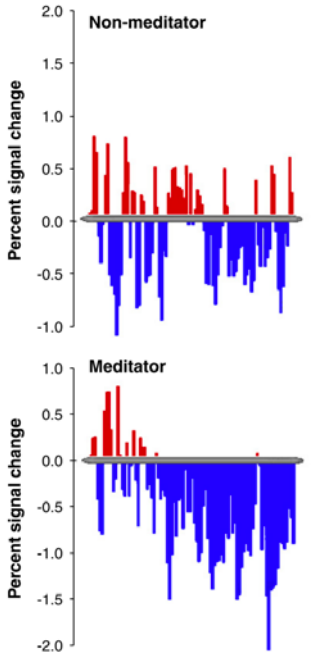
Brain correlates of mindfulness training











Brewer et al., 2011; Garrison et al., 2015; King et al., 2015; Teicher et al., 2016; Tang et al., 2015; Garrison et al., 2015

A-MindREaL: Specific Aims

Aim 1

To establish the AMT protocol and to determine the feasibility of targeted PCC modulation in youth.

Aim 2

To determine whether ELS-exposed youth show greater difficulty engaging the PCC to facilitate mindfulness and whether neurofeedback helps to change the PCC activity.

Aim 3

To determine whether AMT results in improved state mindfulness in ELS-exposed youth.

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A-MindREaL: study design

Visit 1
Core Assessment

Demographic and Medical History

Parent Trauma & Symptomatology

Clinical Interview and Assessment
- MINI
- Life Chart
- Suicidality

Self-report Measures
- Trauma
- Negative valence
- Positive valence
- Substance use
- Physical health and sleep
- Relationships / social support

Neurocognitive Assessment
- Episodic memory
- Executive attention and function
- Working memory
- Language
- Processing speed

Biomarkers
- Lipid panel
- Neuroendocrine panel
- Metabolism panel
- Cardiovascular panel
- Genetics
- RNA/Protein
- Microbiome

Neuroimaging
- Structural
- Resting state
- Functional
- Monetary Incentive Delay
- Fear Conditioning

Visit 2
AMT

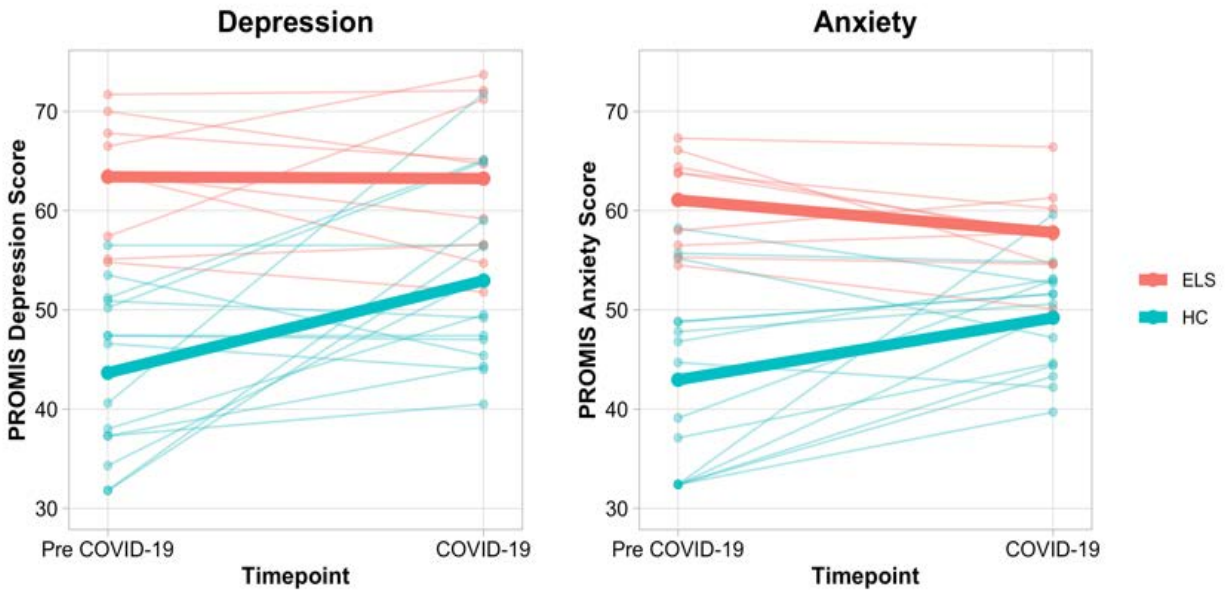
Self-report Measures
- State mindfulness
- State Affect
- Perceived stress

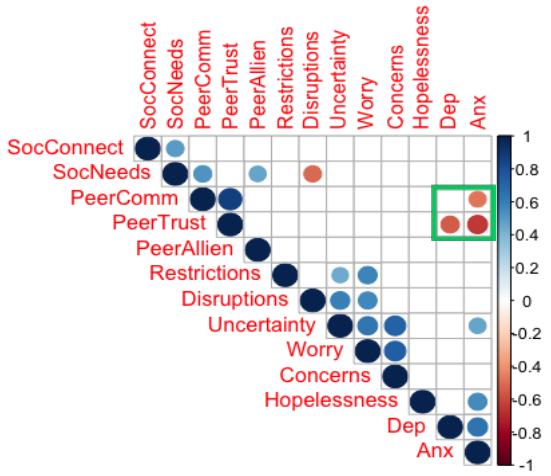
Orientation to mindfulness practice

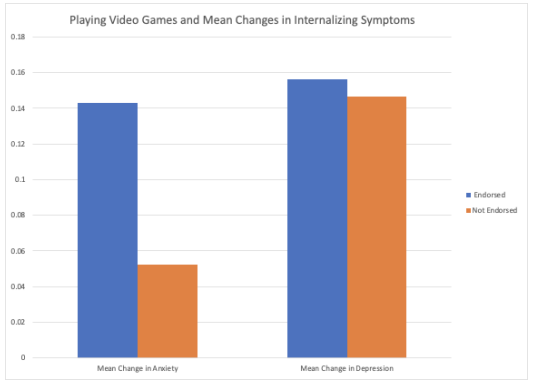
Mindfulness practice in the mock scanner
- Breathing practice

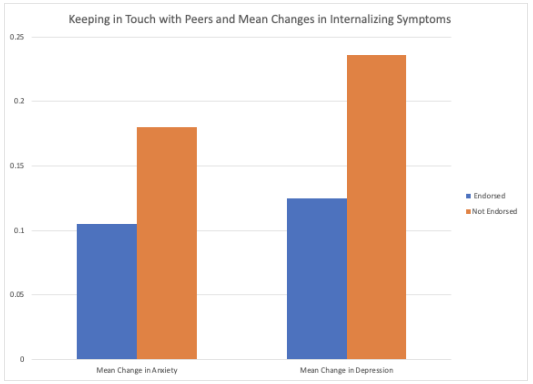
Neuroimaging
- Structural scans
- rtfMRI neurofeedback augmented mindfulness

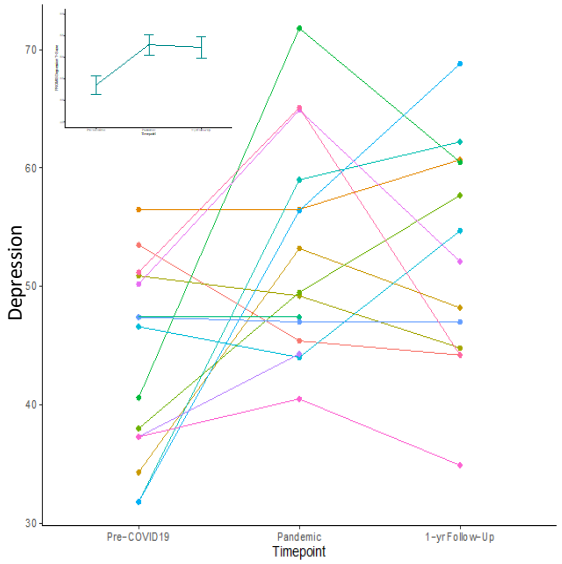
COVID-19 Snapshot

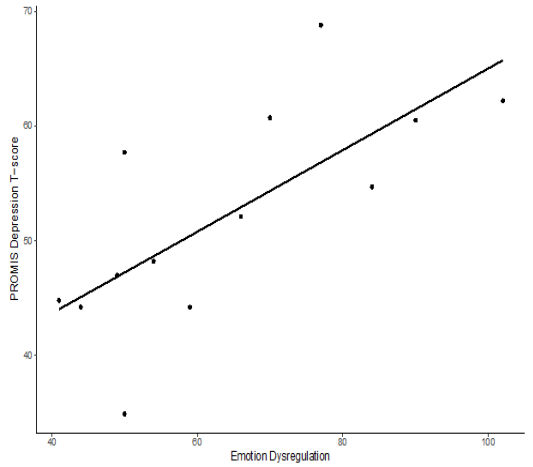












The COVID-19 pandemic has brought on far-reaching consequences for adolescents. Adolescents with early life stress (ELS) may be at particular risk. We observed significant increases in symptoms of depression and anxiety in healthy, but not ELS-exposed adolescents, which were maintained at one-year follow-up.

Cohen et al. (2021b)

A-MindREaL: Experimental Design

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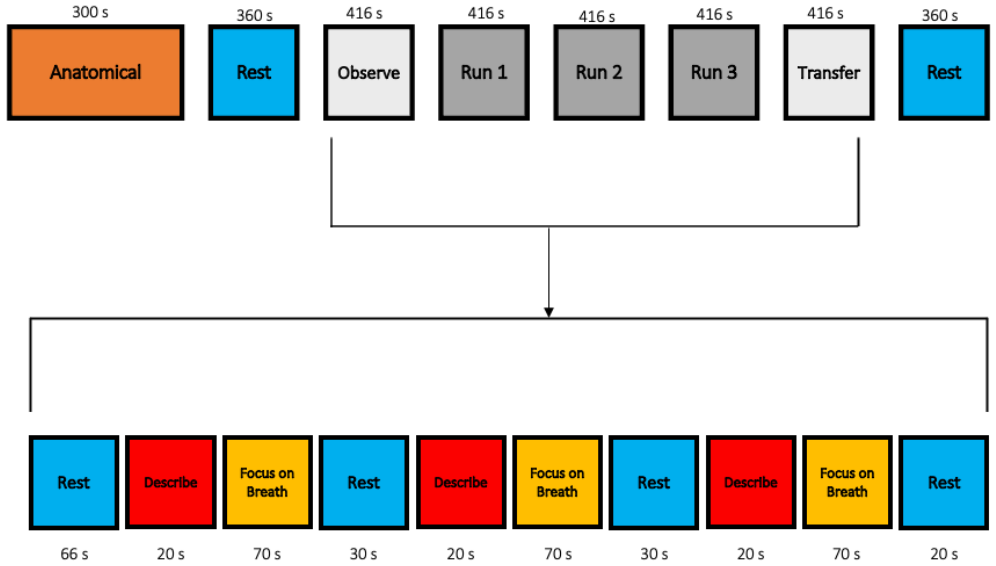
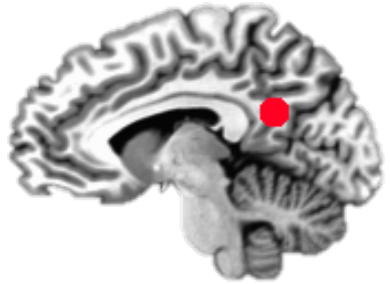
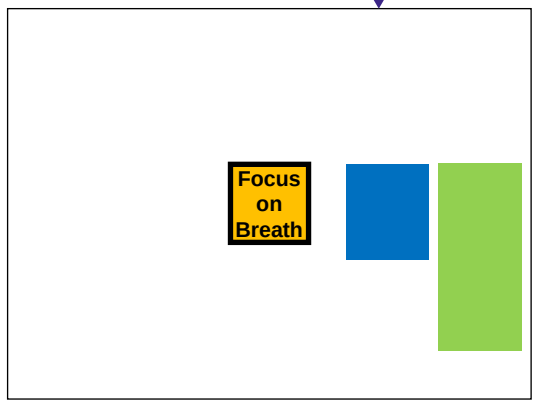
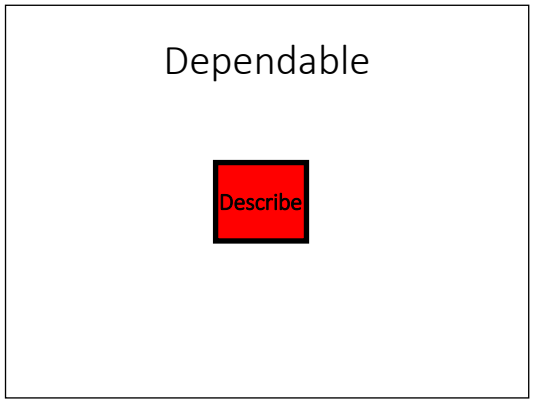


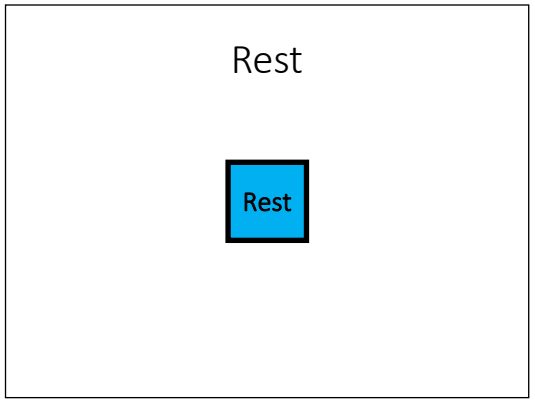
Observe, Runs 1, 2, 3, & Transfer run



Left Posterior Cingulate

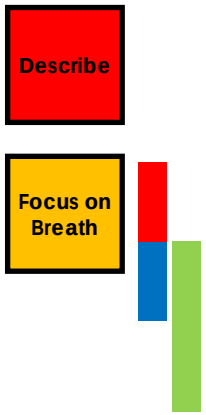


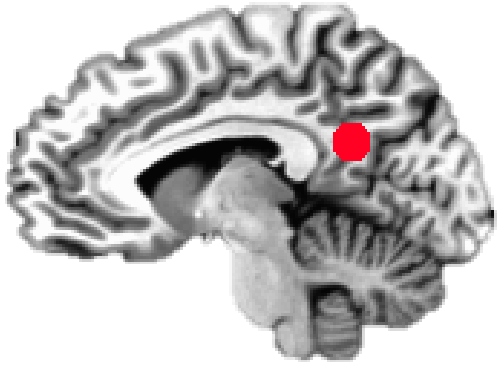


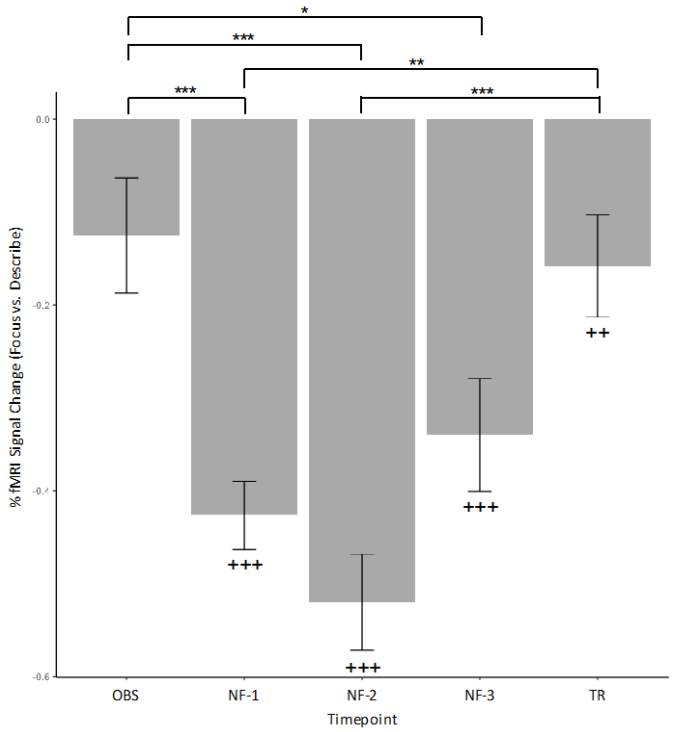


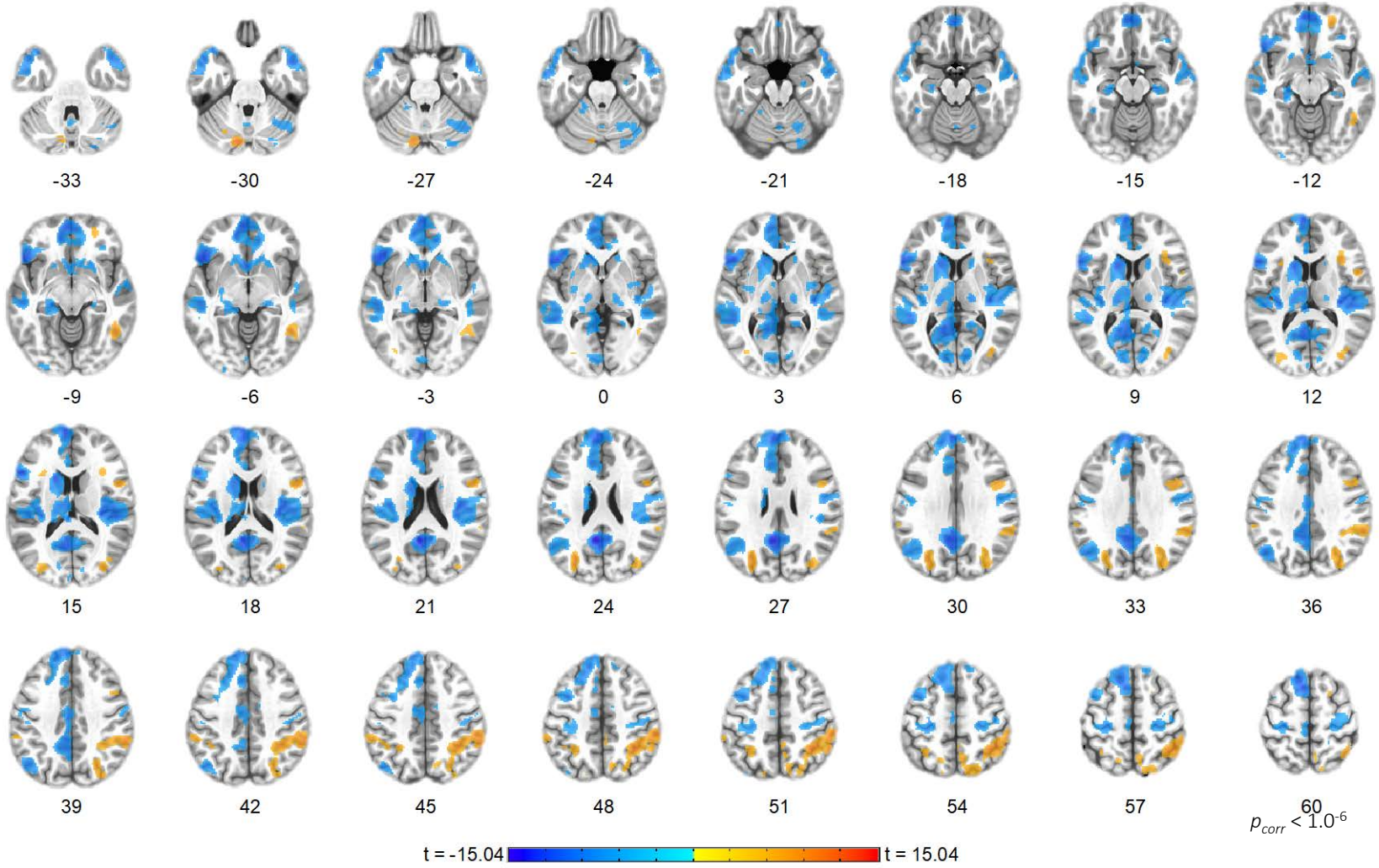
A-MindREaL: Results (healthy adolescents)

Dependable









$p_{corr} < 1.0^{-6}$

Kirlic et al., 2022

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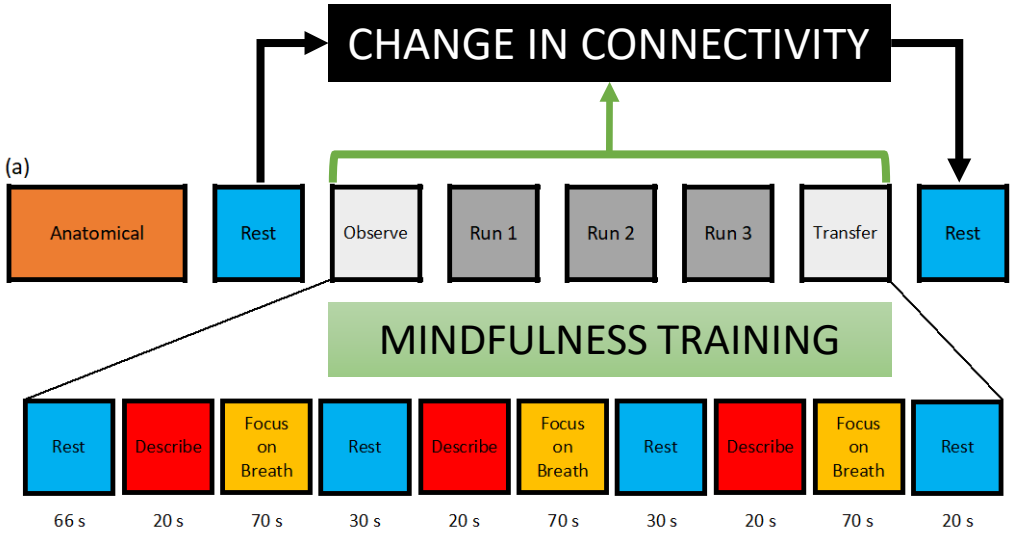
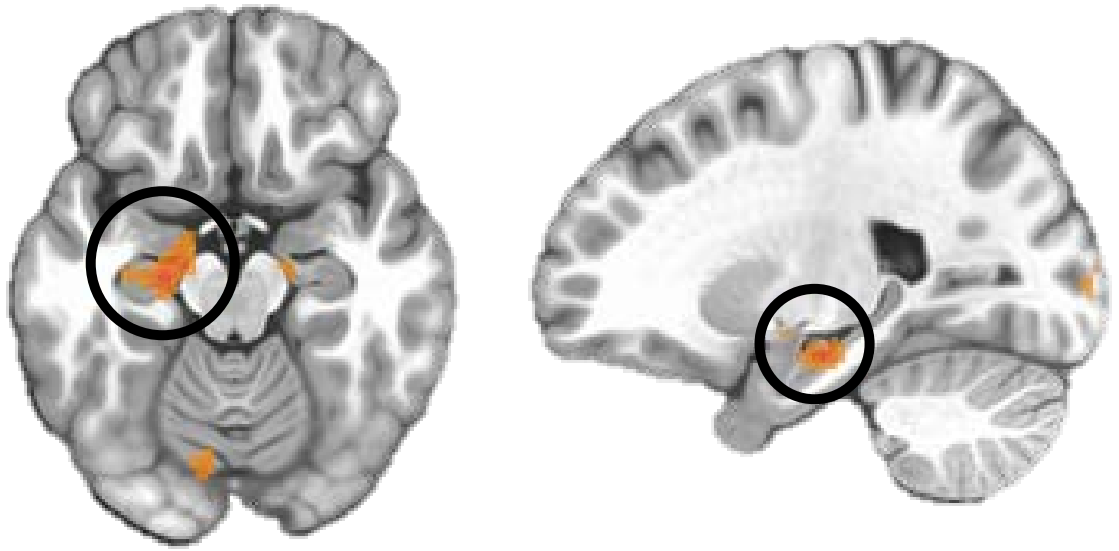
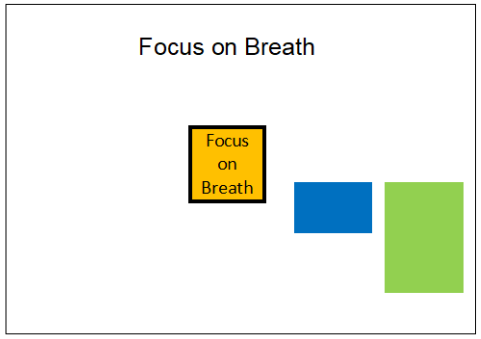
A-MindREaL Results (Functional Connectivity in Healthy Adolescents)

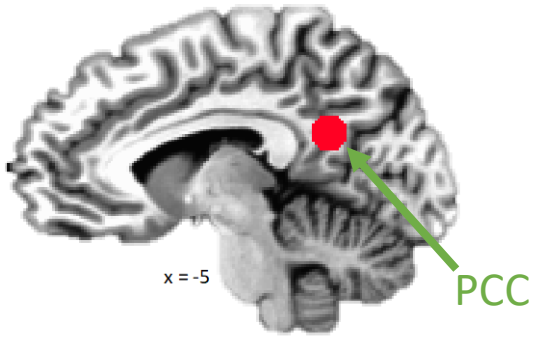


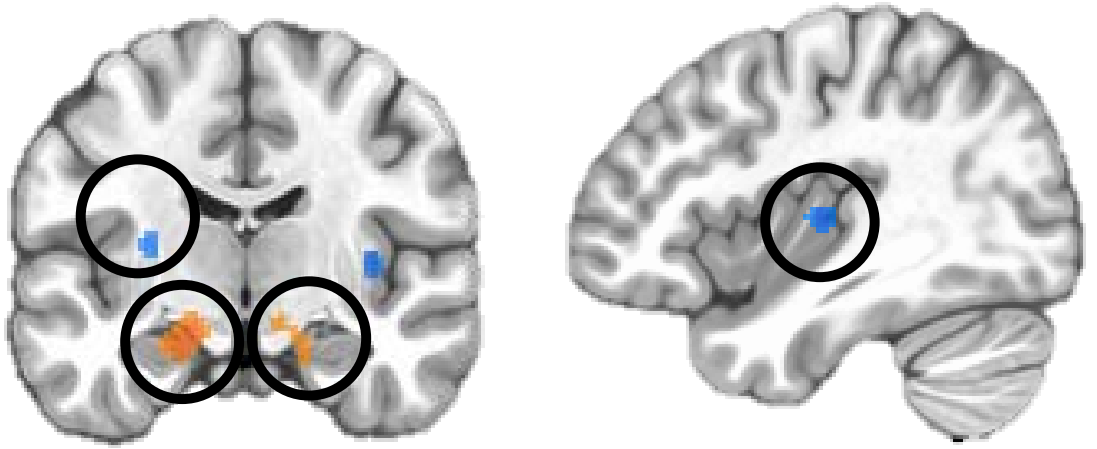


(b)



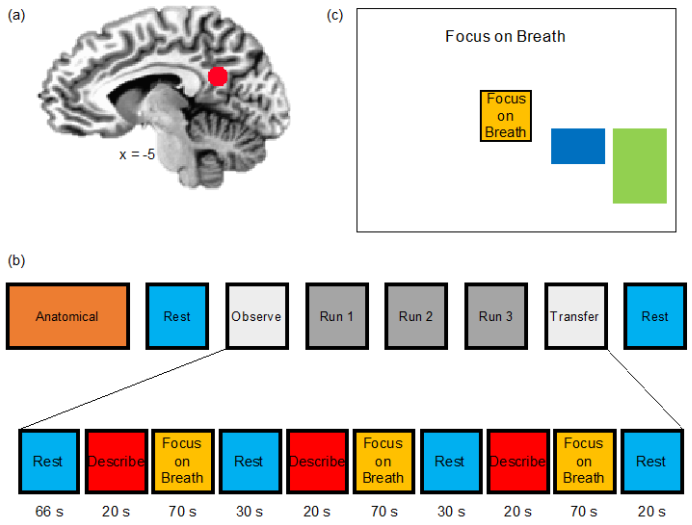
(c)

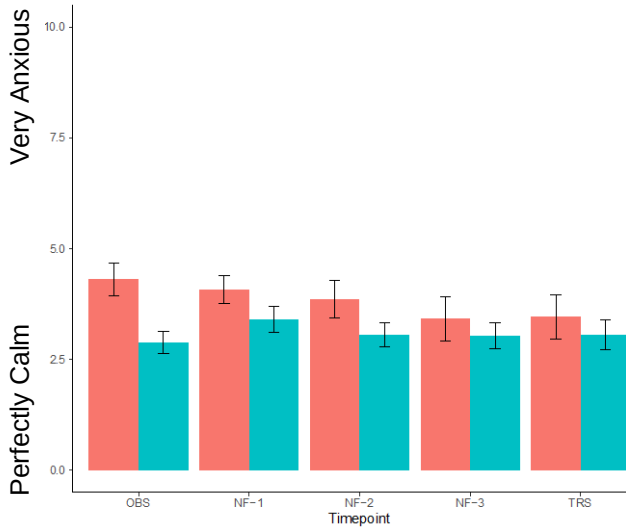


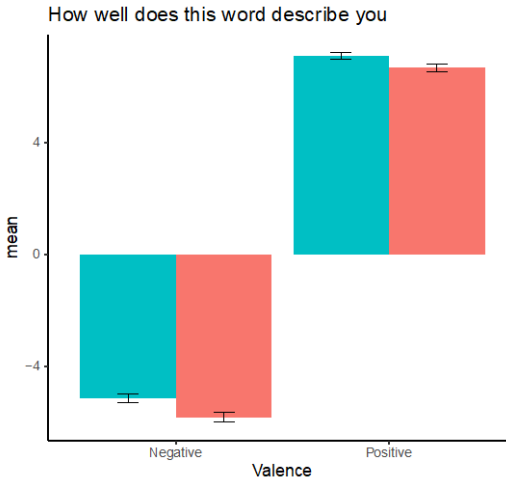


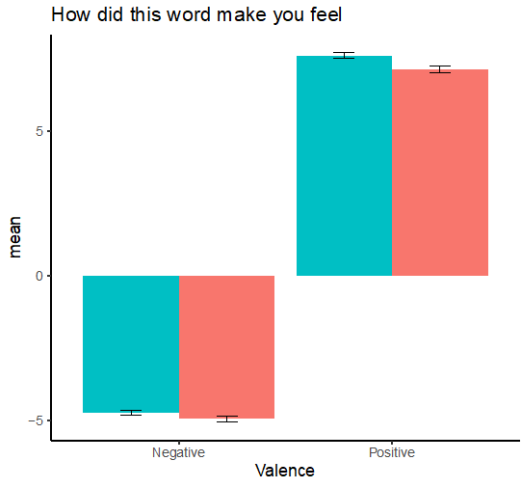
$p_{corrected} < .005$

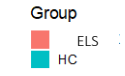
A-MindREaL: Results (Healthy vs ELS-exposed adolescents)

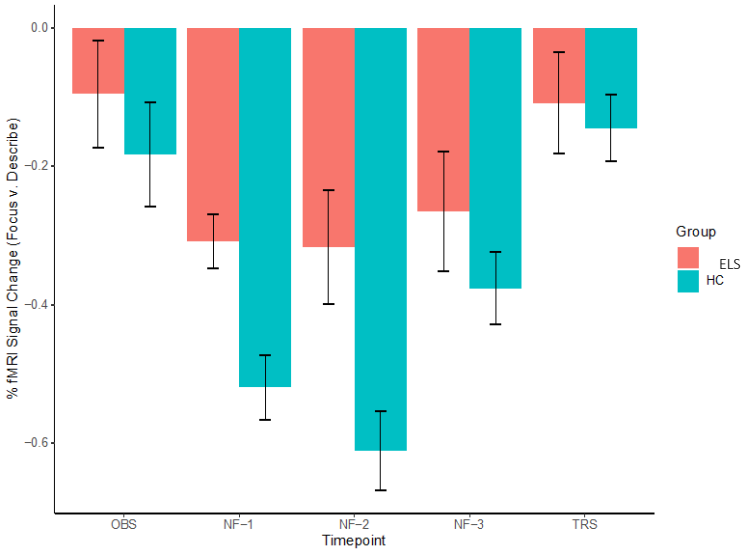




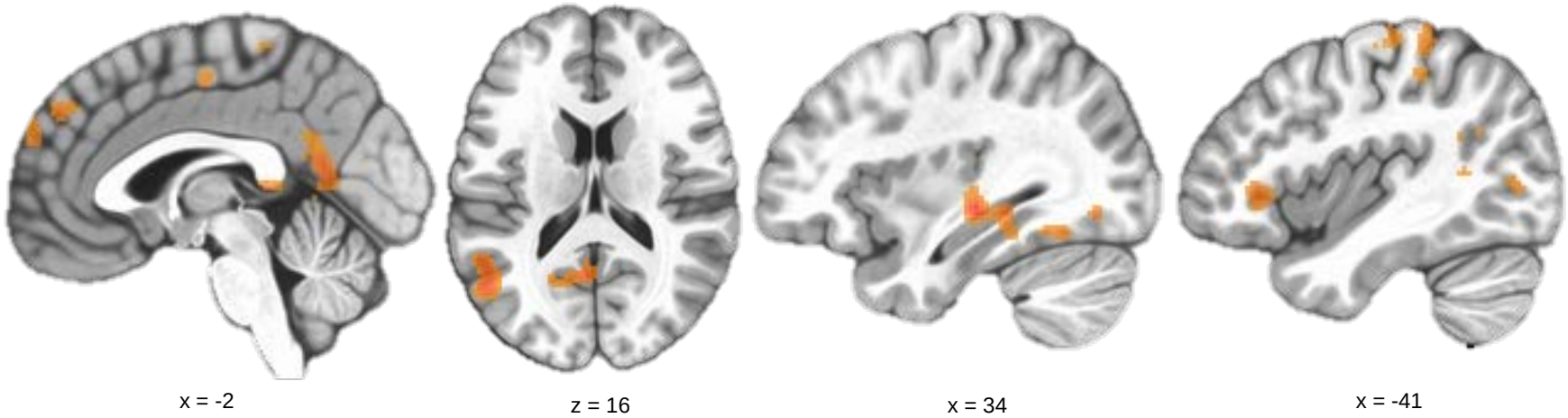








MDD/ANX > HC Breath vs. Describe contrast: p_{uncorr} < .005



Conclusions

- Our data shows that group mindfulness-based training is acceptable and feasible for adolescents with ELS exposure.
  - We found evidence for positive impact of mindfulness-based stress reduction on self-reported symptoms of depression among adolescents with ELS exposure.
  - We further found evidence for changes in cortisol response and stress perception following a stress induction task associated with mindfulness training in adolescents with ELS exposure.
  - ELS-exposed adolescents who completed mindfulness training also evidenced increases in emotional awareness and clarity.

Conclusions

- Real-time fMRI neurofeedback is an acceptable and tolerable approach to self-regulation of brain activity in adolescents.
  - Neurofeedback augmented mindfulness training is effective in deactivating PCC activity relative to self referential thinking.
  - Reduced activity in the PCC is related to activity in regions of the DMN and SN relevant for emergence and maintenance of psychopathology.

- Adolescents exposed to ELS are less successful in downregulating the PCC and show greater brain activity in regions involved in emotional processing during mindfulness practice relative to self-referential thinking.
- This may represent a mechanism by which early life stress exposure leads to psychopathology.

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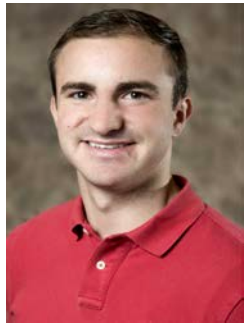
Tim McDermott

Kelly Cosgrove

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