

PTSD: From Neurobiology to Treatment

Arash Javanbakht MD

Director, Stress, Trauma, and Anxiety Research Clinic (STARC)

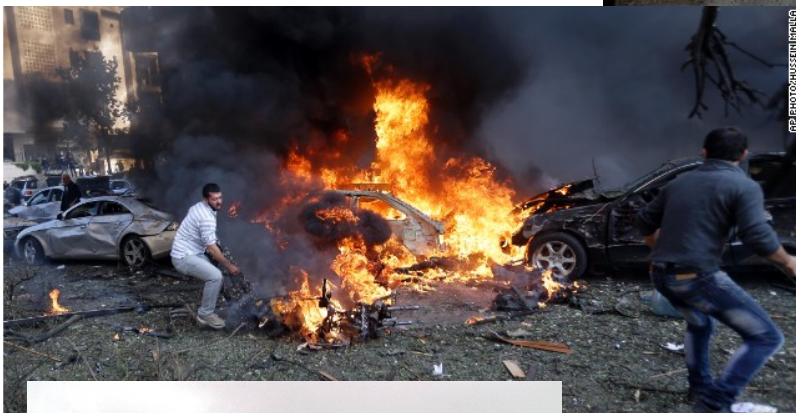
www.starclab.org

Department of Psychiatry and Behavioral Neurosciences
Wayne State University

No conflict of Interest



Neither does Jasper!



PTSD



What I will cover

- PTSD, overview
- PTSD neurobiology: what's new?
- Diagnosing PTSD, and its challenges
- Treatments: old and new
- Trauma in refugees, and creative interventions

PTSD, Why is it important?

- Prevalence

Pretty Common

Lifetime prevalence: 8%

One year prevalence: 3.5%

Females: 10%

Adolescents: Boys: 3.7%, girls: 6.3%

Special groups:

Military: Up to 30%

First responders: Up to 20%

Refugees: 30-80%

Note: These are full blown meeting all the fancy criteria

Compare with 1% schizophrenia

PTSD, Why is it important?

- Prevalence
- Comorbidities
 - MDD: 50-70%
 - Other anxiety disorders
 - Substance use: 20-40%

PTSD, Why is it important?

- Prevalence
- Comorbidities
- Burden
- Its treatable!

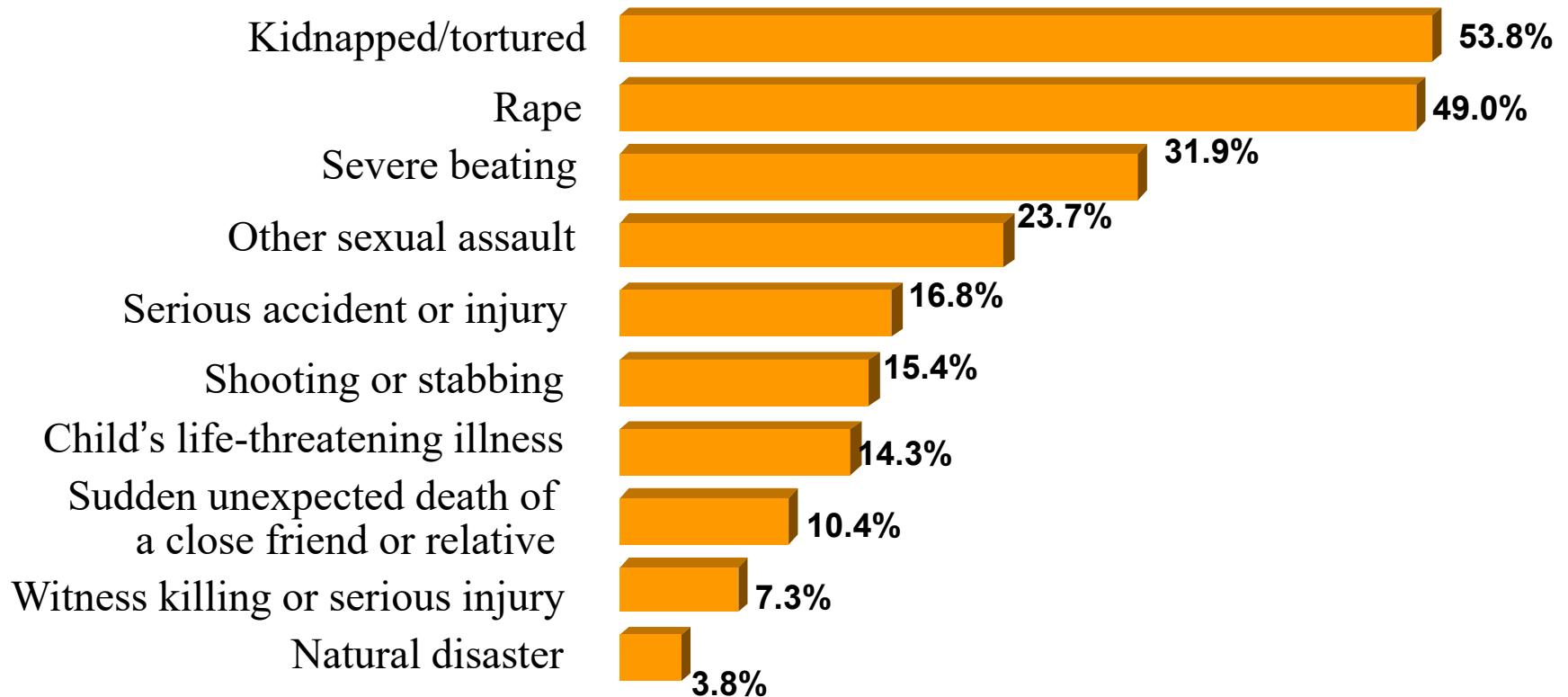
PTSD, do we miss out on it?

- Residency training in diagnosing and Treatment?
- We don't look for it in those with other Dx:
Who is more vulnerable to trauma than a chronically psychotic patient living on the streets of a city?
- Sub-threshold trauma (does it matter to meet ALL the criteria?!)
- Tough guys/girls

PTSD Definition

- Criterion A: Trauma (direct or indirect exposure)

Traumatic Events and Estimated Risk for Developing PTSD in U.S.



PTSD Definition

- Criterion A: Trauma (direct or indirect exposure)
- Criterion B: Intrusion symptoms (memories, nightmares, flashbacks, etc)
- Criterion C: Avoidance symptoms (internal or external reminders)
- Criterion D: Negative cognition/Mood
- Criterion E: Hyperarousal (anger/irritability may be misdiagnosed)
- Do I care if they miss one criterion?!

PTSD and Physical (outside brain) Health

- Reduced perceived health
- Cardiovascular (HPA axis, sympathetic hyperactivity)
- Endocrine (diabetes, metabolic syndrome)
- Pain

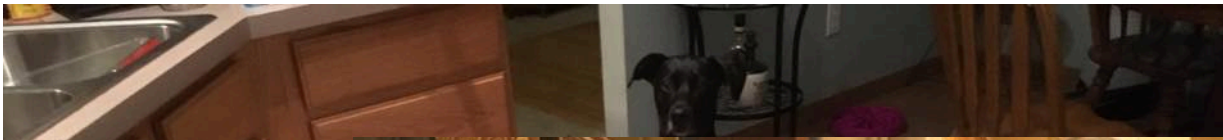
Neurobiology of PTSD

- Fear and Safety Learning
- Neuroimaging
- Contextualization
- Sympathetic system
- Inflammation

How do we learn fear?



We learn safety similarly

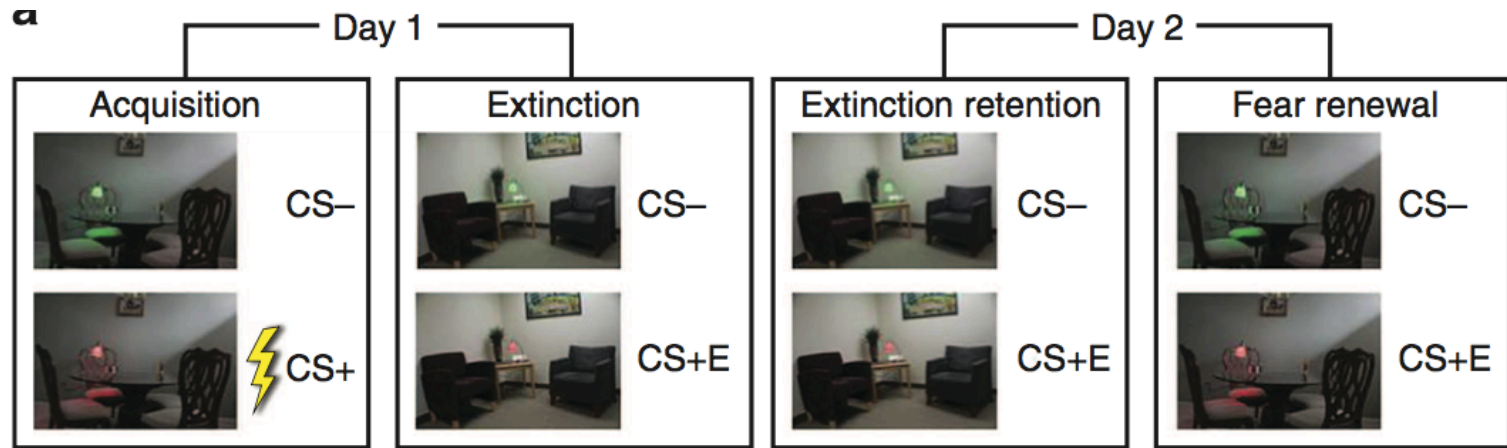


Context & Fear

Fear response, and learning of safety are both context dependent



Associative Fear Learning



- Patients with PTSD learn fear, but have difficulty giving it up!

Fear Learning and PTSD

- Overgeneralization of Fear

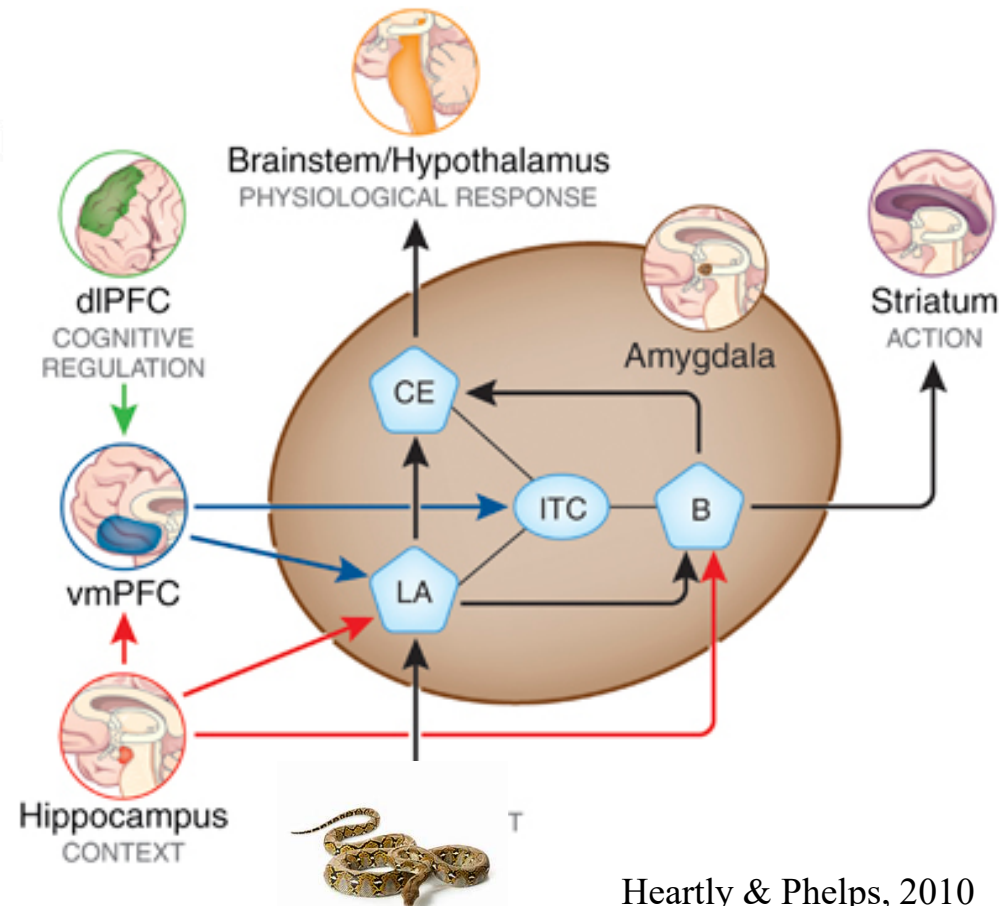
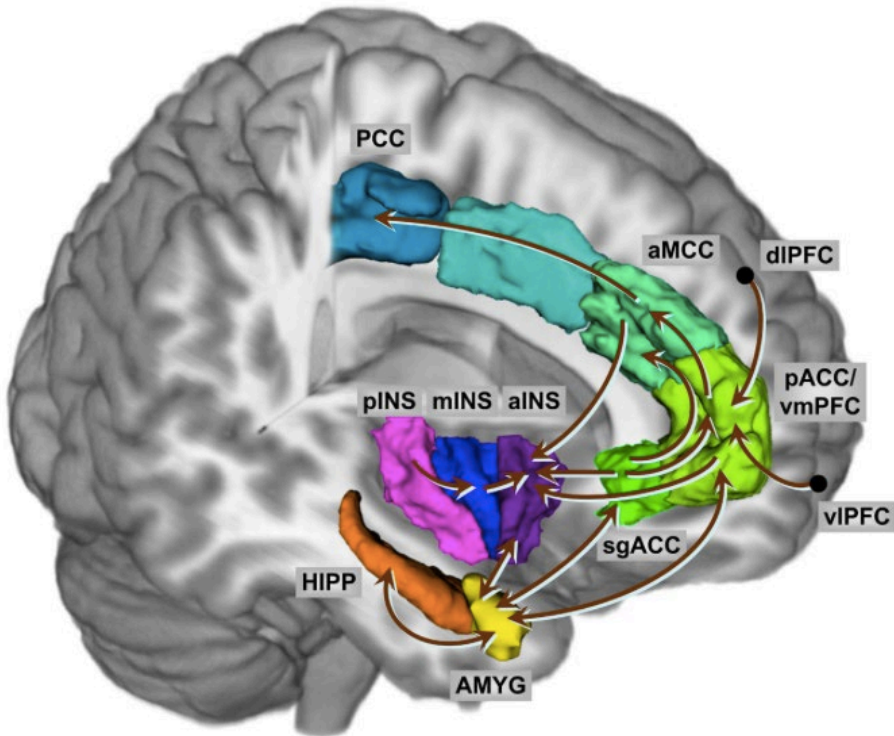


- Failure in contextual processing and safety learning



Neuroimaging

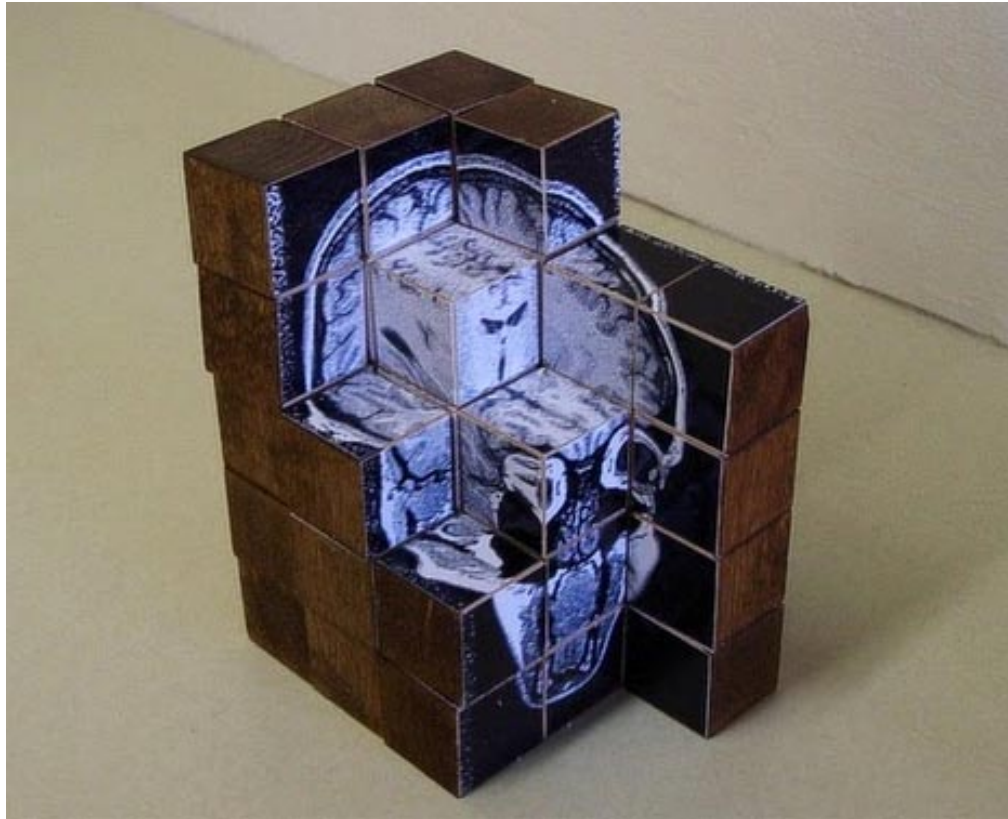
Neuroanatomy of Fear



Neuroimaging methods in PTSD

- Structural
- Resting State
- Fear Conditioning/Extinction Learning
- Response to Trauma narrative, pictures, sounds
- Response to negative images
- Response to fearful faces

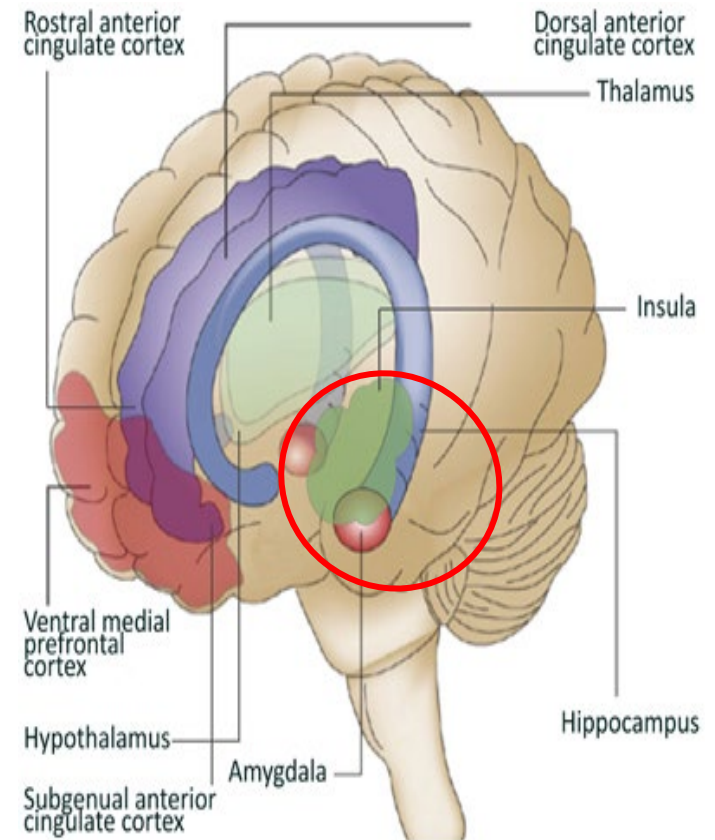
Volumetric Studies



Volumetric Changes

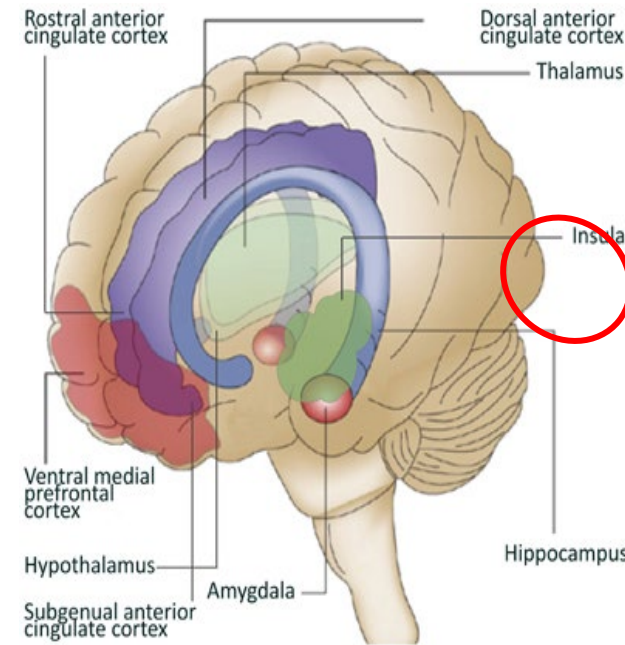
Amygdala: Inconsistent from smaller, to larger compared to the control

Insula: reduced volume



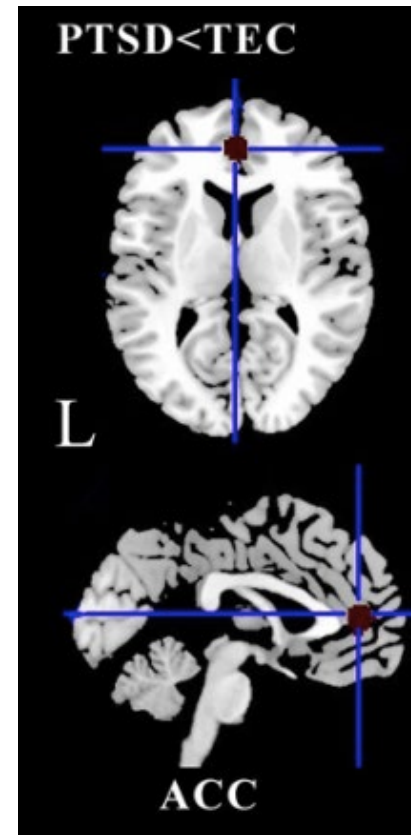
Structural - Hippocampus

- Smaller size both compared to HC and TC.
- More pronounced in more severe cases
- Causality is unclear.
- Twin studies: it may be a vulnerability factor
- On the other hand: PTSD < TEC, & TEC < HC
- Also, loss is larger in chronic PTSD
- May be reversed with SSRI treatment

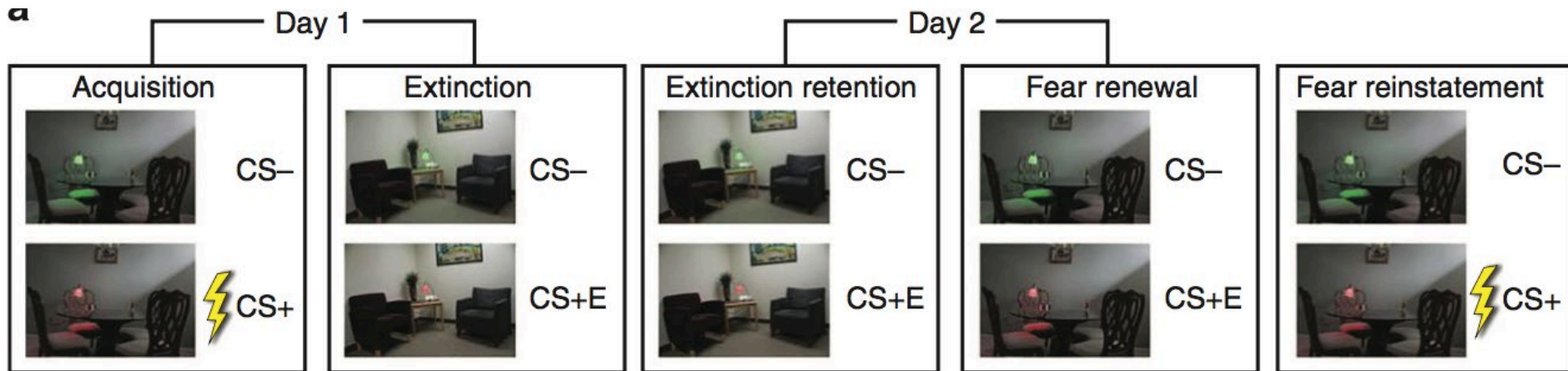


Structural Changes - Regulatory areas

- Reduced volume in Anterior Cingulate Cortex compared to HC and TC, and in twin studies
- DTI: aberrant white matter integrity in ACC=>AMYG pathways
- Could be a result, and also vulnerability
- Can predict response to treatment
- Reduced volume in ventromedial prefrontal cortex

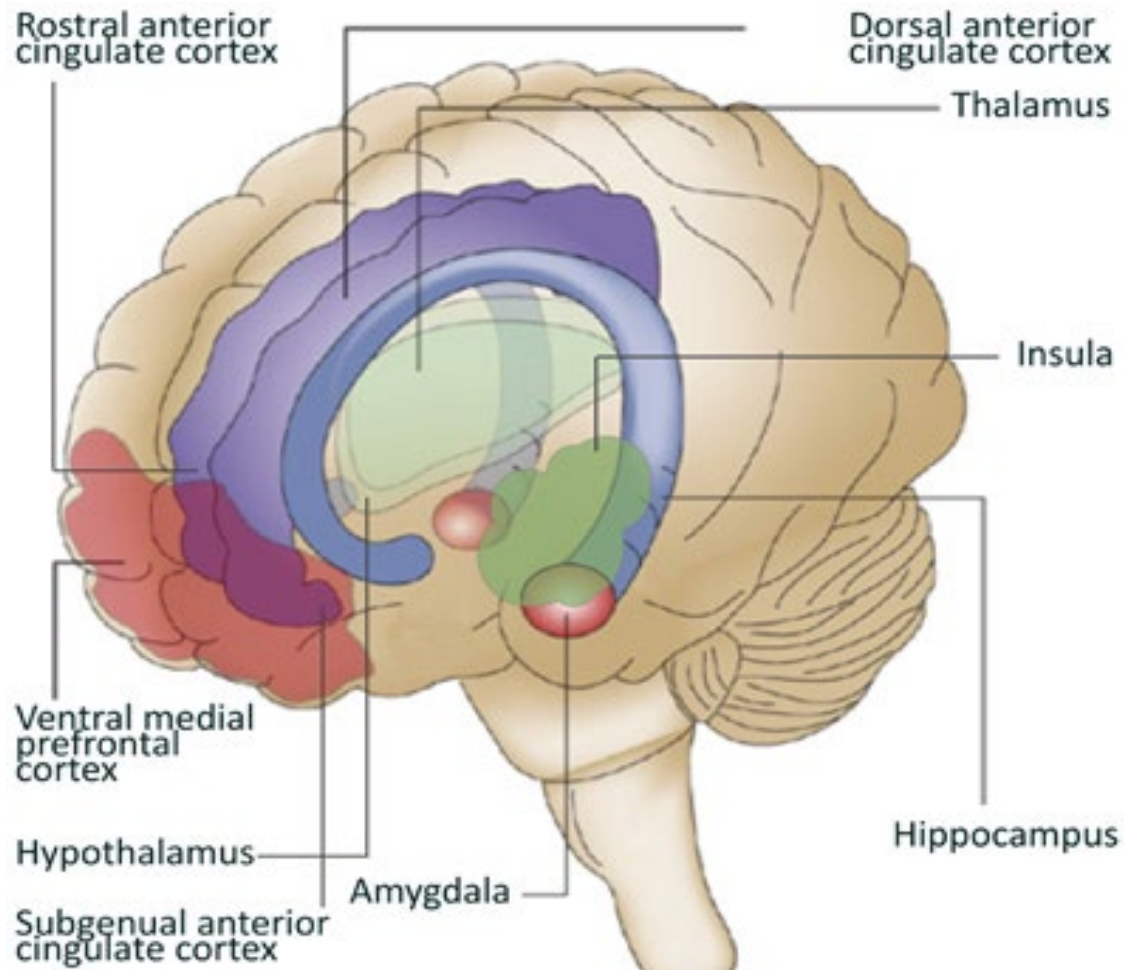


Fear extinction deficits in PTSD



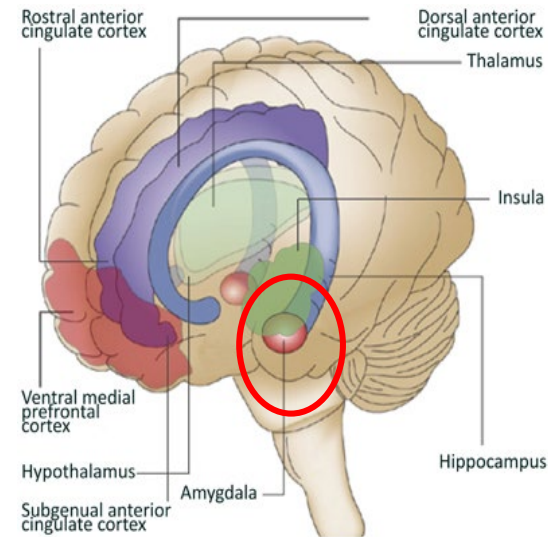
- During extinction recall
 - Lower activation in hippocampus and vmPFC
 - Greater ACC and amygdala activation
 - Indicates lower capacity for regulation of fear response

Refresher on this guy!



Functional MRI studies - Amygdala

- Larger response to trauma-related narrative, pictures, sounds, odors
 - Larger response after trauma, may predict higher chance of developing PTSD
 - Larger response correlates with sxs severity.
- Larger response to fearful faces, trauma-unrelated negative pictures
- Larger response during fear conditioning and extinction learning
- Larger baseline activity, and response to neutral stimuli

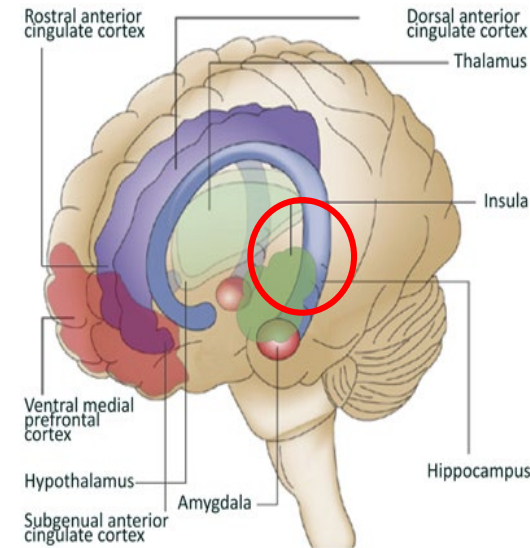


Functional MRI studies - Amygdala

- Treatment:
 - Larger pretreatment activity predicts less response to CBT
 - Treatment response leads to less AMYG activity in response to fearful faces and trauma memories

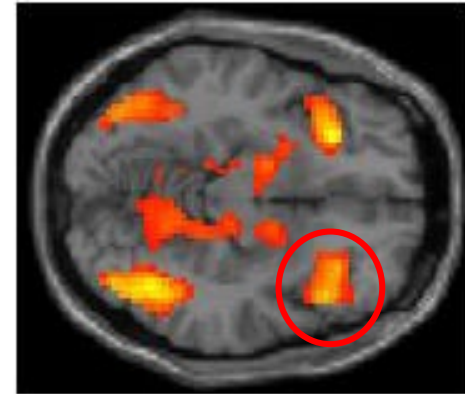
Functional MRI studies - Hippocampus

- Reduced activation during rest, in response to trauma memories, during extinction recall
- Activation is negatively correlated with sxS severity
- Activation is improved with treatment



Functional MRI studies - Insula

- Increased response to trauma related imagery, odors, trauma-related words, anticipation of negative images, fearful faces, and painful stimulation
- Sxs severity correlates with insula activation



Functional MRI - vmPFC

- Lower activation/deactivation during script-driven imagery
- Lower activation in response to trauma pictures, or fearful faces
- Activation is negatively correlated with sx severity
- Activation improves with treatment response

Summary

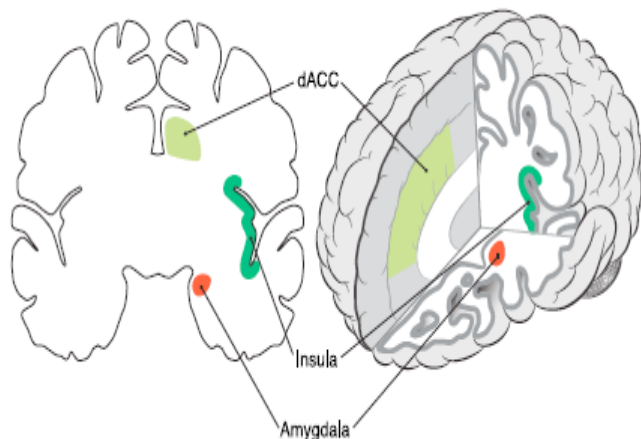
- Increased activation in AMYG, insula, dmPFC
- Decreased activation in HC, vmPFC, rACC

Conclusion: Neurocircuitry model for PTSD

- Abnormal fear learning and exaggerated threat detection
- Diminished emotion regulation and contextual processing

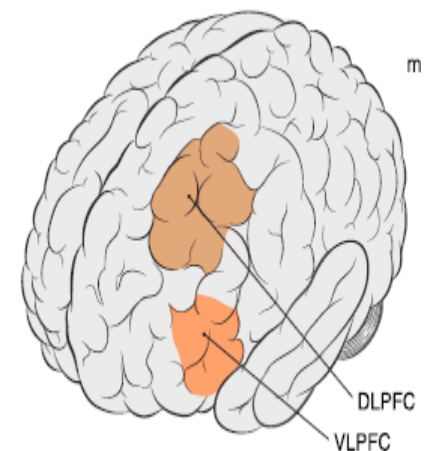
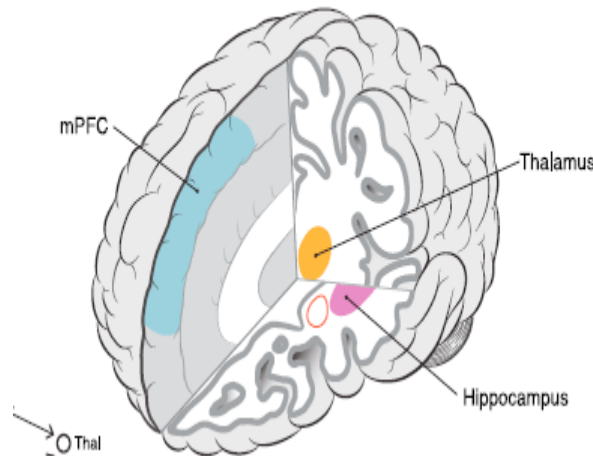
▶ Emotion & salience detection regions

- ▶ Amygdala, insula
- ▶ Dorsal anterior cingulate cortex



▶ Emotion regulatory regions

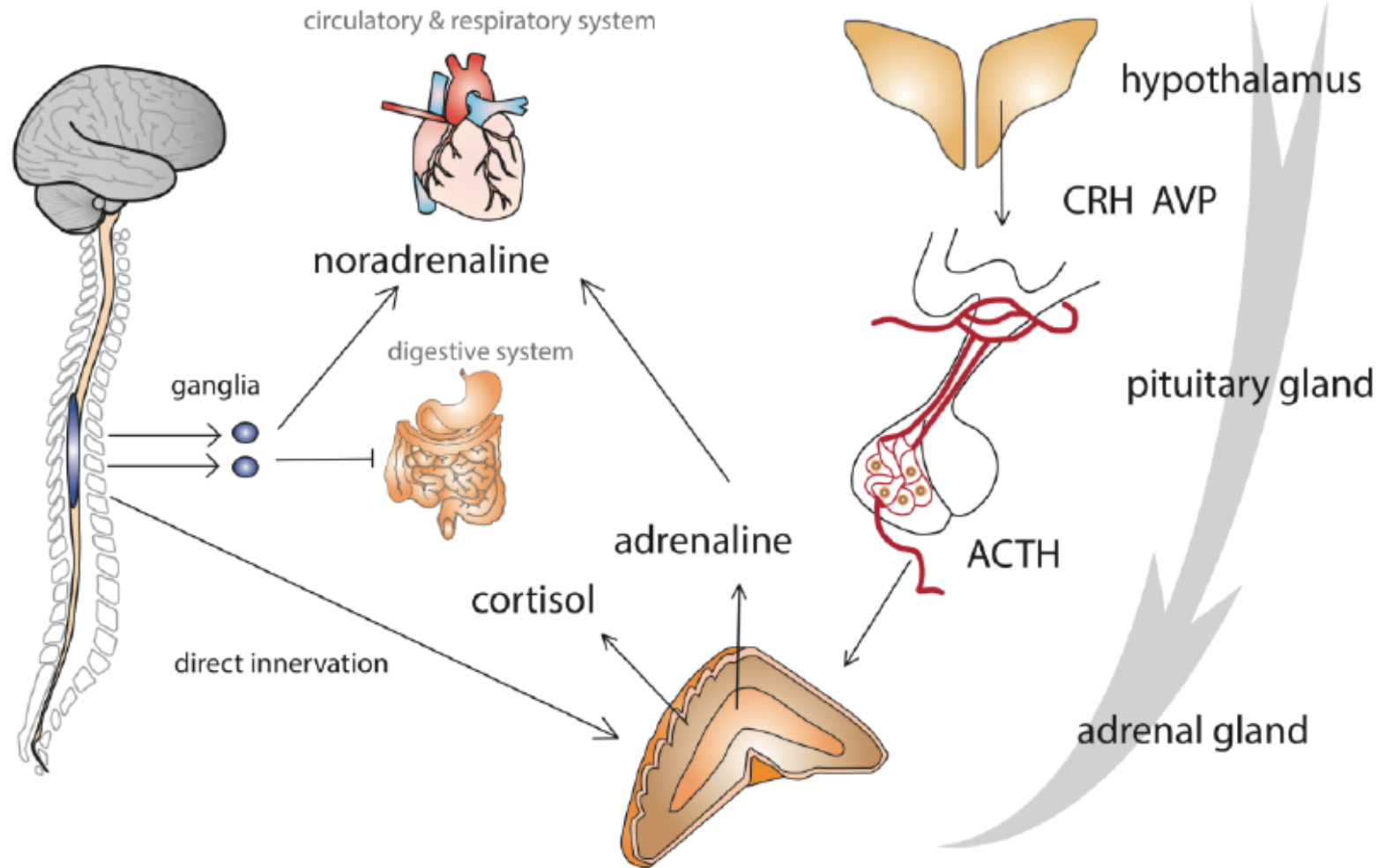
- ▶ ventrolateral and medial prefrontal cortices, rostral ACC
- ▶ Hippocampus



HPA/Sympathetic NS

sympathetic nervous system

endocrine HPA axis



HPA/Sympathetic

Psychophysiology:

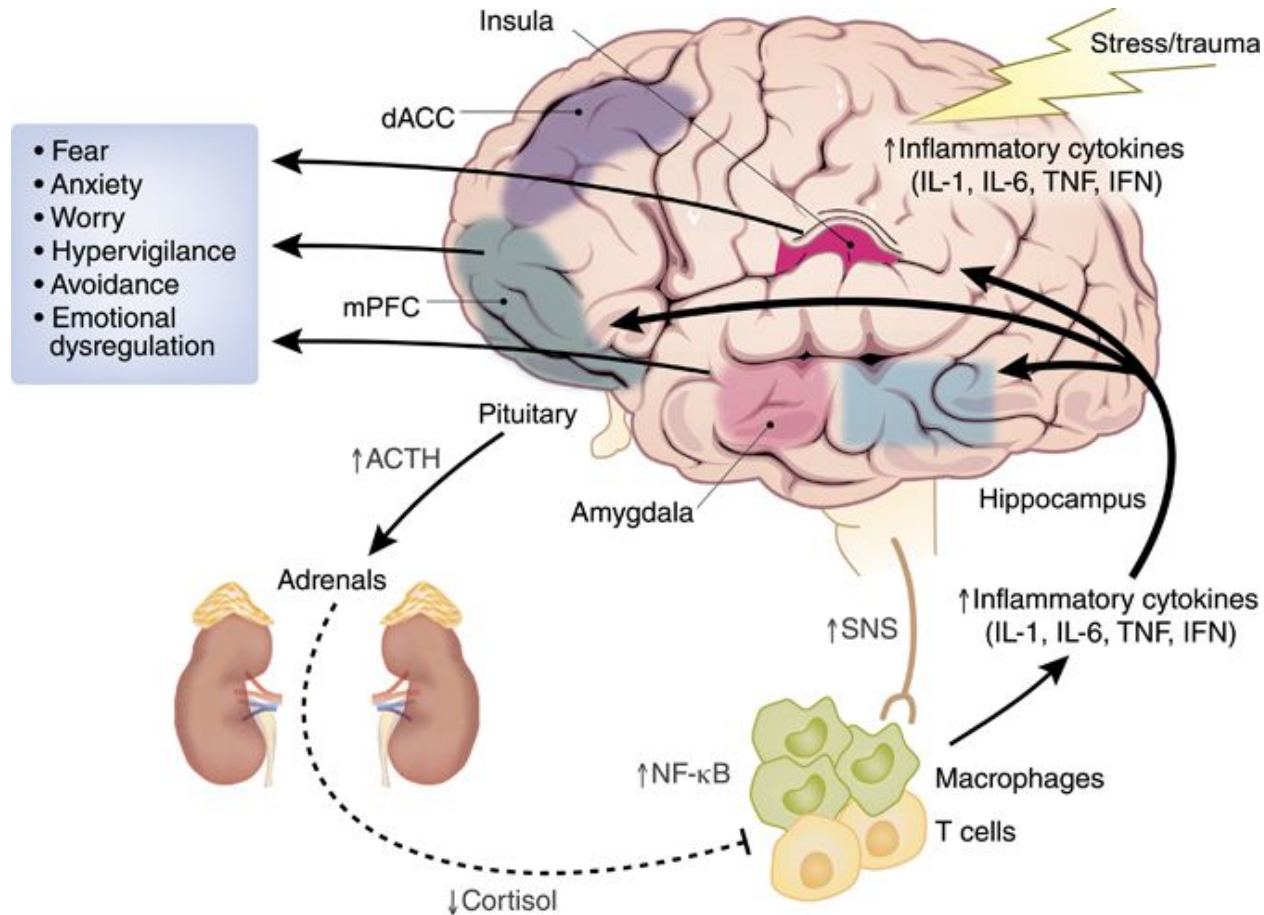
increased baseline HR and BP, enhanced HR, SC and EMG responses, acoustic startle

Sleep abnormalities: disrupted, less efficient sleep

Catecholamines:

increased 24h urinary Epi & NE, enhanced catecholamines response to traumatic stimuli, ADRB2 alpha2 receptor

Inflammation



Adapted from Felger et al. 2016

PTSD: Increased circulating IL-1 β , IL-6, TNF- α , and CRP

Diagnosis

- Like sex, you won't know if you don't ask about trauma!
- How to ask?
 - Trauma
 - Intrusion sxs
 - Hyperarousal
 - Avoidance
 - Negative emotion...
- Don't need all the details the first session (don't be too curious)
- Flashbacks are hallucinations, but are not!

Treatment: Psychopharmacology

- Surprise: SSRIs/SNRIs!
- Care for evidence: sertraline, fluoxetine, venlafaxine
- How I do it: choose based on the side effects!



Don't

- Antipsychotics: no clear evidence; metabolic and sympathetic systems are already messed up
- Benzos and mood stabilizers
- THC: slight evidence for mild effects, but wanna risk the dark side?
- Memory modulating agents such as D-cycloserine: meh
- Ketamine: meh

Prazosin for nightmares?

- We wish we knew.
- There is evidence from small studies, but not large/meta-analyses



Cool reference

- VA/DoD Clinical Practice Guideline

Therapy, Therapy, Therapy!

- Medications can't fix traumatic memories, avoidance, social consequences, with medications!

Cool Technologies

- Virtual Reality

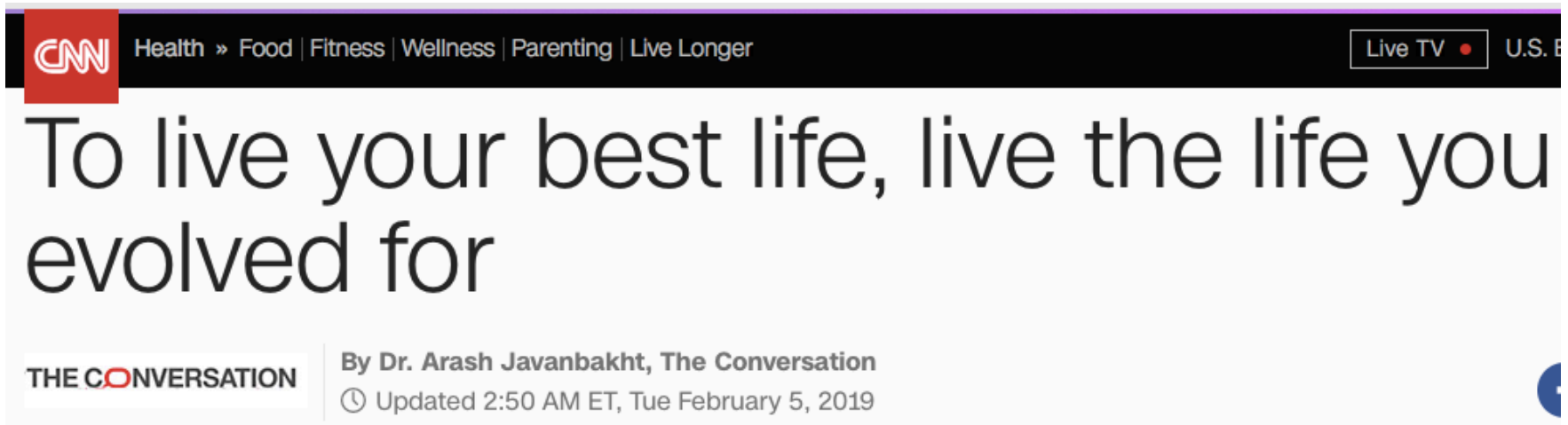


Augmented Reality



Don't forget

- Diet
- lifestyle
- Exercise (specially cardio; evidence for anxiety/depression/PTSD)
- Puppies!



The image is a screenshot of the top portion of a CNN website article. At the top, there is a black navigation bar with the CNN logo on the left and a series of white links: 'Health', 'Food', 'Fitness', 'Wellness', 'Parenting', and 'Live Longer'. On the right side of this bar, there is a 'Live TV' button with a red dot and the text 'U.S. E'. Below the navigation bar, the main headline 'To live your best life, live the life you evolved for' is displayed in a large, dark, sans-serif font. Underneath the headline, on the left, is the text 'THE CONVERSATION' in a bold, black, sans-serif font. To the right of this, it says 'By Dr. Arash Javanbakht, The Conversation' and 'Updated 2:50 AM ET, Tue February 5, 2019'. A small blue Facebook 'f' logo is visible in the bottom right corner.

CNN Health » Food | Fitness | Wellness | Parenting | Live Longer Live TV • U.S. E

To live your best life, live the life you evolved for

THE CONVERSATION

By Dr. Arash Javanbakht, The Conversation
⌚ Updated 2:50 AM ET, Tue February 5, 2019

Bored Yet?



Stress, Risk and Resilience in Syrian Refugees in the US

A Project of Prevalence, Neurobiology, Culture, Environment, and Interventions



Arash Javanbakht MD

Stress, Trauma, and Anxiety Research Clinic (STARC)

Wayne State University Department of Psychiatry

STARC

- Treating trauma in civilians, first responders, & refugees in Detroit Metro Area.
- Researching Neurobiology of anxiety and PTSD: brain imaging, inflammation, autonomic responses, neurobiology of therapy
- Advancing treatment methods: telepsychiatry, augmented reality tech, dance and movement based therapies, art and mindful yoga



<http://www.starclab.org>

Project Stress, Risk and Resilience in Syrian Refugees Resettled in Southeast Michigan

Determine prevalence in children, adults, and families

Genetics/Epigenetics

Stress and Inflammatory biomarkers

Illness trajectory

Environment

Interventions

Collaboration Between WSU & Co



ALJAZEERA



Your NPR News Station **npr**

AMERICAN
PSYCHIATRIC
ASSOCIATION



AMERICAN ACADEMY OF
CHILD & ADOLESCENT
PSYCHIATRY



ANXIETY AND DEPRESSION
ASSOCIATION OF AMERICA

Psychiatric Times



PBS
NEWS
HOUR

KPBSTM
kpbs.org

MEDPAGE
TODAY[®]

Medical  press
medicalxpress.com



Imagine...

Years of Stress

Life in Syria before and after

Life in the camps

Stress of migration and resettlement



Recent publications on Syrian Adult refugees

- Syrian refugees in Lebanon: PTSD 27.2%; Depression: 43.9%
- Camps in Turkey: PTSD 33.5%-83.4%; Depression 37.4%
- None in the US

Acarturk et al, 2017, Alpak et al, 2017, Kazour et al, 2017, Naja et al, 2017

Team, and Methods:

- Where: Arab American Chaldean primary care clinics
- Who: 5 Iraqi/UAE MD and DDS volunteers, research coordinators, and bilingual undergrads
- How: Referral from the PCP
- What: Screening for PTSD (PCL), anxiety & depression (HSCL-25); demographic and self-reported health data; biomarkers

Our cohort:

A total of 432 people recruited between June 2016 and May 2017 with over 90% recruitment success (no unaccompanied minors)

Syrians:

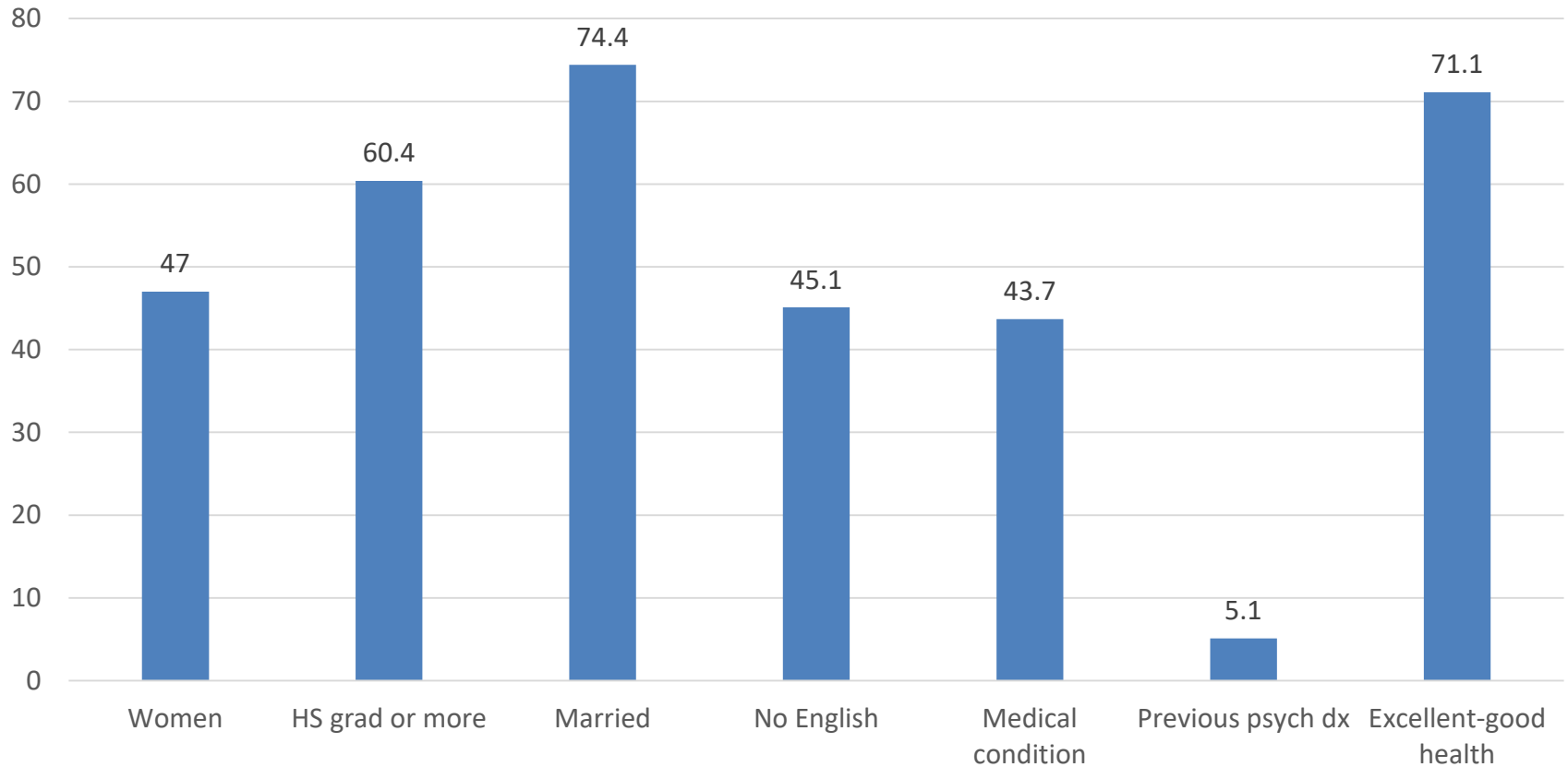
- 157 Adults (18 – 65)
- 131 Children (6-17)
- 77 Families

Iraqis:

- 131 Adults (18-65)
- 40 Children (6-17)
- 51 Families

Findings, Adults

N=157, mean age 36



Thresholds

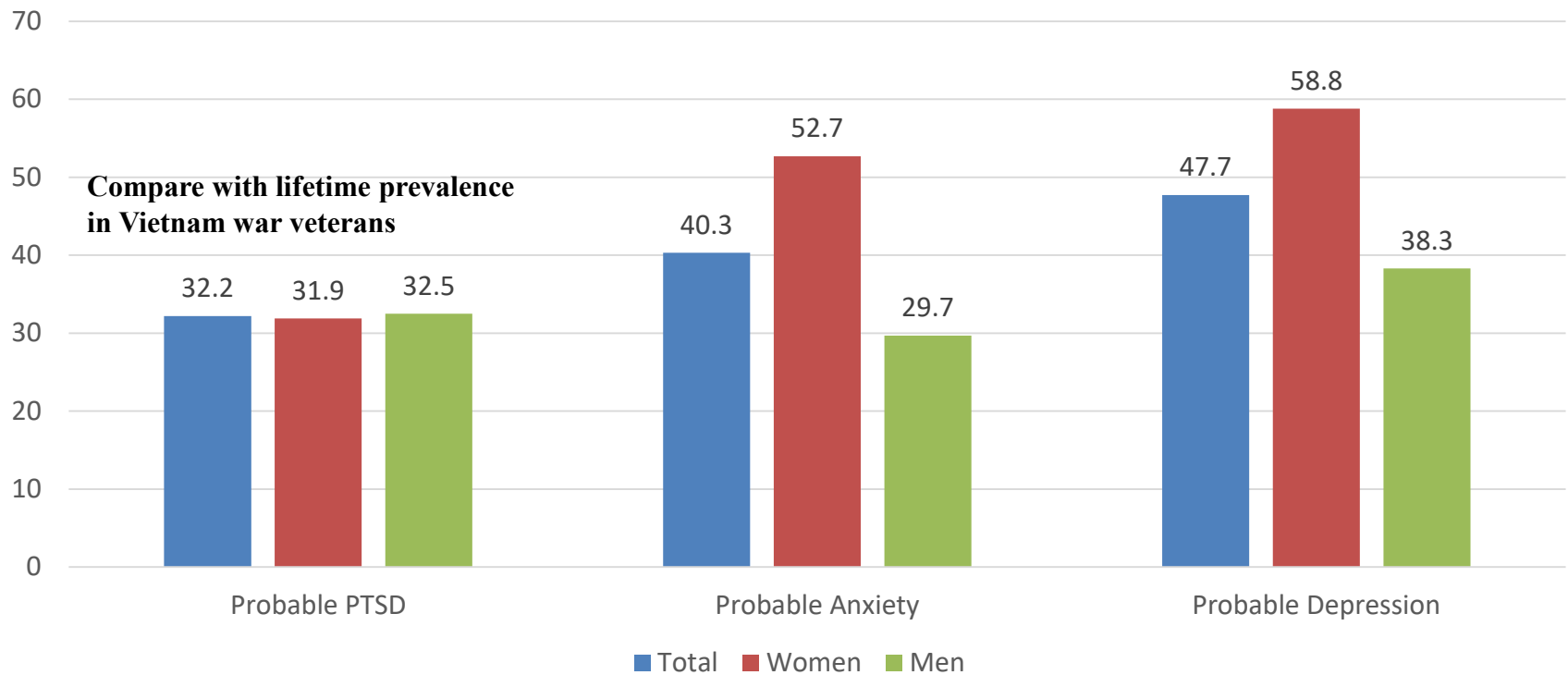
Possible PTSD: DSM-IV criteria (PCL score mostly >40)

High Anxiety: HSCL-anx >1.75

Depression: HSCL-dep >1.75



Prevalence of Possible PTSD, Anxiety and Depression in Adults



Javanbakht et al, 2018

Comorbidities of Possible PTSD

Possible PTSD +	All	Females	Males
Possible Depression	76.5%	88.2%	64.7%
Possible Anxiety	77.1%	88.2%	66.7%
Possible Depression + Anxiety	43.0%	57.9%	31.3%

Gender

	PCL	HSCL-anx	HSCL-dep
Male	41.72 (16.87)	1.92 (0.73)	1.99 (0.67)
Female	37.47 (14.16)	1.62 (0.58)	1.69 (0.58)
	p=0.1	p=0.015	p=0.013

Syrian Refugee Children

- Little is known
- 30% of 96 Syrian children with parents in Germany had PTSD
- Two studies of Yazidi children in Turkey (38 & 55 children): 10.5 & 36% PTSD, and 10.5% and 7.3% high anxiety



Tools: Children

- UCLA post-traumatic stress reaction index
- Screen for Child Anxiety Related Disorders (SCARED)

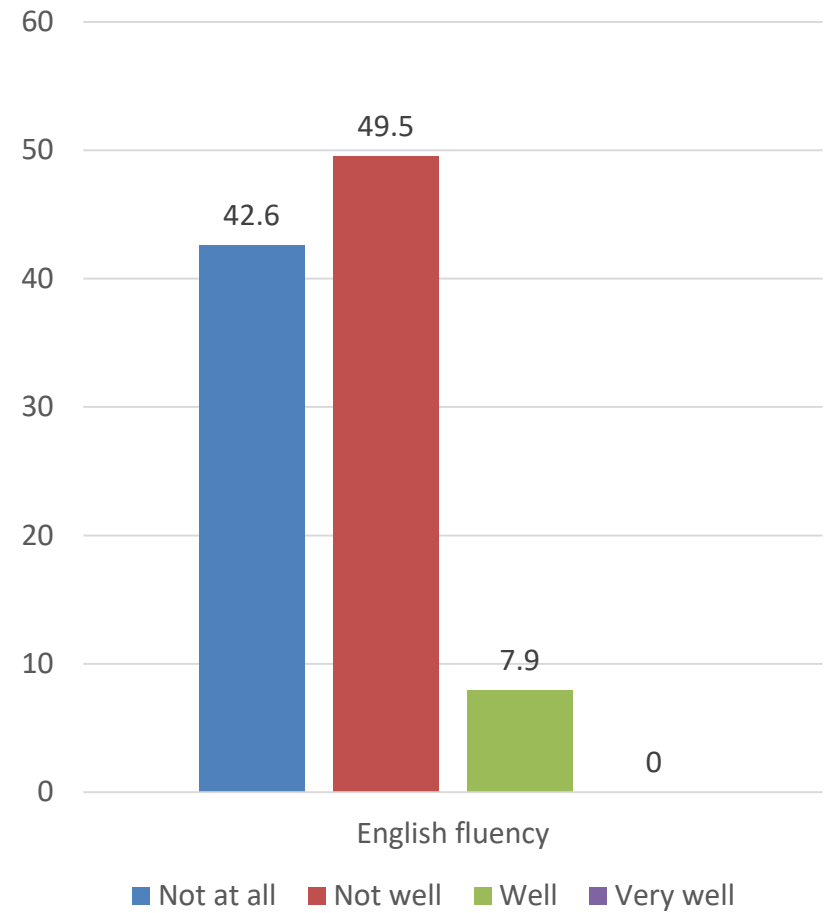
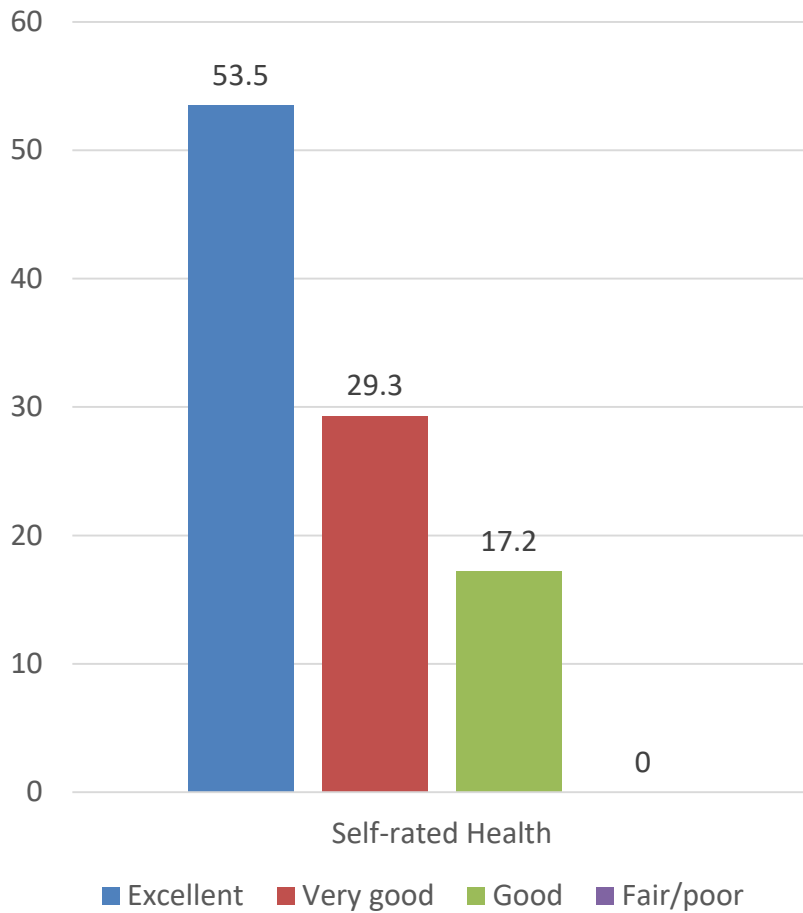


Findings: Children

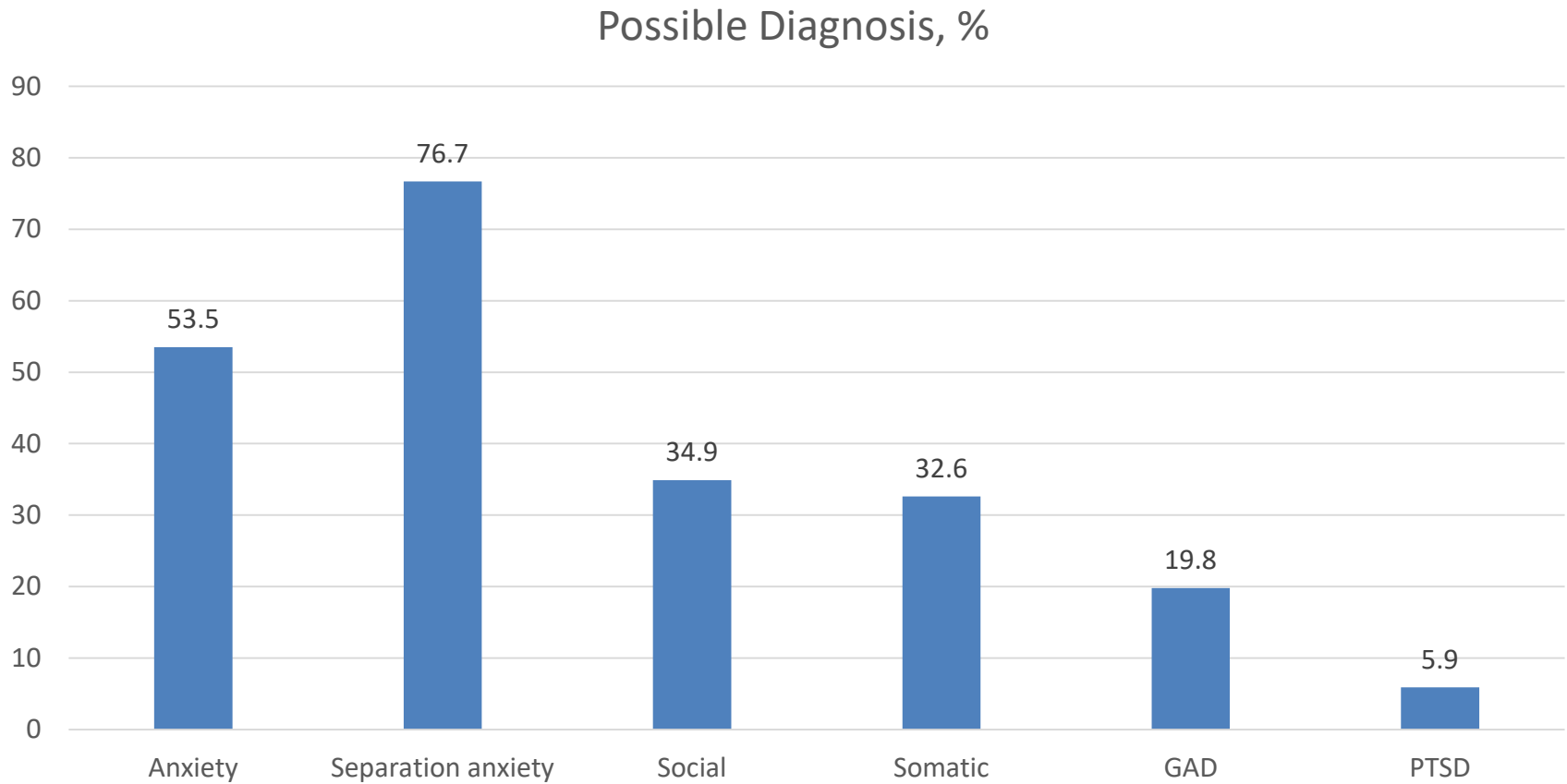
- 131 children age 6 - 17
 - 40.5% girls
 - 11.02 mean age
 - 53 families
 - 83.2% accompanied by 2 parents
- Few with previous psych (6.5%) or medical dx (8.3%).



Self rated Health and Fluency (upon arrival)



Prevalence of Anxiety and PTSD, Children



Javanbakht et al, 2018

All measures of maternal distress correlate with children's anxiety?

TABLE S1 Characteristics and Association Between Symptom Severity Score for Mothers and Fathers and Anxiety Symptom Severity Among Syrian Refugee Children

	Mothers (n = 45)	Fathers (n = 43)
Characteristics		
Age (y), mean (SD)	36.56 (6.01)	42.81 (8.11)
Fair or poor self-rated health, %	30.2	32.5
Anxiety symptom severity, mean (SD)	2.06 (0.80)	1.70 (0.75)
Depression symptom severity, mean (SD)	2.08 (0.69)	1.79 (0.66)
PTSD symptom severity, mean (SD)	43.55 (18.08)	38.44 (15.33)
Possible anxiety diagnosis, %	63.6	34.4
Possible depression diagnosis, %	63.3	34.4
Possible PTSD diagnosis, %	41.5	35.9
Associations, β (p value)		
Anxiety symptom severity	4.66 (.041)	-2.42 (.34)
Depression symptom severity	7.37 (.003)	-0.29 (.91)
PTSD symptom severity	0.33 (<.001)	-0.04 (.78)

Note: PTSD = posttraumatic stress disorder; SD = standard deviation.



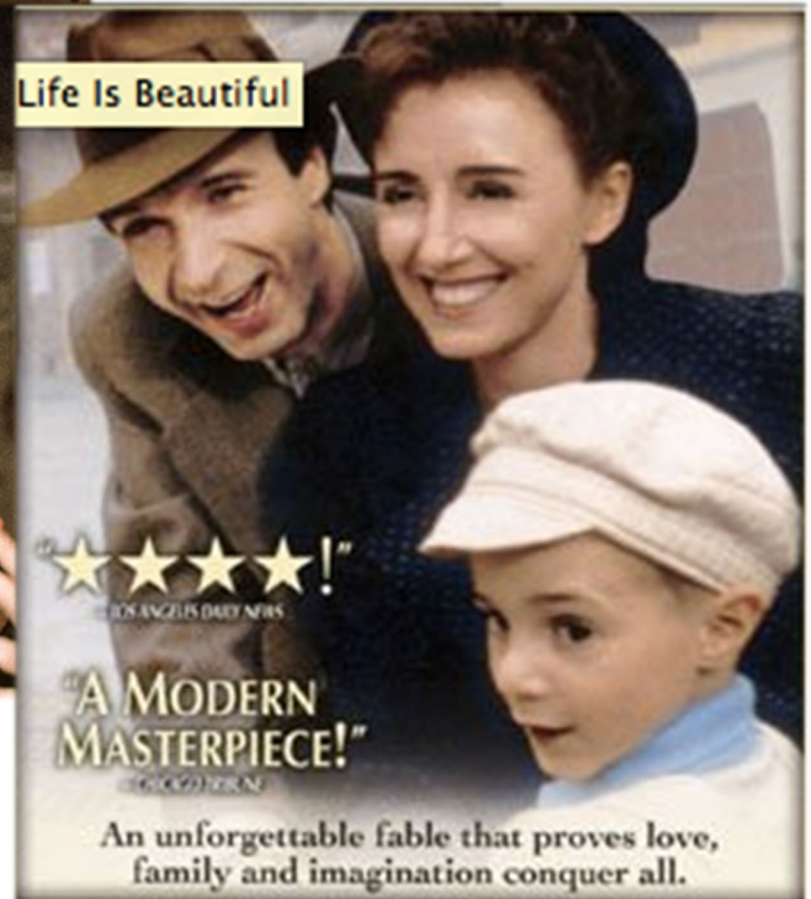
Javanbakht et al (2018), J Am Acad Child Adolesc Psychiatry

Importance of Perception & Meaning

For the meaning of life differs from man to man, from day to day and from hour to hour. What matters, therefore, is not the meaning of life in general but rather the specific meaning of a person's life at a given moment.

Viktor Frankl, 1963/1984

Meaning



<https://www.youtube.com/watch?v=9ITSqc1UnLU>

Perception & Meaning

- How would you rate your general health today? [1] Excellent [2] Very good [3] Good [4] Fair [5] Poor
- On a scale from 1 to 7, 7 being the worst thing that can ever happen to someone, how would you score your experience with war and migration?

Perception & PCL

Health/Hardship Perception	Est Marginal Mean PCL	95% CI	
Worse Health & Worse Perception	54.12	48.02	60.22
Worse Health & Better Perception	37.54	29.66	45.42
Better Health & Worse Perception	38.92	34.82	43.02
Better Health & Better Perception	36.29	31.84	40.73

The group with worse perception and health: PTSD prevalence of 82% (compare with 30% for the whole group)

Y'all still awake?!



Interventions:

We gotta get Creative

- Not enough trauma therapists fluent in language and culture
- Usual high drop out
- Cultural barriers
- Pharmacotherapy
 - Barriers in acceptance of the treatment
 - Side effects

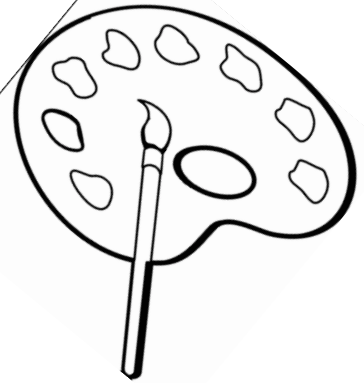
Arts and Movement Based Interventions

- Dance/Movement Therapy (DMT); children
- Art Therapy; children
- Mindful Yoga; moms
- High Intensity Interval Training (HIIT); dads





9 weeks testing for feasibility
100% thanks to volunteers
Barriers: timing, transportation, environment



Summer 2017; 9 Weeks

CYCLE 1



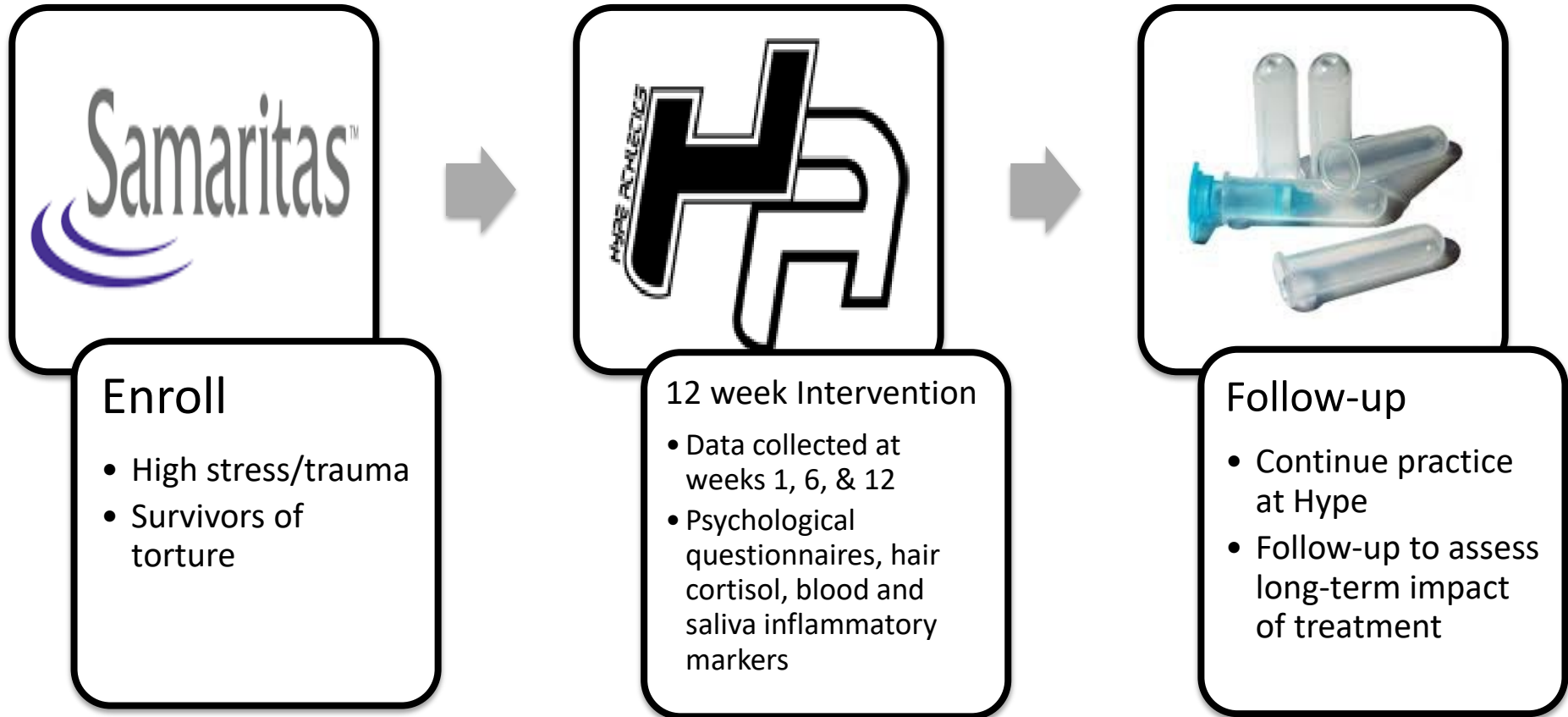
Winter 2018; 12 Weeks

CYCLE 2

- Closer location
- Choice of art or dance for kids
- Weekend sessions
- Culturally friendly rec center
- HIIT program for men



Program Design



Dance Therapy Session Framework

- Check in and mirroring exercise
- Body-mind centering musculoskeletal warmup
- Movement games
- Breath work and mindfulness exercises
- Check out: discussion of experience



Movement Intervention Example

- Mirroring allows leadership and partnership
- Mirroring also allows for cognitive flexibility and active learning



Take-Home Techniques

- Weekly repetition to instill activities for home use
- Body-mind centering musculoskeletal warmup
 - Stretching
 - Balancing
- Breath work and mindfulness exercises
 - Belly breathing
 - Meditation
 - Tension release



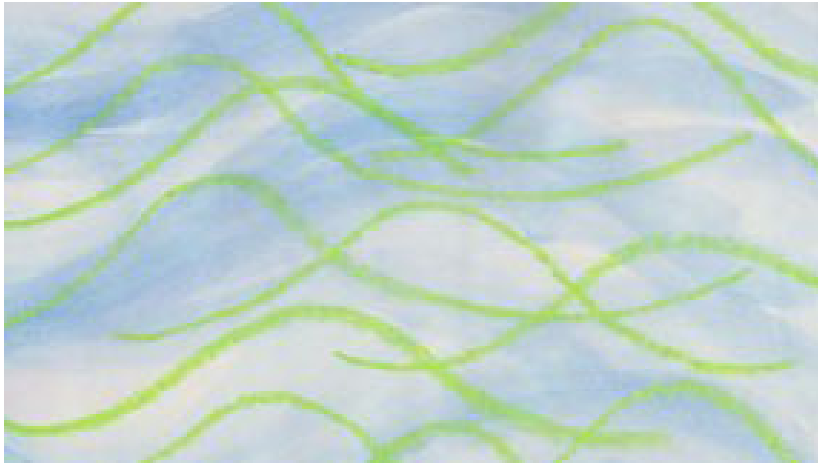
Typical Art Therapy Session

- Check in + snack
- Kinesthetics Engagement
 - Running
 - Deep breathing
- Art intervention w/ modification
- Closure verbal sharing
 - Meditative yoga
 - Breathing



Art Therapy Techniques

- Drawing breaths
- Meditation jars

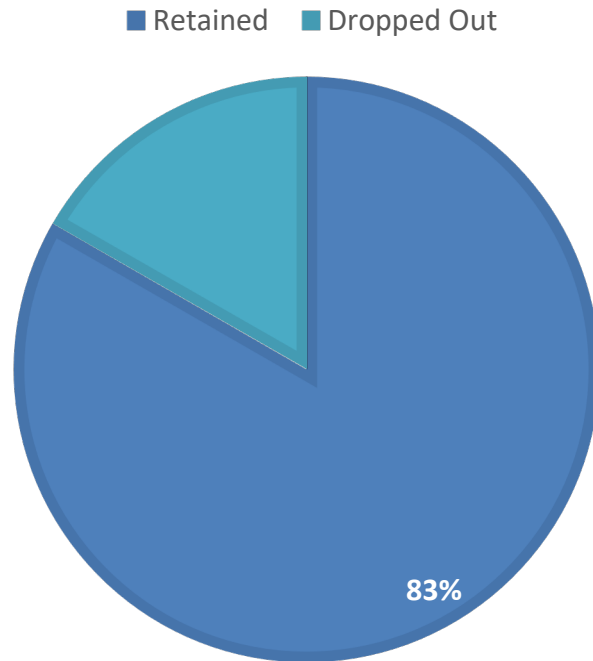


Collage: personal storytelling and creation

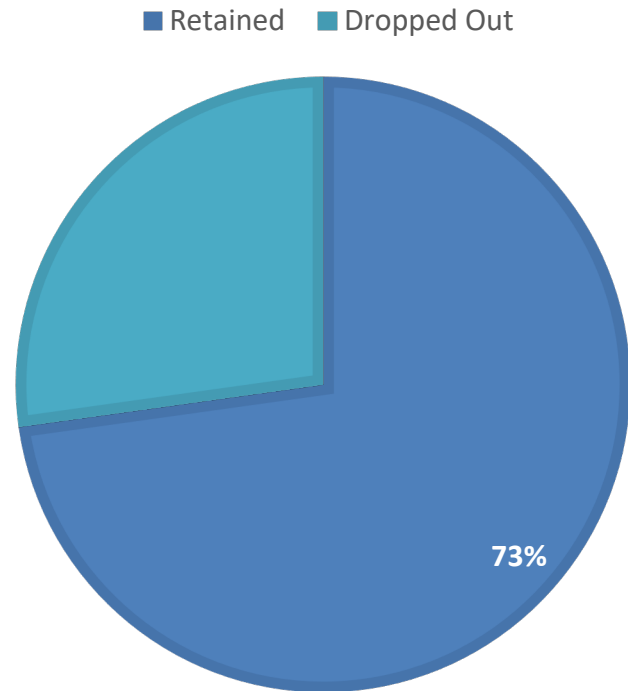


Feasibility

RETENTION, CHILDREN'S ART
THERAPY



RETENTION, CHILDREN'S DMT



Feasibility

- Lower adherence in men likely due to work
- Women were not comfortable with the research part



Results: Dance/Movement Therapy (n=16)

Changes in PTSD Symptoms Over
DMT Treatment

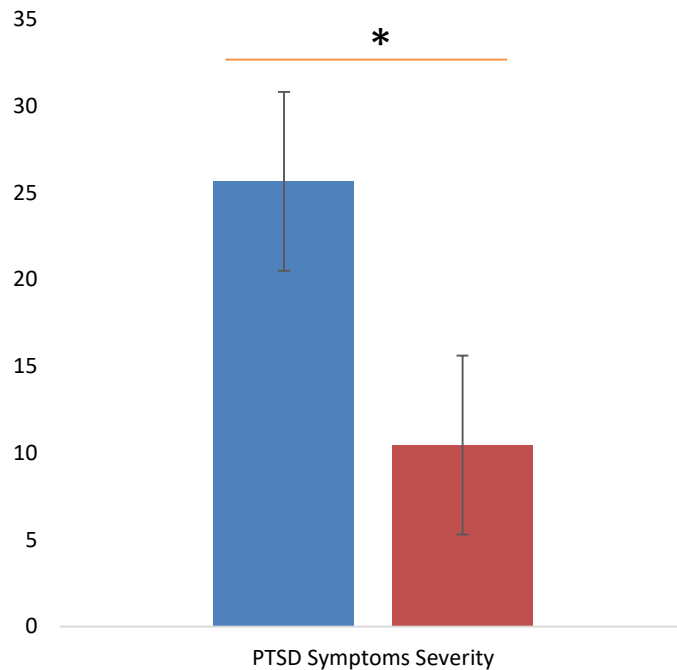


Figure 1. Significant, 15 point reduction in PTSD symptom severity as measured by the UCLA trauma questionnaire; effect size $r=0.451$ (moderate effect)

Changes in Anxiety Symptoms Over
DMT Treatment

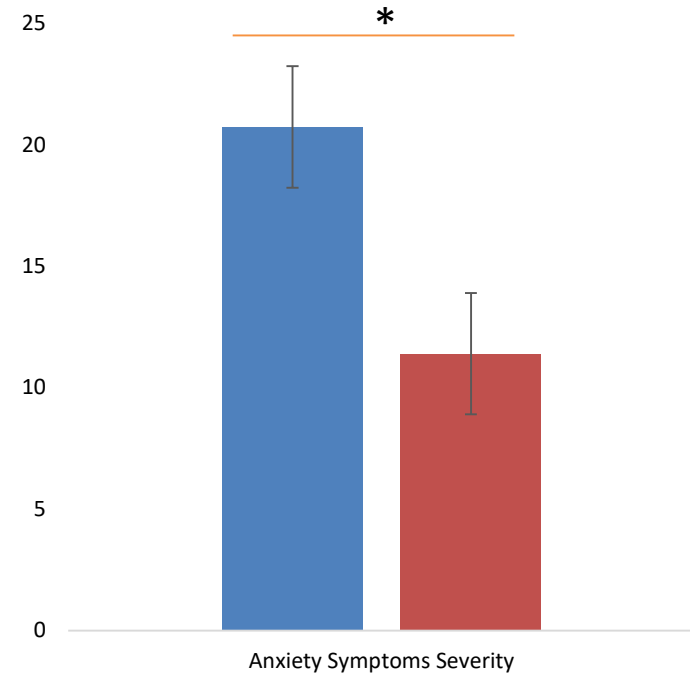
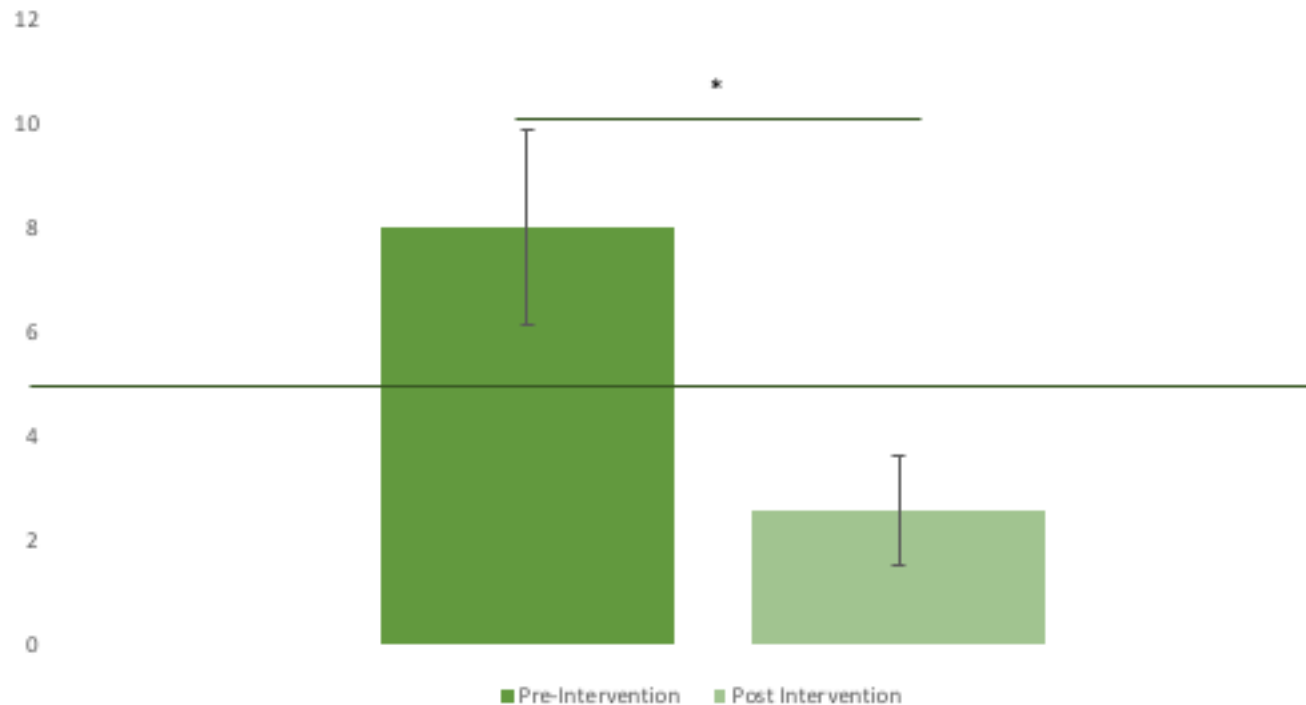


Figure 2. Significant, 9 point reduction in anxiety symptom severity as measured by the SCARED questionnaire; effect size $d=0.964$ (large effect)

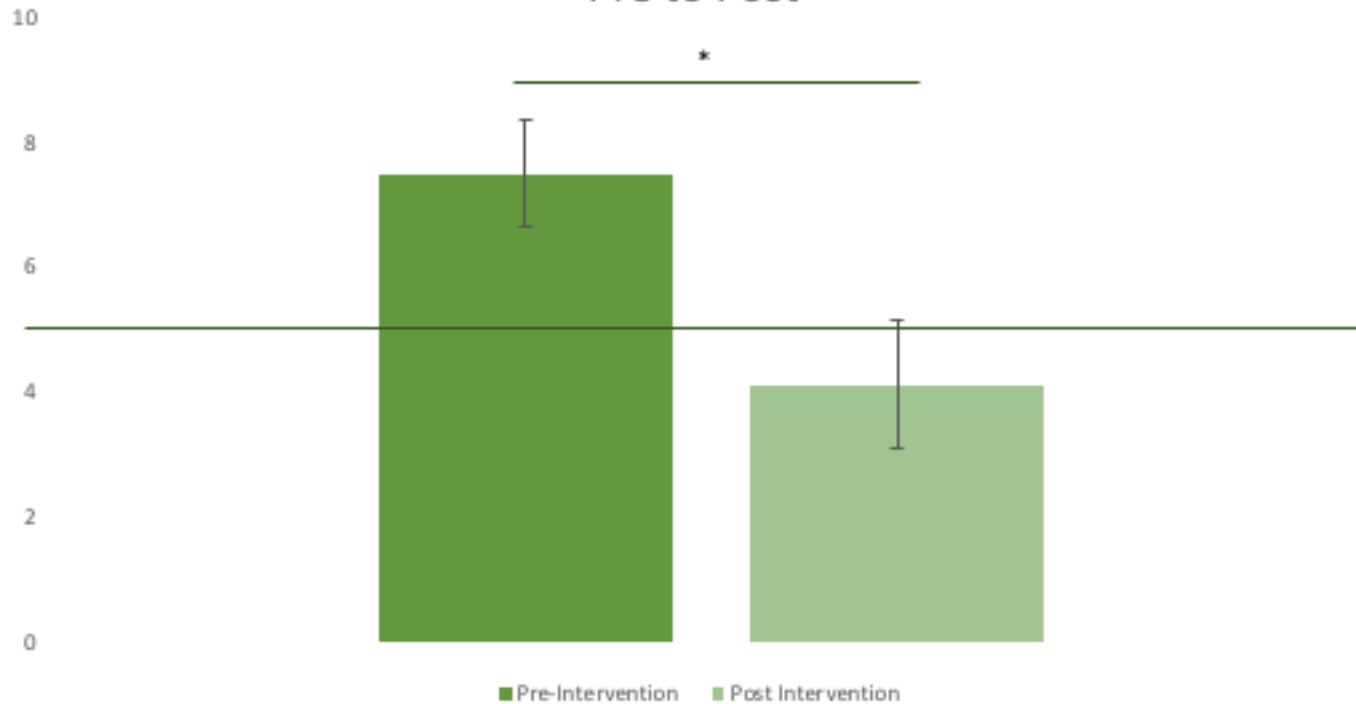
Results: Dance/Movement Therapy

Separation Anxiety Scores for Children in Dance/Movement Therapy; Pre to Post

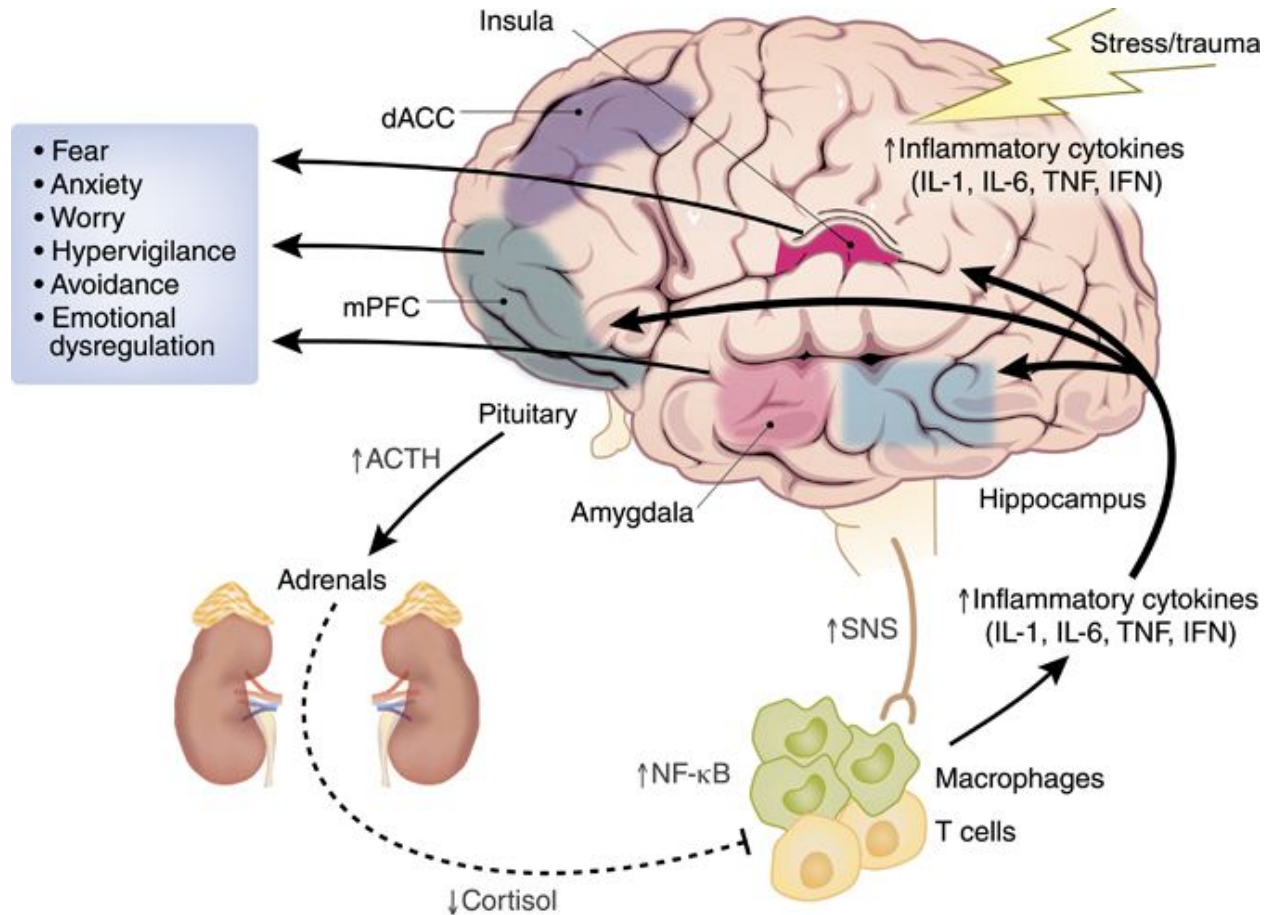


Results: Art Therapy

Separation Anxiety Scores for Children in Art Therapy;
Pre to Post



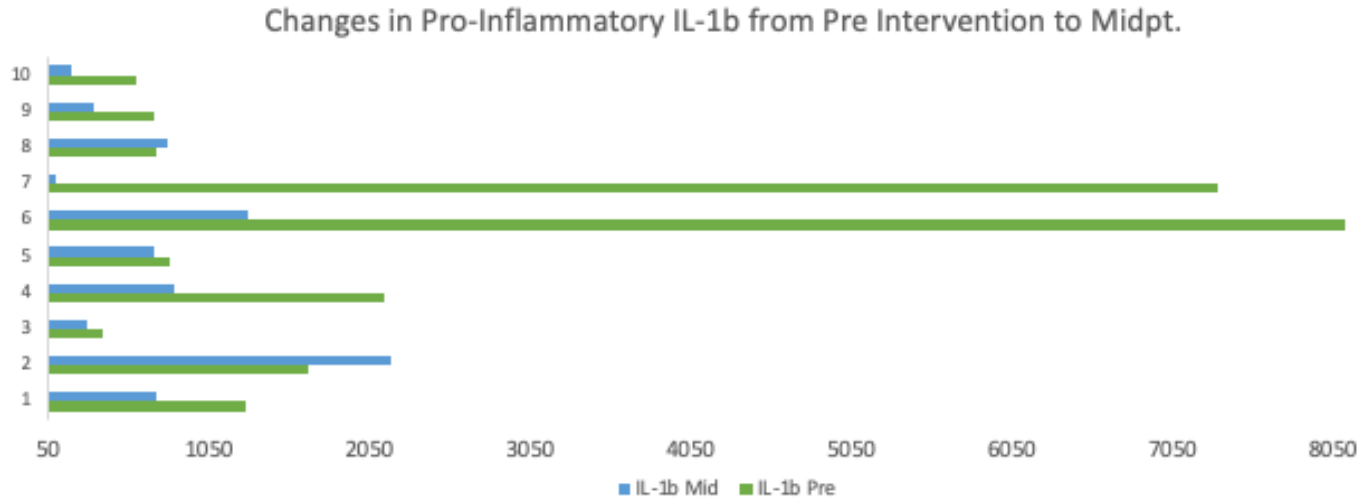
Inflammation



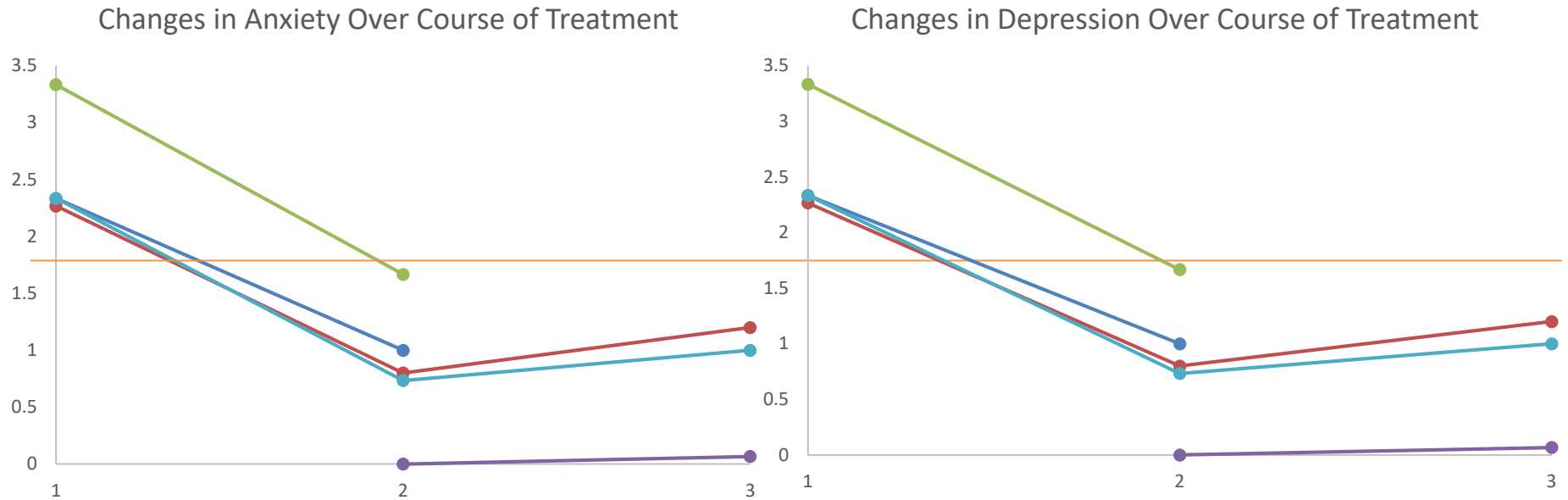
Adapted from Felger et al. 2016

PTSD: Increased circulating IL-1 β , IL-6, TNF- α , and CRP

Children Inflammation



Results: Mothers



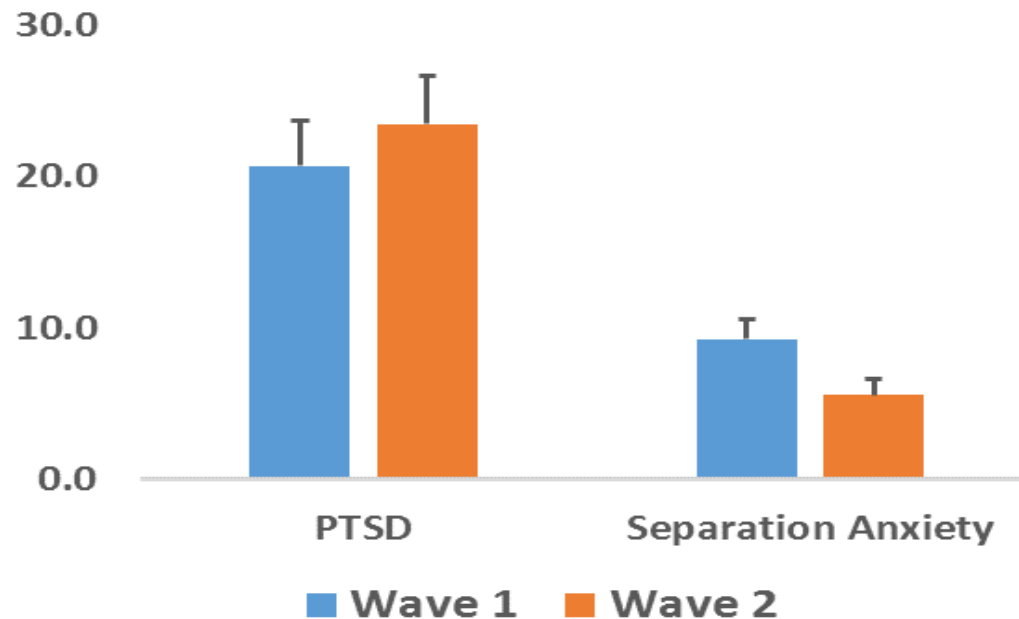
- All adults screened + for anxiety and depression
- All adults screened – following 6 and 12 weeks of yoga or HIIT
- Clinically meaningful reductions in PTSD symptom severity was also observed

One Year Later...

- Symptoms Trajectory
- Epigenetics, Intergenerational Transfer of Trauma
- Family
- Environment
- 39 Children so far

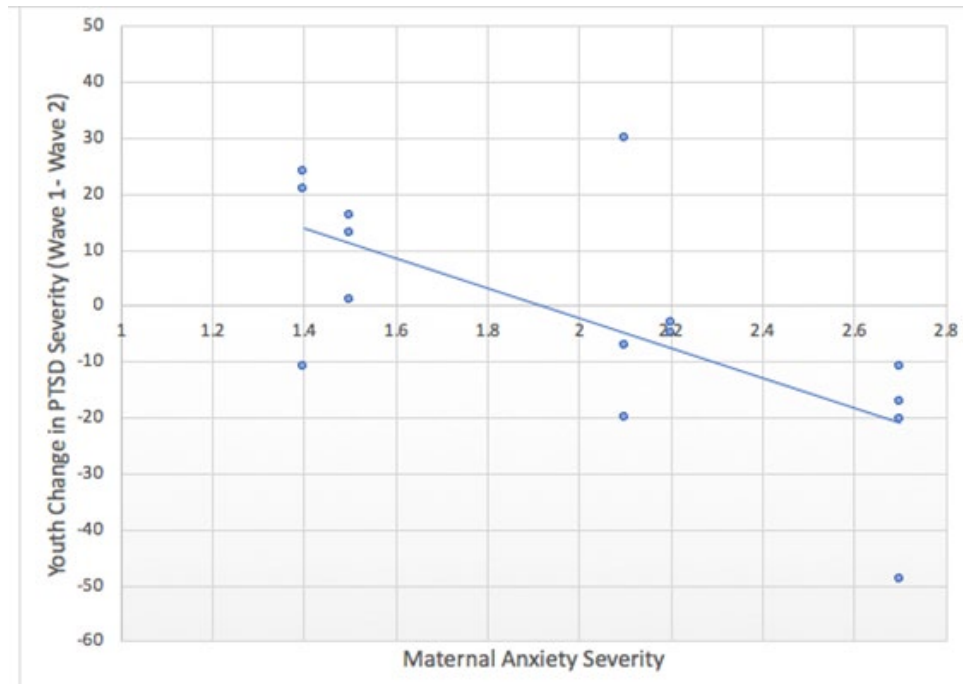
Illness Trajectory, Children

- For 76.2% anxiety severity decreased (Separation—81% — social anxiety—85.7% improve)
- For 71.4% depression symptoms decreased
- For 62.5% PTSD symptoms severity increased



Illness Trajectory, Parents

- PTSD/Anxiety sx's remained stable for both parents.
- The lower the parents' symptoms, the higher the decline in kid's sx's.



Phase I / Phase II

	r	p
Kids' Delta PTSD, Mom's current PTSD	-.534	.007
Kids' Delta PTSD, Dad's current PTSD	-.539	.021
Kids' Delta PTSD, Mom's current anxiety	-.585	.002
Kids' Delta PTSD, Dad's current anxiety	-.464	.019
Kids' Delta PTSD, Mom's current depression	-.516	.005
Kids' Delta PTSD, Dad's current depression	-.492	.013

Perceived Environmental Stress & PCL

1 Year Post-Migration; Parents

Post Migration Living Difficulty Questionnaire (LDQ; 30 adults)

LDQ Subscale	Correlation with PCL	significance
Health services	$r=0.627$	$p<.01$
Housing	$r=0.543$	$p<.01$
finance	$r=0.463$	$p<.01$
Social support	$r=0.526$	$p<.01$
Government support	$r=0.484$	$p<.05$

Parents' Environmental Stress, and Child's Depression

Parental total LDQ scores, Housing, Finances, and Social subscales negatively correlated with changes in children's depression symptoms.

Future Directions

- Continue/Expand/Educate Interventions & Therapies (Refugees, Victims of Torture, Urban Children, Dissemination in Schools)
- Continue follow up on illness trajectory in children and adults; Genetics, epigenetics, inflammatory markers, cortisol environmental correlates
- International collaborations



Collaborators and supporters:

Alireza Amirsadri MD
Paul Burghardt PhD
Holly Feen-Calligan PhD
Luay Haddad MD
David Rosenberg MD
Linda Saab MD
Ed Mischel MSW
Michelle Caton
Israel Liberzon

ACC
Samaritas
Blue Moon Wild Yoga Studio
Center for Yoga, Ann Arbor
Jenna Spinei DMT
Kaity Sinke DMT
Hype Recreation Center
CrossComm

Funding:

BCBSM

Children's Hospital of Michigan
Foundation

DMC Foundation

Lycaki/Young Funds

WSU DPBN NIG

Anonymous Holocaust Survivor

Thanks to the selfless work of the STARC team

Farah Alani
Zeina Alobaidi
Zainba Alrawi
Cynthia Arfken
Heba Alsaghir
Lana Grasser
Mohammed Isam Alsaud
Suzanne Manji
Luna Nasry
Heba Osman
Dalya Saleem
Samantha Sonderman
Hiba Suhaiban



www.starclab.org