PEDIATRIC SYMPOSIUM

OCTOBER 20

Research and Emerging Science on the Physiological Effects of ACEs and Toxic Stress

Presenters:

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TOXIC STRESS IN CHILDREN AND ADOLESCENTS

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Advances in Pediatrics 63 (2016) 403–428
http://dx.doi.org/10.1016/j.yapd.2016.04.002

CENTER FOR YOUTH WELLNESS
health begins with hope

DISCLOSURES

Dr. Bucci is the Director of Clinical Research at the Center for Youth Wellness

The work presented has been recently published

Advances in Pediatrics 63 (2016) 403–428

http://dx.doi.org/10.1016/j.yapd.2016.04.002

I have no relevant financial relationships with commercial interests to disclose.

OVERVIEW

1. Early life adversity and health outcomes
2. Early life adversity and toxic stress
3. Toxic stress and clinical implications

1

Early life adversity and health outcomes

Prevalence

Health Outcomes

TERMINOLOGY

- Early life adversity
- Early life stress
- Early life trauma
- Adverse childhood experiences (ACEs)

Stressful or traumatic events experienced

in childhood or adolescence

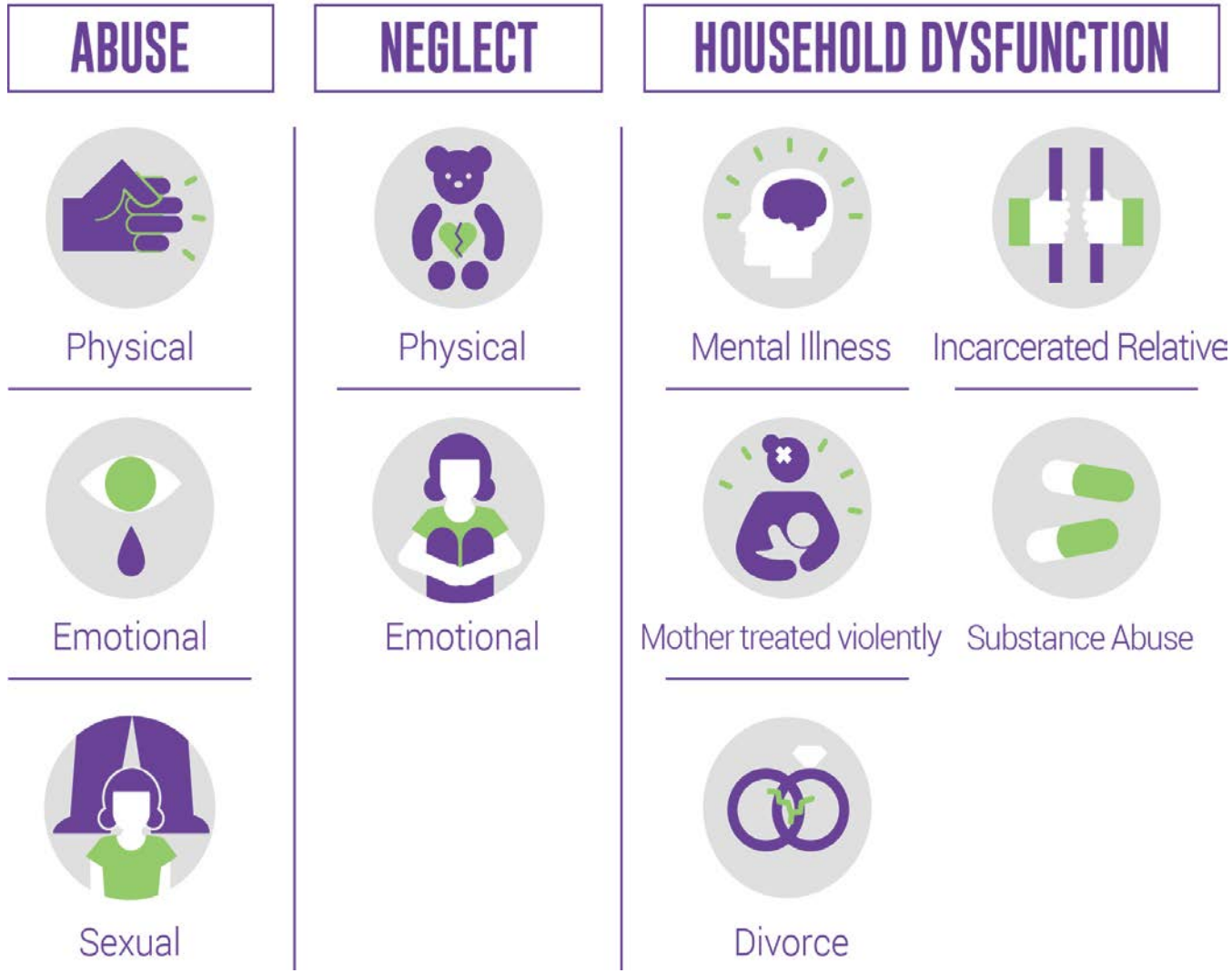
Early Life Adversity and Health Outcomes

The Adverse Childhood Experience Study (ACE Study)

- Kaiser Permanente's Health Appraisal Clinic in San Diego, in collaboration with the Centers for Disease Control and Prevention
- Medical history and data on exposure to ACEs was collected in two waves from 18,175 patients

Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med 1998:14(4): 245–58.

THE ADVERSE CHILDHOOD EXPERIENCE (ACE) STUDY



Robert Wood Johnson Foundation, 2013

From The Adverse Childhood Experiences Study. http://www.acestudy.org/ace_score, *2015*

PREVALENCE OF ACES IN ADULTS

- ACE Study[1]
  - 63.5% of adults had at least one ACE category
  - 12% had four or more

- Behavioral Risk Factor Surveillance Survey (BRFSS) in 10 states[2]
  - 59.4% reported at least one early life adversity
  - 15.3% had four or more

- California BRFSS data from 2008, 2009, 2011, and 2013[3]
  - 61.7% of surveyed adults reported experiencing at least one ACE
  - 16.7% reported having experienced four or more ACEs

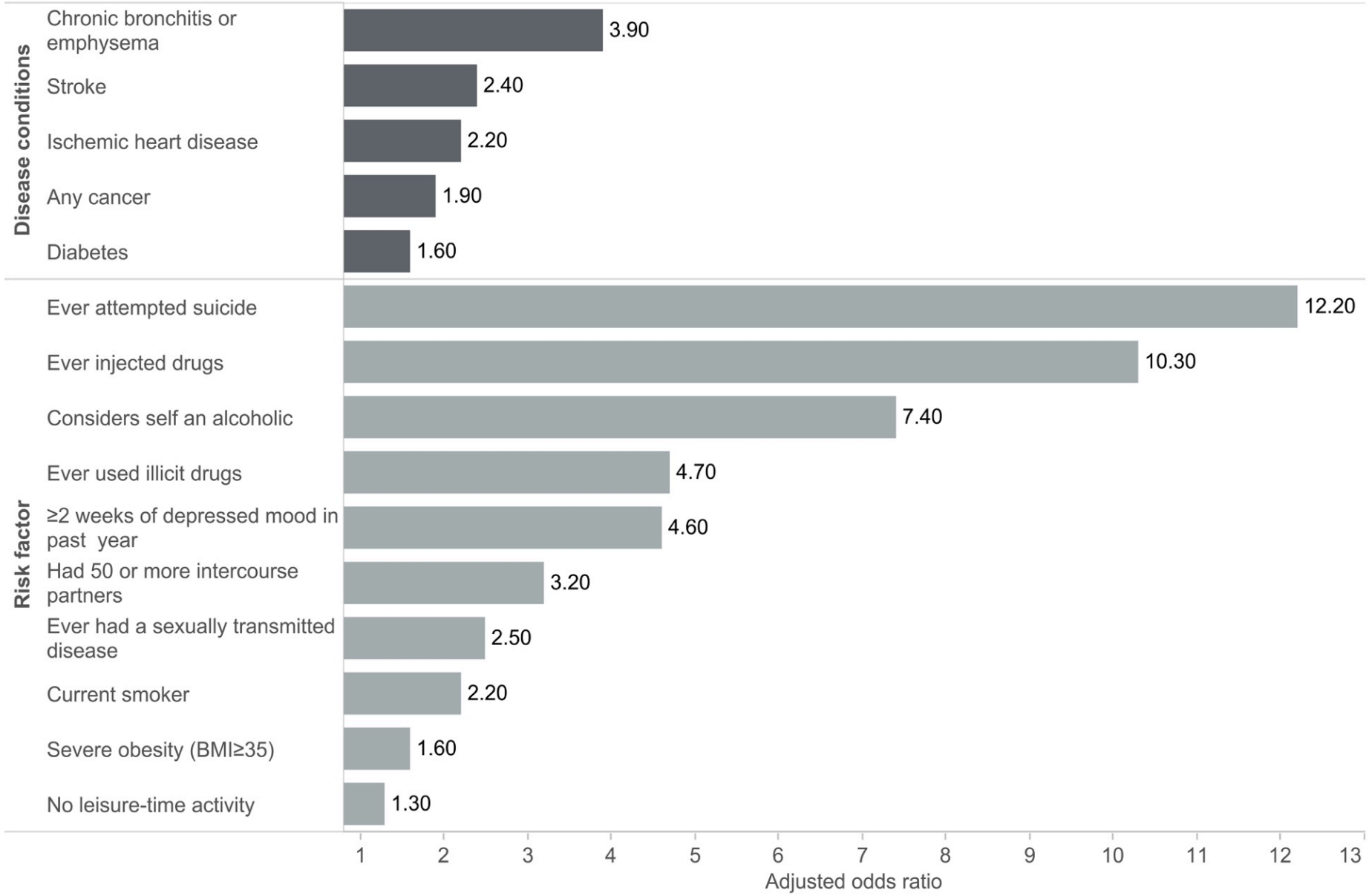
1. Felitti et al., 1998
2. Gilbert LK, Breiding MJ, Merrick MT, et al. Childhood adversity and adult chronic disease: an update from ten states and the District of Columbia, 2010. Am J Prev Med 2015;48(3):345–9.
3. Center for Youth Wellness in partnership with Public Health Institute. 2014. Available at: http://www.centerforyouthwellness.org

PREVALENCE OF ACES IN CHILDREN

- Nationally representative studies show that nearly 50% of children have experienced at least one early life adversity[1-5]
- At a community-based primary care clinic in San Francisco, 67.2% of children had experienced one or more ACE and 12% experienced four or more ACEs[4]
- Among children at high-risk for maltreatment, the rate of having experienced at least one early adversity was found to reach as high as 91%[5]

1. Bethell CD, Newacheck P, Hawes E, et al. Health Aff 2014;33(12):2106–15.
2. Bright MA, Alford SM, Hinojosa MS, et al. Community Dent Oral Epidemiol 2015;43(3):193–9.
3. Wing R, Gjelsvik A, Nocera M, et al. Ann Allergy Asthma Immunol 2015;114(5):379–84.
4. Burke NJ, Hellman JL, Scott BG, et al. Child Abuse Negl 2011;35(6): 408–13.
5. Flaherty EG, Thompson R, Dubowitz H, et al. JAMA Pediatr 2013;167(7):622–9.

HEALTH OUTCOMES – ACE STUDY



2

Early life adversity and toxic stress

Stress response

Dysregulation

Biological alterations

STRESS RESPONSE

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

HPA AXIS

The HPA axis controls the body's response to stress and is a complex interplay of direct interactions. The HPA axis is composed of:

1. The **hypothalamus** which releases AVP and CRH to the pituitary gland
2. The **pituitary gland** which secretes ACTH when stimulated by AVP and CRH
3. The **adrenal cortex** which secretes glucocorticoids (cortisol) when stimulated by ACTH

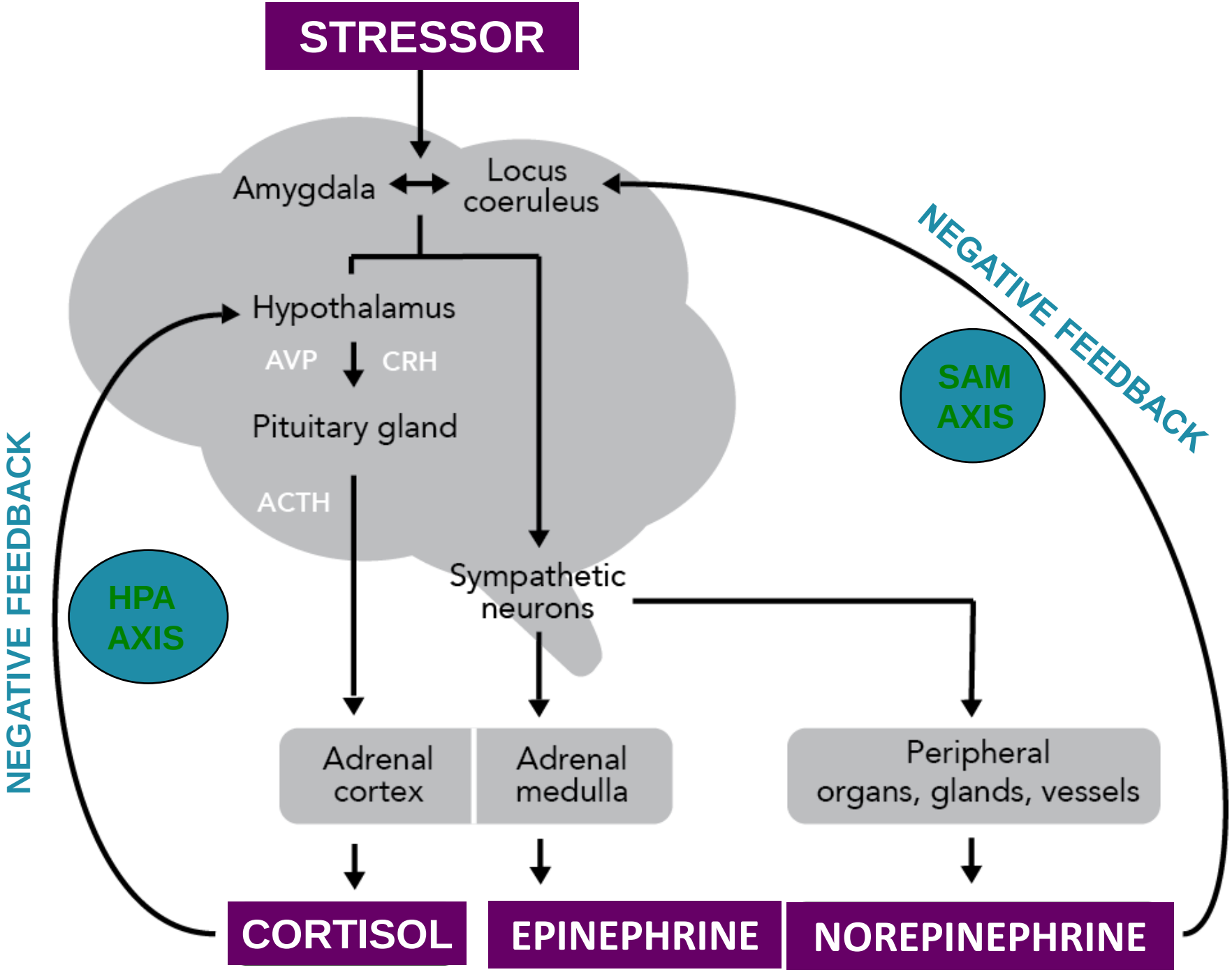
SYMPATHO-ADRENOMEDULLARY AXIS

SAM AXIS

The SAM axis mediates a rapid response to stress through interconnected neurons and regulates autonomic functions in multiple organ systems. The SAM axis is composed of:

1. The **sympathetic neurons** which release epinephrine and norepinephrine and activate the body's "fight or flight" response
2. The **parasympathetic neurons** which withdraw the activity of the sympathetic neurons and promote the body's "rest and digest" response
3. The **adrenal medulla** which when triggered by the sympathetic neurons secretes circulating epinephrine and activate the body's "fight or flight" response

Bucci, Marques, Oh, Burke Harris. Toxic stress in children and adolescents. Advances in Pediatrics 2016



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SAM AXIS ACTIVATION

- **PHYSIOLOGICAL CHANGES:**
  - Blood circulation (HR, BP)
  - Respiration (Hyperventilation)
  - Metabolism (Redirection to noble organs)

SYMPATHO-ADRENOMEDULLARY AXIS ACTIVATION

FIGHT **FREEZE** **FLIGHT**

HPA AXIS ACTIVATION

- Glucocorticoids (cortisol) are the final effectors of the HPA axis

- Physiologically normal HPA axis function depends on the balanced activation mineralocorticoid and glucocorticoid receptors
  - Mineralocorticoid receptors: stress response
  - Glucocorticoid receptors: termination of the stress response (negative feedback)

CENTRAL NERVOUS SYSTEM (CNS) ACTIVATION

- Reward center (mesocorticolimbic system: VTA)
- Emotional center (amygdala-hippocampus complex)
- Thermoregulatory center
- Appetite-satiety center
- Prefrontal cortex (executive functions)

STRESS-INDUCED HORMONES

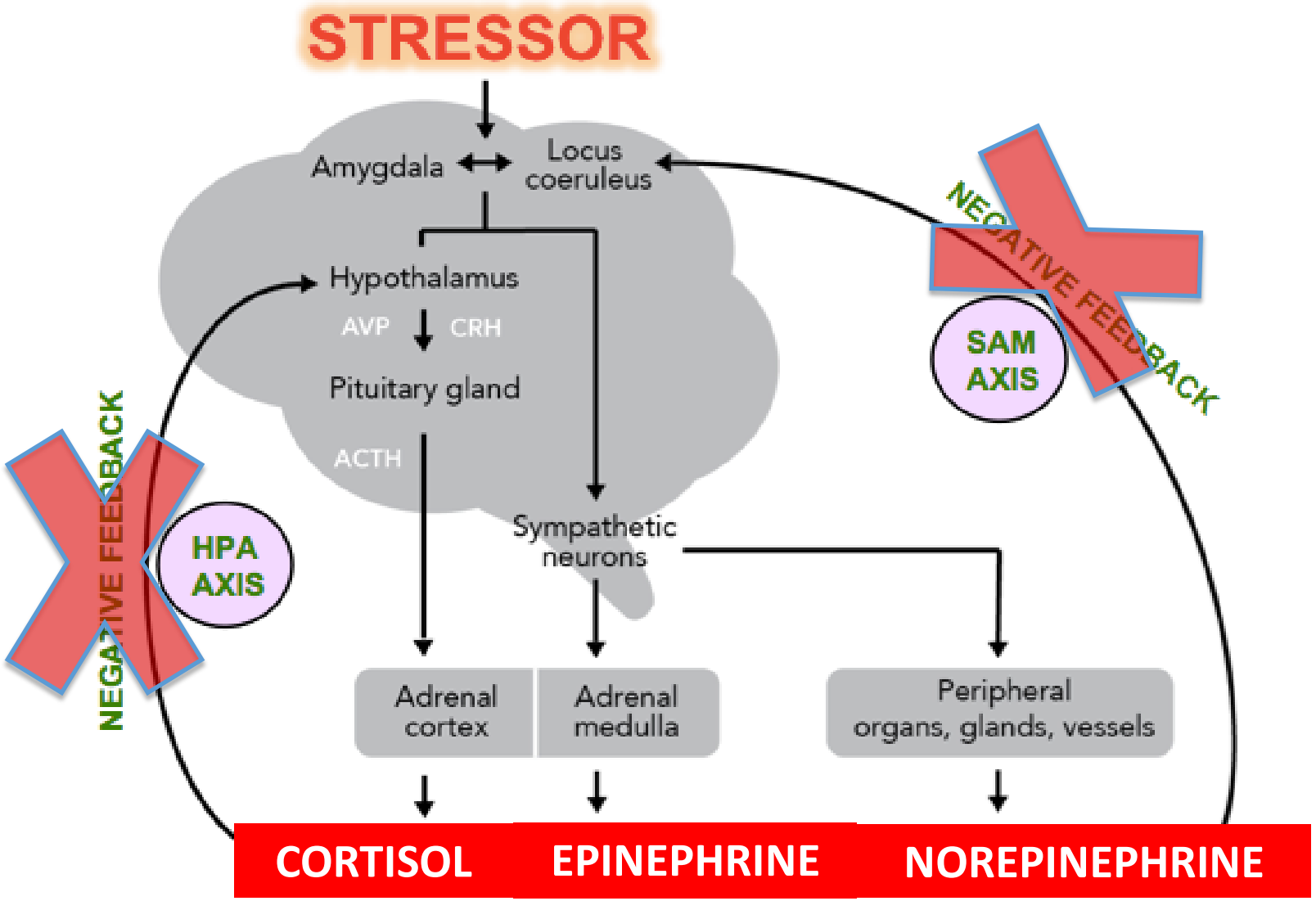
Hormone	Source	Description
Corticotropin-releasing hormone (CRH)	Hypothalamus	Principal regulator of the pituitary-adrenal axis: targets the anterior pituitary
Arginine vasopressin (AVP)	Hypothalamus and posterior pituitary gland	Targets the anterior pituitary and regulates body's homeostasis
Adrenocorticotropin hormone (ACTH)	Anterior pituitary gland	Targets the adrenal cortex to secrete ACTH
Norepinephrine	Sympathetic neurons in the brain stem (medulla and locus coeruleus)	Activates fight-or-flight response
Epinephrine	Adrenal medulla	Activates fight-or-flight response
Glucocorticoids	Adrenal cortex	Final effectors of the LHPA axis. Cortisol is one of the most abundant human glucocorticoid

STRESS RESPONSE

POSITIVE	TOLERABLE	TOXIC
Physiological response to mild or moderate stressor	**Adaptive response to time-limited stressor**	**Maladaptive response to intense and sustained stressor**
Brief activation of stress response elevates heart rate, blood pressure, and hormonal levels	Time-limited activation of stress response results in short-term systemic changes	Prolonged activation of stress response in children disrupts brain architecture and increases risk of health disorders
Homeostasis recovers quickly through body's natural coping mechanisms	Homeostasis recovers through buffering effect of caring adult or other interventions	Prolonged allostasis establishes a chronic stress response
Tough test at school, playoff game	***Immigration, natural disaster***	***Abuse, neglect, household dysfunction***

Adapted from: Shonkoff JP, Garner AS, et al. Pediatrics 2012;129(1):e232–46.
Shonkoff JP, Boyce WT, McEwen BS. JAMA 2009;301(21):2252–9.

STRESS RESPONSE DYSREGULATION



McEwen. Stress, adaptation, and disease. Allostasis and allostatic load. Ann N Y Acad Sci. 1998 May 1;840:33-44.

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NEUROENDOCRINE IMMUNE DYSREGULATION

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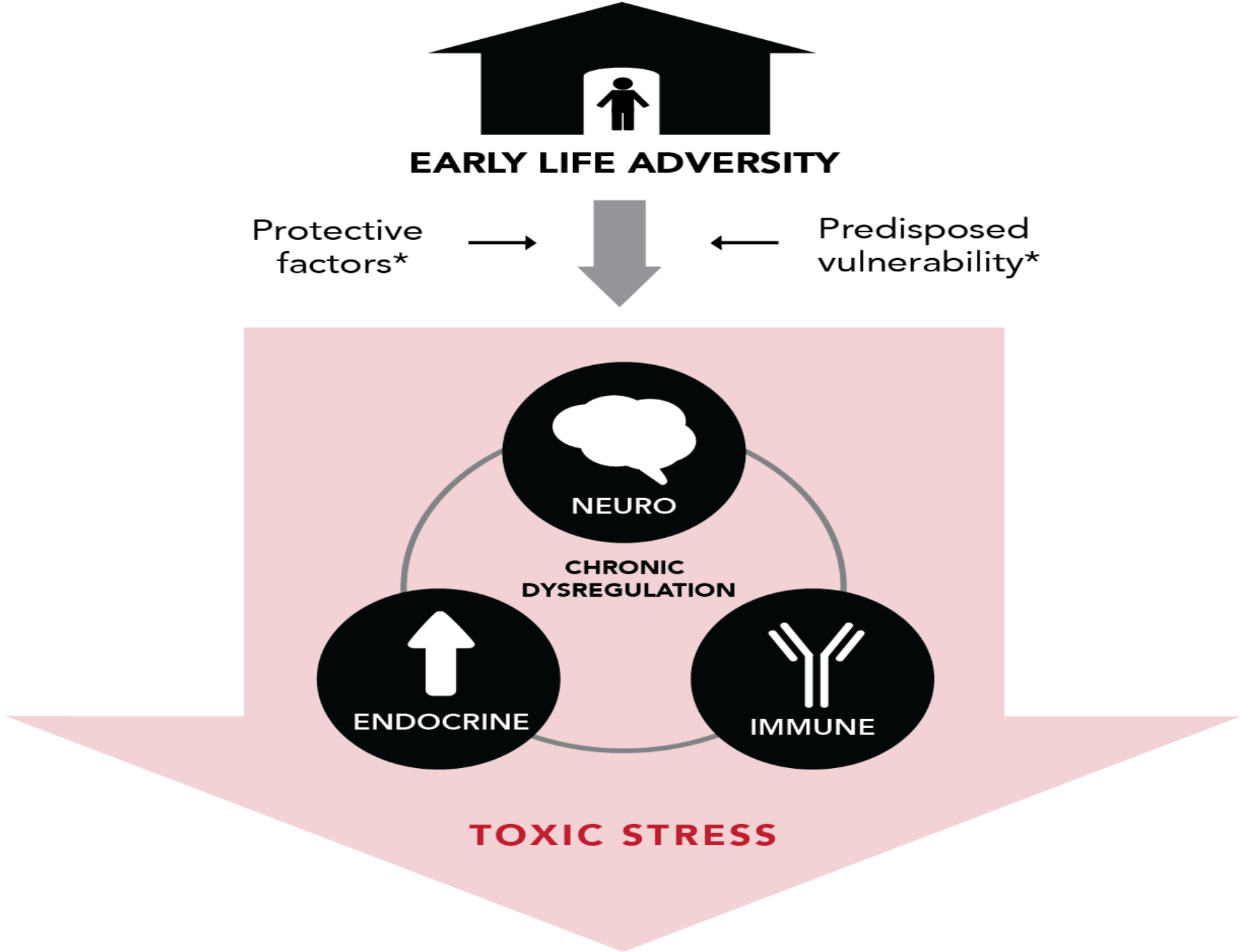
3

Toxic stress and clinical implications

Multisystemic alterations

Genetic factors and epigenetic modifications



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MULTISYSTEMIC ALTERATIONS

NEUROLOGIC

- Prefrontal cortex: reduced synaptic plasticity in children and selective cortex atrophy in adults → executive functions
- Amygdala: increased amygdala volume in children and atrophy in adults → hypervigilance, unlearned fear and fear conditioning
- Hippocampus: reduced hippocampal volume in adults → attention, memory and learning

PSYCHIATRIC

- VTA dopaminergic system →dysphoria and aggression
- Anorexia nervosa, obsessive-compulsive disorder, panic anxiety, excessive exercise, chronic active alcoholism, post-traumatic stress disorder, chronic anxiety, melancholic depression

BEHAVIORAL

- Suicide, eating disorders, substance and alcohol abuse, aggressive and impulsive behaviors

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MULTISYSTEMIC ALTERATIONS

ENDOCRINE

- Chronic activation of the glucocorticoid receptors

METABOLIC

- Thyroid function inhibited
- Obesity/dyslipidemia
- Insulin resistance/glucose intolerance
- Hypertension

REPRODUCTIVE

- Suppression of reproductive function
- Irregularities of the menstrual cycle

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MULTISYSTEMIC ALTERATIONS

IMMUNE

- Deficiency of the humoral and cellular immune responses

INFLAMMATORY

- Allergies and atopic diseases
- Asthma
- Early atherogenesis and vascular remodeling

CARDIOVASCULAR

- Increased plasma endothelin 1, total peripheral resistance, DBP and pulse wave velocity

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GENETIC FACTORS

- Genetic polymorphisms

- Gene-environment interactions

EPIGENETIC REGULATION

- Epigenetic programming of offspring's behavioral and neuroendocrine stress responses: → prolonged stress responses
- Differential gene expression of pro-inflammatory transcription factors and neurotransmitter receptors
- Telomere length
- Increased risk of other chronic diseases

(e.g., asthma, hypertension, heart disease, diabetes)

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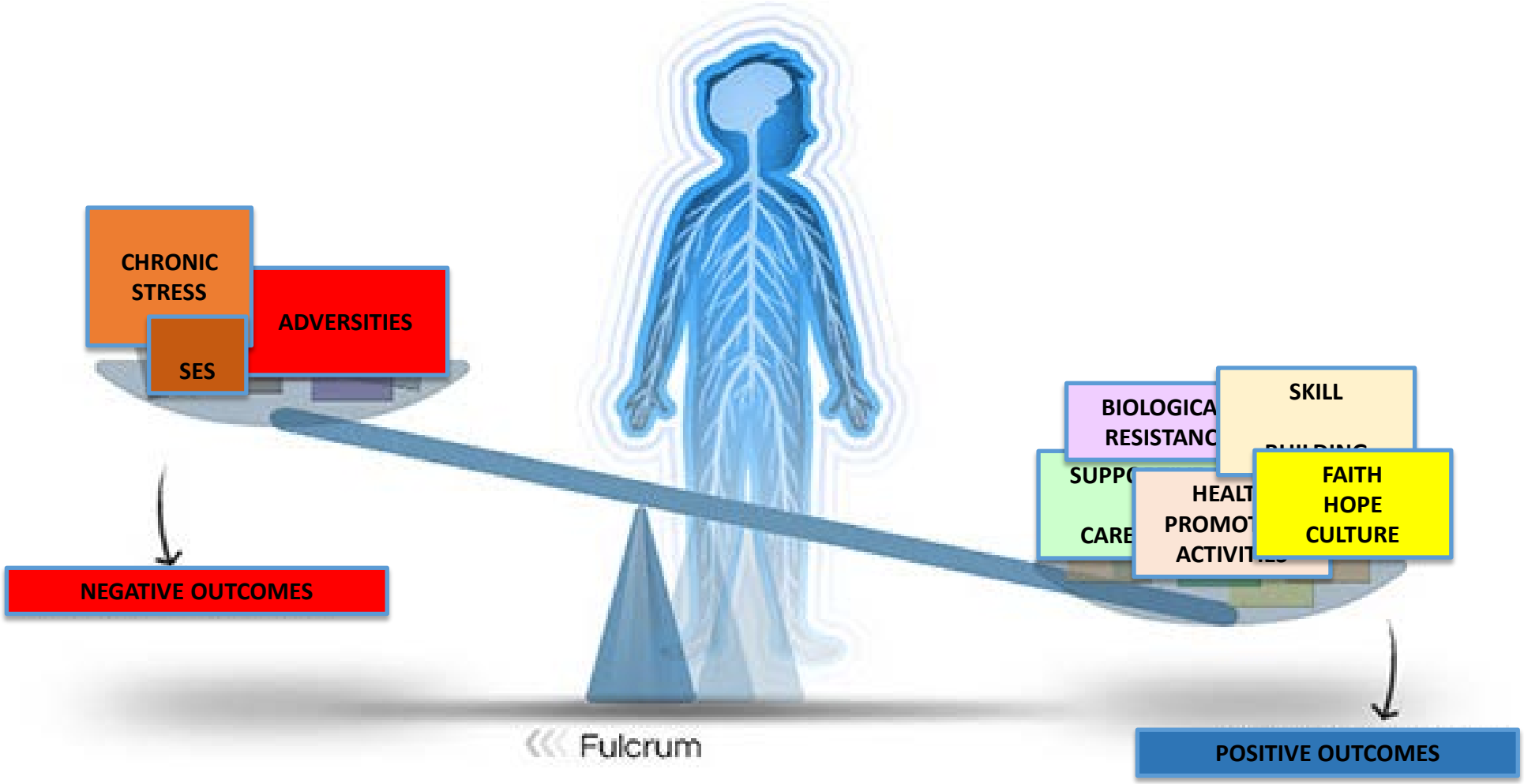
THE ROLE OF RESILIENCE



Adapted from: http://developingchild.harvard.edu/science/key-concepts/resilience/

KEY POINTS

- Stressful or traumatic experiences in childhood are risk factors for negative health outcomes
- In a child exposed to early life adversities, the body's natural stress response can become maladaptive or toxic to the body and brain
- The toxic stress response results from a chronic dysregulation of the circuitry between neurological, endocrine and immune systems and it affects multiple biological systems
- The Role of Resilience

ACKNOWLEDGEMENTS

Debby Oh,
Research Associate

Sukh Purewal,
Research Associate

Kadiatou Koita,
Research Associate

Sara Marques,
Director of Policy

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http://www.centerforyouthwellness.org/

FUNDING: Jeffrey and Barbara Picower (JPB) Foundation, Center for Youth Wellness

Thank you!

Questions?

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