How Adversity Influences Health

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Adverse childhood experiences (ACEs) or early life stress can have lasting impacts on the developmental, emotional and health trajectories of life. To attempt to understand how this happens, we will briefly review the bio-neuropsychological aspects of the stress response.

Stress, is a state of threatened hemodynamic balance of an organism. The response to stress from the body is vital for survival and learning. The prefrontal cortex (PFC), amygdala, hippocampus, hypothalamic-pituitary-adrenal axis, (HPA), sympathetic nervous system (SNS) and immune system are all heavily intertwined in this response.

Perceived psychological or biological stress is picked up by the amygdala, resulting in activation of the HPA axis and SNS. Release of catecholamines from the SNS activation system prepares the body to flee or flight. The activated HPA axis results in the release of glucocorticoids/cortisol from the adrenal gland. Activation of both systems are correlated with the production of inflammatory markers via the immune system. The PFC, known for executive functioning; plays an important role in modulating the perceived stress and thereby affecting the overall stress response produced. The hippocampus (cognition and memory), inhibits the HPA axis, thereby modulating the overall stress response. Vital to the stress response/modulation is the genetic disposition of the individual. Environmental and endogenous stimuli have the ability to determine the way a gene is functionally expressed - epigenetics, and how it interacts with the environment- telomere length

Prolonged stress may increase neural connections in the amygdala and cause structural changes in the PFC, which may in turn cause a hypo or hyper activation of the HPA axis. Elevated or low levels of cortisol cause dysregulation of the immune system and inflammatory markers. Persistently elevated cortisol levels affect the memory making function of the hippocampus and also interfere with its inhibitory/control function of the HPA axis. Chronic persistent stress may cause permanent changes in the functional expression of genes at the bio-neuropsychological level.

The timing, intensity, duration, of the stress response/modulation is significant, when occurring during critical periods of brain development. (**1)** Thus, when significant, prolonged, intense stress exposure occurs during periods of high neuroplasticity, the effects could be over a lifetime.

There's ample literature documenting how this influences health in adulthood. This article will seek to bring together how ACEs influences health from preconception through to the adolescent years.

Epigenetics

Epigenetic changes are a set of heritable changes that are not coded for in the underlying DNA sequence. These change the phenotype (how an organism/cell looks or behaves) without changing the genotype. Environmental and physiological stimuli may change the epigenetic landscape with impacts on normative developmental and age-related physiological capability/adaptability. This could be

through silencing, decreasing or increasing gene expression. In a sense, this is a vital adaptation by the gene in handling ever evolving stimuli. By causing changes in the epigenetic landscape, ACEs could therefore affect gene expression, with direct implications for future bio-neuropsychological health (**2)**

Early life experiences can directly influence genetic function by altering the epigenetic patterns in specific loci on the genome, **(3)** and altering gene expression profiles of neurons in the hippocampus and amygdala **(4).** This means that a child exposed to adverse experiences, could struggle with memory, cognition and have an altered perception of stress, triggering a cascade of dysregulated responses. Epigenetic changes have been tied to mental health, obesity and substance abuse.

Methylation of DNA is one way a cell can create an epigenetic mark. Perroud and colleagues demonstrated that the severity, frequency and type of ACE exposure positively correlated with methylation of NRC31 which codes for the glucocorticoid receptor. Glucocorticoids have been linked to the development and severity of psychiatric illnesses. They found that repetition of exposure correlated with a higher percentage of methylation. They also found a correlation between numbers of traumatic experiences exposed to and methylation of brain-derived neurotropic factor (BDNF) promoter. BDNF is a gene that codes for proteins involved in regulation, growth and plasticity of neuronal tissue. Methylation of BDNF was also found to be associated with increased feelings of hopelessness and impulsivity. **(5, 6)**

Telomere length

To prevent the loss of genetically important information, chromosomes are capped by telomeres. Telomeres protect the ends of chromosomes from deterioration and from fusing with each other, during replication. Emerging literature links accelerated telomere shortening with stress. Some research suggests that the physiological correlates of stress – activation of the HPA axis, inflammation- imposes an increased oxidative burden on the cell, which damages the cell, resulting in accelerated telomere attrition/shortening **(7)** Stress evoked telomeric shortening could evoke physiological weathering in a way similar to aging. Telomere shortening has been associated with depression, harsh parenting, paternal absence and perceived racism. **(8)**

Perinatal

Of note, epigenetic changes and markers in a mother could be passed down to her offspring. Maternal behavior may result in patterns of epigenetic marks in the offspring that reflect those found in the parent **(3)**. Prenatal stressors could therefore, predispose the fetus to a primed response to stress later on in life; fetal programming.

Ceo-Lei and colleagues, in a longitudinal study demonstrated an apparent relationship between objective maternal hardship and methylation levels of genes in their offspring **(9).** Exposure to third trimester depressed maternal mood is associated with methylation status of NRC31 in newborns and altered hypothalamic–pituitary-adrenal stress reactivity at age 3 months. **(10)**

Among the subcategories of adverse childhood experiences, physical abuse, and household substance abuse were associated with higher gestational diabetes mellitus risk and obesity risk in mothers. **(11,15)** A history of childhood maltreatment in a mother was also found to be associated with her child's emotional and behavioral changes in childhood and adolescence. **(16)**

Moog et all suggest that pregnant women who suffered childhood trauma showed a 25% increase in placental corticotrophin hormone at the end of gestation compared to those not exposed to ACEs. Increased maternal and fetal cortisol concentrations in pregnancy were associated with changes in children's temperament and behavior, delay in cognitive development and changes in HPA axis. **(17,20**). They also noted a 6% difference less in brain volume of offspring of mothers exposed to ACES vs non exposed mothers, in the cortical gray matter. **(21)**

Infant and Early Childhood

The hippocampus and amygdala and HPA axis develop gradually in the first 5 years and in a non-linear pattern until early adulthood. For children under 5, some longitudinal studies suggest that stress responsivity decreases with age throughout the preschool period. **(22)** This hyposensitive period may lead to hyper-activity and responsiveness of the HPA axis. This means that primary caregivers play a significant role in mediating threats within the child's environment (social buffering system), helping to calm the nervous system. **(23, 24)** This role is especially significant in children under 24 months. A calm physiologic state or a reliable dependable buffering system is required for optimal learning conditions.

Enlow et al 2012, found that interpersonal trauma (IPT) exposure during 0-24 months was significantly associated with decreased cognitive scores at 24-96 months of age. IPT particularly in the first 2 years of life, was found to have significant and long-lasting effects on cognitive development. Similarly, a significant association exists between maltreatment and cognitive delay at age 4. **(25, 26)** Children whose mothers reported chronic intimate partner violence (IPV) were more likely to be obese at age 5 than those whose mothers reported no IPV **(27)**

Maternal depressive symptoms have been associated with reactive airway disease diagnoses in the preschool years and poor sleep in infants. Children at age 3 seemed to be at a higher risk of reactive airway disease if their mothers were depressed. **(28)** Non depressed mothers had infants who slept longer through the night with fewer nighttime awakenings than those of depressed mothers at 2-24 weeks of age **(29)**

School Age Years

Children exposed to or who have experienced ACEs may hypo or hyper react to threats in their environment, leaving them in states of hypo/hyper arousal for extended periods. These chronic states of dysregulation may cause structural changes in the PFC and alter neuronal signals in the hippocampus. This in turn leads to generalized impairment in learning, memory and struggle with overall academic achievement.

Children who experienced parental death or divorce had lower cognitive ability scores at age 8 and 15.**(30)** Cumulative ACEs (>4) have been shown to be associated with a higher risk of reporting a learning disability, attention and behavioral problems compared to those without exposure **(31-33)**.

Longitudinal neuroimaging studies suggests that early ACEs may cause alterations in the development of the Inferior frontal gyrus, a sub region of the pre frontal cortex involved in inhibitory control and emotion function, resulting in deficits in emotion development and increasing risk for depressive symptoms. **(34)** Behaviorally, ACEs promote hyper vigilance to threat, a focus on immediate gratification and poorer emotion regulation, shaping interactions with the environment and leading to increased health risk behaviors.

Through the prolonged/chronic activation of the SNS and HPA axis, cells produce an excessive inflammatory response, developing into a chronic pro inflammatory phenotype. **(35)** Parental depressive symptoms seem to increase children's profile of asthma relevant inflammatory markers.

Some studies report late menarche associated with being raised in at least one neglectful environment. **(36)**

Studies on household dysfunction show an effect on weight and weight management during childhood, with an increased risk among early adolescent females exposed to maltreatment. **(37)** Wolke and colleagues in a longitudinal study, found parasomnias to be associated with bullying victimization in 8-12y/o **(38)**

Adolescent Years

Numerous studies have linked ACEs to depressed mood, anxiety, PTSD symptoms, risk taking behavior, early pregnancy, eating disorders, weight problems, substance abuse, juvenile delinquency, STI treatment, suicide attempts and mental health treatment in adolescents.

Exposure to 2 or more ACEs increases the odds ratio of having somatic complaints and poor health, while an even increased number of exposures shows a graded relationship with illness requiring a doctor. **(39)** Maltreatment increases the risk for obesity in female adolescents, with abuse and neglect affecting weight in general, during adolescence. **(40)**

In a study looking at the timing of maltreatment and its effect of multiple problem outcomes; adolescents undergoing treatment for substance abuse and juvenile delinquency, seemed to show a significant association between concurrent maltreatment and behavioral problems, than maltreatment earlier in childhood. **(41).**

Neuro-Diverse Children

In typically developing children, ACEs tend to have detrimental effects on their neurobiological, emotional and cognitive development. Children who are developmentally delayed or have ASD, typically

struggle with these at a baseline. They struggle with communicating, are socially isolated and often prone to higher levels of social and familial stress. It may therefore, not be entirely surprising that neuro-diverse kids may be at an even increased risk from the effects of ACEs exposure. **(42, 45)**

Children with more severe ASD symptomatology were associated with elevated risk of ACEs, regardless of poverty and other factors. In children aged 2-17, having at least one ACE has a significant correlation with delay in diagnosis and treatment, regardless of race, ethnicity, health insurance and socioeconomic status **(43)**

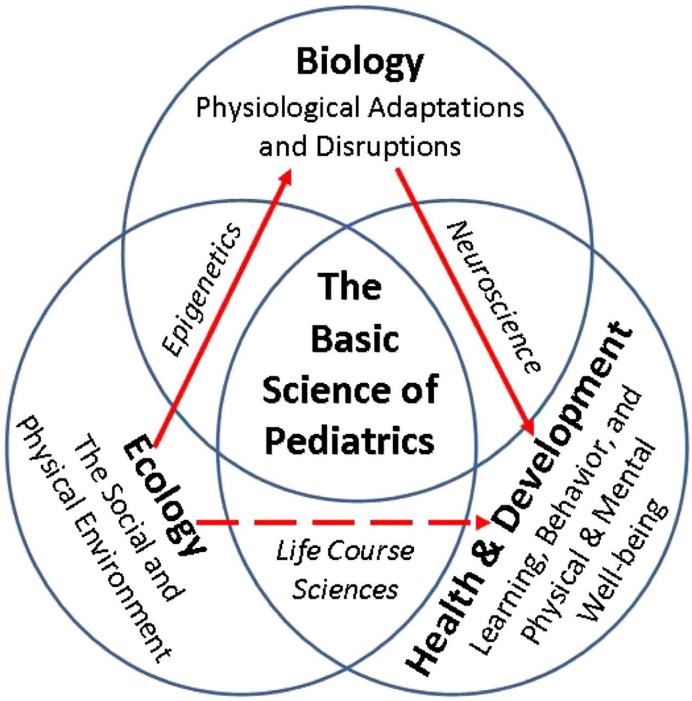
Children with ASD and developmental delays have been shown to be dysregulated in bodily functions such as emotion, stress, mood, and digestion. They have higher levels of salivary cortisol in response to novel and threatening stimuli such as psychosocial stress or sensory stimuli. **(44)** These pre-existing responses may increase vulnerability to ACEs or increase traumatic responses to ACEs, further perpetuating behavioral and biological dysregulation **(45)**

Conclusion

It is quite clear that adverse early childhood experiences do "get under the skin". Ecology, biology, health and development interact in complex ways in a child's life. Adverse childhood experiences (ACEs) or early life stress do have lasting impacts on the developmental, emotional and health trajectories of life.

There is a strong and an urgent case for advocacy, knowledge and intervention, as ACEs continue to impact care of the whole child. The AAP has called for a multidisciplinary approach to the development of this eco-bio-developmental model of care and health planning. The proverbial "it takes a village" couldn't be more succinct at this time.

The Lifelong Effects of Early Childhood Adversity and Toxic Stress



Jack P. Shonkoff, Andrew S. Garner, THE COMMITTEE ON PSYCHOSOCIAL ASPECTS OF CHILD AND FAMILY HEALTH, COMMITTEE ON EARLY CHILDHOOD, ADOPTION, AND DEPENDENT CARE, AND SECTION ON DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS, Benjamin S. Siegel, Mary I. Dobbins, Marian F. Earls, Andrew S. Garner, Laura McGuinn, John Pascoe and David L. Wood
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