Adverse Childhood Experiences and the Effect on the Adult Brain and Heart Health

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Opiate exposure in the developing brain and toxic stress in early childhood: How brain structure and function is altered and impacts lifelong health
Let’s talk development...

Developmental Milestones

- Gross motor
- Fine Motor
- Speech
- Social / communication
Developmental Milestones: Gross Motor

- Holds up head --- 4 months
- Rolls over---5 months
- Sits alone (tripod)---7 months
- Pulls to stand--- 9 months
- Walks with help--- 11 months
- Walks without help--- 13 months
- Runs --- 18 months
- Walks up steps --- 21 months
- Throws a ball --- 24 months
- Rides a tricycle --- 3 years
Developmental Milestones: Fine Motor

- Hands together --- 3 months
- Reaches for objects --- 4 months
- Raking grasp --- 7 months
- Pincer grasp --- 9 months
- Put block in cup --- 12 months
- Scribbles --- 15 months
- Tower of 2 cubes --- 18 months
- Tower of 6 cubes --- 26 months
- Draws circle --- 3½ years
- Draws person (3 parts) --- 4 years
- Draws rectangle --- 5 years
Developmental Milestones: Speech

- Coos --- 2 months
- Imitates sounds --- 7 months
- Dada / mama nonspecific --- 8 months
- Dada / mama specific ---- 11 months
- 3 words --- 16 months
- 6 words --- 18 months
- Combine words --- 24 months
- 6 body parts --- 24 months
- Speech half understandable --- 24 months
- Knows one color --- 3 yrs
- Speech all understandable --- 4 yrs
Development Delay: Social / Communication

- Regards face --- 1 month
- Smiles --- 2 months
- Regards own hand --- 4 months
- Feeds self --- 6 months
- Plays pat-a-cake --- 11 months
- Waves bye-bye --- 11 months
- Imitates actions --- 13 months
- Drinks from cup --- 16 months
- Uses spoon, fork --- 18 months
- Feeds doll --- 19 months
- Puts on clothing --- 24 months
Global Development Delay

- Delay in all types
- Maybe at different levels, but each category is delayed
Patterns we look for

- Normal
- Regression
- Delay, some catch-up
Development Regression

- May have normal development or some delay
- At a certain point in time, lose milestones
- Children continue to lose milestones in
  - Neurodegenerative disease
- Children may regress some, then stabilize and slowly improve in
  - Pervasive Development Disorders
How to approach a patient with development delay

- Which areas are delayed?
  - Helps guide diagnosis
- Birth history
- Family history
- Environmental exposures
  - Neglect / Child Abuse
  - Lead
  - Medical-related (medications, chronic illness, etc.)
- Suspected seizure activity?
- Physical Examination
Myelination is responsible for brain maturation and wiring connections
Progression of Myelination

- Proximal before distal
  - Brainstem before supratentorium
- Sensory before motor
- Central before peripheral
- Posterior before anterior
Myelination at Birth
Myelinated Regions at Birth

- Dorsal brainstem
- Inferior, superior cerebellar peduncles
- Perirolandic region
- Corticospinal tract
  - Central portion of centrum semiovale
  - Posterior limb of internal capsule to cerebral peduncle
- Ventrolateral thalamus
- Optic nerve, chiasm, tract
Birth
Myelination Milestones after Birth:

- T-1 weighted (white matter is bright)
- 3 months
  - Cerebellar WM
3 Months
Myelinated Milestones After Birth:

T-2 weighted (white matter is dark)

- 6 months
  - Splenium Corpus Callosum
Chronology of other Specific White Matter Intensity Changes

- **Infratentorial**
  - Middle cerebral peduncle
  - Cerebellar deep WM

- **Supratentorial**
  - Anterior limb
  - Posterior limb
  - Pre and postcentral gyrus

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6 Months
Myelination (T2)

- 8 months
  - Genu
- 11 months
  - Anterior limb IC
- 14 months
  - Frontal WM
1 Year
18 Months
24 Months
Critical periods

- Maturational time period during which an experience will have optimal impact on development of normal behavior
- Exposure after critical period will lead to a reduced effect
- Also, negative experiences during this time will be more harmful
Critical Periods

- Vision, hearing: birth to 12, peaks around 3
- Language: birth to 16, peaks around 8
- Higher cognitive functioning birth to 24, peaks around 11
Birth to 3 years

- Very important for development!
- Language-rich nurturing
- Responsive care givers (child – adult interaction)
- Children of lower SES (and less parent education) score lower on devt testing by 18 months of age
3-5 years

- Complex social behaviors
- Problem-solving skills
- Pre-reading skills
- Language (grammar)
- Cause and effect
- All a natural preparation for school
Language Development

- Children isolated from language until after puberty have impairments in phonology, morphology, syntax
- Earlier age of exposure to language leads to improved proficiency
- Language best when exposed in infancy
- Similar results with learning a second language
  - Later learners have adequate vocabulary but struggle with phonology, morphology, syntax
Synaptic pruning

- Studies have shown decrease cerebral glucose metabolism from 4 years to 10 years.
- Thought to correlate with synaptic pruning
- Theory: Repeated neuronal activity during critical periods will stabilize circuits and these stable circuits require less energy (glucose metabolism)
Human PET studies

- Newborn highest amount of glucose metabolism in primary sensory and motor cortices, cingulate cortex, thalamus, brain stem, cerebellum
- 2-3 months of age glucose metabolism increases in parietal, temporal, primary visual cortex, basal ganglia, cerebellum
- 6-12 months frontal cortex
- Glucose utilization in brain overall highest birth to 4 (nearly twice that as of adults)
How life can change brain structure
Brain development occurs into early adulthood

- Genes inherited
- Prenatal environment
- Experiences during childhood
- Toxic substances
Human Development

- Prenatal and postnatal environment chemically modifies genes and genes change over time.
Adverse events change the brain

- Malnutrition
- Exposure to chemical toxins or drugs
- Stress
- Impact depends on type of substance, level and duration of exposure, timing
What animal studies have taught us about neural plasticity

- Rats developing in a group environment with social and environmental stimulation have increased brain weight, cortical thickness, more complex dendritic branching.
- Middle-aged rats also showed increase number of synapses with exercise.
Neurotoxins

- Environmental chemicals
- Recreational drugs
- Prescription medications
Environmental toxins: Heavy metals

- Heavy metals disrupt neural cell migration and formation of synapses, Disrupt neurotransmitter function
- Lead impairs formation of neuro circuitry via disrupting dopamine, glutamate, acetylcholine
- Mercury impairs glial formation and brain in a state of higher vulnerability to damage from other toxins
- Organophosphides kill neurons, impair cell migration, reduce synapses.
Recreational Drugs

- Fetus most susceptible to brain damage
- Alcohol interferes with brain, heart, GI, musculoskeletal systems (FAS)
- Alcohol kills neurons or stalls their migration, leads to behavior problems
- Nicotine impairs acetylcholine function, leading to cognitive impairments
- Cocaine/meth/stimulants interfere with monoamines and change maturation of cells that regulate focus and emotion
Neglect

- Rats neglected in early life demonstrate drug seeking behavior as adults.

- Children with poor nutrition have increased risk of CV, respiratory and psychiatric diseases later in life.

- Children in lower SES seem to be more vulnerable to embedding negative factors:
  - Crime, violence, crowded noisy housing, greater air pollution exposure, below average municipal services, fewer parks.
Adverse Childhood Events (ACEs)

- Also known as early life stress (ELS)
  - Smoking
  - Overeating
  - Substance abuse

- Risk factor for chronic disease in adulthood
  - Ischemic heart disease
  - Stroke
  - Diabetes
  - Cancer

- Score predicts adult risk of certain chronic diseases (white males in SD, CA).
Prior to your 18th birthday:
1. Did a parent or other adult in the household often or very often... Swear at you, insult you, put you down, or humiliate you? or Act in a way that made you afraid that you might be physically hurt?
2. Did a parent or other adult in the household often or very often... Push, grab, slap, or throw something at you? or Ever hit you so hard that you had marks or were injured?
3. Did an adult or person at least 5 years older than you ever... Touch or fondle you or have you touch their body in a sexual way? or Attempt or actually have oral, anal, or vaginal intercourse with you?
4. Did you often or very often feel that ... No one in your family loved you or thought you were important or special? or Your family didn't look out for each other, feel close to each other, or support each other?
5. Did you often or very often feel that ... You didn't have enough to eat, had to wear dirty clothes, and had no one to protect you? or Your parents were too drunk or high to take care of you or take you to the doctor if you needed it?
6. Were your parents ever separated or divorced?
7. Was your mother or stepmother:
   Often or very often pushed, grabbed, slapped, or had something thrown at her? or Sometimes, often, or very often kicked, bitten, hit with a fist, or hit with something hard? or Ever repeatedly hit over at least a few minutes or threatened with a gun or knife?
8. Did you live with anyone who was a problem drinker or alcoholic, or who used street drugs?
9. Was a household member depressed or mentally ill, or did a household member attempt suicide?
10. Did a household member go to prison?
ACEs Scoring

**ABUSE**
- Physical
- Emotional
- Sexual

**NEGLECT**
- Physical
- Emotional

**HOUSEHOLD DYSFUNCTION**
- Mental Illness
- Incarcerated Relative
- Mother treated violently
- Substance Abuse
- Divorce
Score of 4 or more:

- COPD risk increases 390%
- Hepatitis 240%
- Depression 460%
- Attempted suicide 1220%
Childhood Experiences vs. Adult Alcoholism

Health Risks

ACE Score

% Alcoholic

0 2 3 4

0 2 4
Childhood Experiences Underlie Chronic Depression
ACE Score and the Risk of *Perpetrating Domestic Violence*

![Graph showing the risk of perpetrating domestic violence by ACE score for men and women.](image)
The ACE Score and the Prevalence of Liver Disease (Hepatitis/Jaundice)
Adverse Childhood Experiences vs. Smoking as an Adult
ACE Score and Indicators of Impaired Worker Performance

Social Function

- Absenteeism (>2 days/month)
- Serious Financial Problems
- Serious Problems Performing job

ACE Score
- 0
- 1
- 2
- 3
- 4 or more

Prevalence of Impaired Performance (%)
Resiliency Factor

1. I believe that my mother loved me when I was little.
2. I believe that my father loved me when I was little.
3. When I was little, other people helped my mother and father take care of me and they seemed to love me.
4. I've heard that when I was an infant someone in my family enjoyed playing with me, and I enjoyed it, too.
5. When I was a child, there were relatives in my family who made me feel better if I was sad or worried.
6. When I was a child, neighbors or my friends' parents seemed to like me.
7. When I was a child, teachers, coaches, youth leaders or ministers were there to help me.
8. Someone in my family cared about how I was doing in school.
9. My family, neighbors and friends talked often about making our lives better.
10. We had rules in our house and were expected to keep them.
11. When I felt really bad, I could almost always find someone I trusted to talk to.
12. As a youth, people noticed that I was capable and could get things done.
13. I was independent and a go-getter.
14. I believed that life is what you make it.
Stress

- Positive stress: brief periods of stress with increased HR, BP, mild cortisol increase. May be meeting a new person, new environment, etc. Helps the child learn self assurance and self control
  - Healthy stress response
  - Brain chemistry returns to baseline
Stress

- Tolerable stress: longer periods of stress or life disruption (death of a parent, divorce, natural disaster). Alters brain structure but in a supportive environment brain returns to baseline.

- Rat model: early weaning (neglect)
  - Explorative
  - Social play
  - Some compensation in brain chemistry
Stress

- Toxic stress: Chronic stress with minimal support from family. Child abuse, neglect, parental substance abuse, violence. Stress hormones are elevated long term and thus alter brain structure and chemistry. Also can lead to increased vulnerability physical disease later on in life.

- Environmental toxins outweigh the ability to adapt to stressor

- Poverty, abuse, neglect, neighborhood violence, substance abuse of caregiver, mental illness of caregiver
EpiGenetics

- Study of heritable, but modifiable, changes in gene expression
- A human can adapt to environment by changing methylation patterns
- Rats: neonatal malnutrition changes gene expression in kidneys and liver
  - Disease phenotype not noted until later in life with high fat diet
- “Genes load the gun and the environment pulls the trigger”
How does this happen?

- Multi – hit process
  - Early life stressors (malnourishment, maternal separation)
  - Vulnerable developmental periods
  - Alcohol, drugs

- Induces glial activation, neurotoxicity and oxidative stress
- Causes cell death, damages brain circuitry
Nutritional Inadequacy

- Unhealthy food habits
  - Under or over nutrition
  - Malnourishment – lack of important vitamins and essential fats for brain development
  - Obesity – excessive protein can cause hyperammonemia and hyperinsulinemia
  - Obese populations show higher rate of depression, impulsivity and lower cognition
How this relates to critical periods

- Cellular development occurs prenatally
  - Damage caused by external stressors at this time can lead to irreversible changes

- Healthy environment during a critical period strengthens neuronal connectivity

- External stressors in a critical period have shown to lead to personality disorders and cognitive impairment
Prenatal Stressors

- Maternal malnourishment
- Maternal stress (glucocorticoids and prostaglandins) cross placenta and can alter brain formation mechanisms
- Infections from poor sanitation, poverty, undernutrition
  - Prolonged immune activation and inflammation in the brain
    - Leads to neuronal malfunction thought to lead to dementia and memory impairment
  - Zika – microcephaly from neural progenitor cells
Prenatal insults effecting homeostasis

- Prenatal protein malnourishment: GFAP over-expression
  - Can lead to oxidative stress
  - Report in rats of changes in hippocampus and amygdala cell size
- Prenatal iron deficiency: GFAP under-expression
- Influenza exposure increases GFAP in mice
  - Link to schizophrenia
- Any immune response increased cytokines which cross fetal BBB
- Bacterial infections can cause disruption in microglial proliferation in mice
Prenatal environment and myelin

- Iron deficiency / malnutrition delays formation and maturation of oligodendrocytes
  - Hypomyelination in rats (CNS and PNS)
- Immune responses during a critical period can down regulate myelin axonal protein
Neurons are not immune during pregnancy

- Malnutrition (protein, iron, iodine)
  - Purkinje neurons have less “arborization"
  - Hippocampus has decreased thickness of mossy fibers
- High fat diet
  - Hypothalamus
    - Increased number, differentiation and proliferation of neurons
- Immune stress (excess cytokines, free radicals)
  - AD: found to have similar receptors for cell death
  - PD: dopamine neurons death
Cognition and Behavior

- Prenatal malnutrition
- Early life nutrient deficiency
  - Low IQ
  - Social isolation
  - Hyperactivity
  - Poor learning and memory
Early Childhood Effects

- Compounding of Stressors
- Malnourished child more likely to have an infection
- Synergistic effect
Reversal of damage in rat model

- Infection can mimic neurodegenerative changes in brain
- Appropriate maternal care can reverse some damage
Stress in a caregiver

- Affects child’s brain
  - Hypothalamic-pituitary-adrenocortical axis
  - Sympathetic nervous system
  - Vasoactive peptides released
    - Vasopressin
    - Endothelin-1
    - Angiotensin II
Neurologic Diseases seen with ELS

- Alzheimer’s Disease
- Schizophrenia
- ALS
- Parkinson’s Disease
AD, ALS, PD Theory

- Glial activation pathways can lead to these neurodegenerative disease
- Neuronal damage post-inflammatory can affect glial cells
- Cellular debris after injury in the CNS removed by microglia
- Add external stressors and this can further effect the environment to promote a cascade of inflammation, microglial activation, cytokine release, free radical presence and thus neurodegeneration
Cardiovascular markers

- ACES induce immediate increase in heart rate and blood pressure
- Also long term effects reaction to stress
  - Higher risk of HTN, CAD
  - High blood pressure persists even after stressful situation resolved
Cardiovascular disease studies

- Dong, et al 2004: Higher ischemic heart disease
- Carroll, et al 2013: Low SES have higher BP in adulthood
- Children of abuse (sexual, physical, emotional) have higher risk of HTN, Cardiovascular disease, obesity
- Finnish children separated from parents during WWII had higher blood pressure as adults
Theories for cardiovascular dysfunction

- Effecting renin–angiotensin–aldosterone system
- Alterations in myocardium
- Changes expression of endothelial cell receptors
Back to home...
Prescription Drugs - WV

- WV has the highest mortality rate from prescription medications
- In past 15 years, rate of drug overdose deaths have increased by more than 600 percent in WV
- Top crime problem in southern WV
- One in 5 babies born were exposed to drug or alcohol in the state in 2009
- Numbers are increasing at an alarming rate
In 2012, WV ranked 39/50 states in lowest “condition of children”

- Measured by birth weight, infant mortality, teen pregnancy rate, children living in poverty and children with no full-time working parent
Overall State Ranks: 2012
WV stats

- Infant mortality rate 7.5 per 1000 (6.7)
- Child death rate 21.9 per 100,000 (18.9)
- Child abuse/ neglect rate 16.4 per 1000 (9.2)
- Percent children in poverty 25.7% (21.6%)
Long term outlook

- Current stressors in our younger population poses increase health care needs in future
- Luckily, these risks being identified
- Resiliency training, early behavioral interventions
- Educate about lifestyle modifications to hopefully limit the multifactorial process
- Treating opioid crisis to prevent future generations
Foster Care Crisis in WV

- Over 6600 children in foster care in WV (2-3% of children in state)
- Half of these in kinship homes
- Up to 6% are out of state in psychiatric facilities or group homes
- Increase in foster children as opioid crisis worsens
What we can do to help:
Resiliency training
Statisticks
Not all children with a high ACEs score will have future health problems.
Opiates during pregnancy

- Neonatal abstinence syndrome
- Effects development of neurons: Cell death, impairs circuitry, glial activation
- Usually confounded with other risks of poor health in pregnancy:
  - Other drugs
  - Medications
  - Tobacco
  - Alcohol
  - Poor prenatal care
Opioid research

- Studies underway
- Many confounding factors
- Infants have thinner cortices
- Oligodendrocites have opiate receptors
- Prenatal morphine exposure negatively affects the migration and survival of neurons in rat embryos
- Morphine increases apoptosis in human fetal microglia and neurons
- Prenatal heroin exposure in mice - memory deficits due to neuronal apoptosis
Current West Virginia challenges in children with history of NAS

**Neonates** –
Low stimulation, swaddled
Motor delays often from “tight muscles” seen in withdrawal

**Toddlers / Preschool**
Hyperactivity
Hyper-oral
Sensory integration abnormalities

**School age**
Hyperactivity, inattention
Studies being conducted on links with ADHD, cognitive delays
Likely genetic predisposition to impulsivity (ADHD, BPD, depression)
Overlay with current social issues

**Neonate – infant**
- Parents not providing appropriate stimulation for development
- Unstable homes

**Toddler / Preschooler**
- Poor parenting
- Inconsistent homes

**School age**
- Poor parenting
- Inconsistent homes
- Life stressors
What we can do to help:

- **Early intervention services**
  - Available for children 0-3 years: state program
  - Early “Head Start” : federal program

- **PreKindergarten classes : state and county programs**

- **Resiliency training in schools for school aged children**
  - Teachers being aware of signs of a child in stress
  - Behavioral health services in schools
  - Making appropriate referrals for other services
Awareness, educating, training
Resiliency Factor

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