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

MITZI PAYNE, M.D.

PEDIATRIC NEUROLOGY

MARSHALL UNIVERSITY

Opiate exposure in the developing brain and toxic stress in early childhood: How brain structure and function is altered and impacts life-long 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 --- 3 ½ 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

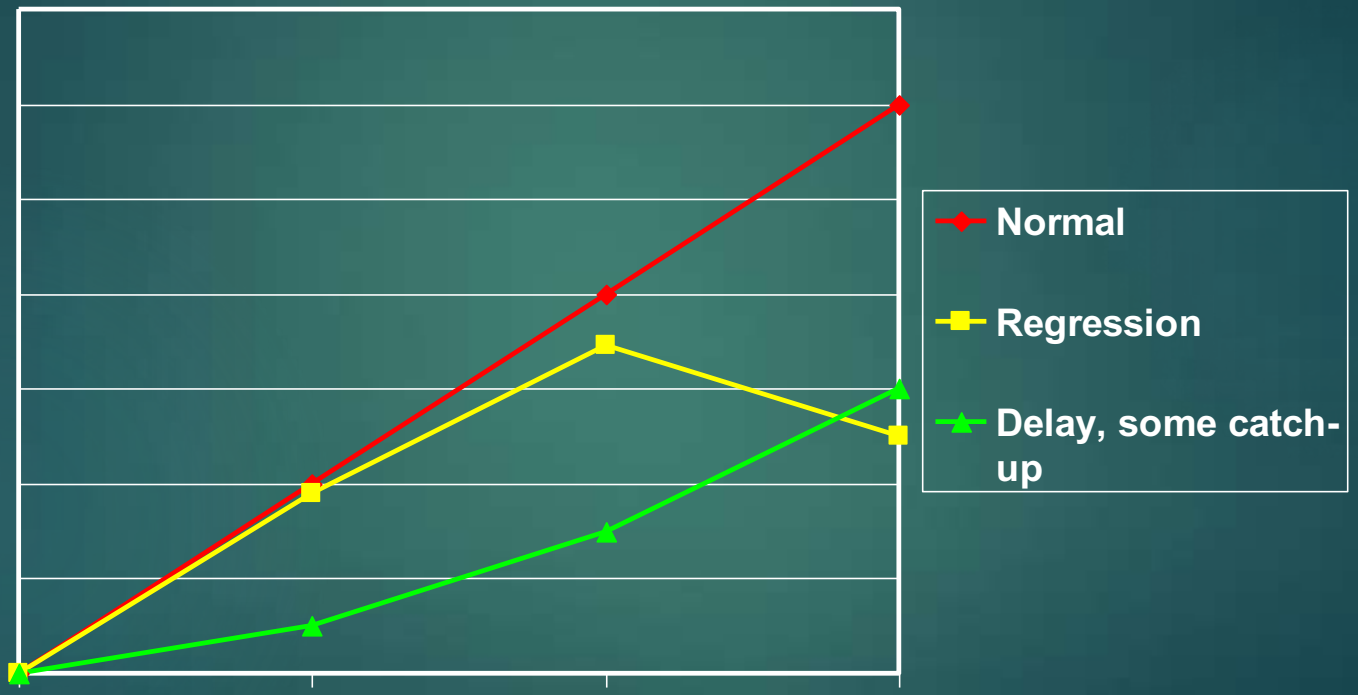
Development Delay: Social / Communication

- 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



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

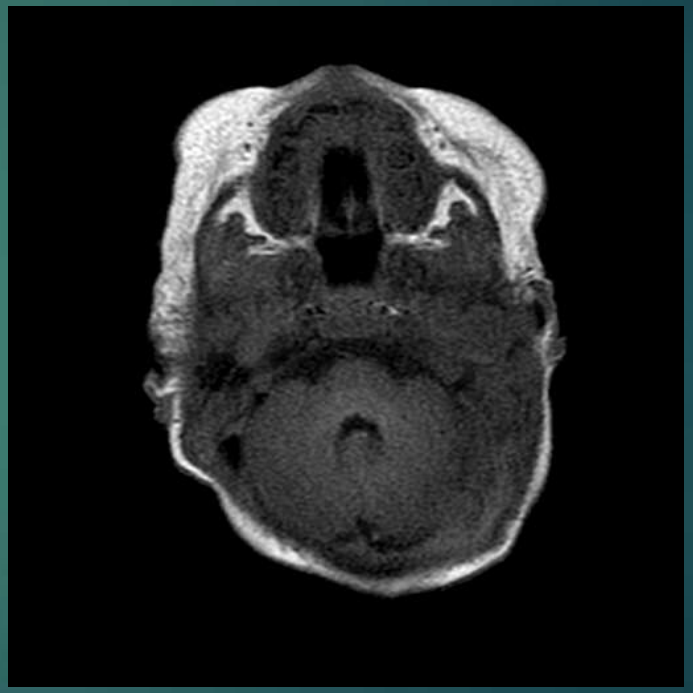
- Proximal before distal
  - Brainstem before supratentorium
- Sensory before motor
- Central before peripheral
- Posterior before anterior

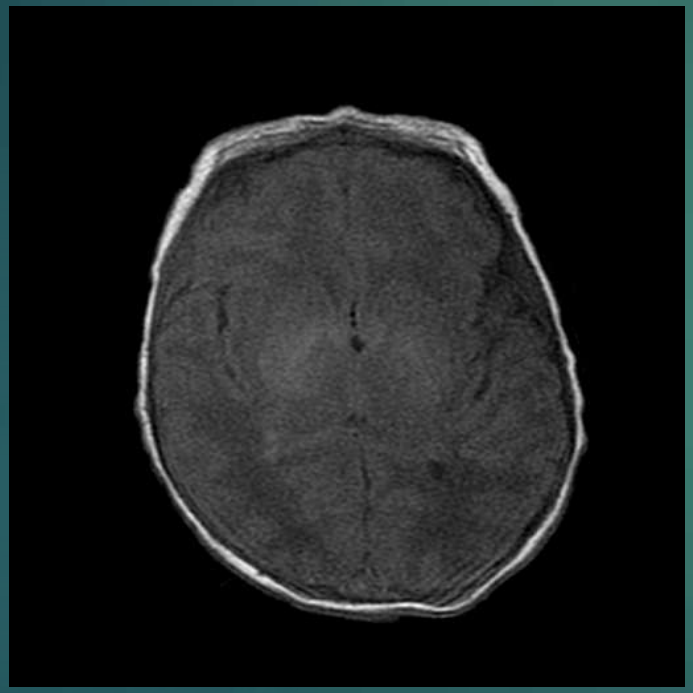
Myelination at Birth

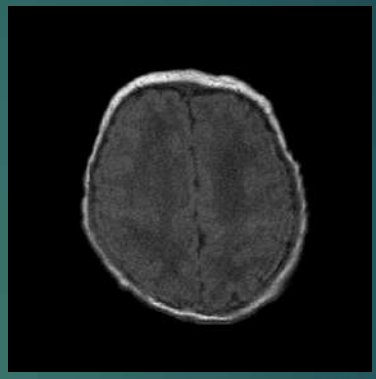
Myelinated Regions at Birth

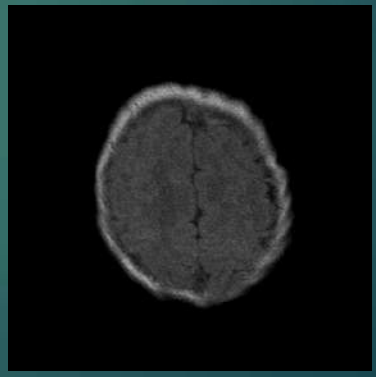
- Dorsal brainstem
- Inferior, superior cerebellar peduncles
- Perirolandic region
- Corticospinal tract
  - Central portion of centrum semiovale
  - Posterior limb of internal capsule to cerebral peduncle
- Ventrolateral thalamus
- Optic nerve, chiasm, tract

Birth





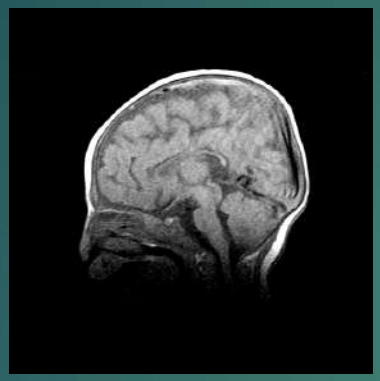


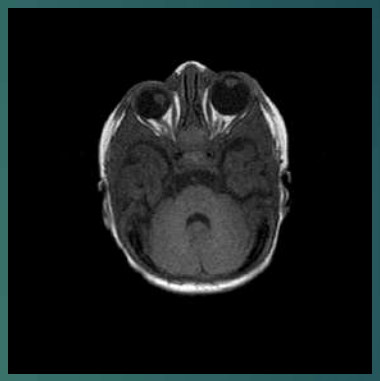


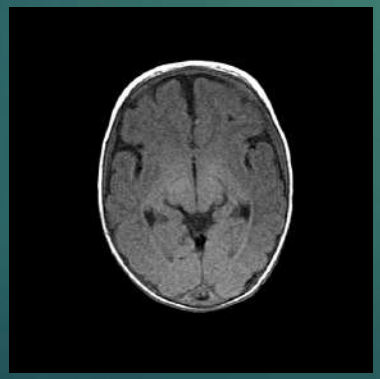
Myelination Milestones after Birth:

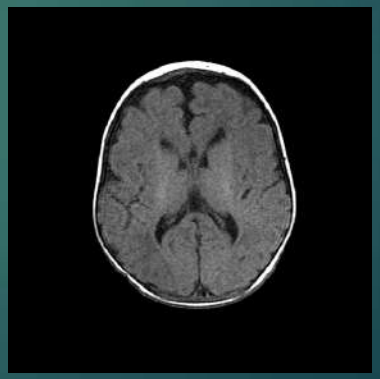
- T-1 weighted (white matter is bright)
- 3 months
  - Cerebellar WM

3 Months





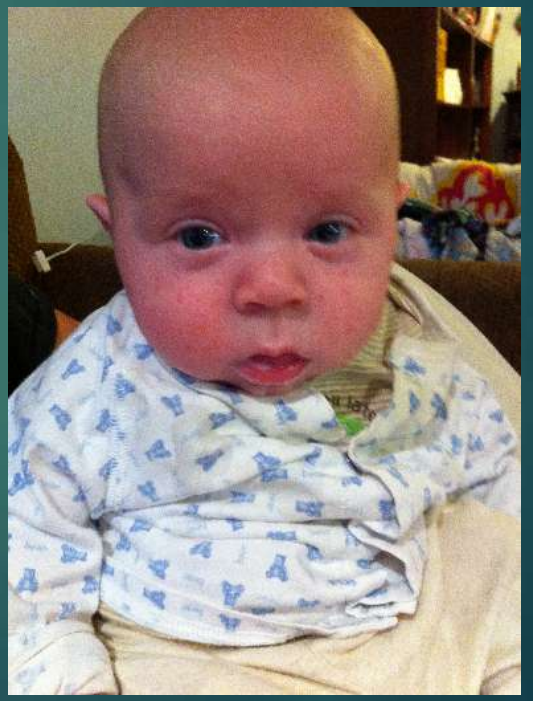




Myelinated Milestones After Birth:

T-2 weighted (white matter is dark)

- 6 months
  - Splenium Corpus Callosum

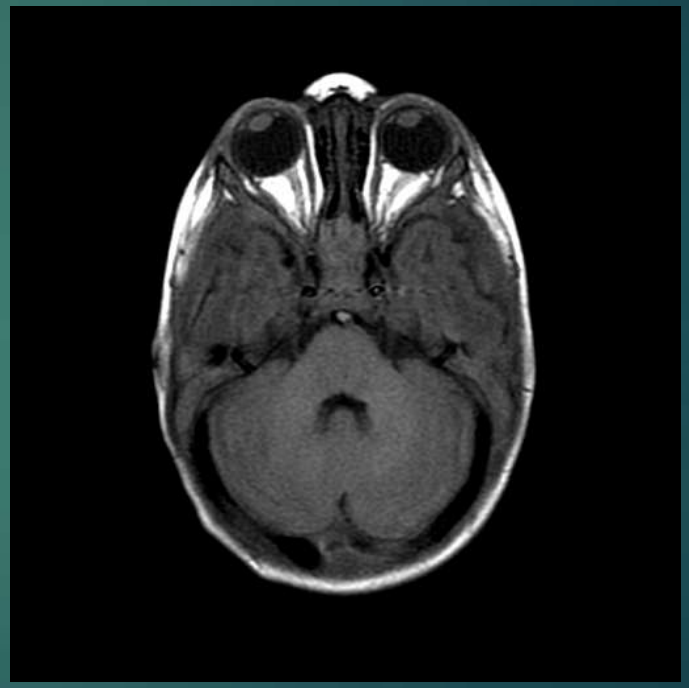


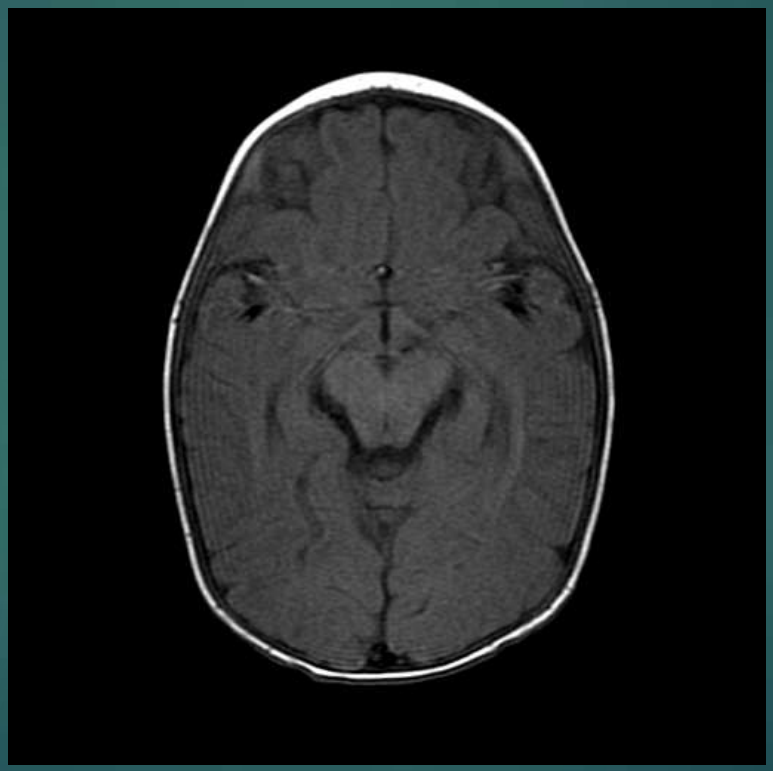
Chronology of other Specific White Matter Intensity Changes

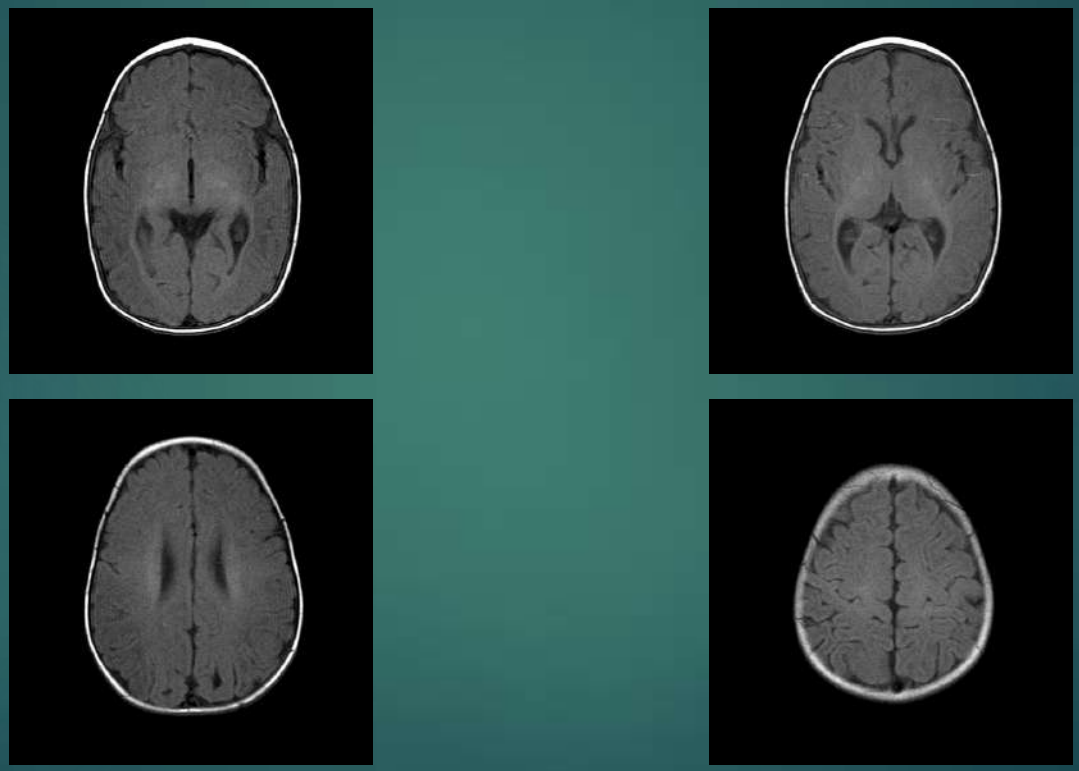
- Infratentorial
  - Middle cerebral peduncle
  - Cerebellar deep WM
- Supratentorial
  - Anterior limb
  - Posterior limb
  - Pre and postcentral gyrus

T1	T2
Birth-1 month	3 - 6 mo
1 - 3 mo	8 - 18 mo
3 mo	7 - 11 mo
Birth	Birth – 7 mo
1 mo	9 – 12 mo

6 Months



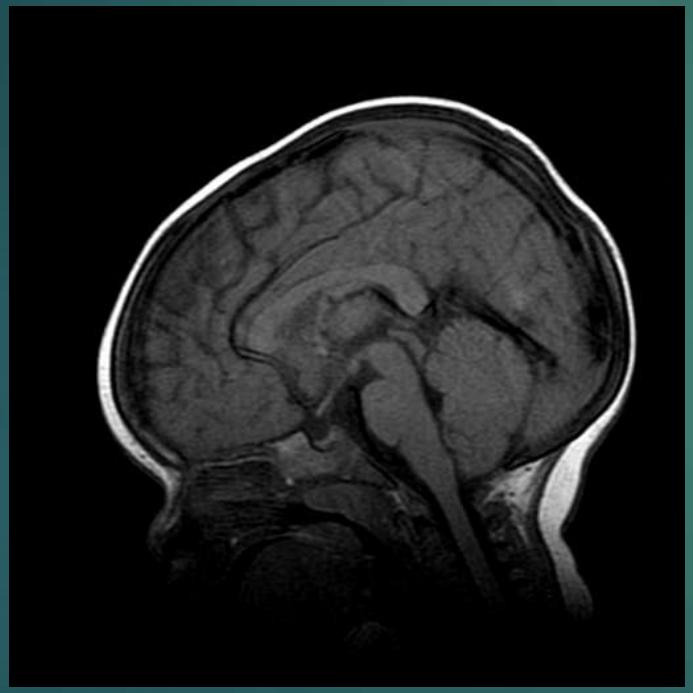


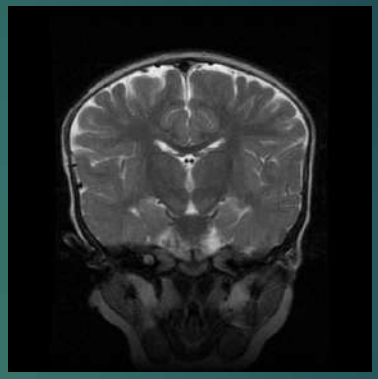


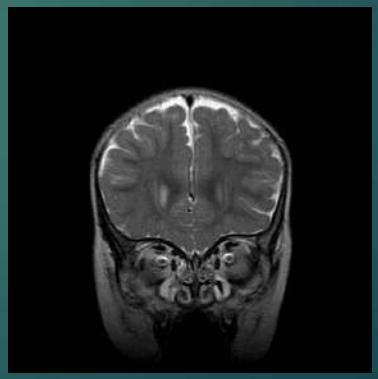
Myelination (T2)

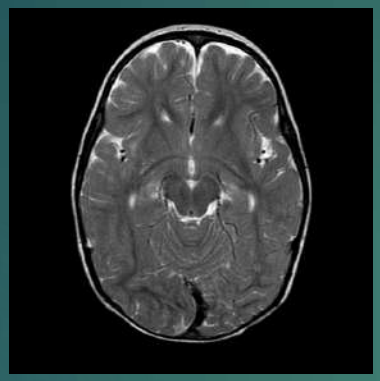
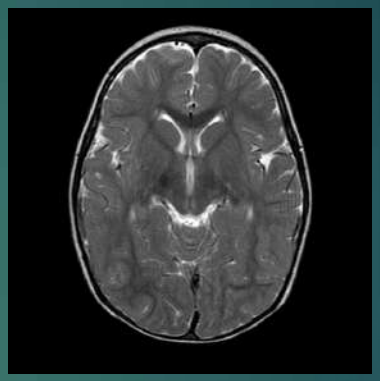
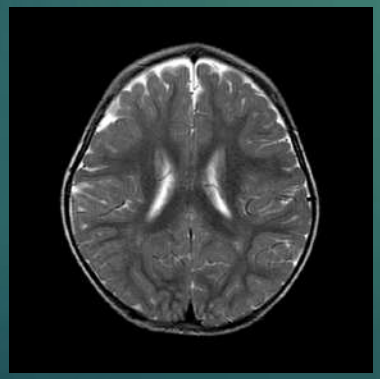
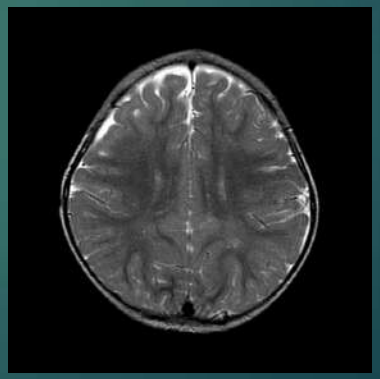
- 8 months
  - Genu
- 11 months
  - Anterior limb IC
- 14 months
  - Frontal WM

1 Year

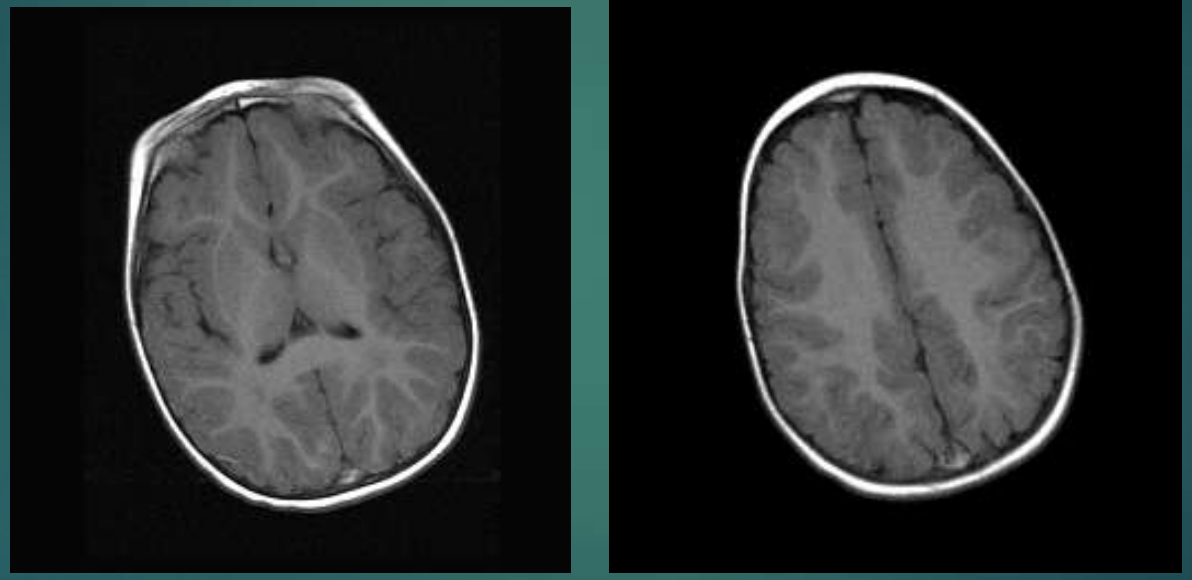


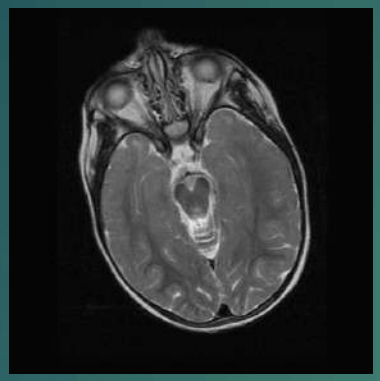


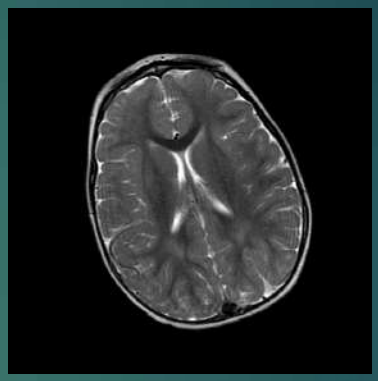


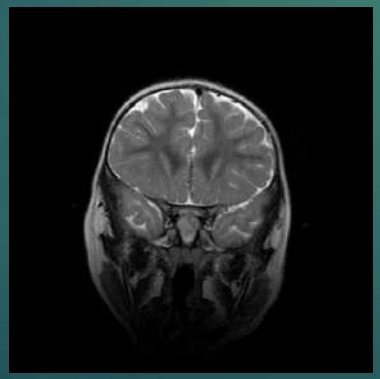





18 Months

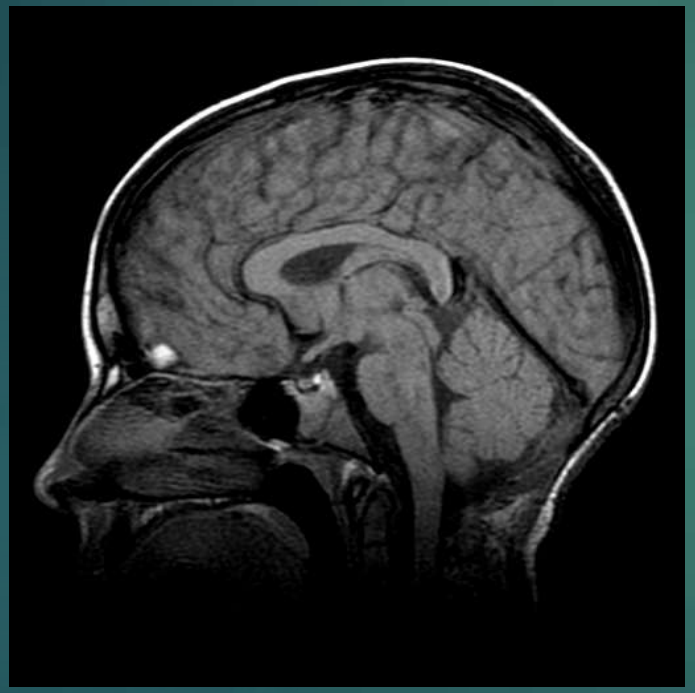


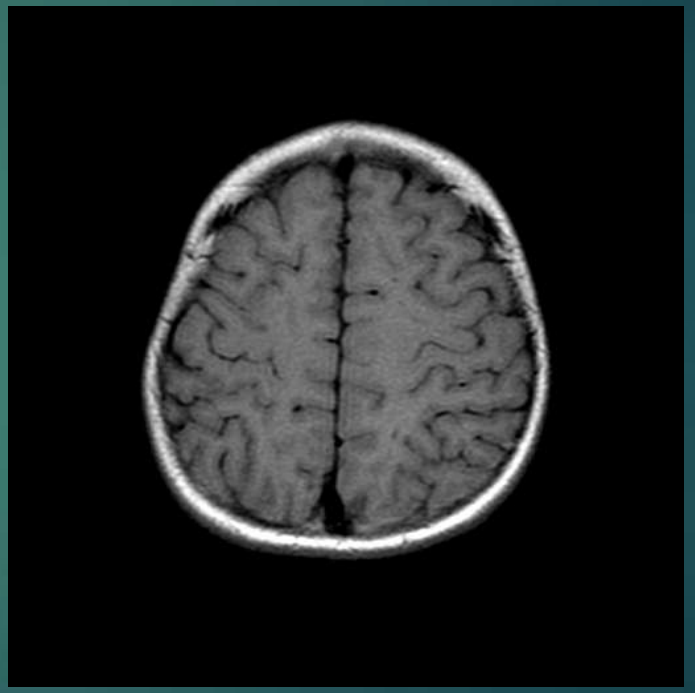


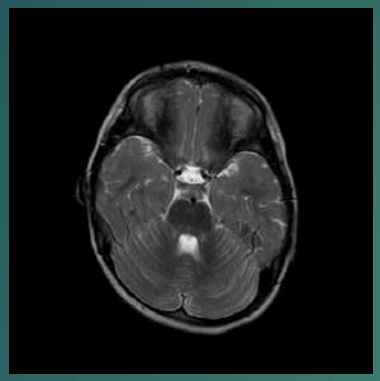
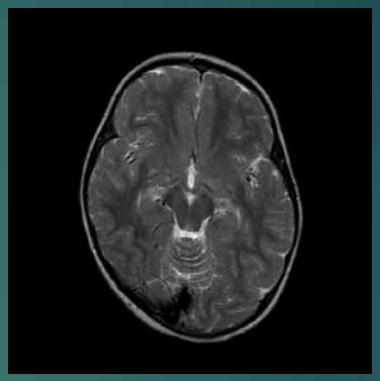
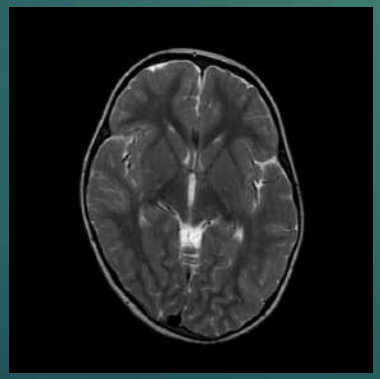
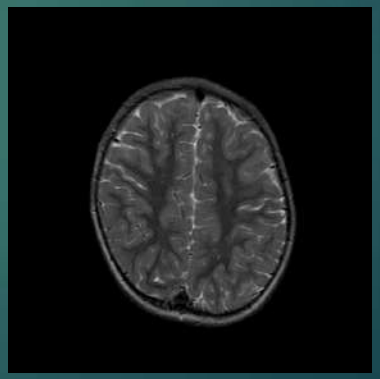




24 Months





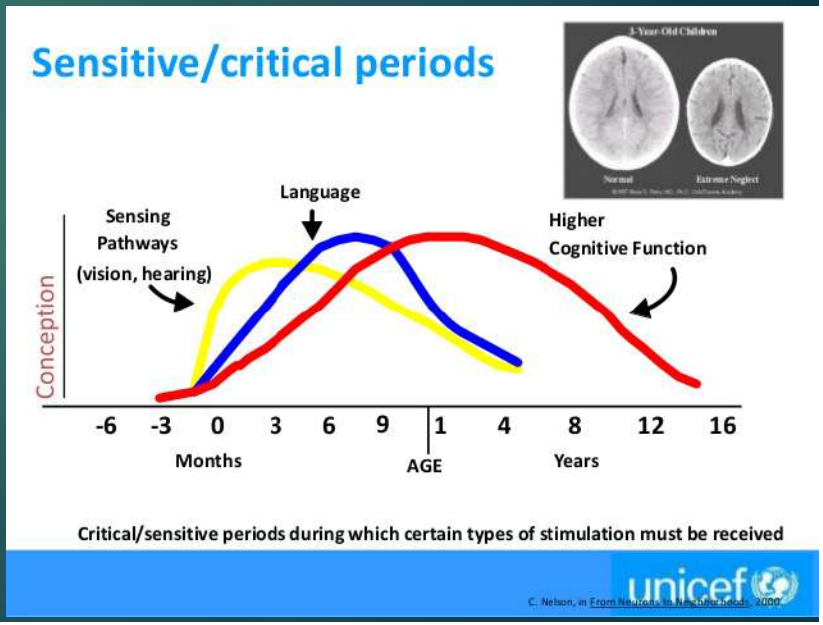





Critical periods

- 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

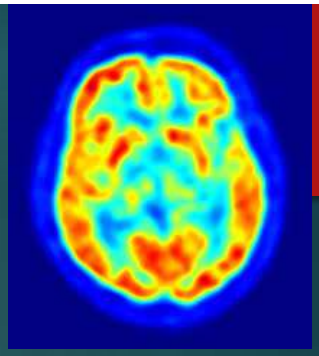
Language Development

- 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:

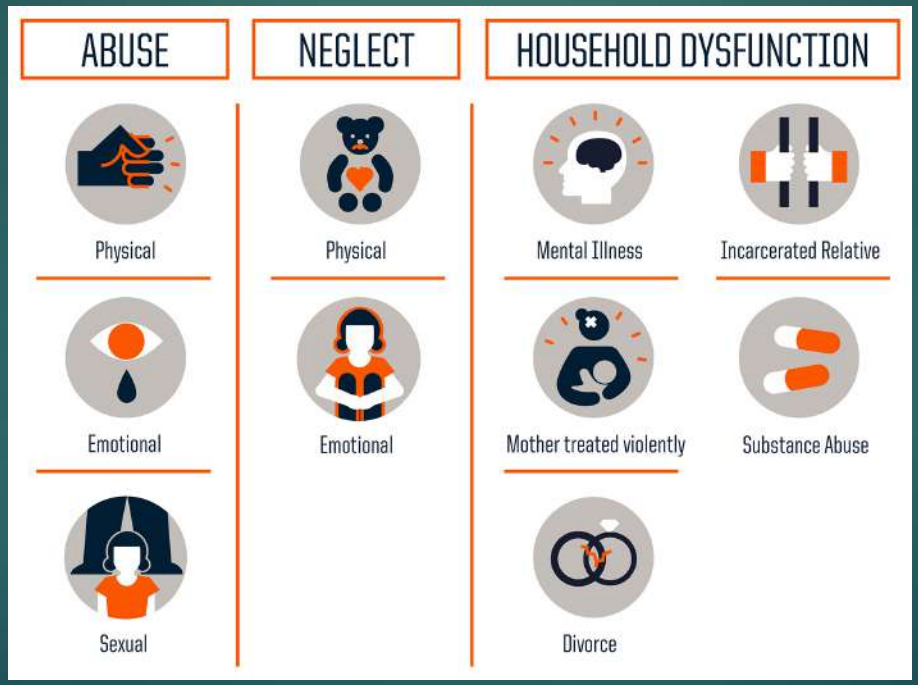
Often or very often pushed, grabbed, slapped, or had something thrown at her? or Sometimes, often, or very often kicked, bitten, hit with a fist, or hit with something hard? or Ever repeatedly hit over at least a few minutes or threatened with a gun or knife?

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?

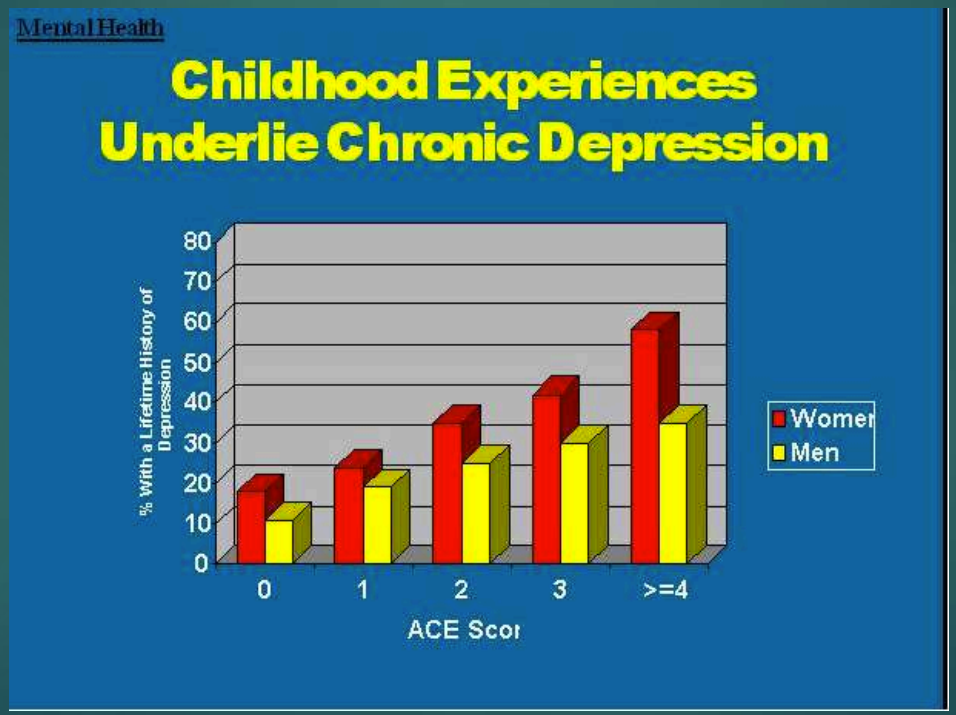
ACEs Scoring



Score of 4 or more:

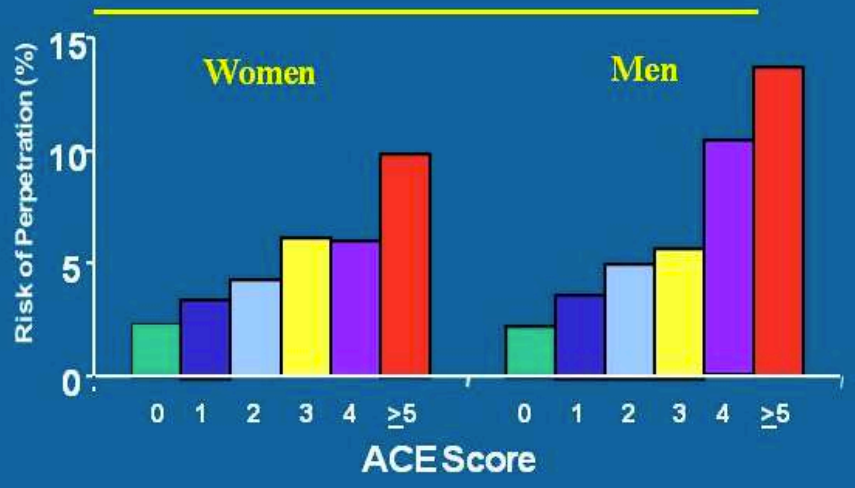
- COPD risk increases 390%
- Hepatitis 240%
- Depression 460%
- Attempted suicide 1220%


Health Risks
Childhood Experiences vs. Adult Alcoholism
% Alcoholic
18
16
14
12
10
8
6
4
2
0
0
1
2
3
4+
ACE Score

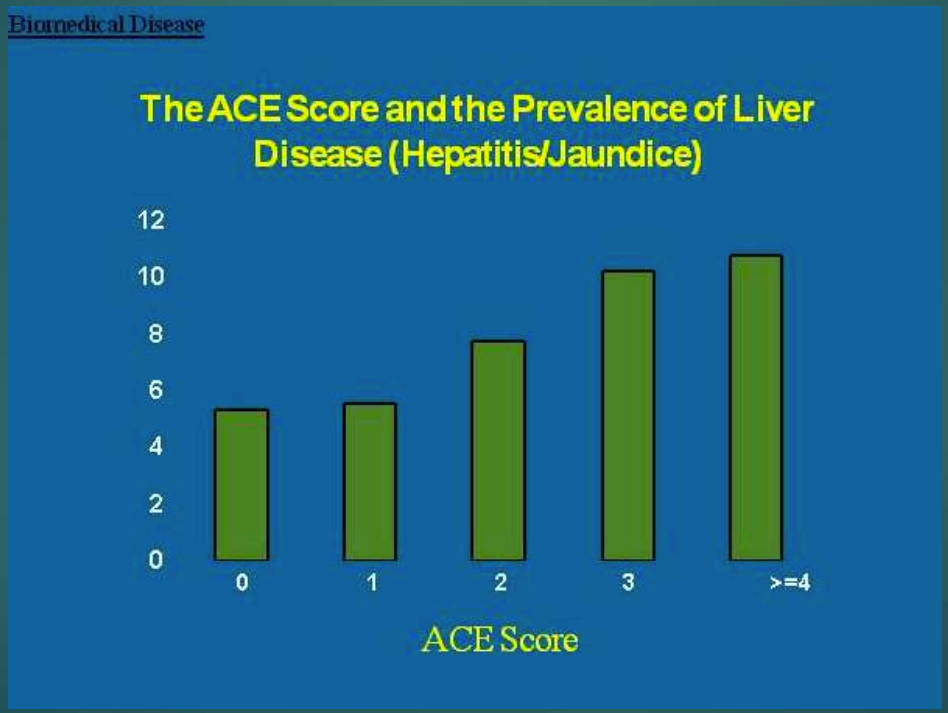

Mental Health
Childhood Experiences
Underlie Chronic Depression
% With a Lifetime History of Depression
80
70
60
50
40
30
20
10
0
0
1
2
3
>=4
ACE Scor
Women
Men

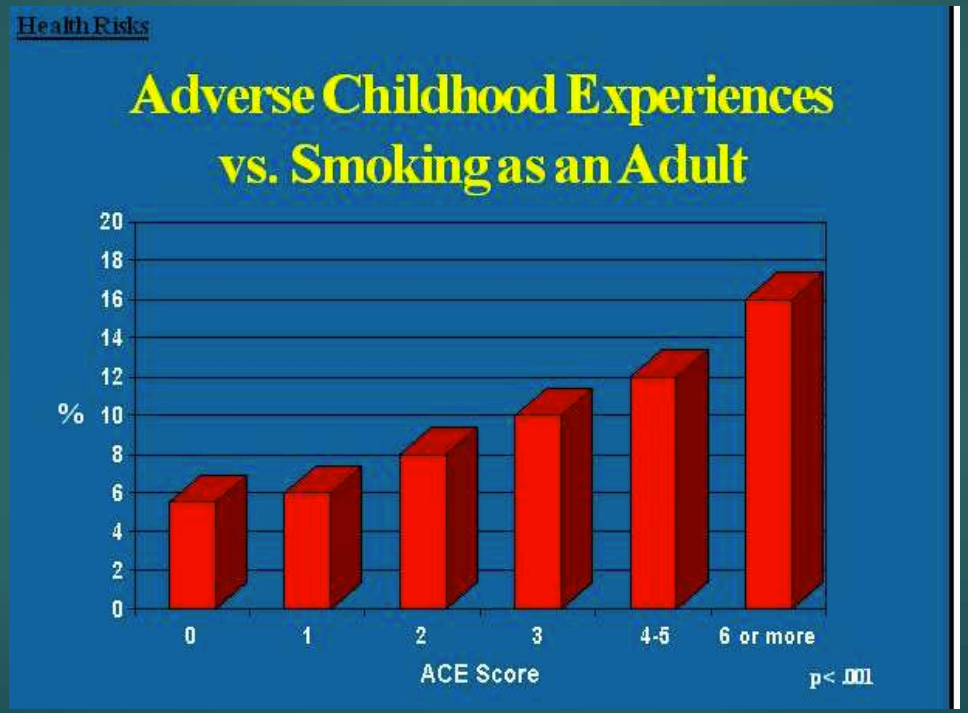
Social function

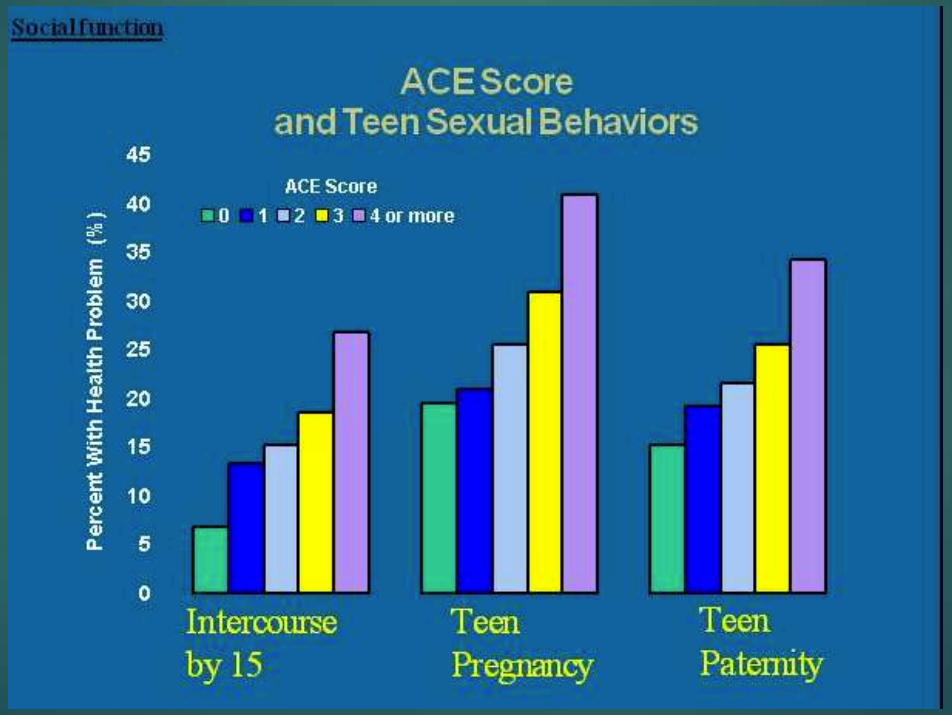
ACE Score and the Risk of *Perpetrating* Domestic Violence



Biomedical Disease

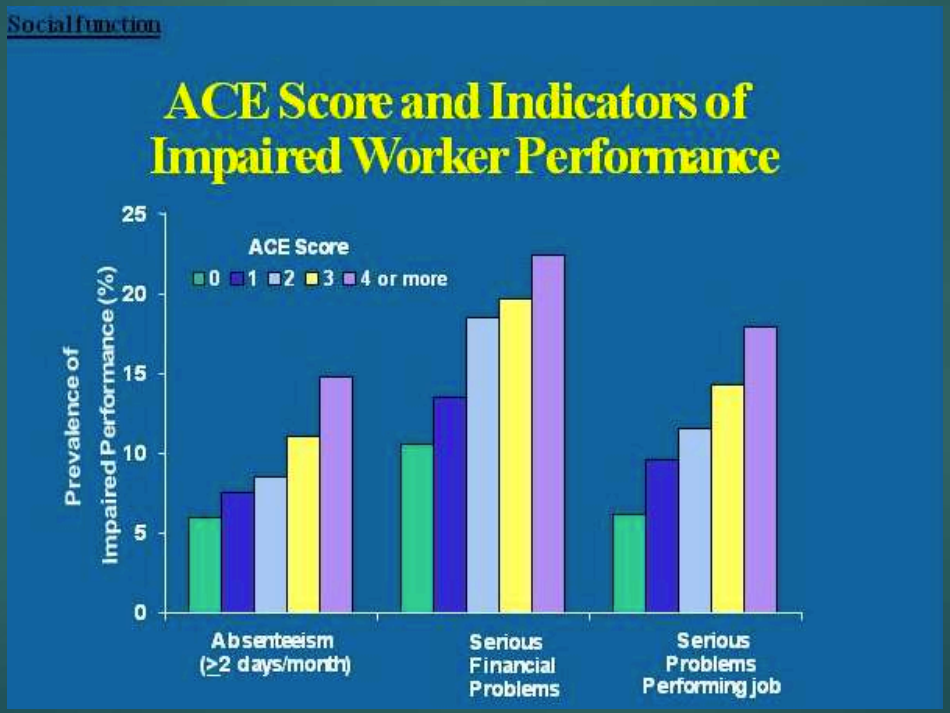



Health Risks
Adverse Childhood Experiences
vs. Smoking as an Adult
20
18
16
14
12
% 10
8
6
4
2
0
0
1
2
3
4-5
6 or more
ACE Score
p< .001


Social function
ACE Score
and Teen Sexual Behaviors
ACE Score
0 1 2 3 4 or more
Percent With Health Problem (%)
45
40
35
30
25
20
15
10
5
0
Intercourse by 15
Teen Pregnancy
Teen Paternity

Social function

ACE Score and Indicators of Impaired Worker 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.
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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 increase 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 cam 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 effect 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

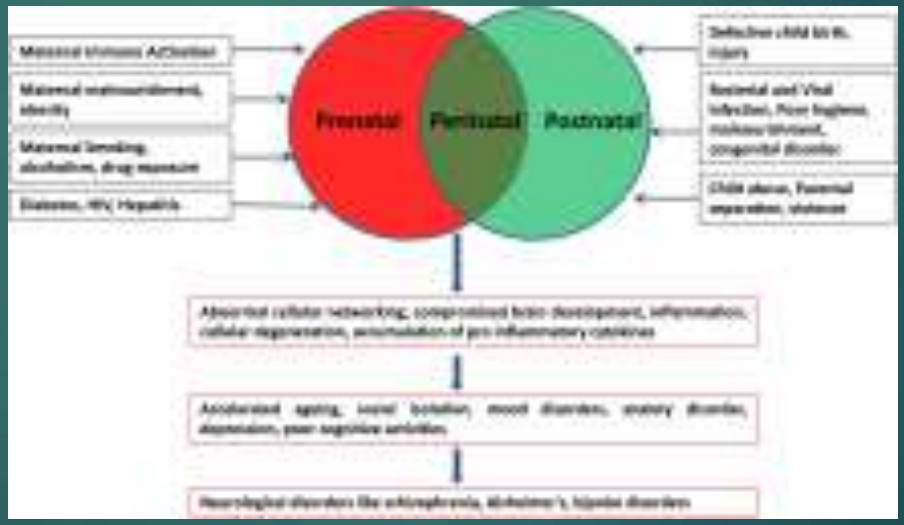
- ACES induce immediate increase in heart rate and blood pressure
- Also long term effects reaction to stress
  - Higher risk of HTN, CAD
  - High blood pressure persists even after stressful situation resolved

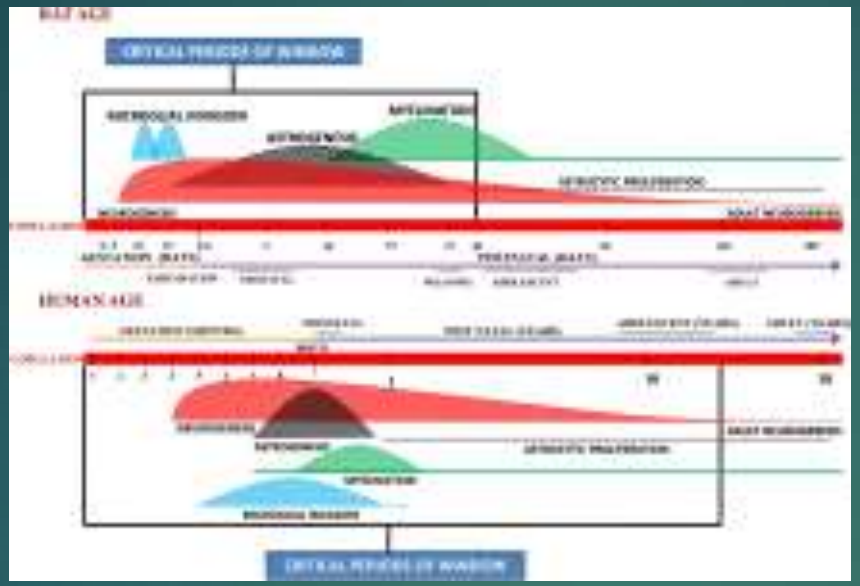
Cardiovascular disease studies

- 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


Prenatal
Perinatal
Postnatal



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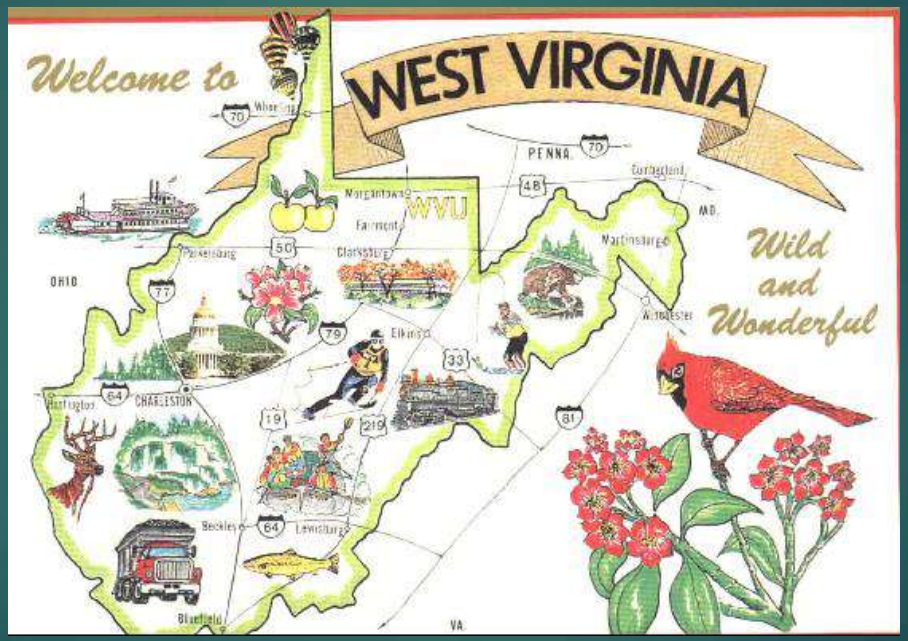

Welcome to
WEST VIRGINIA
Wild and Wonderful
WVU
CHARLESTON
OHIO
PENNA.
MD.
VA.

Prescription Drugs - WV

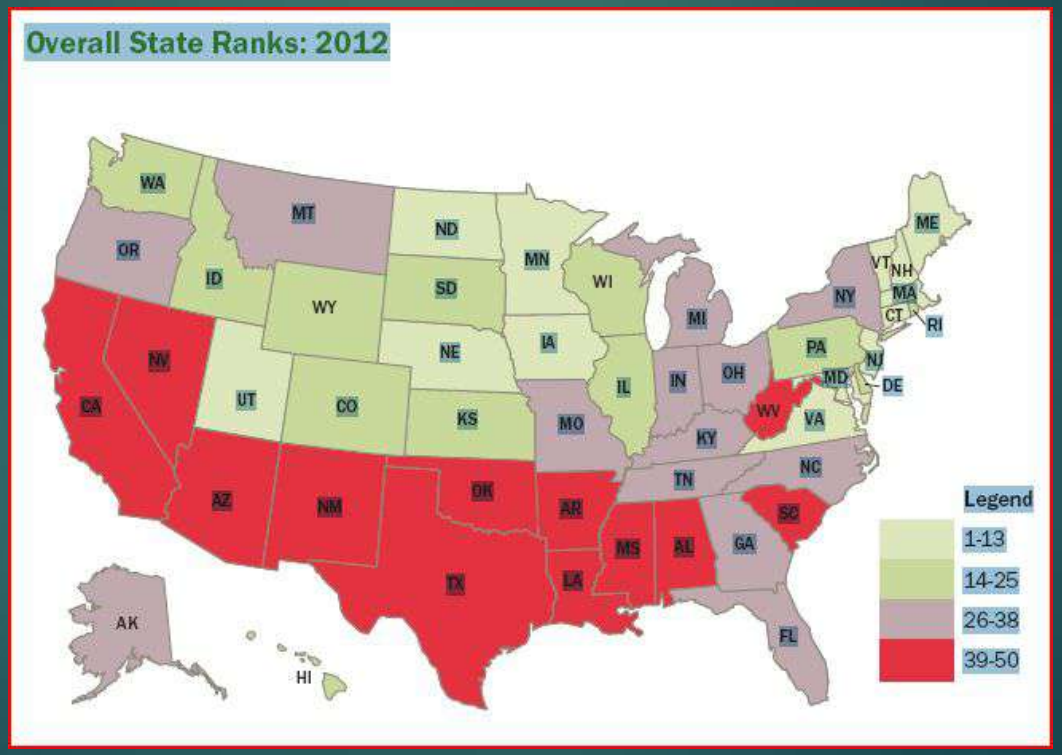
- WV has the highest mortality rate from prescription medications
- In past 15 years, rate of drug overdose deaths have increased by more than 600 percent in WV
- Top crime problem in southern WV
- One in 5 babies born were exposed to drug or alcohol in the state in 2009
- Numbers are increasing at an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

WV "stress"

- 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

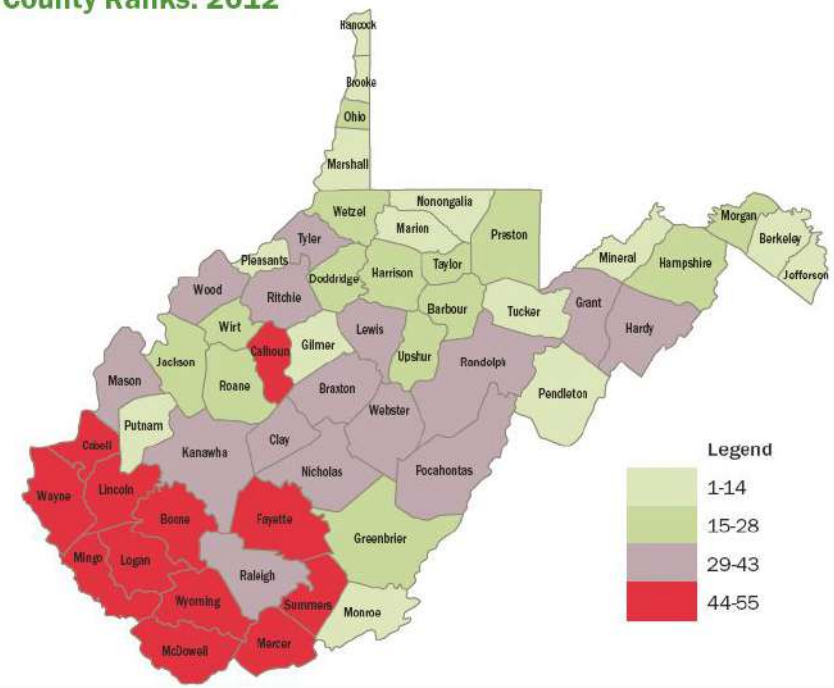
WV KIDS COUNT

WV KIDS COUNT



WV KIDS COUNT

Overall County 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%)

WV KIDS COUNT

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

Stressful events happen

Stress experienced in a supportive environment can promote resilience

Positive stress
Tolerable stress

Stress experienced in a toxic environment can lead to further stress

Toxic stress

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

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.

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?

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