NEURODEVELOPMENT AND NEUROPLASTICITY

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NEURODEVELOPMENT

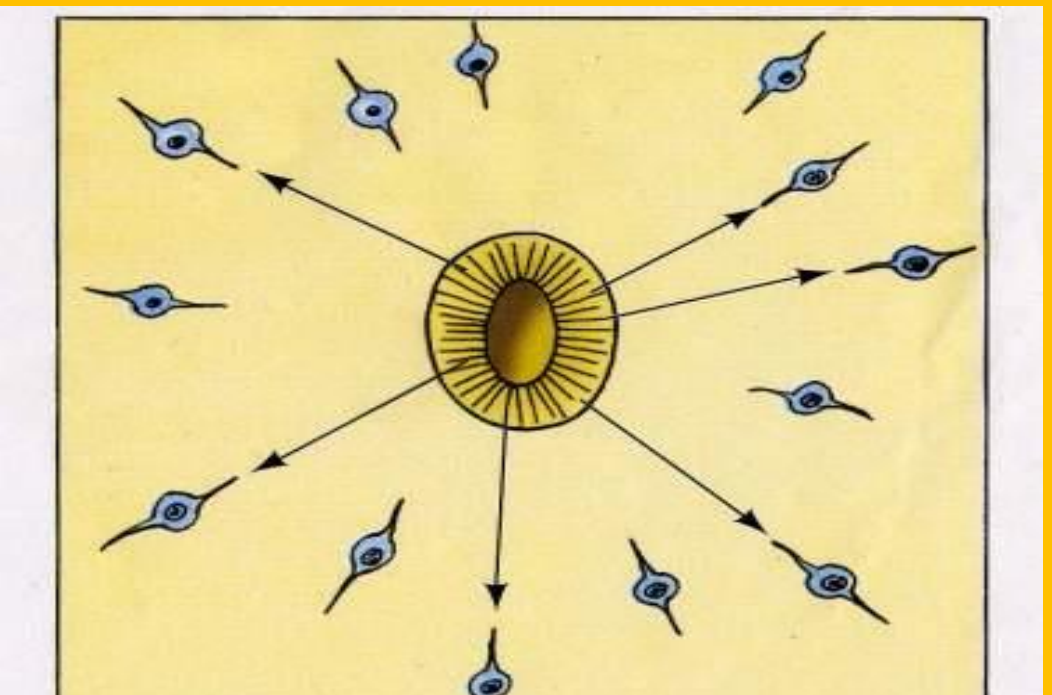
- **Neurodevelopment** is a constantly changing interaction between genes and the environment.

NEURODEVELOPMENT

- **Neurodevelopment** begins at the embryonic stage and continues through adulthood.

NEURODEVELOPMENT

- The brain begins as a neural tube, where cells are born (**neurogenesis)**,
- travel to the proper place in the brain (**migration**)



-undifferentiated at start of migration.

But, differentiation begins as neurons migrate.

NEURODEVELOPMENT

- Neurons sprout branches (**axons for input and dendrites for output**) that enable proximity to other neurons and build pathways and circuits throughout the brain.
- Then, finally, the neuron forms the chemical-electrical connections between cells (**synapses**) to relay information.

NEURODEVELOPMENT

- In mammals, the first phase (prenatal)is *in utero* and reflects a genetically determined sequence of events that can be modulated by the maternal environment.
- The principal developmental stages here are neural generation and migration.

☐Between 40-75% neurons made, will die after migration – death is normal and necessary

NEURODEVELOPMENT

- **Postnatal NeurodevelopmenT** is a consequence of
  - Synaptogenesis
  - Increased dendritic branches
  - Myelination (prefrontal cortex continues into adolescence)

At birth, the human brain weighs approximately 350 grams. By the first year. the brain weighs approximately 1000 grams. The adult brain weighs 1200-1400 grams.

THE ROLE OF ENVIRONMENTAL FACTORS IN NEURODEVELOPMENTAL DISORDERS

- Research has shown that single genetic anomalies can account for a small proportion of cases with neurodevelopmental disorders.

- Neurodevelopmental Disorders are the result of complex interaction between genetic and environmental factors through **neuroplasticity** and **epigenetics**.

NEUROPLASTICITY

- **Neuroplasticity** is a process that involves adaptive structural and functional changes to the brain. It is defined as the ability of the nervous system to change its activity in response to intrinsic or extrinsic stimuli by reorganizing its structure, functions, or connections
- . Brains exposed to different environmental events such as sensory stimuli, stress, injury, diet, drugs, and social relationships show a unique developmental trajectory.

NEUROPLASTICITY

- developmental neuroplasticity : as part of the initial organism stage
- adult neuroplasticity :as a process occurring during the mature form

- Classification based on Molecular and cellular mechanisms of NP phenomena:
- functional NP, which includes changes in the efficacy of synaptic transmissions such as a the activation of silent synapses;
- structural NP, associated to changes in cell structure, as well as changing the complexity of the neurons (dendritic branches)

mechanisms of axonal regeneration, collateralization and reactive synaptogenesis

NEUROPLASTICITY

- Both forms of plasticity are interconnected. The functional activity drives the formation of new morphological features,

NEUROPLASTICITY

- For example, unused neurons (neurons with little neural activity) will die, while used neurons will survive.
- This is a normal process that occurs in the developing brain—too many cells are born and are then pruned—early life deprivation fails to activate neurons, which means that a greater number of neurons will die.

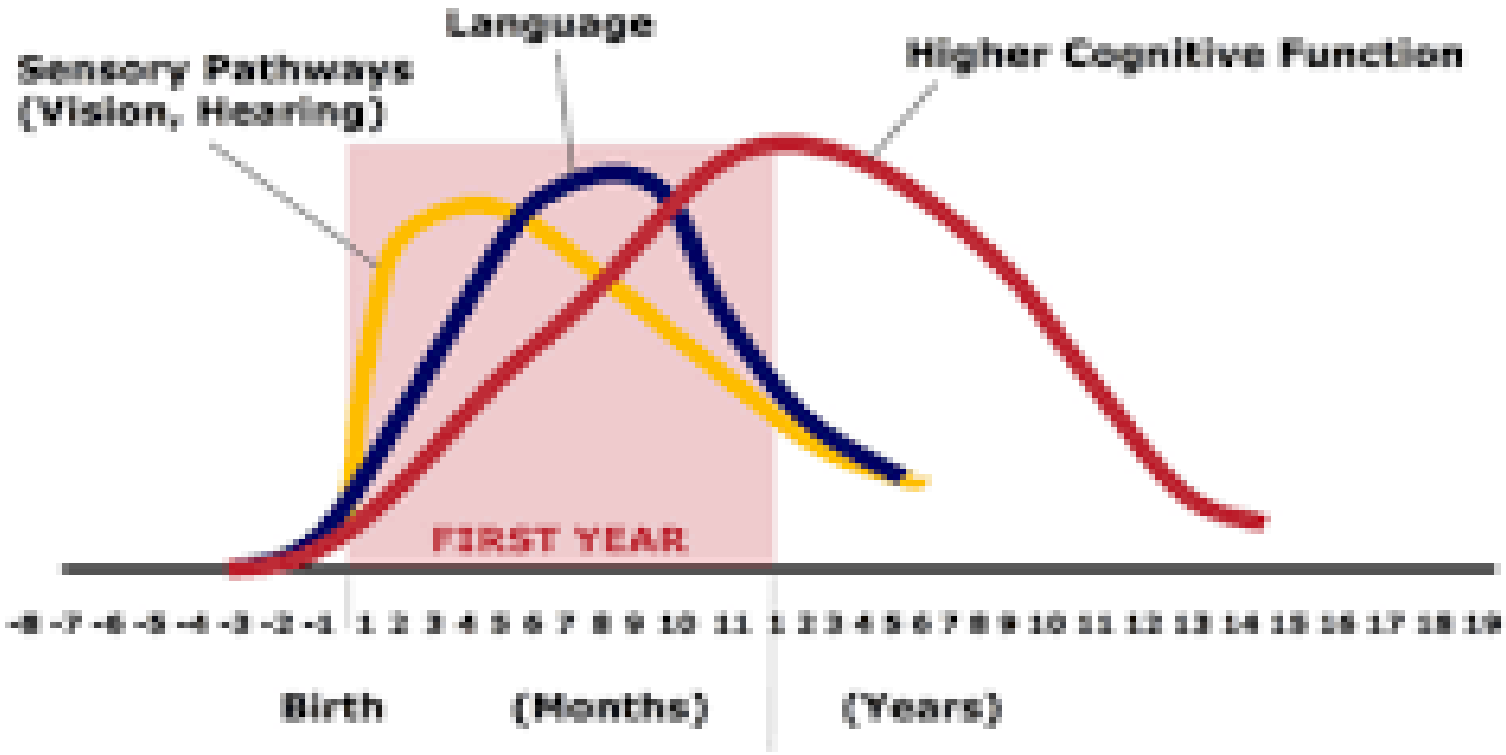
NEUROPLASTICITY

- The early childhood brain is extremely plastic, but this enhanced plasticity also provides an enhanced **vulnerability** to all types of experiences. The nature and timing of these experiences influence the course of the developing brain in many ways, especially if they occur during the **“sensitive or critical periods” .**

- Sensitive periods may be defined as restricted windows of development when experiences have strong influences on the neural circuit formation.

Human Brain Development

Neural Connections for Different Functions Develop Sequentially



Source: In Brief: The Science of Early Childhood Development. Center on the Developing Child, Harvard University.

THE ROLE OF EPIGENETIC MECHANISMS

- “Epi,” the prefix for “on top of” used in the context of genetics, describes mechanisms that work above or in addition to the DNA backbone, influencing the function of the genome without altering the DNA sequence.

- Epigenetic mechanisms influence how accessible certain DNA sequences are to regulators of gene transcription and making specific proteins, **changing the gene expression**.

THE ROLE OF EPIGENETIC MECHANISMS

- Epigenetic modifications can be influenced by genetic and environmental factors, both can be major risk factors for Neurodevelopmental disorders.
- Epigenetic modifications may thus be an important mediator of the effects of environmental risk factors on cell function.

INTERPLAY BETWEEN GENES AND THE ENVIRONMENT

- Summary of three different ways in which the powerful and complex interplay between genes and the environment may happen.

➢ **Gene-environment correlations**: in this case ,genes that influence a trait also influence the exposure to environmental risk. For instance, a mother with high anxiety levels will also display anxious behaviors at home, which will ultimately influence the child

EPIGENETICES AND NEUROPLASTICITY

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- **Genotype environment interactions**: occur when the person's genotype has an effect on the response to environmental factors. Therefore, individuals with a "sensitive" gene polymorphism will be at a higher risk if exposed to a predisposing environment than individuals with an "insensitive" gene polymorphism

EPIGENETICES AND NEUROPLASTICITY

- **Epigenetic gene-regulatory processes**: early life experi-ences can modify the gene expression. One way for this to happen is through DNA methylation that functions as a molecular memory of each individual environment. As an example, maternal smoking during pregnancy influences differences in DNA methylation at birth with effects that can persist during the whole life and can also have potential transgenerational effects.

EPIGENETIC MECHANISMS AND NEUROPLASTICITY

- **The prenatal environment** may trigger modifications on the epigenome of the differentiating cell, leading to changes in the structure and function of the organs.
- For instance, poor fetal grow this an important marker of an adverse intrauterine environment and has been associated with increased risks for developmental delays and/or neurodevelopmental disorders.
- Maternal factors such as the **mothers age, socio-economic status, maternal physical and mental health, and substance abuse** can affect fetal growth and

NEUROPLASTICITY AND EPIGENETIC MECHANISMS

- Intrauterine exposition to substance abuse, smoking, maternal psychological stress, and/or parental psychiatric disorders during pregnancy may have a strong negative impact not only during pregnancy but throughout a lifetime.
- For example ,Prenatal maternal anxiety increases fetal exposure to maternal cortisol. This exposure affects offspring neurodevelopment involving the amygdala, pre-frontal cortex, and hypothalamic-pituitary-adrenal axis which can increase the risk for physical and neurodevelopmental problems later in life.

NEUROPLASTICITY

- **Prematurity** is an adverse event that contributes to poor socioemotional development. The premature brain may present with dysmaturational disturbances such as changes in synaptic efficacy, loss of volume, enlarged ventricles, and alterations in myelination.

NEUROPLASTICITY

- Maternal glucocorticoids are likely to be involved in transmitting the maternal stress and anxiety signals to the developing embryo. Prenatal glucocorticoid overexposure produces long-term changes in offspring cardiometabolic, neuroendocrine, and behavioral outcomes via tissue-specific effects on gene promoter epigenetic changes.
- The importance of the endocrine placenta as the intermediary tissue joining the maternal milieu and the developing embryo must also be considered to mechanistically define genes and antecedents involved in programming of neurodevelopmental disorders

EPIGENETICES AND NEUROPLASTICITY

- Activity-dependent changes in gene expression within neuronal pathways during development may serve as a critical pathway linking experience of the external environment and epigenetic modifications within the cell nucleus.

EPIGENETICES AND NEUROPLASTICITY

- The role of **epigenetic** modification in sustaining the effects of environmental experience has also been demonstrated in the context of **postnatal mother-infant interactions**
- A fundamental study, reported that increased maternal care in young rats leads to decreased DNAm hippocampal promoter of the glucocorticoid receptor gene (*GR*) and increased GR expression, a central regulator of the stress hormone system, and decreased stress reactivity ,an effect that persisted into adulthood.
- Rats with lower maternal care showed higher DNAm in this promoter and decreased *GR* expression. paired with increased stress reactivity of the animals in adulthood and associated behavioral changes

WHY LOVE AND NURTURING ARE SO IMPORTANT IN EARLY LIFE?

- In early life it is the social interactions with the caregiver and the caregiver's stimulation of the child's sensory receptors in the eyes, ears, tongue, nose, and skin that provide the experience-based programming of the brain. In other words, the only possible route for experience to enter the brain is by sensory stimulation,
- .The caregiver is the primary source of this stimulation and is the gateway to other sensory stimulations via access to toys and an interesting and intensity-appropriate environment.

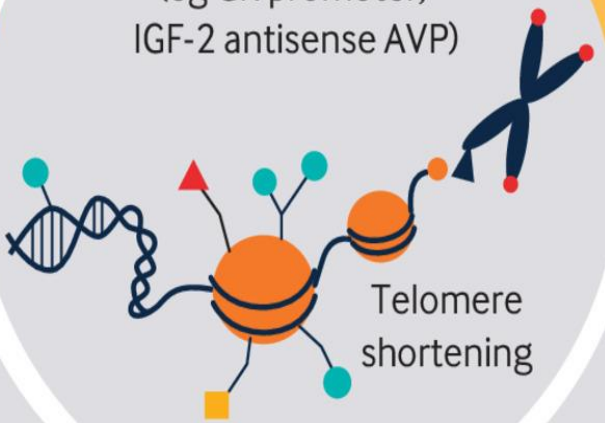
Childhood psychosocial adversity → **Biological change** → **Adult outcomes**

Care environment mediates stress
- Prenatal maternal stress, depression
- Postnatal caregiver unavailability/ absence (mental illness, substance abuse, death)
- Depriving environments (eg institutional care)
- Child abuse or neglect

Genetic endowment
Genetic variants alter susceptibilty to advesity
- eg 5-HTTLPR, BDNF, $FKBP_5$, MAOA poly-morphisms

Epigenetic changes

DNA methylation (eg GR promoter, IGF-2 antisense AVP)



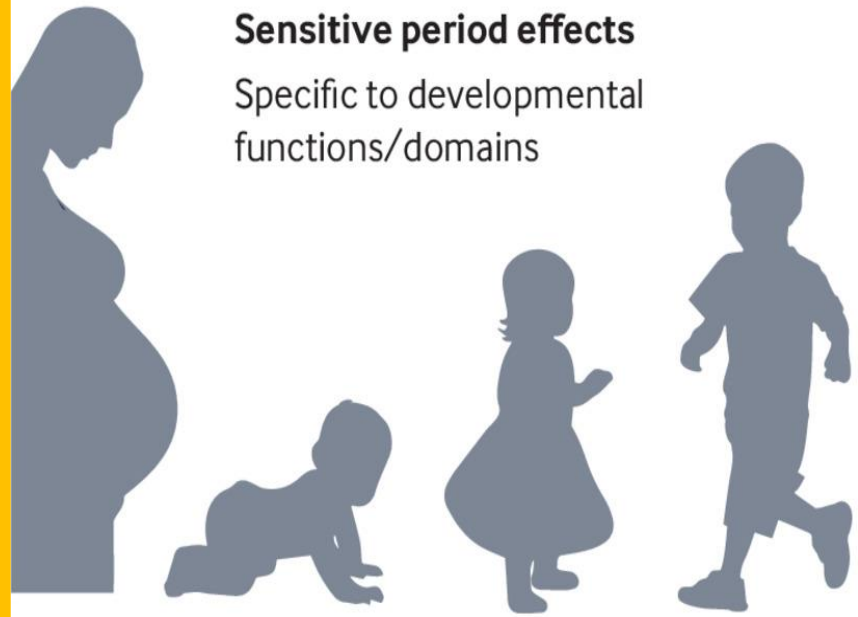
Telomere shortening

Developmental trajectory
- Biological change is embedded in behaviour (e.g. substance use, exercise, diet, stress management)

Increased risk of:
- **Cognitive deficits**
- **Disease**
- **Psychopathology**
- **Social problems, (unemployment, incarceration)**

Sensitive period effects

Specific to developmental functions/domains



6–12 months HPA axis (SHRP)

15 months Language

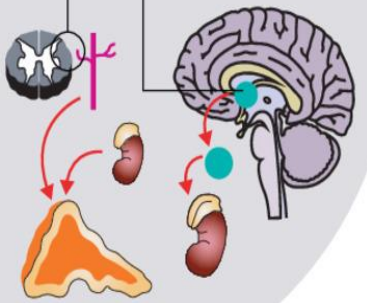
24 months Attachment, IQ

- Reduced volume of key regions
- Neurotransmitter changes
- Altered functional activity, tract connectivity

Neurodevelopmental disruption

Inflammation

Altered HPA and sympatho-medullary axes



Reprogramming of stress and immune regulatory systems

thebmj Visual summary

From bitter experience

Lifelong implications of adverse childhood experiences

Today's youth face challenges unforeseen in previous generations. Adversity in the first years of life may deleteriously affect the course of human development. This graphic presents some of these challenges and introduces the biological and psychological mechanisms by which they can affect health throughout a child's development and journey into adulthood

Context

Each child's situation is unique, and their particular circumstances can have an important impact on how they are affected by their experiences

- Type of adversity
- Duration of adversity
- Number of adversities
- Interactions between adversities
- Timing and developmental status
- Child's temperament and reaction to adversity
- Pre-existing characteristics
- Family environment
- Health status and comorbidities

Experiences and responses can compound one another

Biological changes

Exposure to adversity early in life interacts with a child's genetic endowment, which in turn leads to a host of biological changes across multiple levels. These changes, in turn, influence adult outcomes

Epigenetic

DNA methylation, such as glucocorticoid receptor promoter, IGF-2 antisense vasopressin

Neurodevelopmental

Changes to cortical volume, functional activity, tract connectivity, or neurotransmitters

Response systems

Health problems that have been observed more commonly in people that have experienced adversity in childhood

Pre-existing characteristics

Family environment

Health status and comorbidities

DNA methylation, such as glucocorticoid receptor promoter, IGF-2 antisense vasopressin

Neurodevelopmental

Changes to cortical volume, functional activity, tract connectivity, or neurotransmitters

Response systems

Reprograming of stress and immune regulatory systems

Behavior embedding

Biological changes embedded in behavior, such as substance misuse, exercise, diet, or stress management

Health problems that have been observed more commonly in people that have experienced adversity in childhood

Examples of **physical** impacts	Examples of **behavioral** impacts
Somatic symptoms	Learning and/or behavioral problems
Headaches	Early use of illicit drugs
Poor dental health	High school absenteeism
Asthma	Early use of alcohol
Allergies	Attention deficit hyperactivity disorder
Increased infections	

Childhood exposure to adversity may lead to increased risk of adverse health conditions. Physical problems often stem from inadequate nutrition, restricting growth and increasing disease risk. Neurobiological and psychological effects can also increase risk of a range of behavioral and mental health problems

Childhood impacts

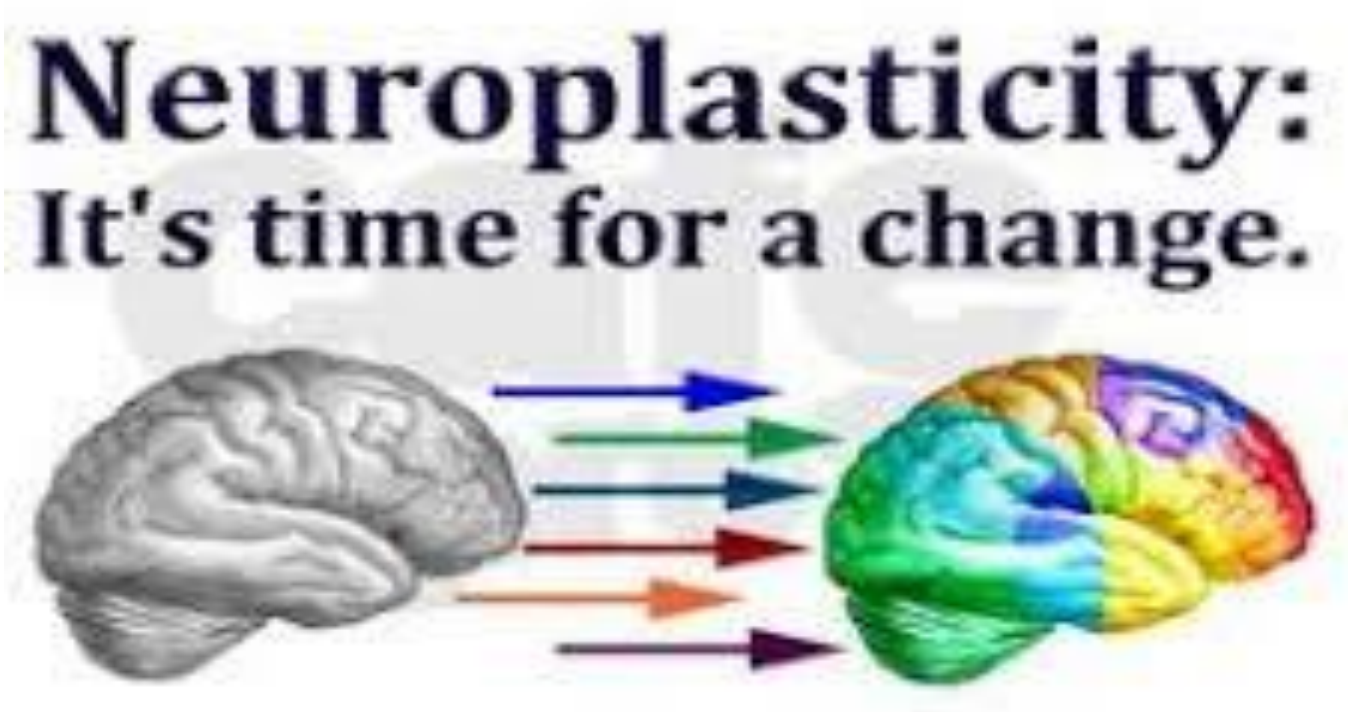
Chronic obstructive pulmonary disease	Suicide attempts
Somatic symptoms	Cannabis use
Skeletal fracture	Suicidal ideation
Hepatitis or jaundice	Injected drug, crack cocaine, or heroin use
Cancer	Violence perpetration
Cardiovascular disease	Violence victimization

Disruption of the development of brain architecture and other organ systems can increase lifelong risk for physical and mental disorders. Such impacts can be observed across multiple systems, affecting cardiovascular, immune, metabolic and brain health, and may extend far beyond childhood, affecting life course health

Adult impacts

- A balanced approach to understanding how genes and environmental conditions interact, is to focus on the study of resilience and risk factors.
- When there is a balance between protective and risk factors there is a healthy neurodevelopmental pathway. On the contrary, when there are delays or deviation on the neurodevelopmental pathways the person has a much higher chance of having a neurodevelopmental disorder, which may start in the first childhood years or much later in life.

- **Early life programing** can be the target for prevention of neurodevelopmental disorders by manipulating the environmental protective and risk factors.


Neuroplasticity:
It's time for a change.