

A Detailed Review of Factors that Influence Early Brain Development

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AUTHOR BIO

Kishan Patel is a student in Houston, Texas and has lived there all his life. In school, he is part of the Pre-Medical Sciences program and has taken the following classes: Medical Terminology and Public Health. He is also a member of the Medical Mindset and American Red Cross clubs, in which he further enriches his passion for medicine. Outside of school, he attended the University of Texas at Austin Sports Medicine Camp, in which he learned about the anatomy and physiology of the musculoskeletal system and about several techniques used in the field of sports medicine. Most recently, he was accepted into a research practicum program in neuroscience and psychology. He participated in seminars about the role of the brain in memory and prepared a seminar presentation himself. Through this, he authored this research paper about the factors that influence early brain development.

ABSTRACT

This paper aims to explore the different factors that affect brain development. Early neurodevelopment hinges on several brain processes. Neurons and supporting glial cells have to form inside the neural tube and migrate after doing so. An insulative layer forms around the midsection of the neuron as a part of its maturation and further development. From matured neurons, neural networks are formed which store information that is first learned, then repeatedly retrieved. However, overproduction leads to cell death, which keeps networks functioning efficiently. External influences can be manipulated to help the efficacy of brain development. The factors that influence neurodevelopment on the neurological scale and that are crucial in paving the way for ideal brain maturation will be analyzed.

Keywords: *Brain development, Brain maturation, Neurodevelopment, Glial cells, Neurons, Neural networks.*

INTRODUCTION

Millions of neural connections are created every second during the years of brain development, from birth up until the late stages of adolescence. In these early stages, the brain is vulnerable to a variety of factors that can all impact the instrumental processes that must occur. By ensuring that adequate brain development occurs in the few formative years of life, one can be guaranteed to have a fully functioning brain with ample neural activity during adulthood.

Having ample neurodevelopment is crucial, because although one may not always be cognizant of the processes of the brain, it is constantly having to adapt to the environment. Such adaptations revolve around a singular concept: the neural network. Within this complex, there are billions of nerves; on an even smaller scale, however, there are neurons, the cells or building blocks of nerves.

In order to understand the developmental processes of the brain (Prado and Dewey, 2014) and how certain factors can affect such processes, one needs to know the basic anatomy and function of a neuron. On one end of a neuron is the dendrite, which receives informational signals from neighboring neurons. These signals, known as chemical substances called neurotransmitters, are sent from the axon, which is the middle section of a neuron. When a neuron's resting potential is brought to a high enough voltage by excitatory inputs, an action potential, which is electrical activity, fires across the entire length of the axon, causing the neurotransmitter to be released. After this has occurred, the signal passes through the ends of the nerve ending, called axon terminals, and into the synapse. This is a junction between two neurons where the signal travels and is received by the dendrite of an adjacent neuron, starting

the cycle again.

Returning to the topic of neurodevelopment, the above illustrated functioning of neurons, and, in turn, of nerves and neural networks is what the vital processes of brain development center around. Starting from infancy, they all occur to build and rebuild a complete brain throughout the lifespan. If neurodevelopmental processes were to not happen, entirely formed neural networks would be nonexistent, and information could not be properly retained and retrieved. Because of the intricacy of the brain, as was mentioned before, certain factors play into the efficacy of brain processes, and, therefore, neurodevelopment itself. Prenatal and postnatal nutrition, infections, and social exposure are all factors that heavily influence early brain development.

Prenatal and postnatal nutrition

One factor in neurodevelopment is prenatal and postnatal nutrition. Having adequate nutrition is key to ensure that early brain processes are able to occur with as much success as possible. Five processes and a select amount of nutrients correlating to the efficacy of such processes will be discussed. Proliferation, occurring primarily during the pregnancy period and shortly after, is brain cell division.

The two overarching categories of brain cells are neurons and glial cells, which are a part of neurons and regulate their function. The start of proliferation happens in the neural tube after it is formed from the neural plate, a process called neurulation. Within neurons, axons and dendrites must mature in order to communicate with each other and form neural networks. This process, similar to proliferation, begins in utero, but continues into early infancy. Important components of neural networks are the synapses that allow for neurotransmission.

Formation of synapses in different brain areas takes varying amounts of time, which is the explanation for why certain functions are fully learned at certain ages. Because the number of synapses formed is more than necessary, synaptic pruning occurs, in which many are eliminated based on their usage frequency. This happens in parallel with synapse formation, throughout life until adolescence, to reach the desirable amount (Oppenheim, 1991).

For neurotransmitters to efficiently pass-through axons, an insulative myelin sheath needs to form around it. Myelination occurs from the gestational period and continues until infancy, as certain brain areas and corresponding skills develop. For example, because myelin forms around axons in the parts of the brain responsible for spatial awareness before those oriented with the senses and communication, such skills mature in accordance with how the brain develops. Lastly, brain cells are overproduced similar to how synapses are. Apoptosis, the final of the neurodevelopmental processes going to be discussed, is intentional cell death that occurs to ensure that the ideal number of both neurons and glial cells are present. As synapses are produced between neurons, certain neural paths become obsolete, leading to apoptosis, which refines neural networks down to only what is necessary. The intake of specific nutrients during both the prenatal and postnatal stages can affect the above explained processes (Prado and Dewey, 2014).

Deficiency of Energy

Fetuses with Intrauterine Growth Restriction (IUGR) have been shown to have less brain cells and, therefore, less neuron proliferation (Tolsa et al., 2004). IUGR is caused by a lack of nutrients for the fetus, explaining why a lack of energy nutrients might result in this and disrupt a vital neurodevelopmental process.

Young infants with energy malnutrition have had less dendritic maturation and branching. This can lower the activity and complexity of neural networks, which can harm the early acquisition of skills associated with brain development. In rodents, having a lack of energy during both pregnancy and the early postnatal period causes changes in the amount of synapses present, damaging neural activity (Jones and Dyson, 1981). Myelination has been found to be less prevalent in animals with IUGR and with mothers who have been malnourished. Lastly, a decrease in neurotrophic factors (e.g., BDNF and IGF-1) that are associated with neuron production and development has an inverse effect on apoptosis. A restricted diet, in baboons, caused such factors to deplete and, in turn, increased cell death (Prado and Dewey, 2014).

Fatty Acids

Neurogenesis (neuron production) requires phospholipids, derived from fatty acids, to occur. A deficiency in DHA, a type of fatty acid, for a fetus has been shown to decrease neuron proliferation. In addition, omega-3 fatty acids situated in cell membranes near synapses modulate the formation of synapses and transmission through them. Lastly, because myelin is a substance rich with fatty acids, myelination declines in correlation with a deficiency of fatty acids during the prenatal and postnatal stages of rodents (Prado and Dewey, 2014).

Iron

The enzyme, ribonucleotide reductase (RNR), is responsible for proliferation and DNA synthesis, which is vital for any cell to function. Because RNR requires iron, a deficiency of iron during the gestational and newborn periods of rodents produces a smaller hippocampus. Similarly, dendrites are shortened (Jorgenson et al., 2003), and synapses remain undeveloped

and inefficient (Jorgenson et al., 2005) in the hippocampus, as a result of an iron deficiency, in rodents. Myelination rates do also correlate with iron intake. That is, sub-optimal iron levels decrease myelination. It is important to note that the harm induced on dendrite and synapse maturation and myelination by iron depletion could not be repaired with iron repletion (Prado and Dewey, 2014).

Iodine

Fetuses exposed to insufficient amounts of iodine were shown to have a smaller brain mass, which connects with the fact that neuron proliferation influences the size of the brain. In addition, an iodine deficiency in utero has been shown to reduce dendritic activity and connections to other neurons in several parts of the brain. Similarly, a deficiency of iodine in sheep caused a smaller number of synapses to be present. Regarding the thyroid gland, because iodine intake influences its activity, hypothyroidism, as a result of iodine deficiency, depletes synapse levels and activity. An iodine deficiency, lastly, causes little to no myelination in fetuses, sheep, and rodents (Prado and Dewey, 2014).

Zinc

Zinc is important in DNA synthesis, and, therefore, neuron proliferation. This concept is reflected by the fact that a zinc deficiency of a fetus results in decreased neuron proliferation. Also, in rodents, less dendritic branching was witnessed due to a zinc deficiency. On the contrary, an increased concentration of zinc in the cerebral cortex and hippocampus causes a decrease in synapse formation and function, rather than having a direct correlation on synapse production. This is so because zinc can prevent synapse strengthening (Huang, 1997). Lastly, a deficiency in zinc causes a decline in IGF-1, in turn, altering natural apoptosis (Prado

and Dewey, 2014).

Choline

Choline is a nutrient vital in stem cell production, which can be later differentiated into brain cells. By supplementing choline intake, in rodents, proliferation further increases. On the other hand, a deficiency in choline affects synapse function, namely, neurotransmission. Acetylcholine, a derivation of choline, can power neurotransmission; choline deficiency, therefore, lowers neurotransmission. Apoptosis also unnaturally increases in the hippocampus of rodents due to choline inadequacy (Prado and Dewey, 2014).

B-vitamins

Although folic acid and vitamin B12, two types of b-vitamins, do not have a direct effect on proliferation, they do on the formation of the neural tube. Because cells differentiate within it and a deficiency of such vitamins is known to cause defects of the neural tube, b-vitamins are necessary for adequate proliferation. Vitamin B6 deficiency reduces dendritic connections in multiple parts of the brain of rodents, decreases synaptic density, and reduces myelination. Overall, the deficiency of just one vitamin has been shown to disrupt the entire structure and function of neurons and neural networks (Prado and Dewey, 2014).

Infections

When an infant is exposed to an infection, neurodevelopment can be greatly affected. Almost half of the infants born from HIV-infected mothers have a chance of being vertically infected (Newell et al., 2004). As this issue became increasingly prevalent, solutions were brought about and adapted. Currently, what is recommended is a lifelong antiretroviral treatment for all pregnant females with HIV. Regarding brain development, HIV-exposed

children have had higher rates of suboptimal birth conditions before antiretroviral treatment. An increased chance of neurological mitochondrial dysfunction in HIV-exposed children was also present in one study. What HIV exposure does maternally is elicit immune responses, which, in turn, cause uncontrollable immune responses in children. This relates to neurodevelopment in that alterations in white matter and unusual neuron projections were seen. Relating to the effect of infection on brain development, the differences noticed between HIV-exposed and HIV-unexposed children will be discussed (Toledo et al., 2021).

Outcomes of Children who are HIV-exposed and HIV-unexposed

Studies have been conducted that report impaired development in HIV-exposed children compared to the general population. Young HIV-exposed children have been shown to perform worse cognitively and in terms of motor skills. On the topic of abnormal birth conditions, HIV-exposed children with autism spectrum disorder (ASD) have greater amounts of white blood cell mitochondria (Budd et al., 2018). This associates a seen dysfunction in HIV-exposed children with disease related to affected brain development. In utero, important brain processes are occurring, but HIV-exposed children have a higher likelihood of being born preterm, disrupting vital maturation. Despite antiretrovirals having success in treating HIV, cognitive and motor neurodevelopmental aspects were seen to be inhibited in exposed infants. Deficits in understanding and expressing language were also seen in HIV-exposed infants (Toledo et al., 2021).

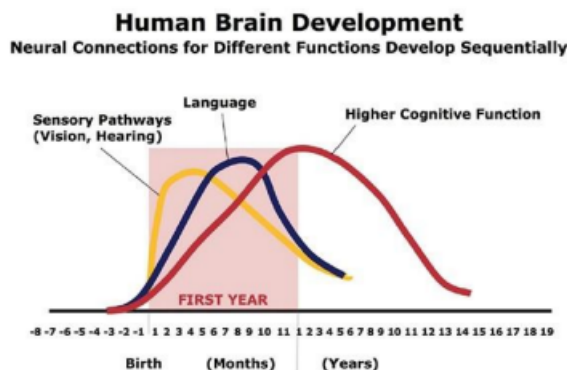
Contrary to the impairments of HIV-exposed children outlined above, other studies, having used treatment, have witnessed no major differences. When Nevirapine, a non-nucleoside reverse transcriptase inhibitor (NNRTI) or

non-competitive enzyme inhibitor, was used for protection against vertical transmission, postpartum brain outcomes were reported to be identical between HIV-exposed and unexposed children. General antiretroviral therapy equalized the developmental performances of the two as well. Lastly, when brought to terms, HIV-exposed children presented without any deficits in brain development (Toledo et al., 2021).

Social Exposure

Social exposure is another, very different factor that affects neurodevelopment in that it hinges on interactions and experiences with others and the outside world. A child cannot be isolated in order for them to have complete brain development. Rather than staying idle, children learn best by being active. Actions representative of certain language better translates to understanding such language than just reading or hearing it (Pica, 2014). For example, engaging a child in climbing *up* a ladder or crawling *through* a tunnel may better stimulate learning of such prepositions, rather than just reading to a child those words. Social interactions should also take place to build vital parts of the brain and the neural networks within them. This basic learning serves to build a brain foundation that can later be modified and expanded upon. Primary brain development occurs in the first five years of life; the overarching processes at certain age periods (see Figure 1) and how aspects of social exposure relate to them will be outlined (E. Berkley and R. Berkley, 2016).

Figure 1 (First Discoverers, 2022)



3 to 9 months

During this early postnatal period, apoptosis is occurring. Engagement is crucial in order to repeatedly activate and strengthen neural pathways. If this did not occur frequently enough a foundation would not be properly built to be accessed in the future. Because the infant is acclimating to the environment, the five senses (seeing, hearing, smelling, tasting, and touching) are used greatly. This, in turn, strengthens the neural connections between each sense organ and the brain. Specifically, regarding the eye, cells in the retina become developed and start transmitting photons through synapses to the occipital lobe, which is correlated with vision (E. Berkley and R. Berkley, 2016).

10 to 14 months

Shortly after the five senses become utilized, their neural associations still continue to build. The actions of crawling and walking, with assistance, are reinforced, improving motor skills and the corresponding brain cortices. Further environmental familiarization builds the immune system and several organ systems as they have to fight illnesses. Not only is one's overall health fortified, a memory of the internal actions and external feelings associated with sickness is created, which can be retrieved. More communication occurs, primarily by gesturing, that leads to language acquisition from associations made with actions. At this

stage, improving on the developmental skills explained above and building full-body function is difficult without adequate exposure. Everything learned and remembered is associated with a memory, but they cannot be formed without attributes to correspond them with. Experiences derived from exposure are such attributes (E. Berkley and R. Berkley, 2016).

15 to 24 months

At this point, not just the legs are being involved, but the hands more so, as well. Synapses and neural pathways associating actions with the hands to the brain are activated just as they were and are continuing to be with the legs. Memories of learning movements with the hands are created and will be constantly accessed and strengthened as motor skills improve, turning into habit. In correspondence with the increased usage of the hands, play becomes more vital as infants aim to understand how objects work ("15-18 months: toddler development," 2022). Experimentation with the environment translates into memories of how certain objects function, which will be retrieved again and again as one comes into contact with such objects. Lastly, social activity becomes increasingly important as infants learn to stimulate areas of the brain for language (E. Berkley and R. Berkley, 2016).

2 to 3.5 years

Development gets to be more complex during this stage as the infant starts to associate the five senses with experiences. One obtains a deeper understanding of objects in the environment by learning their unique attributes and stimuli. Pertaining to the environment, a toddler becomes more spatially aware; one's motor skills are advanced enough to move and view objects in all dimensions. As in the prior periods, social interactions are vital. However, now children must retrieve and

express past experiences to resolve problems, whose memories will be stored in neural pathways as well (E. Berkley and R. Berkley, 2016).

3.5 to 5 years

Although interactions with other children, not just through language but with gestures as well, have already been occurring, during these years, the concepts of negotiation and sharing are learned. As with all the previously acquired skills, these two are associated with experiences and stored as memories which are called upon in the future. The brain continues evolving to function in everyday life and to react and grow from experiences. Synapses strengthen and prune (synaptic plasticity) in accordance with knowledge being both recalled and unused. One becomes more independent alongside the neurodevelopment that occurs from exposure. In all, development over the ages is information being learned and either retrieved or purged. Social exposure is indispensable when it comes to having a well rounded brain development. The structure of neural networks constantly adapts to experiences faced in everyday life (E. Berkley and R. Berkley, 2016).

Conclusion

Having an adequate amount of certain nutrients, protecting from neurodevelopmentally harmful infections, and staying active and socially engaged are important to ensure that the brain grows to become and adapts to remain fully matured. Firstly, the primary processes of brain development were discussed. The effect of not having the optimal amount of certain nutrients, both during the prenatal and postnatal periods, on such processes was explained. Secondly, a comparison between HIV-exposed and unexposed children was made, in regard to their overall success in neurodevelopment. Lastly, a timeline, from early postpartum to age

5, of the importance of social exposure as it relates to brain maturation was displayed. The brain, despite much research, still remains one of the most mysterious organs in the human body. What really are the “perfect” decisions to make, taking into account all the known and unknown factors of neurodevelopment, to yield the ideal, fully formed brain?

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