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Early nutrition and cognitive functions

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Abstract
Majority of the brain growth and development occurs during the first 1000 days of life i.e. from conception till two years. This period is known as the critical period. Animal and human studies suggest that under nutrition during this critical period can adversely affect brain growth and development. Human studies carried out among preterm/full-term infants born with IUGR/VLBW/SGA reveal that early under nutrition may impact key cognitive functions such as – attention, memory, visuo-motor, visuospatial and executive functions. Nutritional supplementation during the critical period along with psychological stimulation may aid in preventing cognitive deficits in undernourished children and those at-risk.

Keywords: critical period, brain, nutrition rehabilitation, environmental enrichment

Introduction
The first thousand days of life i.e. from conception up to two years of age are regarded as a 'critical period' for adequate growth and development, both physical and mental. Worldwide, 22.2% of the children are stunted [1]. Most of undernourished children are from under-developed and developing countries. They are highly susceptible to infections and are likely to experience delay in attaining the developmental milestones. As a result of this, children may have poor scholastic performance which adversely influences their productivity and economic growth in the later years of life. Chronic malnutrition also endangers the nation's economic growth. In view of this, it is necessary to understand the relation between nutrition during the early years and cognition.

Growth and Development of the Brain
The growth and development of the brain begins *in utero*. Human gestation is divided in to - the embryonic stage (conception till eighth week) and fetal stage (ninth week till term). The brain begins to develop in the embryonic stage i.e. from third week post conception. By the end of the embryonic stage, the main structures – brain, spinal cord and peripheral nervous system (PNS) are established [2, 3, 4]. The fetal stage is a critical period for the development of the neocortex, the outer layer of the cerebral hemispheres. The fetal stage is marked by extensive neurogenesis, migration of neurons, formation of neuronal processes (axons and dendrites), arborization (dense population of dendritic branches in and around each cell) and synaptogenesis [2, 5, 6].

Brain development continues in the postnatal life too. In the postnatal period, major development occurs from birth up to first two years of life. At birth, the infant's brain is approximately 400 grams i.e. 25% of the adult brain by weight [7]. The total brain volume increases by 101% in the first year followed by 15% rise in the second year of life. Likewise, the volume of cerebral hemispheres increases by 88% during infancy and by 15% in the second year of life. Amongst the various brain structures, maximum increase during the first year is seen in the cerebellum (i.e. by 240%) [8]. By the age of two, the brain reaches almost 80-90% of the adult size [9]. Neurogenesis that begins in the prenatal period continues after birth although the pace is slower than earlier[6]. The highlight of the postnatal brain development is the proliferation and differentiation of glial cells which proceeds rapidly after birth and continues even in the adult brain. Glial cells support and insulate the neurons by creating the myelin sheath. The main function of myelin is to accelerate the conductivity of impulses along the axon [2, 5, 6]. The general pattern of adult myelination develops by the end of two years [10].

Synapses grow rapidly during the prenatal and postnatal life. Alongside, there is systematic elimination of some of synapses through a process called synaptic pruning or sculpting. In simple words, it is the 'use it or lose it' process. This depends heavily on the levels of presynaptic activity. For instance, with minimal activity/stimulation, synaptic connections get diluted. On the other hand, stimulation releases neurotrophic factors that help the presynaptic and postsynaptic interconnections to grow more tightly [3, 11]. This is the basis of learning and memory and hence, essential for neurodevelopment [2]. Sculpting continues throughout the lifecycle but the rate decreases with age.

Critical Period of Brain Growth
As early as 1969, Winick [12] analyzed brains of 31 dead foetuses and/or infants ranging from 13 weeks gestational age to 13 months postnatal age. The DNA content of the brain was seen to increase linearly in the prenatal period, which tapered down at around birth and again peaked at about one year of age. In humans, the period of brain spurt or 'the vulnerable period' or 'critical period' is said to begin in the third trimester and extends to almost two years of age. The period of growth spurt excludes the phase of neuronal proliferation. This does not mean that the phase of neuronal proliferation is unimportant or less critical. In humans, neuronal growth occurs under a highly protected environment and hence it is not included in the brain spurt. Therefore, many do not recognize neuronal proliferation as a 'vulnerable period'.

Early under nutrition and the Brain

Under nutrition during critical periods of brain growth (prenatal and postnatal) can adversely affect various structural facets of the brain. This may bear an impact on the development of cognitive functions.

Effect of Prenatal Growth Restriction on the Brain

Owing to ethical and practical concerns, animals and not humans have been used as models for experiments to study growth and development of the brain. Therefore, findings of the animal studies have been used to understand the human brain development.

Studies have been undertaken to examine the effect of prenatal under nutrition on brain development and structure in animal models of intrauterine growth restriction (IUGR) and maternal protein restriction. Cha *et al*. [13] studied the effect of mild and severe IUGR on brain growth at birth in rats. On the first day of life, the brain weight of control and mild IUGR was similar. But, the weight of the brain of severe IUGR rats was significantly lower than that of controls. Moreover, the DNA, protein and lipid content of brain of IUGR rats were significantly lower than that of controls. Mallard *et al.* [14] induced IUGR at 30 days gestational age in guinea-pigs. At one week of age, as compared to the control group, the IUGR-induced animals showed 16% reduction in total brain weight ($p < 0.01$). In the hippocampal region, there was a significant decrease in CA1 pyramidal neurons ($4.19\pm0.43\times105$ v $5.20\pm0.44\times105$, $p < 0.01$) and 21% drop in the volume of stratum oriens layer above CA1 region which contains apical dendrites. In the cerebellum, there was significant decrease in the number of Purkinje neurons, internal granular layer and the volume of cerebellar white matter.

In another study on rats, Gressens *et al.* [15] studied the effect of early maternal protein restriction on the postnatal brain development. The rats were fed either 5% or 20% casein diet at conception and during first two weeks of the gestation period. In the first two weeks after birth, the animals showed delayed astrocytogenesis, abnormal neuronal differentiation, abnormal synaptogenesis and delayed apoptosis.

Thus, when models of prenatal protein restriction as well as IUGR were immediately analyzed after birth (day 1 or within a week), they showed reduction in brain weight, decreased neuronal number and alterations in the structure of dendrites in the hippocampus region.

Effect of under nutrition during the Critical Period on the Brain

Animal Studies: In rats, under normal and healthy circumstances, the critical period is said to occur when the DNA content and the protein: DNA ratio (i.e. the protein content in each cell) increases in the postnatal period day 10 to day 21 after which it tapers off [16]. The increase is observed earliest in the cerebellum followed by cerebrum and hippocampus and brainstem. Considering this, the brains of the experimental animals were structurally analyzed at varying postnatal ages to study the effect of under nutrition.

Fish and Winick [16] restricted the food intake of newly born rats who were later sacrificed by day 21. The increase in the cell number was curtailed in the areas of cerebellum, cerebrum and hippocampus. In addition, the increase in the protein/DNA content was hindered in the brainstem.

Ahmad and Rahman [17] studied the effect of moderate and severe under nutrition during suckling on rats born to normally fed and undernourished mothers. When rats born to normally fed mothers were subjected to moderate under nutrition during suckling, no significant difference was seen in the brain weight, nucleic acid content and phospholipid levels. Thus, the pups appeared to be resistant to mild nutritional deprivation imposed during suckling period. However, in response to severe under nutrition during suckling period, significant reduction was seen in the body weight, brain weight, nucleic acid content and phospholipid levels of the brain. But these significant reductions were not corrected with nutritional rehabilitation during the weaning period. Similar findings were noted when rats born to malnourished mothers were subjected to moderate or severe under nutrition during suckling.

Likewise, Cha *et al.* [13] observed that when mild IUGR pups were under fed for the first two weeks of life, their brain weights were similar to normally fed control pups with higher DNA content and lower protein: DNA content. However, under fed severe IUGR pups had lower brain weight than normally fed control pups with higher DNA content, lower protein and lower protein: DNA content. This emphasizes on the impact of under nutrition during the critical period of suckling. Thus, severe under nutrition during the critical period of suckling altered the brain composition in both groups of the pups, those who were undernourished and adequately nourished during gestation.

Diaz-Cintra *et al.* [18] studied the hippocampus of rats born to undernourished mothers who were fed on 6% casein diet. These rats after birth were fed by well-nourished mothers who received 25% casein diet up till day 15. Rats were sacrificed by day 15. They observed a drop in the number of neurons, somal size and length of the apical dendrites in the CA3 pyramidal cells of the hippocampus. It is important to note that the pups in this study were nursed by well-nourished mothers till day 15. However, as discussed earlier, the critical period of growth lasts from day 10 to 21. This means that the pups did not receive optimum nutrition throughout this vulnerable period and were sacrificed early during this period. This could have influenced the findings of the study.

In simple words, when under nutrition occurred during suckling or if it continued from the prenatal period in to the immediate postnatal period, it adversely affected the brain growth. Thus, under nutrition during suckling can hamper the brain growth and chemistry.

Human Studies

Human studies conducted in late 1960s and early 1970s suggest that severe malnutrition during infancy resulted in reduction in the number of cells in the cerebrum, cerebellum and brain stem [19, 20]. Further, infants with severe malnutrition who died in the first year had reduced amount of total lipid content, cholesterol and phospholipid in the cells [21].

In the previous decade, studies were undertaken to examine the structural abnormalities of brain in preterm infants or children with IUGR and/or those who had very low birth weight (VLBW). The IUGR infants at birth showed significant reduction in cortical gray matter (CGM) and intracranial volume (ICV) as compared to the controls [22]. Lodygensky *et al.* [23] observed that the total hippocampal volume was significantly reduced in the IUGR group. Hippocampal volume also showed a significant correlation with birth weight ($r=0.507$; $p=0.008$). Furthermore, the head circumference correlated with ICV ($r=0.86$; $p<0.01$) and

CGM (r=0.76; p<0.01) [22]. In the above discussed studies, the participants were born at a gestational age of < 32 weeks. Thus, prematurity and IUGR appear to have a significant impact on the brain development. In contrast to this, Fearon *et al.* [24] found no significant difference in the whole brain volume, cortical gray matter and hippocampal volume of VLBW adults with the control group. This study however, did not specify if the subjects were born preterm or at term. This suggests that preterm babies are more likely to have a sustained structural deficit than the term infants. The final trimester of gestation is indeed crucial for structural development of the brain.

Effect of IUGR/VLBW/SGA/LBW on Cognitive Functions in Humans

Several prospective studies on cognition have been conducted among children born with IUGR, VLBW, SGA and LBW.

Table 1: Effect of IUGR/VLBW/SGA/LBW on Cognitive Functions in Humans

Author	Subjects	Tools	Outcome
Tolsa *et al.* [22]	28 preterm infants	Assessment of Preterm Infant Behaviour (APIB)	IUGR infants recorded lower scores than controls in attention-interaction. CGM at term significantly correlated with the attention-interaction capacity (r=0.45; p<0.05)
Geva *et al.* [25]	110 IUGR born children	Visual Auditory Digit Span tasks (VADS), Rey Auditory Verbal Learning Test (Rey-AVLT), and Rey Osterrieth Complex Figure Test (ROCF).	At 9 years, IUGR born children at had significantly lower digit span (p < 0.001), immediate recall (p = 0.024) and delayed recall (p < 0.002), lower in certain executive functions – visual attention (p < 0.001), form fluency (p < 0.001) and Tower of London (p < 0.014) than the controls
Lodygensky *et al.* [23]	13 preterm infants	APIB	The total hippocampal volume significantly correlated with mental developmental index (MDI) at 24 months corrected age (r=0.516; p=0.034)
Chaudari *et al.* [26]	161 LBW infants	Raven's Progressive Matrices	At 18 years, preterm SGA children had the lowest IQ than the full-term SGA and AGA, though it was within the normal range
Lohangen *et al.* [27]	59 SGA and 81 controls adults aged 20 years	Wechsler Adult Intelligence Scale	SGA group had lower full IQ scores than the control group (−6.3; 95% CI, −2.8 to −9.7; P = .001)
Ostgard *et al.* [28]	58 SGA and 81 non-SGA	Comprehensive neuropsychological test battery	SGA-born adolescents had significantly lower visuo-motor and visuo-spatial functions (p < 0.01), lower auditory immediate memory scale (p < 0.01), lower excutive functions than the non-SGA participants at 19 – 20 years of age (p < 0.01)
Starnberg *et al.* [29]	285 LBW children (2.0 – 2.5 kg)	Wechsler Intelligence Scale for Children (WISC IV), Beery–Buktenica developmental test of Visual–Motor Integration (Beery VMI), and Test of Everyday Attention for Children (TEA-Ch)	At 7 years, LBW children had lower verbal comprehension IQ (104 vs. 107, P=0.004), lower VMI scores (96.5 vs. 100, P=0.028), and lower total mean TEA-Ch scores (8.5 vs. 9.7, P=0.006), compared to controls

Overall, children born with IUGR, VLBW and SGA scored lower than the normal birth weight controls in several cognitive functions. Systematic review and meta-analyses carried out among IUGR/VLBW children have also reported similar findings [30, 31, 32]. Some studies indicate that these deficits may last even during adolescence and later. Thus, under nutrition in fetal i.e. during the critical period were vulnerable to poor cognitive outcomes.

Effect of under nutrition after the Critical Period on the Brain: Evidence from Animal Studies

Ahmad and Rahman [17] observed that when the pups born to and nursed by malnourished mothers in large litters were deprived of protein after the weaning period (postnatal day 21), they had significantly lower brain weight, DNA and RNA content than the controls. On the other hand, post weaning under nutrition in pups born to and nursed by normally nourished mothers, had a fall in the cholesterol content of brain but not the levels of phospholipids. The accretion of sphingomyelin is believed to occur from 10 to 70 days and that of ethanolamine happens till 100 days. The total process of myelination continues throughout the adult life. As a result, absence of nutrition hampered the lipid content of the brain. Furthermore, significant reductions were seen in the RNA content of the brain. It was suggested that the decrease in the RNA content led to reduction in the cell size and resulted in lower brain weight. However, no significant difference was observed in the DNA content as compared to the controls. The lack of difference in the DNA content can be attributed to the fact that cell division in pups is completed by day 21. Under nutrition induced after this critical period bears no influence on the cell number (i.e. DNA content). Thus, under nutrition post weaning resulted in a decrease in the lipid content and the cell size (RNA content) but not the cell number (DNA content).

Likewise, the pups born to malnourished mothers had recovered from the early insult when they were nursed by normally-fed mothers. This suggests that the effects of prenatal malnutrition disappeared with rehabilitation during the suckling period. The brain thus, appears to positively respond to rehabilitation immediately after birth. The suckling period i.e. up till day 21 is referred to as the critical period of brain growth in rats. The process of cell division is almost complete by this time and hence no difference was noted in the cell number (i.e. DNA content). Thus, post-weaning under nutrition in previously well-nourished rats

only negatively influenced the cell size and not the cell number.

Effect of Nutritional Rehabilitation on Brain Development: Evidence from Animal Studies

Some studies have examined the effect of nutrition supplementation on the brain growth in undernourished rats. The brain being heterogeneous in nature, different regions may be affected differently. It all depends on the cellular events that occur when the stimulus (under nutrition) was active.

Gressens, *et al.* [15] studied the effect of early prenatal under nutrition (5% casein diet) imposed during conception and first two weeks of gestation. At the end of the period of malnutrition, the fetal body weight and brain cortical thicknesses were lower than the control. At birth, body weight and brain weight had normalised. Moreover, it was observed that in the prenatally protein-restricted adult animals, all the features of brain growth and development - astrocytogenesis, neuronal differentiation, synaptogenesis and apoptosis had normalized. Thus, it was seen that prenatal protein restriction may induce transient period of multiple alteration in brain size and development. But in spite of this early insult, all the alterations observed early in the fetal life were seen to normalize in the adulthood. This suggests that the brain is capable of enormous plasticity in the postnatal life after an early insult.

Diaz-Cintra *et al.* [18] fed female rats with either 6% or 25% casein diet five weeks before conception. After delivery, the pups were randomly cross-fostered to 25% casein-receiving dams. At day 90 and 220, there were significant reductions in the length of the apical dendrites, basal dendritic branching and dendritic spine density in the hippocampus in the pups born to malnourished dams. At the same time, there was significant increase in apical dendritic branching. In this case under nutrition began in the prenatal period and was followed by nutritional rehabilitation. In spite of the rehabilitation, significant structural reductions were noted in certain parameters. This indicates that prenatal malnutrition can have long-term effects on the developing brain. Nutritional rehabilitation did show positive effects in the branching of apical dendrites. This suggests that the rate of cell division and the pattern of growth is region specific and cannot be generalized [16]. Bedi [33] studied the impact of nutritional rehabilitation on rats who were undernourished between 16th day of gestation and 30 postnatal days of age. Nutritional rehabilitation was initiated after 30 days of birth. By 212 days of age, the control group (adequately nourished) had significantly higher number granule cells in the dendate gyrus than the undernourished group. Under nutrition was induced in the prenatal period and lasted through the suckling period (till postnatal day 21) i.e. the vulnerable period. The critical timing of the insult thus resulted in long-term deficit in the total number of dendate gyrus granule cells.

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Lessons from the Animal Studies

Animal studies indicate that when malnutrition occurs in the critical period i.e. during the period of cell division, it disrupted the process of cell division.

- If rats were rehabilitated during this phase, catch-up was evident in certain areas especially cell number and lipid content.
- If rehabilitation was initiated after the period of cell division, recovery does not take place.
- If under nutrition occurred post the end of cell division then, there was no effect on the cell number or DNA content of cell. However, there was decrease in the protein: DNA ratio. But this change can be reversed on subsequent refeeding [17].

In another study, previously undernourished rats were nutritionally rehabilitated between 150 to 250 days of age. The number of synapses in the dorsal lip of dendate gyrus was estimated. Findings showed that up to 75 days of age (i.e. prior to rehabilitation) the control group had significantly higher number of synapses than the undernourished group. By the end of the study period, the previously undernourished rats who received nutritional rehabilitation showed significantly higher number of synapses and synapse: neuron ratio than the controls [36]. This suggests that previously malnourished rats were capable of some 'catch-up' in the ratio of synapse: neurons post nutritional rehabilitation.

Impact of Catch-Up Growth on the Cognitive Functions in Humans

Cognitive deficits pertaining to IQ were seen to be attenuated when the IUGR infants achieved complete catch-up growth [25]. Geva *et al.* [25] observed that academic achievements were much lower in IUGR children who failed to document catch-up growth by the third year of life. Moreover, children whose either height or weight or head circumference caught up but the catch-up growth was not evident in all the parameters (i.e. weight, height and head circumference) performed worse than the children who documented catch-up in all the three parameters at the age of 9 years.

Further, Crookston *et al.* [35] analysed the complete data of 8062 children of Young Lives study (Peru, Ehtopia, Vietnam and India). The children were classified as – not stunted, stunted in infancy but not in childhood, stunted in childhood and stunted in infancy as well as childhood. At 8 years, as compared to those who were never stunted, the Maths scores of the persistently stunted and recovered groups were significantly lower (effect sizes: 0.22 – 0.48 and 0.12 – 0.21 respectively). Also, the children who were stunted in childhood and those who were persistently stunted had significantly lower reading comprehension scores (effect sizes: 0.24 – 0.38 and 0.05 – 0.37 respectively).

Sokolovic *et al.* [36] studied the effect of government subsidized lunch of 300 grams of cooked rice and lentil for a period of six months on children aged 6 – 12 years. At baseline, significant differences were seen in short-term memory ($p = 0.023$), retrieval ability ($p = 0.026$), visuospatial ability ($p = 0.028$) and overall cognitive score ($p = 0.006$) in the stunted and the non-stunted children. However, no difference was seen in the magnitude of change between the two groups in any of the domains.

The critical period of growth for humans begins in the third

trimester of pregnancy and continues till two years of life. The deficit in growth if not corrected during this period can adversely affect the brain growth and functions. Sokolovic *et al.* [36] failed to document any difference in the stunted and the non-stunted groups. This could be due to the age of of the children and the short duration of supplementation.

Impact of 'Nutritional Supplementation Alone' on Cognition

Earlier, the relationship between under nutrition and cognitive development was believed to be linear. Researchers assumed that under nutrition in early life caused structural damage to the brain leading to poor cognition. Levitsky and Barnes [37] conducted experiments on rodents to study the effect of nutrition and environmental interactions on behavioural development. They observed that the malnourished rodents lacked energy, withdrew from the peers and other objects. Mothers of these rodents cuddled them thus preventing further growth and independence.

Based on these observations Pollitt and colleagues [38] designed a longitudinal study in rural areas of Guatemala, Central America. Pregnant women and children under the age of seven participated in the study received either 'Atole' (11.5 g protein; 163 kcals) or 'Fresco' (59 kcals) from 1969 – 77. As compared to the infants born to the Fresco group, infants born to the Atole consuming group showed a 69% drop in the infant mortality. Furthermore, growth rates of children under three improved with Atole. These children were again followed up during 1988 – 89 to examine the effects of nutritional supplementation during pregnancy on intellectual development in the long-term. Children who received Fresco grew slowly, experienced gradual recovery from infection as compared to Atole group. In addition, their motor development (for eg. crawling, walking and so on) was hindered resulting in limitations in exploring their physical and social environment. This delayed the acquisition of cognitive skills. Contrary to this, the Atole consuming group grew faster, had lower incidence of malnutrition, received more challenges from the physical and social environment which in turn promoted social and cognitive skills. In spite of this, when compared with the children of the middle-income households of the same area, the Atole group, who lived in extreme poverty did not perform as well as them. Thus, nutritional supplementation alone could not completely compensate for the negative effects of poverty on cognition.

Role of Environmental Enrichment on the Cognition

The brain is considered to be malleable during infancy and early childhood than later in life. This malleability enhances the ability and capacity to learn and overcome the earlier deficits in brain functioning. This is also known as plasticity of the brain [2]. Plasticity is defined as the adjustment of the brain to internal and external milieu. Plasticity has been seen in many 0neural systems but, is most evident in the immature cerebral cortex. In the cerebral cortex, neural plasticity is more prominent in regions related to higher-mental-processes such as – language, mathematical ability, music and executive functions. On the other hand, areas concerning voluntary motor movements, visual and auditory information processing are said to be less malleable [2].

Derrington *et al.* [39] reported that rats in the 'enriched environment' had an increase in the total cortical thickness and length of the cortex as compared to those in the standard condition. This increase was attributed to the rise in the nerve cell size, number of cells, dendritic arborization, length of the dendrites, size and number of synapses and length of postsynaptic thickening in the occipital cortex and the visual cortex [40, 41]. There was increase in the hippocampal neurogenesis and decrease in the apoptotic cell death. In addition to this, there was increase in spine densities in hippocampal CA1 pyramidal cells in hippocampus [40].

Researchers have studied the impact of environmental enrichment (EE) provided up to two years of age on the cognition of children with severe malnutrition [42, 43, 44, 45]. Stimulation showed marked improvements in the cognition of malnourished children. Follow-up studies evaluated the benefits of providing stimulation at a young age and it's effect on IQ, educational attainment during childhood [45], middle [43] and late adolescence [44]. Significant improvements were seen in verbal scores, performance IQ and school performance of the malnourished children. Also, these children had fewer behaviour difficulties than the groups that did not receive stimulation [45]. Similar improvements have been documented when such interventions were used in poorly resourced areas [46] and when mothers of undernourished babies received the intervention [47]. Thus, it is clearly evident that early psychological stimulation positively influences and bears long-lasting impact on the cognitive function in malnourished children.

Conclusion

Nutritional supplementation during the vulnerable period (i.e. from third trimester to two years of age) is seen to be effective in preventing stunting below age of two years and also cognitive deficits in childhood and later. Supplementating children who are already stunted at two years may not be effective. However, providing psychological stimulation to stunted children does appear to improve the cognitive functions and educational attainment. This beneficial effect of stimulation on cognition can be attributed to the unique feature of neural plasticity. Plasticity is also reported in adult brain. Nevertheless, it is true that plasticity decreases with the increasing age.

In view of this, timing of corrective and/or preventive measures to avoid permanent cognitive deficits is extremely crucial. The 'vulnerable period' should in fact be viewed as a 'window of opportunity' to prevent and/or correct under nutrition and the cognitive deficits. Thus, efforts need to focus on the nutrition and care during first 1000 days of life, in particular third trimester to two years of age, to ensure a healthy and enriching future for every child.

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