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Issues in the timing of integrated early interventions: contributions from nutrition, neuroscience and psychological research

Theodore D. Wachs[a], **Michael Georgieff**[b], **Sarah Cusick**[b], and **Bruce McEwen**[c]

[a]Purdue University

[b]University of Minnesota

[c]The Rockefeller University

Abstract

A central issue when designing multi-dimensional biological and psychosocial interventions for children who are exposed to multiple developmental risks is identification of the age period(s) in which such interventions will have the strongest and longest lasting impact (sensitive periods). In this paper we review nutritional, neuroscience and psychological evidence on this issue. Nutritional evidence is used to identify nutrient sensitive periods of age-linked dimensions of brain development, with specific reference to iron deficiency. Neuroscience evidence is used to assess the importance of timing of exposures to environmental stressors for maintaining neural, neuroendocrine and immune systems integrity. Psychological evidence illustrates the sensitivity of cognitive and social-emotional development to contextual risk and protective influences encountered at different ages. Evidence reviewed documents that the early years of life are a sensitive period where biological or psychosocial interventions or exposure to risk or protective contextual influences can produce unique long-term influences upon human brain, neuroendocrine and cognitive or psychosocial development. However, the evidence does not identify the early years as the sole sensitive time period within which to have a significant influence upon development. Choice of age(s) to initiate interventions should be based on what outcomes are targeted and what interventions are used.

Keywords

Early Intervention; sensitive periods; iron deficiency; stress; developmental risk; brain

Introduction

Evidence documents that children from low income families in both wealthy[1] and low income countries [2] have greater exposure to multiple biological and psychosocial risks that can significantly compromise their development. These findings emphasize the importance of integrating and implementing multi-dimensional biological and psychosocial

Corresponding author: Theodore D. Wachs, Dept of Psychological Sciences, Purdue University, West Lafayette, Indiana. 47907. 765: 494-6992 (office), 765: 496-1264 (fax), wachs@psych.purdue.edu.

interventions to compensate for exposure to multiple risks.[3] A critical and long-standing question involves identifying the age period(s) in which such interventions can have the strongest and longest lasting impact. The concept that the early years of life are a time when children are particularly sensitive to extrinsic influences has deep seated roots, dating back to the writings of Plato.[4] In the present era questions involving timing of events and change over time in relations between contextual elements are central issues in major developmental theories such as Developmental Systems Theory [5,] and the Bio-ecological Model. [6.]

Initial empirical support about the importance of the early years of life came from 20th century embryological research on fetal development and ethological research on imprinting, which culminated in the concepts of "critical" and "sensitive periods" of development. While both concepts refer to age periods characterized by plasticity in development, where the impact of exposure to facilitative experiences or developmental risks is particularly strong and lasting, the concepts are not identical.[7] Critical periods are characterized by enhanced sensitivity to exposures which are restricted to a sharply defined time period such that the impact of exposures during this time period are irreversible. In contrast, when sensitive periods are occurring the exposure time windows for enhanced sensitivity are broader, there can be continued, though reduced, plasticity both before and after the sensitive period and exposure during sensitive time windows are not necessarily irreversible. [8]

Evidence from human level studies favors the operation of sensitive rather than critical periods.[9–12] Research findings also indicate that there may be multiple sensitive periods depending upon the domains of development assessed. [9,10,13] Illustrating the operation of multiple sensitive periods is evidence that sensitive periods for neural development may be narrower than sensitive periods for behavioral development [14,15] and that different sensitive period windows are seen for cognitive/academic versus social-emotional outcomes[16,17]. For example, the impact of exposure to poverty (or to interventions designed to reduce poverty) upon later cognitive or academic outcomes appears to be strongest in the period from infancy to early childhood, whereas such exposure appears to adversely impact on social-emotional development or behavior problem outcomes across the age span from infancy through adolescence [18]. One implication of this pattern of findings is that different time periods may be needed for biological versus psychosocial interventions or for different psychosocial outcomes.

The primary question addressed by this paper is whether the early years of life are a sensitive time period for implementing integrated biological and psychosocial interventions to promote the development of children living in poverty in low and middle income countries? To address this question we will review evidence from nutrition, neuroscience and developmental psychology on timing of exposures to biological or psychosocial influences and neural, physiological and behavioral outcomes. In this paper the early years are defined as the time span between fertilization and the end of the fifth year of life. Our rationale for age 5 years is based on evidence that lower developmental trajectories during this time period are a significant precursor for poor school readiness and subsequent inadequate school performance as well as later cognitive and social-emotional problems.[2] In addition, although we relate defined time periods to specific outcome dimensions, we

recognize the validity of the conclusion drawn by developmental systems theorists that different outcome dimensions are linked in such a way that changes in one outcome can result in changes in other outcomes.[5]

The Timing of Nutrition and Brain Development

Optimal overall brain development in the prenatal period and early years of life depends on providing sufficient quantities of key nutrients during specific sensitive time periods. While all nutrients are important for brain development, certain nutrients (eg, protein, long chain polyunsaturated fatty acids, iron, copper, zinc, iodine, folate, choline and vitamins A, B6 and B12) have particularly large effects early in life and exhibit critical or sensitive periods for neurodevelopment (for more details see supplementary on-line table A). These periods coincide with the times when specific brain regions are developing most rapidly and have their highest nutrient requirements. Because the brain is not a homogeneous organ there is not a single common growth trajectory or a single sensitive period.[9] Rather, different brain regions (e.g., the hippocampus, striatum, cortex) and brain processes (e.g., myelination) exhibit growth trajectories that span and peak at different times, each with specific nutrient requirements. These periods of peak growth are also those times when the deficiency of a specific nutrient, particularly one that supports basic neuronal/glial metabolic processes (e.g., protein, iron, glucose), is most deleterious. Supplementation of a deficient nutrient after these sensitive windows of development have passed usually results in incomplete correction of the brain insult and thus in an increased risk of long-term neurodevelopmental deficits. Defining the timing of these peak periods of nutrient requirement for certain brain areas is critical for the successful implementation of nutritional interventions to prevent harmful, potentially permanent effects of deficiency on brain development.

Sensitive periods for specific nutrients (Table 1) are typically identified in controlled studies of pre-clinical models at different stages of early development and subsequently validated with successful nutritional intervention studies in humans that yield beneficial neurobehavioral outcomes in the domains identified in the preclinical models. The literature on early iron nutrition serves as an example of how such multi-disciplinary studies work in concert to demonstrate that timing affects a nutrient's relationship with the developing brain.

Iron Deficiency

Iron deficiency is the most common nutritional deficiency worldwide, with an estimated one billion people having iron deficiency anemia.[19] The developing brain requires iron for enzymes and hemoproteins that regulate cellular processes, including fatty acid production, dopamine neurotransmitter synthesis, and neuronal energy production.[20,21] The peak periods of brain vulnerability to iron deficiency are those where a high demand for iron coincides with a time period when iron balance is likely to be negative (Table 1). This includes the fetal/neonatal period and infancy/toddlerhood (6 months to 3 years), two time periods where iron deficiency has profound and long-lasting effects and where supplementation has proven to be an effective deterrent of later impairment. It is important to note that while early adulthood is also a period of high risk for negative iron balance, brain development at this time is slower, and thus brain demand for iron is relatively low. Accordingly, iron deficiency in women between 18 and 35 years may cause acute effects, but these effects appear to

resolve with restoration of iron status, with no apparent long-term neurobehavioral consequences.[22]

Newborn infants with iron deficiency from late gestation demonstrate recognition memory deficits indicative of impaired hippocampal function, slower processing speed potentially indicative of reduced myelination, and altered temperament characterized by poorer infant-mother interaction and suggestive neurobiologically of altered dopamine metabolism.[23–25] Infants with postnatal iron deficiency anemia show fewer learning and memory effects, but do display slower speeds of neural transmission in auditory brain stem responses and visual evoked potentials, consistent with hypomyelination.[26, 27] Iron deficiency later in toddlerhood leads to impaired social emotional behavior, including maintaining closer proximity to caregivers, increased irritability, and decreased positive affect.[28,29] Iron deficiency at this time appears to particularly affect the brain's monoaminergic system, i.e. neurochemistry, and these behavioral changes may not be remediable with iron therapy.[20, 30]

Animal studies corroborate the effect that the timing of iron deficiency in infancy vs. toddlerhood has on neurobehavioral outcomes. Rodent models of gestational/lactational vs postnatal dietary iron deficiency reveal variable impairments in spatial navigation, trace fear conditioning, and procedural memory, all consistent with functional and structural abnormalities in the hippocampus and striatum, as well as abnormalities in myelin formation and monoamine regulation based on the timing of the deficiency.[31–39] A differential timing effect is also seen in rhesus monkeys, where late gestational iron deficiency results in a less fearful and more impulsive animal, while postnatal iron deficiency results in a more inhibited and anxious one.[40]

Iron Supplementation

Studies of iron supplementation in pregnancy and childhood reinforce these findings and demonstrate that the importance of timing in intervention studies cannot be overstated.[41–44] When the period of high brain demand for iron coincides with a period of high risk for iron deficiency, as in the fetal and toddler periods, neurodevelopmental consequences are more likely to occur. Accordingly, these periods are optimal for iron intervention (for more specific details see supplementary on-line table B). Prenatal iron supplementation appears to particularly set the stage for postnatal iron and brain health. Iron/folic acid supplementation during pregnancy results in significantly better scores in working memory, inhibitory control, and fine motor functioning in children at 7 to 9 years of age.[43] In contrast, daily iron/folic acid with or without zinc supplementation of children from age 12 to age 35 months, whose mothers do not receive micronutrient supplementation during pregnancy, has no effect on intellectual, executive, or motor function at age 7–9 years.[44] Moreover, supplementation of children from 12–36 months whose mothers receive iron/folic acid during pregnancy confers no additional cognitive benefit over prenatal iron/folic acid alone.[42]

While 12–36 months of age is both a period of peak vulnerability to iron deficiency and brain demand for iron (supplementary on-line table B), the brain system exacting the greatest need for iron at this age is the monoaminergic system. Iron supplementation between 12–36 months would thus potentially lead to improvements in socioemotional

behavior, but significant improvements in cognitive, intellectual, and motor functioning--the domains tested by the researchers—would necessitate earlier supplementation.

Implications for interventions

The established sensitive periods of brain development for each nutrient should guide the timing of implementation of nutrition interventions to ensure optimal brain development. Nutritional health of the offspring is related to maternal nutritional health even prior to the time the child is conceived. Many important brain systems (eg, the hippocampus, myelination, synaptogenesis) that are dependent on adequate nutritional supply are maturing in the fetus in the last trimester. Thus, nutritional, medical and social interventions that ensure a healthy, low-stress pregnancy optimize nutrient delivery to the developing fetal brain. In the postnatal period, earlier screening and identification of nutrient risks/deficits is critical since the preponderance of data shows earlier nutritional intervention is more effective in promoting long-term brain health. When developing these interventions, four key principles must also be considered to achieve significant neurobehavioral results:

- 1). The nutritional intervention must be given concordantly with when the nutrient is most needed, e.g., iron supplementation during pregnancy or early infancy to achieve improved cognitive or motor outcomes in later childhood;
- 2). The target population must not already be sufficient in the nutrient. No evidence exists that nutrient delivery greater than that which is needed to ensure sufficiency will provide additional neurobehavioral benefit;
- 3). The behavioral or cognitive battery used to assess outcomes later in childhood must be appropriately specific (i.e., assess potentially affected neural circuits) and not be too global such that subtle differences will not be detected;
- 4). The timing of the assessment battery must also be carefully considered. A null result in response to intervention may be found if the test is administered too late, and the child outgrew a previous nutritionally induced brain deficit, either by neural plasticity or catch-up growth.

Text Box 1

Nutrition and brain development in the first 1000 days

1. Brain growth and development is highly dependent on adequate nutritional substrates for that growth. While all nutrients are necessary for the growth of cells, including those in the brain, certain nutrients appear particularly influential: protein, energy sources including glucose, fats including long-chain polyunsaturated fatty acids (aka fish oils), iron, zinc, copper, iodine, folic acid, choline and vitamin A. Deficits in nutrients can cause the brain to function abnormally during the period of the deficit. These deficits appear to be related to alterations in brain metabolism.
2. Some nutritional deficits confer long-term structural and functional abnormalities well beyond the period of deficit suggesting that the brain has been permanently altered. These deficits appear to be related to structural

changes (i.e., not having built the brain correctly) and genomic (e.g., epigenetic) changes that alter long-term regulation of brain function.

3. The brain is not a homogeneous organ. Rather it is characterized by interconnected regions each of which has a different developmental trajectory. The times of most rapid development (i.e., cell growth and differentiation) define the time of greatest nutrient needs. Thus, the timing of nutrient provision or deficiency determines how the structure develops and ultimately how it functions. A given nutrient deficit at one age may result in quite different developmental effects than the same nutrient deficit at another age. These findings imply that critical/sensitive windows exist for many of these systems and that these windows are tightly linked to periods of rapid regional brain growth and differentiation.

4. The majority of brain growth that is nutrient sensitive occurs in the first 1000 days from conception. Ensuring the delivery of specific nutrients coincident with growth spurts that are dependent on those nutrients should shape dietary and nutritional intervention policy. As a blanket approach, overall nutrient sufficiency is most important for the pregnant woman, the newborn infant and the toddler to ensure long-term brain health in the offspring.

5. Provision of nutrients represents only the supply side of the equation. The metabolic status of the recipient, including the presence of illness and psychological stress, will alter how growth factors are regulated and how nutrients are utilized. Thus, factors that mediate stress (see next section) are also important with respect to the effectiveness of nutritional therapy in promoting brain growth.

Timing of stress for brain and neuroendocrine development and function

Stressful experiences throughout the life-course and resulting health promoting or damaging behaviors have an impact on metabolism and can be regarded as “nutrition sensitive”. In response to a changing social and physical environment, the body and brain respond to novelty and potential threats by activating autonomic, neuroendocrine, metabolic and immune system responses that promote adaptation. This process, called “allostasis” helps to maintain homeostasis and is primarily dependent on the brain to perceive and react to novelty and potential threats and activate the coordinated mediators of allostasis. When this mechanism is overused by many stressful events, and especially when the balanced responses of the network of allostasis are dysregulated, then wear and tear on the body ensue, referred to as “allostatic load”. This concept has relevance to the intersection between metabolism, stress responsiveness, and malnutrition in the sense of both quality and quantity of food, are very much involved.

Text BOX 2

Allostasis and allostatic load

The brain is a target of allostatic load as is the rest of the body. Depression, anxiety disorders and substance abuse are expressions of this load along with cardiovascular disease, Type 2 diabetes and metabolic syndrome and other disorders that reflect the consequences of chronic stress in terms of poor sleep, overeating, smoking, drinking and lack of physical activity.[45] Allostatic load changes architecture of regions of the brain involved in cognition and emotional regulation, including shrinkage of the hippocampus that can be reversed by regular, moderate exercise.[46,47] In animal models, chronic stress is also associated with shrinkage of dendrites in the medial prefrontal cortex as well as hippocampus and dendritic growth in the basolateral amygdala and orbitfrontal cortex.[46,48]

Chronic stress becomes toxic and has its greatest impact to produce the greatest allostatic load when the individual lacks sufficient control of his or her life due to inadequate social, emotional or material resources.[49] Moreover, adverse events in early life predispose the brain and body to greater vulnerability to stress throughout the life course.[49,50] Prenatal stress of the mother is known to increase anxiety behavior of the offspring and alter brain structure and function, including impaired development of the hippocampus.[51,52] Prenatal stress in humans is associated with shorter telomeres in offspring along with behavioral and metabolic dysregulation that includes increased risk for metabolic disorders related to low birthweight.[53–55] There are also possible epigenetic effects that are transmitted from the parents to the offspring.[56,57]

Early life events related to maternal care in animals, as well as parental care in humans, play a powerful role in later mental and physical health, as demonstrated by the adverse childhood experiences (ACE) studies and other recent work. A summary of evidence on findings from animal studies are seen in supplementary on-line text box A. At the human level one of the consequences of ACE is an increased prevalence of metabolic disorders, obesity and diabetes that may reflect both quantity and quality of food as well as how the body processes it.[50] Food insecurity may be an added factor [58] along with the stressful nature of an ugly and dangerous neighborhood living environment influencing obesity and increasing allostatic load.[59,60] In studies on ACE in human populations, there are reports of increased inflammatory tone, not only in children, but also in young adults related to early life abuse, that includes chronic harsh language, as well as physical and sexual abuse.[61,62] Chaos in the home is associated with development of poor self-regulatory behaviors, as well as obesity.[63] An ACE study carried out in a middle class population indicates that poverty is not the only source of early life stressors.[50]

Nevertheless, low SES does increase the likelihood of stressors in the home and neighborhood, including toxic chemical agents such as lead and air pollution.[63–65] Low SES children are found to be more likely to be deficient in language skills, as well as self-regulatory behaviors and also in certain types of memory that are likely to be reflections of impaired development of parasylvian gyrus language centers, prefrontal cortical systems and

temporal lobe memory systems.[66,67] Low SES also correlates with smaller hippocampal volumes.[68] Lower subjective SES, an important index of objective SES, is associated with reduction in prefrontal cortical gray matter.[69] Growing up in a lower SES environment is accompanied by greater amygdala reactivity to angry and sad faces, which, as noted above, may be a predisposing factor for early cardiovascular disease that is known to be more prevalent at lower SES levels.[70,71] Furthermore, depression is often associated with low SES, and children of depressed mothers, followed longitudinally, have shown increased amygdala volume while hippocampal volume was not affected.[72]

On the positive side, there are the “reactive alleles” that, in nurturing environments, lead to beneficial outcomes and even better outcomes compared to less reactive alleles, even though those same alleles can enhance adverse outcomes in a stressful early life environment.[73–75] Regarding adverse outcomes and good and bad ”environments”, it must be recognized, as stated in the Active Calibration Model, that allostatic processes are adjusted via epigenetic influences to optimize the individuals adaptation to, and resulting fitness for, a particular environment, whether more or less threatening or nurturing.[76] Yet, there are “trade-offs” in terms of physical and mental health that, on the one hand, may increase the likelihood of passing on one’s genes by improving coping with adversity and enhancing mental health and overall reproductive success, but, on the other hand, may impair later health, e.g., by eating of “comfort foods”.[77] Nowhere is this all more important that during adolescence, which is a time of transition in physiology and brain development and maturation.[78,79]

Adolescents have a propensity for risk-taking that is related to the capacity to exert self-control, as can be assessed by tests of delayed gratification such as the “marshmallow test” that have considerable predictive power for social, cognitive and mental health outcomes over the life course.[80,81] The neural basis of self-regulation involves frontal-striatal circuitries that integrate motivational and control processes and appear to be stable for a lifetime, based upon studies of the same individuals over 4 decades.[82] A key feature is an exaggerated ventral striatal representation of appetitive cues in adolescents relative to the ability to exert control. The connectivity within the ventral frontostriatal circuit including the inferior frontal gyrus and dorsal striatum is particularly important to the ability to exert self-regulation.[83] Moreover, adolescents are typically somewhat impaired in fear learning but at the same time impaired in fear extinction, which implies that they may take more risks [84] and that, when there is a traumatic event, they may be more affected by this including the possibility that this carries over into adult life. [85,86]

Box 3

Brain development transitions in adolescence

Animal models are giving important clues. During adolescence, chronic juvenile stress consisting of 6h daily restraint from postnatal day 20 to 41, produced depressive-like behavior and significant neuronal remodeling of brain regions likely involved in these behavioral alterations, namely, the hippocampus, prefrontal cortex and amygdala. Chronically stressed males and females exhibited anhedonia, increased locomotion when exposed to novelty, and altered coping strategies when exposed to acute stress. Coincident with these behavioral changes, there was stress-induced shrinkage of

dendrites in the hippocampus and prefrontal cortex and concurrent hypertrophy of dendrites in the amygdala and impaired development of the hippocampus carrying into adult life. [87,88]

The human prefrontal cortex undergoes a prolonged course of maturation that continues well after puberty and parallels a slowly emerging ability for flexible social behavior.[89,90] Interestingly, there are differences within the cerebral cortex in heritability. Primary sensory and motor cortex, which develop earlier, show relatively greater genetic effects earlier in childhood, whereas the later developing dorsal prefrontal cortex and temporal lobes show increasingly prominent genetic effects with maturation.[91]

It is also noteworthy that the prefrontal cortex (PFC) to amygdala connectivity changes from positive to negative between early childhood and adolescence and young adulthood.[70] Indeed, young children are wary of strangers as secure attachment to the mother develops. One index of this sensitive period is that, early in life, ambiguous facial expressions are perceived as conveying negative meaning.[92] However, during adolescence, there is a restriction on extinction of fear learning, suggesting that negative experiences may have greater impact during that developmental period, although it is not yet known whether fearful events during adolescence may be more difficult to extinguish later in adult life.[85]

Finally, it is important to note that early life adversity in rhesus and humans impairs development of the PFC, among other effects in the brain and body. In rhesus, peer rearing causes changes in 5HT1A receptor density in a number of brain regions including PFC and is associated with an enlarged vermis, dorsomedial PFC, and dorsal anterior cingulate cortex without any apparent differences in the corpus callosum and hippocampus.[93,94] In humans, adverse childhood experiences were associated with smaller PFC, greater activation of the HPA axis, and elevation in inflammation levels compared to non-maltreated children, while adults with a history of childhood maltreatment showed smaller PFC and hippocampal volume, greater activation of the HPA axis, and elevation in inflammation levels compared to non-maltreated individuals.[95]

There is also increased risk for obesity and metabolic disorders, including Type 2 diabetes. Indeed the developing as well as adult brain is vulnerable to metabolic dysregulation such as occurs in Type 2 diabetes and pre-diabetes. The brain responds to metabolic hormones such as insulin, leptin, ghrelin and IGF-1.[96] In adults both pre-Type 2 diabetes and diabetes causes the hippocampus, a brain region important for learning and memory and mood regulation, to shrink and, with it, there is impairment of memory and mood.[97–99] There is also increased risk for later Alzheimer's disease.[100] Moreover, many of these problems begin in childhood and teenagers with pre-Type 2 diabetes and diabetes have impaired neural architecture and cognitive function.[101,102] This has potentially huge implications for success in school and acquiring skills for the increasingly technical workforce, with a growing impact on national competitiveness as well as soaring health care costs.

Major conclusions- stress and adaptation

1. The brain is the central organ of stress and adaptation to stress and does so through the autonomic, neuroendocrine, immune and metabolic systems, via the active

process of allostasis. The brain is itself a target of the dysregulation and overuse of allostasis resulting in allostatic load and overload, which also is manifested in the body as cardiovascular disease, diabetes, arthritis and other disorders that commonly increase with age.

2. Brain architecture is altered by stress so as to weaken brain regions involved in learning, memory and self-regulation but strengthen brain regions important for anxiety and aggression. However, the brain is normally resilient and able to recover after stress, but this resilience is impaired with aging and also in mood and anxiety disorders.

3. Adverse experiences in childhood exert lasting effects on physical as well as mental health. Animal models reveal long lasting changes in brain architecture via epigenetic processes that involve behavioral transmission from the parent to the child as well as modifications of DNA without changing the genetic code that are passed on in the germ cells and *in utero* in the developing fetus. Early life adversity also increases the level of inflammation in the body that lasts into adulthood and contributes to increased incidence of mood and anxiety disorders, substance abuse, sexual precocity, cardiovascular disease and diabetes.

4. Adolescence is a time of major changes in brain architecture, particularly the prefrontal cortex that controls self-regulatory behaviors and, as a result, adolescence is a time of vulnerability to stress. Childhood obesity and diabetes that may result, in part, from early life adversity, affects brain development, cognitive function and learning ability as well as increasing the risk for dementia later in life.

5. Metabolic dysregulation related to poor quality of diet and also stress-related patterns of health behaviors, including how ongoing stress and resulting allostatic load alters food consumption and metabolic processing, have profound effects on brain development and function that are only now beginning to be appreciated.

Implications for intervention

Interventions that create a stable, consistent and nurturing parent-child bond foster the development of vital self-regulatory behaviors in which the late-developing prefrontal cortex plays a key role. The continuing plasticity of the brain offers some hope that behavioral intervention may have some beneficial effect throughout the life-course. In addressing the growing problem of obesity and diabetes, beginning in childhood, it must be recognized that these disorders take a toll on the brain, affecting the ability of individuals to function in our complex society. A promising strategy to prevent obesity involves teaching self-regulation to Head Start preschoolers [103], although including parents in such therapy is also important [104]. In addition, programs such as the conditional cash transfer in Oportunidades in Mexico offer some hope in helping poor families rid themselves of infections and adopt healthier life styles, with some reported improvements in developmental markers of cognition and improved mental health [105,106], although such programs have shown uneven effects on educational learning outcomes [107].

Timing issues in contextual contributions to cognitive or social- emotional development

As discussed previously significant neural development continues after the early years of life, particularly during the adolescent period. [84,108] Similarly, later neural changes can be influenced by current contextual characteristics.[14, 109,110] A parallel pattern of findings emerges when we consider the impact of contextual influences on cognitive and social-emotional development. Evidence on contextual influences illustrates that: (a) important developmental landmarks or precursors for later development occur both in the early years and at later ages; (b) both early and later contextual influences or interventions can influence subsequent functioning; (c) later influences or interventions may sometimes be necessary to maintain the impact of early influences or interventions. Each of these conclusions is documented in the following sections.

Rates of behavioral development

The early years. Examples of important developmental landmarks appearing during the first two years as well as precursors of later development which emerge over the first 5 years of life are shown in table 2.

Later onset of important developmental characteristics—While precursors of later development can be seen in the infancy and toddler periods early specific skills or behaviors can be lost, expanded or replaced by later developing skills. [119] For example, experience-dependent brain development in adolescence and early adulthood is thought to mediate the emergence of and increases in later appearing social-emotional, communication and cognitive functions. Developmental characteristics appearing past the early years are also shown in table 2.

Do early contextual influences or interventions impact upon children's development?

Evidence for a direct impact—As seen in table 3 findings from early intervention studies document that the early years of life are a sensitive period for preventing long-term sensory problems, for facilitating social-emotional development and for promoting child cognitive and academic competence. Results from meta-analytic studies, reviews and randomized control trials also document that interventions involving parents and carried out during the first several years of a child's life can significantly improve parental sensitivity, cognitive stimulation, discipline strategies and supportive warm parenting.[113, 128,130,131, 134] Findings also emphasize the potential importance of intervention quality [130] or parent involvement (for home based interventions) [135], given that long exposure to a sub-standard early intervention program may have limited benefits.

While findings from some studies suggest that social-emotional development may be particularly sensitive to interventions or experiences experienced during the first 3 years [113, 127–129] other studies indicate that there is no specific time window during the first 5–6 years where cognitive or social-emotional intervention effects are uniquely strong. [129,132, 136, 137] Isolation of unique sensitive time windows during the early years of

life are complicated by evidence indicating that significant early intervention effects may not show up until well after the intervention has been completed. [136, 138,139]

Evidence supporting an indirect impact—Early contextual influences also may have long-term consequences through constraining or enhancing later reactivity either epigenetically or through neural mechanisms. [49,50, 140] Similarly, developmental researchers have described five behavioral processes through which early exposure to stressors or protective factors can influence later reactivity:[141,142]

- Facilitation: positive early experiences increase the child's receptivity to positive later experiences;
- Buffering: positive early experiences protect the individual against later stress;
- Sensitization: early risk exposure increases the individual's reactivity to later occurring risks;
- Steeling occurs when successfully dealing with early stress increases later stress resistance;
- Blunting: exposure to early risks also can reduce the ability of the individual to benefit from subsequent positive influences.

Examples of each of these processes are found in supplementary on-line table C. What these five processes illustrate is that we cannot understand the impact of later occurring contextual influences or interventions without also considering the nature of the child's early context.

Are early influences or interventions uniquely sufficient?

While early experiences or early interventions can have direct or indirect long-term consequences, the evidence also shows that experiences or interventions occurring well after the early years of life also can alter subsequent development.[143] For example, interventions such as computer or martial arts training designed to promote children's executive functioning appear to have more benefit when used with 8–12 year old children than when used with 4–5 year olds. [144] Research reviews also document that increased levels of schooling can promote knowledge based skills (crystallized intelligence), biologically based information processing skills ("fluid intelligence) and specific components of intelligence such as reasoning and memory) for children from both high and low-middle income countries. [145–148] Additional findings illustrating the impact of later occurring experiences or interventions are also seen in table 3.

Are later influences necessary to maintain the impact of prior influences?

Evidence from follow-up studies—Findings from both meta-analyses and systematic reviews, encompassing both U.S, and non-U.S. small and large scale intervention studies, indicate that the stability of long-term cognitive gains, even if still remaining significant, tends to weaken over time. [131, 132, 138] Attenuation of initial cognitive gains following early intervention may result from non-intervention children catching-up in cognitive skills once they start attending primary school [131] or, alternatively, from a fadeout of initial gains by intervention children from low income groups if they attend low-quality primary schools [138]

In either case primary school influences are implicated as relevant to the stability of intervention based early cognitive gains. Educational, economic and behavioral gains or reductions in anti-social behavior resulting from exposure to small scale high dosage early interventions are more likely to be maintained over time [161] whereas gains in these areas associated with large scale shorter dosage programs are more likely to attenuate, though still remaining significant for some outcomes. [129, 132, 138,]

In addition to program dosage and scale child characteristics also play a significant role in influencing stability of early intervention gains. While children at higher levels of biological or psychosocial developmental risk have greater need for, and perhaps greater responsivity to, early intervention programs [130] there also is evidence suggesting that the impact of early intervention programs may be attenuated for children with higher levels of biological or psychosocial risk. [3, 128,162] The fading of early intervention gains in high risk populations is consistent with evidence showing that high levels of developmental risk can overwhelm the impact of normally protective influences.[163] One implication of these findings is that it may be necessary to continue interventions or provide follow-up interventions beyond the first 5 years for children with significant levels of cumulative biological or psychosocial risk exposure or children with a history of compromised development. [128, 164–167] For children with high levels of cumulative risk exposure there is a greater likelihood that initial intervention gains are more likely to be lost over time without some type of subsequent high quality follow-up intervention experience,[158, 168, 169] particularly when such children were enrolled in scaled up lower dosage early interventions. [169]

The role of "causal chains"—Whether or not there is a long term impact of early interventions also may depend on the degree to which the early intervention initiates causal chains of later occurring events which serve to maintain the impact of the early event.[142] For example longitudinal findings show not only how children's participation in a quality preschool program directly enhances cognitive skills at age 6 but also how, over time, intervention children also had a higher probability of subsequently receiving more parental and teacher educational support and involvement, were more likely to attend higher quality schools, and were are at lower risk for parent abuse or neglect, repeatedly changing schools or grade retention. [170] Path analyses illustrate how these later naturally occurring parental and school causal chain links associated with early interventions serve to influence the child's educational attainment through early adulthood.

Other examples of naturally occurring causal chains include evidence that; (a) early exposure to developmental risk factors can increase the probability of children encountering other risks later in life [142,171]; (b) early exposure to developmental risks or protective influences can shut down or open up later opportunities [128]; (c) Children's participation in early enrichment programs can increase the probability of young children being involved in follow-up interventions and can initiate changes in parental rearing styles, such as more reading to their child, or parental life changes, such as getting more education, all of which can in turn promote children's subsequent development.[128,172] When the long-term impact of early interventions depends upon exposure to later supportive experiences the concept of a single early time bounded sensitive period becomes problematical. This is because causal

chains mean that the child also must be sensitive to later occurring events if the impact of the early intervention is to be maintained.

Developmental contributions to the question of sensitive periods: conclusions

1. Critical aspects of neural and social-emotional development or precursors for later development occur during the first 5 years of life.
2. There are long-term consequences for both concurrent and later cognitive-educational and social-emotional functioning from experiences or interventions occurring during the first 5 years. Such consequences can result from either direct or indirect influences of early experiences or interventions.
3. More intense early interventions during the first 5 years or longer duration interventions may be necessary to increase the probability that early gains will be maintained over time. This is particularly true for children with a history of high levels of exposure to biological or psychosocial developmental risk factors.
4. There are significant changes in cognitive and social-emotional development occurring at least through adolescence which are linked to later developing brain regions.
5. There can be significant experience driven enhancement of cognitive and social-emotional competence in later childhood, adolescence and adulthood.
6. Some of the long-term impact of early experiences or interventions will depend on subsequent changes in the child's proximal context.

Implications for intervention

The first several years of life may be a sensitive period for promoting social-emotional development and parenting quality. The overall pattern of evidence also suggests that for cognitive/academic outcomes interventions could start during the preschool years without necessarily impacting on their effectiveness. However, when designing interventions to promote positive parenting, cognitive development or school competence a wider time window may be necessary to maintain initial gains when dealing with high risk children or multi-risk contexts. For high risk children or high risk families, the impact of early psychosocial interventions will be stronger and more durable when there are built-in experiences or follow-up interventions during the early school years as well.

Integrated conclusions and implications

Evidence from multiple disciplines documents that there can be unique long-term influences upon human neural growth, health and cognitive or social-emotional development from early biological or psychosocial interventions and exposure to risk or protective contextual characteristics. The first 3–5 years of life (including the prenatal period) appear to be a sensitive time window for ensuring adequate nutrition to promote brain development, for promoting consistent, responsive, sensitive parenting, for promoting social-emotional competencies and for providing cognitive stimulation to promote school readiness.

However, the evidence does not support the hypothesis that the early years are the sole sensitive time period within which to have a significant influence upon human development. Adolescence also is a sensitive period for continued growth of the prefrontal cortex, for vulnerability to stress and for the development of critical dimensions of executive function, perspective taking and abstract thought. Rather than a single sensitive period the evidence indicates multiple sensitive periods, with the sensitive time windows depending on rate of development of specific neural regions or behavioral functions, outcomes assessed, and the nature of the experiences encountered or interventions provided. The implication from findings reviewed here suggests that choice of age at which to begin interventions should be based on what outcomes are targeted and what interventions are used.[173] For example, for interventions involving iron supplementation (table 1) or promoting secure attachments [113] it will be important to start as early as possible, certainly within the first year, whereas starting around age 3 years would not be too late for interventions involving stimulation to promote school readiness. [128]

Further, for children living in high stress environments, or encountering multiple high risk events, or receiving lower early intervention dosages there may need to be systematic follow-up interventions to maintain the gains resulting from early interventions. For example, the functional consequences of gains in early brain development resulting from early nutritional supplementation may require building in subsequent psychosocial stimulation experiences if the nutritional intervention is to impact upon the child's school readiness and subsequent school performance. Finally, in evaluating the long-term impact of interventions it will be critical to look for both main effects and person x intervention interactions, given evidence showing that children with different developmental histories, different genotypes or different individual characteristics may react in very different ways to the same intervention package [3].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Brain regions affected by critical nutrients for brain development in the first 1000 days*

Nutrient	Period(s) of particularly high brain demand for nutrient	Principal brain region or circuitry affected
Protein	**1** Gestation **2** 4 – 12 months postnatal	**1** Global, hippocampus, striatum, myelin, cerebellum **2** Cortex (esp prefrontal), myelin
LCPUFAS	Last trimester of gestation- 2–3 months postnatal	Global, retina
Iron	**1** Last trimester of gestation **2** 6 months-3 years postnatal	**1** Myelin, striatum, hippocampus **2** Myelin, frontal cortex, basal ganglia (motor)
Zinc	**1** Last four months of gestation **2** 6 months – 10 years	**1** Autonomic nervous system, cerebellum, hippocampus **2** Cortex
Iodine	**1** First trimester of gestation **2** Last trimester of gestation **3** Infancy-12 years	**1** Global **2** Cortex, striatum, cerebellum, hippocampus **3** Myelin, prefrontal cortex
Copper	Last trimester of gestation	Occipital and parietal cortex, striatum, cerebellum, hippocampus

*All nutrients listed are critical in the first 1000 days and have their largest effects on brain development at that time; some nutrient-brain developmental time frames extend into middle childhood with milder effects of effects on different neural systems.

Table 2

Ages of emergence of critical developmental landmarks and precursors of critical developmental markers.

Early appearing developmental landmarks (birth-24 months):	Normally developing visual function such as visual acuity (primarily first 6 months, with gradual improvement to 4 years) and eye movements following repetitive movement through the visual field (optokinetic nystagmus-3–24 months). [13] Certain domains of language such as phononetic perception (seen in the first 10 months) [111] Acquisition of taste preferences (first 3 months). [112] Acquisition of basic trust and attachment (primarily seen in the 6–12 month period). [113]
Early appearing precursors (preschool and early childhood years) of later developmental landmarks	Internalization of committed compliance to adult requests as a precursor for effortful self-regulation (initially seen in the time period between 14–56 months). [114.] Developing a "theory of mind" as a precursor for taking another person's perspective (emerges around 4 years of age).[115] Understanding of the "wrongness" of moral transgressions as a precursor for later moral reasoning (initially seen in the time period from 2.5–4 years).[116] Language based perceptual categories as a precursor for later word learning (appearing around 18 months). [111] Deferred imitative play as a precursor to the development of abstract thinking (appears between 18–24 months).[117] Development of an internalized conscience or inhibiting aggressive outbursts as a precursor to effortful self-regulation (seen between 4–7 years) [118].
Later appearing developmental functions appearing in middle childhood, adolescence or adulthood.	Evaluating the comparative values of risks versus rewards as a marker of effortful self-regulation (appears between 12–20 years).[84,108.] Orientation to future goals and considering long- term consequences (appears between 11–17 years). [120] Interpersonal competencies such as taking another person's perspective (12–15 years).[117] Distinguishing between effort versus ability as primary causes or outcome success or failure (9–12 years). [121] Cognitive competencies such as: working memory (7–15+ years). [122,123] Knowledge based cognitive dimensions- "crystallized intelligence" (peaks in middle adulthood). [124,125]

Table 3

Impact of early and later interventions or exposures upon children's development.

Child outcomes:	Early exposures or interventions (infancy-early childhood):	Later exposures or interventions (middle childhood-adolescence):
Perception.	Cochlear implants for children with severe hearing deficits can have maximal impact on promoting normal sound reactions if implanted before age 3 ½ years, with diminishing gains thereafter.[126]	
Social-emotional development	Meta-analytic findings involving previously institutionalized adopted infants document the latter half of the first year as a sensitive period for promoting attachment security.[113,127] Findings suggest that the early years of life are a particularly salient time period for preventative interventions to reduce negative emotionality and behavioral problems or promote self- regulation or pro-social behaviors[128,129]	Adverse long-term consequences associated with exposure in childhood or adolescence to developmental risks such as: Societal violence;[149]; Alcohol;[150] Culturally based socialization for aggressive behavior;[151] Positive consequences associated with exposure in childhood or adolescence to positive developmental influences such as: Social support, which facilitates children's resilience after occurrence of a major natural disaster;[152] Community acceptance, which supports the adjustment of former child soldiers;[153] Treatment programs for abused children;[154] Programs to increase child pro-social behavior and reduce aggression;[155] School based programs to promote better inhibitory control; [144] Drug prevention programs[156] Programs for reducing the impact of parental divorce on offspring.[157]
Cognitive/academic competence.	Meta-analytic and review findings document that intervention during the early years carried out in either high or low-medium income countries can have long-term cognitive-academic benefits.[129–132] Meta-analytic findings and results from individual studies show at least partial benefits in cognitive and academic performance for institutionalized children adopted into high quality homes in the early years of life. [127, 133]	Attending high quality elementary schools, can promote academic achievement for children who did not attend preschool programs.[158] Validated programs to reduce learned helplessness or increase self-efficacy beliefs in children with poor academic achievement. [121] Validated interventions to promote reading skills in elementary school children.[159] School feeding programs promote some aspects of educational performance.[160]