Chapter __. Evidence on Brain Development and Interventions

Elena Grigorenko

Yale Child Study Center, Yale University, New Haven, USA

Introduction

The landscape of the child public health literature in the 21st century has been strongly influenced by the Developmental Origins of Health and Disease (DOHaD) hypothesis (Van den Bergh 2011). The hypothesis proposes that human complex diseases and disorders, regardless of their age-of-onset, have their roots in childhood and adolescence and are products of the dynamics of various forces that substantiate human development.

The human brain is arguably the most complex biological system, embodying a diversity of functionally distinct regions, structurally distinct neural circuits, and morphologically distinct cell types. Its lifespan is highly dynamic, encompassing continuity and changes at both the structural and functional levels. The brain has a unique developmental trajectory compared to the rest of the body. Whereas at birth an infant is approximately 6 percent of its adult body weight, the brain is already 25 percent of its adult weight; by age two years, these proportions are 20 percent and 77 percent, respectively (Dekaban and Sadowsky 1978). This rapid rate of growth is accompanied by a slow rate of functional maturation that extends into early adulthood. One of the major premises of the DOHaD is that both structural and functional characteristics of brain development are highly informative predictors of the lifespan ratio of health and disease**.** As the brain substantiates the behavior change, understanding its development is key in constructing and disseminating interventions that maximize healthy development and minimize the impact of disabilities and disorders.

This chapter briefly outlines aspects of the brain literature that pertain to public health interventions, programs, and policy approaches to protect, augment, and maximize the healthy development of the brain. First, the essential characteristics of brain development are outlined. Second, brain development changes associated with public health in different research are briefly discussed. The relevance of this research, conducted predominantly in high-income countries (HICs), is considered, with a view to its applicability in low- and middle-income countries (LMICs).

Development of the Human Brain

Anatomical Maturation

The human brain's maturation is remarkably prolonged and characterized by ongoing dynamic changes throughout the lifespan (Giedd and Rapoport 2010). The two main dimensions of brain development postnatally (figure __.1) are inverted U-shaped trajectories of the volumes of gray matter and white matter. Gray matter is composed chiefly of neuronal cell bodies, which determine the color, as well as dendrites, unmyelinated and relatively few myelinated axons, glial cells including astroglia and oligodendrocytes, synapses, and capillaries. White matter is composed chiefly of myelinated axons; the myelin, which determines the color; and relatively few neuronal cell bodies. In general and simplifying terms, the gray matter forms structures of the brain, whereas the white matter assures that these structures are connected; both are essential for any and all functions the brain substantiates. The gray and white matter have differential developmental trajectories; their relative proportions and rates of accumulation differ at different developmental stages and in healthy and disordered brains.

Figure 1 (pp 1-3). Developmental trajectories of brain morphometry. The data were collected from a sample of males (n = 475 scans) and females (n = 354 scans) aged 6–20 years. The figure presents mean volume by age in years by sex (boys are shown in orange). The middle lines in each set of three lines represent mean values; the upper and lower lines represent upper and lower 95% confidence intervals. All curves differ significantly in height and shape. (A) total brain volume, (B) gray matter volume, (C) white matter volume. Adapted from (Giedd and Rapoport 2010) which says Reprinted from (Lenroot et al. 2007).

By age six years, the brain reaches approximately 95 percent of its adult volume. Its size in boys is approximately 10 percent bigger than for girls; this gender difference persists throughout the lifespan, although the bodies of boys do not become larger than bodies of girls until adolescence, suggesting a decoupling of the maturation trajectories of brain and body size (Giedd and Rapoport 2010). The developmental trajectory of gray matter peaks in early childhood, preceding a peak in total brain volume, and then gradually decreases unevenly throughout the brain. The areas where the amount of gray matter peaks the earliest is in the primary sensorimotor areas, and the latest is higher-order association areas. The volume of white matter increases gradually into early adulthood. Myelination not only enhances the parameters of signal transmission; it also boosts the connectivity and networking properties of the brain. Some evidence indicates that white matter increases are coupled with the emergence of specific psychological functions, such as language (Paus and others 1999).

There has been a rapid accumulation of data on the developmental trajectories of the brain in HICs within several initiatives, such as the Brain Initiative, (https://www.whitehouse.gov/share/brain-initiative). Selected findings from these initiatives include the following:

- The shape of the age-by-size trajectories appears to be a better predictor of functional characteristics of the brain than the brain's absolute size; for example, the age-by-cortical thickness developmental curves were observed to be better predictors of IQ at age 20 years than cortical thickness (Shaw and others 2006).
- Subtle deviations from normal developmental trajectories of the brain anatomy appear to be at least associated with—if not causal factors of—a number of developmental disorders (Giedd and Rapoport 2010).
- A remarkable amount of variability of individual brain size occurs, whether across or within groups, making individualized clinical predictions difficult.
- Different areas of the brain have differential maturational dynamics. For example, the developmental imbalance between the earlier-maturing limbic system networks and later-maturing frontal systems might explain the psychological and behavioral texture of adolescence when this imbalance is being resolved (Casey, Duhoux, and Cohen 2010).
- The maturing brain is characterized by the reshaping its functional properties, particularly its connectivity, which peaks during adolescence and is defined through the physical links between co-developing brain areas, the co-activational patterns between brain areas engaged in specific tasks, and the etiological connections between brain areas that are co-influenced by the same genetic and/or environmental factors.

Functional Development

The human brain is commonly represented as a system of tiered networks of highly organized neurons, where spatiotemporal biochemical and bioelectrical activity gives specialized functionality to structural anatomic components of the brain (Power and others 2010). The connection between structure and function is bidirectional, so that specific anatomical characteristics—such as lesions, synaptic development, and myelination—parameterize the function of a particular network. The functional dynamics of the network can change physical characteristics of the underlying brain structure. From conception through the lifespan and into senescence, this system is on a developmental trajectory that is shaped by the continuous co-influence of each individual's genome and the environome (i.e., a system of environmental factors that influence human health and behavior)**.** Understanding the stability and malleability of the system is a fundamental task of modern science and the focus of a number of large-scale projects, such as the Human Connectome Project (http://www.humanconnectomeproject.org/).

As the system as a whole and each network in particular emerge developmentally, studies have traditionally assumed research into *where* in the brain a network may be localized and *how* it operates. Such research historically utilized methods of anatomical localization, for example, through brain surgery or autopsy, but these methods are of limited value in living humans. More recent methods (EEG, PET, (f)MRI, and NIRS) based on various technological advances study the brain in living humans, where the focus, along with anatomical structure, is on functional connectivity. These methods, which first appeared as technology-, skill-, cost-, and safety-demanding, have been evolving to minimize these demands and maximize safety (such as applicability to pediatric populations), transportability (such as use in minimally equipped settings), and utilization (such as usability in low-resource settings).

The current view of the developmental trajectory of the brain's functional networks and their system converges on the following:

- From infancy into young adulthood, the properties of the network change in such a way that initially strong correlations between brain activity in closely located anatomical regions tend to weaken, while initially weak correlations between more distant regions tend to increase (Power and others 2010), allowing, presumably, for the substitution of the mental and behavior functional repertoire of a newborn with that of an adult.
- This change in the distribution of correlations may be related to anatomical developmental changes in the brain: synaptic pruning (Huttenlocher 1979), i.e., the process of eliminating synapses connecting different neurons, may be the driving factor substantiating the decrease in proximal correlations; whereas myelination (Paus and others 2001), i.e., the process of forming a myelin sheath around a nerve to allow nerve impulses to move more quickly, may be the driving factor for the increase in distal correlations.
- Developmental increases in functional connectivity appear to be, at least in part, due to spontaneous or orchestrated co-occurrences of activity (Lewis and others 2009), i.e., the co-activation of different brain structures in the context of, for example, implicit or explicit learning, based on which functional connections within the brain might be established as new skills are acquired.
- Characteristics of functional networks have been associated in adulthood with indicators of intellectual performance (van den Heuvel and others 2009) and executive control

(Seeley and others 2007). Although comparable data for children are limited, a careful investigation of the developmental trajectories of brain functional networks in conjunction with other maturing systems—for example, language, cognition, and self-regulation—might enhance the understanding of human development as a systemic transformation of a maturing individual guided by the brain.

Genome-Environome Dynamics of Brain Development

Blueprint of the Genome

The development of the brain is intricately based on the apt expression (that is, the transcriptome) of integral gene products coded by sequences of DNA, the genome, specifically, protein and RNA (Tebbenkamp and others 2014). Recent analyses of the human brain transcriptome (http://www.brainspan.org) have, for the first time, allowed the construction of a comprehensive picture of the trajectories of genes associated with specific neurodevelopmental processes (figure __.2). There are time-specific strong correlations between the characteristics of the transcriptome and the morphological and functional specialization of brain regions. Alterations to DNA sequences can result in modifications of gene expression, which can cause changes in the brain and the development of brain-based disorders.

Yet, the brain is a highly open and modifiable system, as neuronal circuits, established early in life, undergo remodeling as they develop their adult functional properties in response to both genomic and environmental cues. This room for varying interpretations of a single genotype—that is, when the same genotype can exhibit different phenotypes in variable environments—is referred to as *plasticity*. The capacity of the human brain to respond to the environment and its fluctuations represents an adaptive system that allows individuals to better survive and reproduce. In other words, the brain, metaphorically, is the hub between the genome and the environome that allows for the organism's interpretations of and adaptations to genetic and environmental forces.

Figure 2 (p. 4). Timeline of major human neurodevelopmental processes based on gene expression trajectories. Expression trajectories of genes associated with major neurodevelopmental processes reflect the occurrence and progression of these processes in the human neocortex. PCW: postconceptional weeks; M: months; Y: years. Adapted from (Tebbenkamp et al. 2014), which says: The expression levels and trajectories have been adapted from Kang et al. [5].

Nutritional Requirements

As the most metabolically active organ, adequate balanced nutrition of the brain prenatally and postnatally is essential for its development and the proper maturation of the neural mechanisms substantiating child development (Gómez-Pinilla 2008). Overwhelming evidence demonstrates that malnutrition, especially when severe, has significant and lasting implications for development (Laus and others 2011). Malnutrition slows the brain's development, thinning the cerebral cortex and reducing the numbers of neurons, synapses, dendritic arborization, and myelination—all of which decrease brain size, which, in turn, challenges the brain's functional properties. Specifically, numerous cranial imaging studies of the brains of patients with protein energy malnutrition (for example, Atalabi and others 2010) have demonstrated cerebral atrophy and ventricular dilation (which, potentially, might lead to inadequate patterns of brain activity). Nutritional rehabilitation can reverse these effects, at least partially.

Similarly, adequate specific microelements are essential for developing brains. For example, both severe lack of iodine and severe exposure to neurotoxins such as lead result in irreversible brain damage (Benton 2010). Adequate concentration of vitamin A is essential for the development of the visual system; levels that are too high or too low prenatally can be teratogenic (Reifen and Ghebremeskel 2001). Moreover, complex dynamics occur among different vitamins; a prenatal imbalance between folate and vitamin B_{12} can increase the risk of postnatal insulin resistance, which is associated with poorer cognitive development (Yajnik and others 2008). The differential developmental trajectories of the brain's features means there are differential sensitive periods when the violation of nutritional requirements is most detrimental. As the brain most rapidly develops prenatally and postnatally, these two periods are especially important; yet, as brain development does not stop until the early 20s, different microelement deficiencies and malnutrition can have a lasting impact, even after early childhood.

Specific strategies—such as salt iodization to prevent iodine deficiency, home fortification to prevent iron deficiency, and food and specific micronutrient supplementation in food-insecure populations—have been shown to be effective in preventing nutritional deficiencies. Yet, the research literature that qualifies and quantifies the impact of these strategies on brain development is limited (Prado and Dewey 2014).

Environmental Experiences

Substantial evidence indicates that both gray and white matter are susceptible to environmental perturbations (Lupien and others 2009). Although the direction of the causality—from brain to behavior or from behavior to brain—is often unclear, it is indisputable that environment is a critical ingredient of change in the structure and function. For example, children who have experienced severe exposure to air pollution in South Mexico City were reported to have prefrontal white matter alterations and the precursors of Alzheimer disease (Calderon-Garciduenas and Torres-Jardon 2012).

Two environments that contextualize brain development are particularly prominent: social-economic status (SES), especially poverty (Hanson and others 2013), and early life experience in general and parenting quality in particular (Kundakovic and Champagne 2015). There is a growing field of studies into socioeconomic neurogradients, defined as neural differences associated with differences in SES (Schibli and D'Angiul 2013). For example, it has been demonstrated that low SES environments in general and poverty in particular influence the rate of human brain development (Hanson and others 2013). Specifically, children from lower SES environments differ in their gray matter accumulation in the frontal and parietal lobes, such that differences widen throughout development as the exposure to impoverished environments continues (figure __.3). Of note was that volumetric brain differences were associated with the emergence of disruptive behavioral problems (Hanson and others 2013).

Anatomical brain differences have also been associated with characteristics of prenatal and postnatal environments. For example, maternal stress prenatally is associated with decreased dendritic spine density in multiple brain areas (such as the hippocampus and the anterior cingulate and orbitofrontal cortex) substantiating emotional regulation (Murmu and others 2006). Conversely, early maternal support postnatally is strongly predictive at school age of healthy development of the hippocampus, a brain region key to memory and stress modulation (Luby and others 2012).

Figure 3 (pp. 5-7). Brain growth trajectories by age and SES. Age in months is shown on the horizontal axis, spanning from 5 to 37 months. Brain volume (A—total gray matter; B—frontal gray matter; C—parietal gray matter) is shown on the vertical axis. The colored lines differentiate children from different SES households. Adapted from (Hanson et al. 2013).

Neuroplasticity

The overriding principle of neuroplasticity is that behavioral change is associated with a specific gain or loss of synapses within neuronal networks (Caroni, Donato, and Muller 2012). Multiple factors differentiate different types of neuroplasticity in the typically developing brain (Kolb and Gibb 2014).

Neuroplasticity can be characterized as follows:

- **Experience-expectant**: when structural or functional changes in the brain require specific types of experience, for example, the maturation of binocular vision
- **Experience-independent**: when changes in the brain occur spontaneously and override its initial structure and function, for example, the development of the lateral geniculate nucleus in the maturation of the visual system
- **Experience-dependent**: when changes in the brain allow the acquisition of new behaviors, for example, all types of learning.

Neuroplasticity is related to the relevance, frequency, intensity, and sequences of experiences. It can be adaptive, as in the acquisition of a new skill, or maladaptive, as in the formation of a dependency or disorder. Of note is that changes in the brain that result from the same environmental impact, such as the injury, vary remarkably, depending on when in the developmental process the impact occurred. An experience can generate qualitatively different changes in different regions within the same brain. In addition, plastic changes themselves change over time; for example, the overproduction of synapses in the early stages of development is reversed by pruning in adolescence, which continues well into adulthood.

Skill Acquisition and Changes in the Brain

This section focuses on different behavioral loci associated with brain changes that have been or can become targets for specific public-health interventions. Only four selected loci are discussed here—early attachment, language development, acquisition of literacy and numeracy, and self-regulation.

Early Environment and Attachment

Substantial evidence demonstrates that atypical early development, in which the presence of the attachment bond between children and significant others—mothers, fathers, or primary caregivers—is disrupted, is extremely detrimental for brain and behavior development. One source of such evidence comes from research into orphanhood, when children are raised in institutions, often characterized by nutritional, physical, stimulational (that is, cognitive, linguistic, and emotional), and care deficiencies. Institutionally reared children tend to be characterized by deviations from typical brain development, in particular, a distributed network of alterations in the white matter—limbic and paralimbic pathways, frontostriatal circuitry, and sensory processing pathways (see, for example, Bick and others 2015). No comparable studies have been completed in LMICs; yet, the frequency of orphaned children in LMICs—given conflict zones, child labor, deadly epidemics and other maladies—is much higher than in HICs and, therefore, should be a priority for research.

Another source of such evidence comes from studies into the prevalence of childhood maltreatment in LMICs. For example, it has been reported that 25-50 percent of young South Africans are maltreated by family members (Pieterse 2015). In HICs, maltreatment has been consistently shown to be detrimental to brain development (Painter and Scannapieco 2013). Given the widespread opportunities for maltreatment in LMICs (Tomlinson, Cooper, and Murray 2005) due to early pregnancies, extended sibships (i.e., large numbers of children in the same home), high levels of poverty, and low levels of education, it is extremely important to identify programs demonstrated to be effective and efficacious in HICs and transportable, at least potentially, to LMICs. One such program is the Nurse-Family Partnership (Olds and others 1997), which is being transported to South Africa (Pieterse 2015).

Language Development

Language acquisition occurs during a sensitive period of brain development (Knudsen 2004). The neural signatures of language acquisition are detectable at very early stages of development (Rivera-Gaxiola, Silvia-Pereyra, and Kuhl 2005). These neural signatures, although themselves dynamically transforming, are highly predictive of numerous other indicators of child development, both linguistic and nonlinguistic.

However, children require several key elements to progress through the language acquisition process:

First, children need to be immersed in environments where they have high-frequency exposure to the language, as the mechanism thought to be most utilized is that of statistical learning, which assumes an ongoing exposure to language data so that linguistic mental representations can be inferred and automatized (Saffran, Aslin, and Newport 1996). Yet, simple exposure to linguistic stimuli, no matter how intense, is not enough.

Second, the motivation to learn language is social and requires the presence of a social context for language acquisition (Kuhl 2007). The acquisition of language engages and impacts the computational and social areas of the brain. To master language, children both capitalize on and enhance systems of cognitive and social skills (Meltzoff and others 2009). Thus, the brain-behavior pathways that underlie and follow language acquisition are highly dynamic and future-oriented as their properties predict subsequent steps in child development (Pascoe and Smouse 2012; Prathanee and others 2010a).

These conditions—statistical exposure and social context—form appropriate targets for policies to enhance typical and remediating atypical brain-behavior development. Such policies, which have been developed in HICs and are being introduced to LMICs, include the following:

- Raising public awareness of atypical development (Mahmoud, Aljazi, and Alkhamra 2014)
- Promoting professional training of specialists able to diagnose, remediate, and support individuals with developmental difficulties (Cheng 2010)
- Facilitating early identification of developmental difficulties (Glumbic and Brojcin 2012; Hamadani and others 2010; Sidhu, Malhi, and Jerath 2010)
- Advocating inclusive preschool education
- Providing additional support to children with developmental language delays (Rakap 2015) and implementing specialized intervention programs (Amato and others 2015; De Cesaro and others 2013; Erasmus and others 2013; Fernandes and others 2014; Fernandes and others 2012; Pascoe and others 2010; Prathanee and others 2010b; Kotby, El-Sady, and Hegazi 2010).

These systemic changes reflect the emerging emphasis on early child care and education in LMICs in general and language development in particular, as all are extremely important for brain development. The relevant research accumulating in LMICs has replicated findings from HICs and reinforces the crucial significance of these systemic changes (Cheng 2010; Günhan 2011; Pascoe and Smouse 2012).

Literacy and Numeracy

Numerous studies have been conducted to isolate and map the specific brain pathways or functional systems that support literacy (Dehaene and Cohen 2007) and numeracy (Butterworth and Walsh 2011). Clearly, the acquisition of these skills is based on the utilization of existing areas of the brain, which are reorganized structurally and functionally while being recycled and recruited into systems of acquisition (Dehaene and Cohen 2007). Large and burgeoning fields of research are investigating the impact of literacy and numeracy on brain functioning via (1) longitudinally tracking of children as they transition from pre-literacy and pre-numeracy stages into stages of mastery; (2) comparing groups of literate and numerate and illiterate and innumerate adults; and (3) comparing individuals with typical and atypical pathways of acquisition for literacy and numeracy. Each of these approaches is associated with its own methodological challenges, so limitations exist in the interpretations of the relevant data and findings. Yet, there is a remarkable convergence of multiple studies from different countries, including LMICs, specifying the impact of skill acquisition on brain structure and function.

Literacy

Literacy systems appear to involve brain areas substantiating early vision, script analysis, language analysis, and their mutual associations (Dehaene and others 2015). Literate individuals have been reported to demonstrate numerous advantages, compared to illiterate individuals, in the speed and accuracy of processing both letter-based and picture-based materials. The specificity of reading as a skill distinguishing literate and illiterate individuals is reflected by the fact that reading recruits a specific brain area located in the left ventral occipito-temporal cortex to become a visual word form area (VWFA)—an area that demonstrates specific, universal, and reproducible responses to script. The patterns of activation in the VWFA are correlated with the degree of mastery of reading.

Importantly, adult plasticity in this area underlies the ability to acquire print (i.e., the graphic representation of a spoken language) either in a first or subsequent languages. Also of the essence is that the VWFA is strongly connected, both structurally and functionally, to the brain areas that support spoken language. As reading assumes a conversion from vision to language, it requires an activation of the language network, or at least its component. Indeed, literate, compared to illiterate, individuals demonstrate an increased and modified activation of the language-related cortical and subcortical network (in particular, the planum temporale, PT—an area of the brain that supports, along with surrounding areas, the neuronal representations of the consonants and vowels of spoken language) while engaged in specific language- and reading-related tasks. This means that literacy acquisition not only results in creating specific systems supporting reading; it also changes other systems supporting related functions, enhancing and automatizing them. To illustrate (figure __.4), literacy enhances the connectivity between the ventral temporal lobe (including VWFA) and the inferior parietal and posterior superior temporal regions (including PT) via enhanced myelination. This strengthening may enable the automatization of the grapheme-to-phoneme conversion, crystallization of reading skills, and subsequent development of related higher-order cognitive processes, such as reading comprehension. Moreover, reading mastery has been shown to increase gray-matter density in several regions of the brain that contribute to the establishment and function of the brain system that supports literacy.

Figure 4 (p. 8). Impact of reading acquisition: Enhanced connectivity between PT and VWEA. The structural link between the visual orthographic (visual word form area; VWFA) and the auditory phonological (PT) systems is enhanced with literacy: there is an increase in the fractional anisotropy (FA) in the posterior branch of the left arcuate fasciculus in literate and ex-illiterate (i.e., individuals who learned to read in adulthood) relative to illiterate participants. This increase in FA with literacy correlates with the activation of the PT in response to spoken sentences. Error bars represent one standard error. *$p < 0.05$; **$p < 0.001$. Adapted from (Dehaene et al. 2015) which says adapted from Thiebaut de Schotten, M., Cohen, L., Amemiya, E., Braga, L. W. & Dehaene, S. Learning to read improves the structure of the arcuate fasciculus. *Cereb. Cortex* (2012) 24 (4), 989–995.

Numeracy

Although this field is considerably smaller than that of literacy studies, systemic findings include the following (Butterworth, Varma & Laurillard 2011):

- It appears that there are groups of “multiple duty” neurons located in the intraparietal cortex that respond to object dimensions such as space, time, object size, and number.
- These neurons are part of an extensive distributed network, as, similar to literacy, numeracy engages multiple processes such as early vision, motor, spatial, and mnemonic functions.
- Neuroimaging studies have converged on the intraparietal sulcus (IPS, novel numeric operations) and the angular gyrus (AG, previously learned numeric operations) as the loci of numeric processing.
- Fourth, the IPS is viewed as the foundational structure in the construction of numeric brain networks; it demonstrates structural abnormalities in individuals with the

developmental disorder of mastering numeracy—dyscalculia—and changes in gray-matter density in expert mathematicians.

The evidence that education in general and the acquisition of literacy and numeracy alters the brain structure and function comes primarily from HICs. The relevance research in LMICs is focused predominantly on documenting the manifestation of difficulties in acquiring literacy and numeracy in different languages and societies (Pouretemad and others 2011); frequencies of these difficulties (Ashraf and Najam 2014; Hsairi Guidara and others 2013; Jovanovic and others 2013) ; and the development of relevant intervention approaches (Lee and Wheldall 2011; Obidoa, Eskay, and Onwubolu 2013).

Self-Regulation

One of the ultimate goals of development is to master the skill of self-regulation (SR)—goal planning, inhibition, mental flexibility, sustained motivation, executive control, and self-agency. SR is a critical element in the dynamic system of health and disease and the key to productive adulthood and successful aging. SR is supported by a distributed brain system, whose main task is to support the adequate appraisal of the system of demands of all relevant factors on individuals and the subsequent formulation of behavior to satisfy these demands. The executive load is developmentally uniquely intensified in adolescence, and corresponding changes occur in the brain (figure __.5). These changes are related primarily to the maturation of the prefrontal cortex (PFC) and its connectivity with other brain areas as it recruits them to substantiate the system of SR.

Figure 5 (p. 9). Developmental course of brain maturation. Behavioral attributes are paralleled by hormonal and neurobiological changes that target specific brain regions and cell populations (shown in shaded gray to capture the dynamic influences of hormones, various brain processes, and myelination). Adapted from (Lee et al. 2014).

Specifically, the following changes peak in the adolescent brain (Luciana 2013).

- A general thinning of the cortex and pruning in subcortical structures (gray matter) and an increase in the volume and enhanced organization of brain connections (white matter) crescendo. This results in increasingly efficient functioning within and across brain networks.
- Heightened distinctions occur in regional brain volumes and functional brain responses to reward intensify.
- Maturation of the PFC and the SR network requires exposure to key environmental experiences, such as positive incentive and reward. Such exposures are particularly important in adolescence, because they are coupled with age-dependent experience-expectant increases in dopaminergic tone (i.e., the amount of distribution of the neurotransmitter dopamine) in the brain.

Dopaminergic signaling (i.e., the engagement of dopamine-based reward systems), exposure to uncertain and risky environments, behavioral explorations, and independence seeking are all contributors to the maturation of the PFC and the related distributed system in general and the cross-talk between subcortical (limbic) and cortical (prefrontal) regions in particular. As consolidation through learning occurs, a brain system emerges whose role is to support decision-making based on calculations of the probability and magnitude of risk and reward.

Our current knowledge regarding the development of the brain systems substantiating SR, although largely empirically based rather than explanatory, suggests several approaches for intervention. These are connected to the nature of reward responsivity, its intersection with social strivings, and socioemotional context and content. Numerous relevant intervention approaches have been developed in HICs (Rothbart and Posner 2015), but their distribution has been limited in LMICs.

Conclusions

The DOHaD hypothesis assumes continuity between the adulthood profile of health and disease and the dynamics of child development in general and brain development in particular. The hypothesis also assumes another continuity—that between interventions and sensitive periods, sicne the presence of such periods is not limited to early childhood. Although the DOHaD hypothesis has been increasingly supported by empirical evidence in HICs, the corresponding evidence in LMICs is limited.

As this empirical evidence is being accumulated, it is becoming clear that one of the ensurers of both types of continuity is the brain. The brain is an ever-changing system whose structure and function reflect, at any given time, both the endowment of the genome and the investment opportunities available in various environmental contexts, including educational systems, public-health policies, and specific intervention programs. As knowledge of the brain's developmental trajectories accumulates, the extent of the brain's modifiability, especially in response to targeted interventions, will become clearer. This understanding, in turn, will help to guide the development of intervention approaches suitable for and most effective at the sensitive periods of brain development that occur across the lifespan.

Author Note
The work on this essay was supported by NIH grants R01 HD085836 (Elena L. Grigorenko, PI) and P50 HD052120 (Richard Wagner, PI). Grantees undertaking such projects are encouraged to express freely their professional judgment. This essay, therefore, does not necessarily reflect the position or policies of the abovementioned agencies, and no official endorsement should be inferred. I am grateful to Ms. Mei Tan for her editorial assistance.

References

Amato, C. A. H., T. H. F. Santos, I. Y. I. Sun, L. Segeren, and F. Fernandes. 2015. "Serving the underserved: Language intervention to children with disorders of the autism spectrum in Brazil." *European Psychiatry* 30: 438.

Ashraf, F., and N. Najam. 2014. "Validation of Learning Disabilities Checklist in public sector schools of Pakistan." *Pakistan Journal of Psychological Research* 29: 223-44.

Atalabi, O. M., I. A. Lagunju, O. O. Tongo, and O. O. Akinyinka. 2010. "Cranial magnetic resonance imaging findings in Kwashiorkor." *International Journal of Neuroscience* 120: 23–27. doi:10.3109/00207450903315727.

Benton, D. 2010. "The influence of dietary status on the cognitive performance of children." *Molecular Nutrition & Food Research* 54: 457–70.

Bick, J., T. Zhu, C. Stamoulis, N. A. Fox, C. Zeanah, and C. A. Nelson. 2015. "Effect of early institutionalization and foster care on long-term white matter development: a randomized clinical trial." *JAMA Pediatrics* 169: 211-19. doi:10.1001/jamapediatrics.2014.3212.

Butterworth, B., Varma S., and D. Laurillard. 2011. Dyscalculia: From Brain to Education. *Science* 332(6033): 1049-1053. doi: 10.1126/science.1201536

Butterworth, B., and V. Walsh. 2011. "Neural basis of mathematical cognition." *Current Biology* 21 (16):R618-R621. doi: http://dx.doi.org/10.1016/j.cub.2011.07.005.

Calderon-Garciduenas, L., and R. Torres-Jardon. 2012. "Airpollution, socioeconomic status, and children's cognition in megacities: the Mexico City scenario." *Frontiers in Psycholology* 3: 217. doi:10.3389/fpsyg.2012.00217.

Caroni, P., F. Donato, and D. Muller. 2012. "Structural plasticity upon learning: regulation and functions." *Nature Reviews Neuroscience* 13: 478-90.

Casey, B. J., S. Duhoux, and M. M. Cohen. 2010. "Adolescence: What do transmission, transition, and translation have to do with it?" *Neuron* 67: 749–60.

Cheng, L. R. 2010. "Emerging issues in health and education in Asia-Pacific: a focus on speech-language pathology." *Folia Phoniatrica et Logopaedica* 62:238-245. doi:10.1159/000314787.

De Cesaro, B. C., L. G. Gurgel, G. P. Nunes, and C. T. Reppold. 2013. "Child language interventions in public health: a systematic literature review." *Codas* 25: 588-94. doi:10.1590/s2317-17822014000100012.

Dehaene, S., and L. Cohen. 2007. "Cultural recycling of cortical maps." *Neuron* 56: 384–98.

Dehaene, S., L. Cohen, J. Morais, and R. Kolinsky. 2015. "Illiterate to literate: behavioural and cerebral changes induced by reading acquisition." *Nature Reviews Neuroscience* 16: 234-44.

Dekaban, A. S., and D. Sadowsky. 1978. "Changes in brain weights during the span of human life: Relation of brain weights to body heights and body weights." *Annals of Neurology* 4: 345–56.

Erasmus, D., L. Schutte, M. van der Merwe, and S. Geertsema. 2013. "Speech-language therapy for adolescents with written-language difficulties: the South African context." *South African Journal of Communication Disorders* 60: 50-58.

Fernandes, F. D. M., C. A. H. Amato, D. A. Defense-Netrval, and D. R. Molini-Avejonas. 2014. "Speech–language intervention for children with autism spectrum disorder in Brazil." *Topics in Language Disorders* 34: 155-67. doi:10.1097/tld.0000000000000011.

Fernandes, F. D. M., C. A. De La Higuera Amato, and D. R. Molini-Avejonas. 2012. "Language therapy results with children of the autism spectrum." *Revista de Logopedia, Foniatría y Audiología* 32:2-6. doi:10.1016/j.rlfa.2011.12.001.

Giedd, J. N., and J. L. Rapoport. 2010. "Structural MRI of pediatric brain development: What have we learned and where are we going?" *Neuron* 67: 728-34. doi: http://dx.doi.org/10.1016/j.neuron.2010.08.040.

Glumbic, N., and B. Brojcin. 2012. "Factor structure of the Serbian version of the Children's Communication Checklist-2." *Research in Developmental Disabilities* 33: 1352-59. doi:10.1016/j.ridd.2012.03.010.

Gómez-Pinilla, F. 2008. "Brain foods: the effects of nutrients on brain function." *Nature Reviews. Neuroscience* 9: 568-78. doi:10.1038/nrn2421.

Günhan, N. E. 2011. "Review of communication disorders in Turkish." *Clinical Linguistics & Phonetics* 25 (4): 335-37.

Hamadani, J. D., H. Baker-Henningham, F. Tofail, F. Mehrin, S. N. Huda, and S. M. Grantham-McGregor. 2010. "Validity and reliability of mothers' reports of language development in 1-year-old children in a large-scale survey in Bangladesh." *Food and Nutrition Bulletin* 31: S198-206.

Hanson, J. L., N. Hair, D. G. Shen, F. Shi, J. H. Gilmore, B. L. Wolfe, and S. D. Pollak. 2013. "Family poverty affects the rate of human infant brain growth." *PLoS ONE* 8: e80954.

Hsairi Guidara, I., I. Ayadi, E. Ellouz, I. Abid, F. Kamoun, and others. 2013. "Study of a Tunisian population of children with learning disorders." *Tunisie Medicale* 91: 382-86.

Huttenlocher, P. R. 1979. "Synaptic density in human frontal cortex - developmental changes and effects of aging." *Brain Research* 163: 195–205.

Jovanovic, G., Z. Jovanovic, J. Bankovic-Gajic, A. Nikolic, S. Svetozarevic, and D. Ignjatovic-Ristic. 2013. "The frequency of dyscalculia among primary school children." *Psychiatria Danubina* 25: 170-74.

Knudsen, E. I. 2004. "Sensitive periods in the development of the brain and behavior." *Journal of Cognitive Neuroscience* 16: 1412–25.

Kolb, B., and R. Gibb. 2014. "Searching for the principles of brain plasticity and behavior." *Cortex* 58: 251-60. doi:http://dx.doi.org/10.1016/j.cortex.2013.11.012.

Kotby, M. N., S. El-Sady, and M. Hegazi. 2010. "Thirty-five years of care of child language in Egypt." *Topics in Language Disorders* 30: 84-91.

Kuhl, P. K. 2007. "Is speech learning 'gated' by the social brain?" *Developmental Science* 10: 110–20.

Kundakovic, M., and F. A. Champagne. 2015. "Early-life experience, epigenetics, and the developing brain." *Neuropsychopharmacology* 40: 141-53. doi:10.1038/npp.2014.140.

Laus, M. F., L. D. M. F. Vales, T. M. B. Costa, and S. S. Almeida. 2011. "Early postnatal protein-calorie malnutrition and cognition: A review of human and animal studies." *International Journal of Environmental Research and Public Health* 8: 590-612.doi: 10.3390/ijerph8020590.

Lee, F. S., H. Heimer, J. N. Giedd, E. S. Lein, N. Šestan, D. R. Weinberger, and B. J. Casey. 2014. "Adolescent mental health—Opportunity and obligation." *Science* 346: 547-49. doi:10.1126/science.1260497.

Lee, L. W., and K. Wheldall. 2011. "Acquisition of Malay word recognition skills: lessons from low-progress early readers." *Dyslexia* 17: 19-37. doi:10.1002/dys.421.

Lewis, C. M., A. Baldassarre, G. Committeri, G. L. Romani, and M. Corbetta. 2009. "Learning sculpts the spontaneous activity of the resting human brain." *Proceedings of the National Academy of Sciences* 106: 17558–63.

Luby, J. L., D. M. Barch, A. Belden, M. S. Gaffrey, R. Tillman, and others. 2012. "Maternal support in early childhood predicts larger hippocampal volumes at school age." *PNAS* 109: 2854-59.

Luciana, M. 2013. "Adolescent brain development in normality and psychopathology." *Development & Psychopathology* 25: 1325-45. doi:10.1017/S0954579413000643.

Lupien, S. J., B. S. McEwen, M. R. Gunnar, and C. Heim. 2009. "Effects of stress throughout the lifespan on the brain, behaviour and cognition." *Nature Review Neuroscience* 10: 434–45.

Mahmoud, H., A. Aljazi, and R. Alkhamra. 2014. "A study of public awareness of speech-language pathology in Amman." *College Student Journal* 48: 495-510.

Meltzoff, A. N., P. K. Kuhl, J. Movellan, and T. J. Sejnowski. 2009. "Foundations for a new science of learning." *Science* 325: 284-88. doi:10.1126/science.1175626.

Murmu, M. S., S. Salomon, Y. Biala, M. Weinstock, K. Braun, and J. Bock. 2006. "Changes of spine density and dendritic complexity in the prefrontal cortex in offspring of mothers exposed to stress during pregnancy." *European Journal of Neuroscience* 24: 1477-87. doi:10.1111/j.1460-9568.2006.05024.x.

Obidoa, M. A., M. Eskay, and C. O. Onwubolu. 2013. "Remedial help in inclusive classrooms: Gender differences in the enhancement of mathematics achievement of students through PAL (Peer-Assisted Learning)." *US-China Education Review* 3:172-180.

Olds, D. L., J. Eckenrode, C. R. Henderson, Jr, and et al. 1997. "Long-term effects of home visitation on maternal life course and child abuse and neglect: Fifteen-year follow-up of a randomized trial." *Journal of the American Medical Association* 278: 637-643. doi:10.1001/jama.1997.03550080047038.

Painter, K., and M. Scannapieco. 2013. "Child maltreatment: The neurobiological aspects of posttraumatic stress disorder." *Journal of Evidence-Based Social Work* 10: 276-84.

Pascoe, M., Z. Maphalala, A. Ebrahim, D. Hime, B. Mdladla, N. Mohamed, and M. Skinner. 2010. "Children with speech difficulties: an exploratory survey of clinical practice in the Western Cape." *South African Journal of Communication Disorders* 57: 66-75.

Pascoe, M., and M. Smouse. 2012. "Masithethe: speech and language development and difficulties in isiXhosa." *South African Medical Journal* 102: 469-71.

Paus, T., D. L. Collins, A. C. Evans, G. Leonard, B. Pike, and A. Zijdenbos. 2001. "Maturation of white matter in the human brain: a review of magnetic resonance studies." *Brain Research Bulletin* 54: 255–66.

Paus, T., A. Zijdenbos, K. Worsley, D. L. Collins, J. Blumenthal, J. N. Giedd, J. L. Rapoport, and A. C. Evans. 1999. "Structural maturation of neural pathways in children and adolescents: in vivo study." *Science* 283: 1908–11.

Pieterse, D. 2015. "Childhood maltreatment and educational outcomes: Evidence from South Africa." *Health Economics (United Kingdom)* 24 (7): 876-94. doi:http://dx.doi.org/10.1002/hec.3065.

Pouretemad, H. R., A. Khatibi, M. Zarei, and J. Stein. 2011. "Manifestations of developmental dyslexia in monolingual Persian speaking students." *Archives of Iranian Medicine* 14: 259-65. doi:0011144/aim.007.

Power, J. D., D. A. Fair, B. L. Schlaggar, and S. E. Petersen. 2010. "The development of human functional brain networks." *Neuron* 67: 735-48. doi:http://dx.doi.org/10.1016/j.neuron.2010.08.017.

Prado, E. L., and K. G. Dewey. 2014. "Nutrition and brain development in early life." *Nutrition Reviews* 72: 267-84. doi:10.1111/nure.12102.

Prathanee, B., P. Lorwatanapongsa, K. Makarabhirom, and W. Wattanawongsawang. 2010a. "Thai speech and language norms for children 2 1/2 to 4 years of age." *Journal of the Medical Association of Thailand* 93 (Suppl 4): S7-S15.Prathanee, B., P. Lorwatanapongsa, K. Makarabhirom, R. Suphawatjariyakul, R. Thinnaithorn, and P. Thanwiratananich. 2010b. "Community-based model for speech therapy in Thailand: implementation." *Journal of the Medical Association of Thailand* 93 (Suppl 4): S1-S6.

Rakap, S. 2015. "Quality of individualised education programme goals and objectives for preschool children with disabilities." *European Journal of Special Needs Education* 30: 173-86. doi:http://dx.doi.org/10.1080/08856257.2014.986909.

Reifen, R., and K. Ghebremeskel. 2001. "Vitamin A during pregnancy." *Nutrition and Health* 15: 237–43.

Rivera-Gaxiola, M., J. Silvia-Pereyra, and P. K. Kuhl. 2005. "Brain potentials to native and non-native speech contrasts in 7- and 11-month-old American infants." *Developmental Science* 8: 162–72.

Rothbart, M. K., and M. I. Posner. 2015. "The developing brain in a multitasking world." *Developmental Review* 35: 42–63.

Saffran, J., R. Aslin, and E. Newport. 1996. "Statistical learning by 8-month old infants." *Science* 274: 1926–28.

Schibli, K., and A. D'Angiul. 2013. "The social emotional developmental and cognitive neuroscience of socioeconomic gradients: laboratory, population, cross-cultural and community developmental approaches." *Frontiers in human neuroscience* 7: 788. doi:10.3389/fnhum.2013.00788.

Seeley, W. W., V. Menon, A. F. Schatzberg, J. Keller, G. H. Glover, and others. 2007. "Dissociable intrinsic connectivity networks for salience processing and executive control." *Journal of Neuroscience* 27: 2349–56.

Shaw, P., D. Greenstein, J. Lerch, L. Clasen, R. Lenroot, and others. 2006. "Intellectual ability and cortical development in children and adolescents." *Nature* 440: 676–79.

Sidhu, M., P. Malhi, and J. Jerath. 2010. "Multiple risks and early language development." *Indian Journal of Pediatrics* 77: 391-95. doi:10.1007/s12098-010-0044-y.

Tebbenkamp, A. T. N., A. J. Willsey, M. W. State, and N. Sestan. 2014. "The developmental transcriptome of the human brain: implications for neurodevelopmental disorders." *Current Opinion in Neurology* 27: 149-56.

Tomlinson, M., P. Cooper, and L. Murray. 2005. "The mother–infant relationship and infant attachment in a South African periurban settlement." *Child Development* 76: 1044–54.

Van den Bergh, B. R. 2011. "Developmental programming of early brain and behaviour development and mental health: a conceptual framework." *Developmental Medicine & Child Neurology* 53: 19-23.

van den Heuvel, M. P., C. J. Stam, R. S. Kahn, and H. E. Hulshoff Pol. 2009. "Efficiency of functional brain networks and intellectual performance." *Journal of Neuroscience* 29: 7619–24.

Yajnik, C. S., S. S. Deshpande, A. A. Jackson, H. Refsum, S. Rao, and others. 2008. "Vitamin B12 and folate concentrations during pregnancy and insulin resistance in the offspring: the Pune Maternal Nutrition Study." *Diabetologia* 51: 29-38. doi:10.1007/s00125-007-0793-y.