Fine-Tuning the Baby Brain

By Harry T. Chugani

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Nature invented a remarkable way to create a human brain. First, provide it with far more cells and circuits than it will eventually need. Next, be sure that this neural equipment is supplied with abundant energy. Then, one by one, initiate functions such as eye-hand coordination, and let them lay claim to the brain pathways they need; other pathways, less used, will die. This way, brain circuits are created and strengthened, in part, by whatever environment and experiences the baby encounters. Here, then, is the master plot of brain development now emerging from research in a new era of neuroimaging technology. A pioneer in that research tells us how the brain brings the human mind “online”—a robust, resilient process, but one that can go seriously wrong for children deprived of basic social and emotional nurturing.

Why does a child’s brain demand twice the energy of an adult’s brain? Why do some areas in the brain mature before others? And what about one of the most fascinating aspects of brain development—the discovery that the brain produces “too much” of various neural elements and then eliminates the excess? In some ways, this is analogous to the sculptor who begins with more material than is required and then subtracts the excess material to obtain a desired form. Unlike the sculptor, however, who eventually achieves a final form, the brain is able to undergo some remodeling throughout life.¹

The answers to these and other exciting questions, being explored with neuroimaging and other new techniques available to the developmental neuroscientist, are important to parents, teachers, policymakers, and everyone concerned with our children’s healthy development and future. Scientists studying the relationships among brain development, brain function, and behavior in infants and young children have discovered how the cellular architecture of the brain is changed through environmental exposure and experience. As a result, we are also learning how certain kinds of extreme early social deprivation can have an adverse effect on emotional and social behavior.

IMAGING THE BABY’S BRAIN

One important tool that has pushed this field forward is the positron emission tomography (PET) scan, which can be used to measure and take pictures of physiologic and biochemical processes within the brain and other organs through the use of radiolabeled tracers. The actual amount of radiation received from a PET scan is small. For example, a child living at sea level who receives three PET scans in a year would be exposed to no more radiation than a child living in Aspen, Colorado, because the child at the higher altitude in Aspen receives more background radiation from cosmic rays. PET scans are widely used to measure glucose metabolism in the brain and other organs, thus providing a measure of the energy requirement of the organ and its degree of activity.

As early as 1982, Charles Kennedy, M.D., Louis Sokoloff, M.D., and their coworkers (the group that I trained with) predicted that a relationship might exist between behavioral development and the energy demand of various brain regions. They arrived at this conclusion when they studied glucose metabolism in the developing rhesus monkey.² When, two decades ago, my research team and I first performed PET scans of glucose metabolism in newborn human babies, the results were stunning. Most of what we consider the higher brain, the cerebral cortex, showed little activity, with the exception of the primary sensorimotor cortex. The greatest activity was in the thalamus, brain stem, and cerebellar vermis, which are all relatively old structures from an evolutionary perspective.³

This pattern of activity probably accounts for the less complex behavior of newborns, compared with older infants. For example, reflexes that we are well acquainted with in babies, such as startling in response to a sudden noise or motion, “rooting” of the mouth toward a nipple, or an involuntary grasping by the baby’s hand around a finger are all reflexes that we are born with, and
all are mediated by subcortical brain regions. These reflexes will later disappear as they are suppressed by the increasing influence of the cerebral cortex. As an unfortunate aside, these same reflexes can re-emerge later in life if the person becomes demented (for example, with Alzheimer’s disease), because cortical suppression of the reflex fails. I have seen many such patients in whom it is quite easy to elicit a grasp or even a root reflex.

As PET devices improved and smaller brain structures in babies could be visualized, we encountered further surprises. Brain structures such as the amygdala, hippo-campus, and cingulate cortex were also already active in the newborn, something that was not known before. We are now seeking to learn whether these limbic structures show the same level of activity if the baby is born prematurely, say at 26 to 28 weeks’ gestation. At our center, a microPET scanner intended for scanning monkeys was adapted for human use and placed in our neonatal intensive care unit. We shall see later how understimulation of this limbic network in early life can lead to abnormal behavior and attachment difficulties.

As the newborn develops into an infant and increases its level of behavioral sophistication, so too do the PET scans change. In the second and third months of life, visuo-spatial and visuosensorimotor integration improve. For example, the infant is now able to follow visually an interesting object, reach for it, and bring it to his mouth. This level of coordination requires the participation of several brain regions that are now activated, such as the frontal eye fields, the parietal cortex with its tracking centers, the basal ganglia, and the cerebellar cortex. We know that infants demonstrate a capacity to learn through exposure to language before their ability to speak, and this is consistent with the earlier functional maturation in receptive language areas of the brain, compared with expressive areas.

![PET scans of human newborn and one-year-old child](image)

The upper row of PET scans of a human newborn show the typical pattern of glucose uptake by the brain (dark indicates higher uptake). In the first image, the highest activity is in the sensorimotor cortex, in the second image in the amygdala (top arrow) and brainstem (bottom arrow), and in the third image in the hippocampus (top arrow) and cerebellar vermis (lower arrow). Compare these images with those of a one-year-old child, as shown in the lower panel. Courtesy of Harry T. Chugani

Between six and eight months, the remaining frontal cortex begins to show a maturational rise in glucose metabolism, which continues until the infant is a year old. Even within the frontal cortex, there is a fixed order and hierarchy of maturation, which suggests strongly that these events are genetically programmed. Indeed, functional maturation of the frontal cortex begins in the side and lower portions, later proceeds to the middle, and finally to the dorsal prefrontal areas. Functional maturation of these frontal cortical regions coincides with the emergence of improved cognitive competence. For example, although the five-month-old infant is quite content to play with, smile at, and even be picked up by a stranger, the eight to ten-month-old is cautious and clings to a parent when the stranger attempts to engage the infant. Even grandparents and relatives need to go through a period of familiarization with the infant before this behavior slowly abates.

Do both hemispheres mature in synchrony or do hemispheric differences exist in humans? In 1997, Catherine Chiron, M.D., and her colleagues in Paris reported regional cerebral blood flow changes in children and found that between one and three years of age, cerebral blood flow appeared to be higher in the right hemisphere compared with the left. After the age of three, the left hemisphere showed higher cerebral blood flow. Those researchers suggested that functional maturation of the right hemisphere might precede that of the left hemisphere. Future studies are required to replicate these findings, although the results are consistent with measures in 1987 of electroencephalographic (EEG) activity from Robert Thatcher, Ph.D., and colleagues, which also support the notion that the left and right hemispheres develop at different rates.
Why does the human brain go through a period from about three years to late adolescence during which glucose consumption and blood flow so much exceed that of the adult? What is all this extra fuel or energy being used for? To figure this out, we first asked whether such a process is unique to humans or whether it also occurs in other species. The latter proved to be true. In 1991, we discovered a
glucose consumption and blood flow so much exceed that of the adult? What is all this extra fuel or energy being used for?

Although not a lot of research data were available from humans, Peter Huttenlocher, M.D., and his associates at the University of Chicago studied the question for many years. They were able to obtain postmortem human cortical tissue specimens from children who died of various non-neurologic causes and were the first to show that between birth and age three to four years there was a rapid increase in the numbers of synapses in the cerebral cortex—what we call “synaptic exuberance.” Furthermore, this coincided with the rise in glucose metabolic rates seen on PET scans. These phases of exuberance and elimination of synapses do not parallel the general growth of the brain as measured by weight. Synaptic numbers remain high until adolescence, when they gradually begin to decline, as do glucose metabolic rates.

This intriguing similarity in the patterns of synaptic exuberance and energy consumption in the human brain led us to hypothesize that PET scanning might provide a tool for assessing, albeit indirectly, the period of synaptic excess. Indeed, this hypothesis is supported by studies that examined more closely the relationship between the two processes in both kitten and monkey brains. Such a relationship is perhaps not surprising, considering how, under normal circumstances, most of the glucose used by the brain after birth goes toward maintaining the electrical processes of the myriad connections and membranes that make up the “dendritic tree” of nerve fiber branches. Therefore, in the resting state, the energy demand of the brain must be related to the number of synapses; it will increase or decrease during development, depending on the production or pruning of synapses.

Why did Mother Nature design a system of synaptic exuberance followed by elimination of many of those same synapses? What is the biological advantage of this master plot? Scientists generally agree that transient exuberant connectivity reduces the amount of information that would otherwise need to be encoded in the genes. This process allows the environment to affect brain development. Each individual brain can retain and increase the efficiency of connections that, through repeated use during sensitive periods, are deemed to be important, whereas connections that are used less are more susceptible to elimination. This allows for a fine-tuning of neuronal circuits, based on early exposure and environmental nurturing, that makes the neuronal architecture of each person unique.

We can see this fine-tuning in the process of learning to play a musical instrument. A child who learns to play the piano between 5 and 10 years of age, but then gives up the instrument for the next 20 years, will still have an advantage at age 30 years over the novice who did not have the benefit of such an early exposure. I am not implying that an adult cannot learn to play well, but there is clearly an advantage when the exposure is early in life. There are some exceptional adults who might even master the instrument beginning in adulthood, but success is not as easy to predict and is probably more related to genetic factors.

It is tempting to speculate that the two periods of the most dramatic change in glucose metabolism (ages two to three years and adolescence) could be related to the dynamic behavioral fluctuations seen in our children during these periods. If you survived raising children, as I have, I probably do not need to remind you of the impulsive behavior of a two to three-year-old (whose brain is for the first time reaching a state of huge synaptic numbers) or the sometimes strange behavior of adolescents.

THE PERIOD OF SUPREME PLASTICITY

The brains of infants and children not only consume more energy than the brains of adults, but they are also more plastic, more able to change or to compensate for damage. Doctors have long known that after brain injury, recovery is easier in a nervous system that is still developing, as compared with one that is fully mature. The four-year-old boy who sustains an injury to his left brain (including his language centers) typically goes through a period of global aphasia (inability to speak), but then, as though miraculously, he recovers as the right brain takes over these language functions. Other dramatic examples of plasticity are seen
in children who undergo surgery for epilepsy that could not be controlled with drugs. The recent increase in such surgery resulted in studies that document language recovery after removal of the entire language-dominant hemisphere of the brain as late as 14 years of age, but not after.

Even in the adult brain significant plasticity exists, but it is not as robust as in the immature brain, and the biological mechanisms that control it are probably different. The degree of plasticity after injury depends on complex factors such as the size of the lesion, brain regions damaged, state of maturation at the time of injury, and type of injury. But it appears, from many studies in both animals and humans, that exuberant connectivity (associated with high glucose consumption) of the developing brain can be the key to robust plasticity in response to injury. Children who have an eye removed (usually because of cancer) before they are eight years old perform better on depth perception tasks than those who have the surgery at an older age. We know also that a decline in glucose metabolic rates in the human visual cortex coincides with a notable decrease in plasticity, so that certain types of eye disorders or injuries result in irreversible loss of vision from one eye if not corrected in a timely manner.

We saw how brain plasticity during development can be a blessing in the case of brain injury, but sometimes the same plasticity can be a problem. How is this possible? Consider a child with the kind of epilepsy in which a particular focal point in the brain causes seizures. Typically, the seizures begin with a stare or a jerking of just one extremity, but, over time, the seizures worsen to include more jerking or even a full-blown convulsion. This is because more brain regions or pathways have become incorporated into the epileptic network as a result of recurrent seizures. The incorporated pathways can “learn” how to seize and establish what is known as a “secondary epileptic focus.” Because of this danger, seizures in young children should be suppressed with medication in the early stages. Once a secondary focus is created, it can generate seizures independently regardless of whether the primary focus has been surgically destroyed or removed. My colleagues and I used PET scans to measure the abnormal glucose metabolism associated with the epileptic focus in children. We found that the size of the disturbance in the cerebral cortex changes depending on whether the seizures are controlled or remain refractory to medications.

The implications of the unique brain plasticity during development are much debated, and not just by scientists. Look in any magazine for new parents and see advertisements for products that claim to stimulate and “enrich” the child’s brain. I see no scientific basis for such claims and certainly do not advocate using the sometimes ridiculous commercial props. Yes, society should take advantage—appropriate advantage—of the learning possible during infancy and childhood. I believe that most reasonable parents and guardians provide the necessary exposure and nurturing to support development and achievement of a child’s genetic potential. Certainly, there are many children whose environmental circumstances are suboptimal for various reasons, such as poverty, war, or a disrupted home environment. The admittedly difficult task of identifying these children and providing appropriate interventions should be a high priority. As we shall see, the costs of neglecting this task can be formidable.

THE NEWBORN REACTS TO FACES AND FEELINGS

As we mentioned earlier, the amygdala and hippocampus, which are part of the brain’s limbic system, already seem to be “turned on” at birth, and the anterior cingulate cortex and orbital frontal cortex mature early in life’s first year. We know that the time during development when a particular brain region becomes metabolically active marks the time when that structure contributes to the behavioral repertoire of the person. So what activities are going on in these brain regions so early in life, and how are they reflected in the infant’s behavior?

The amygdala, among its other functions, is associated with processing of faces that show emotion. We believe that the amygdala, together with the hippocampus (associated with memory) and cingulate cortex (associated with emotional processing and bonding), forms an important network that comes into play as soon as the baby is exposed to other people. The amazing capacity of a newborn to “read” the emotional content of the mother’s face likely involves processing within this network. Imagine even the young infant’s reaction when a parent conveys through facial expression the emotions of joy, displeasure, frustration, or surprise. These are powerful means of connecting with or engaging the baby.

Our understanding of the importance of brain networks for social interactions was greatly enhanced by animal experiments. For example, the notion that damage to temporal lobe regions (including the amygdala and hippocampus) occurring early in life has
We learned by studying Romanian orphans how abnormal early socioemotional development can lead to measurable changes of glucose metabolism in the brain.

This is just one of many examples of how biological and psychological factors in early development can have a strong effect on adult life. As we become better able to understand and, indeed, measure the effect of these factors on the young brain, we can delineate the immediate and long-term results in children of growing up under both normal, “good enough” conditions and conditions that put them at high risk. A case in point is social deprivation, in which we learned by studying Romanian orphans how abnormal early socio-emotional development can lead to measurable changes of glucose metabolism in the brain.

SOMBER LESSONS FROM ROMANIAN ORPHANAGES

Children have always been neglected and mistreated, but the effect of childhood social deprivation on brain function could not really be studied in humans until non-invasive tools were sufficiently sensitive. The deleterious effects of early deprivation were studied in animals, however, and we are beginning to understand that there are both short-term and long-term changes in brain function associated with early neglect and deprivation. From the classic studies of infant monkeys conducted by Harry Harlow, Ph.D., in the 1950s and ’60s, it became clear that isolation from birth—extreme deprivation of social contact—leads to severe behavioral maladjustment after a sensitive period of about eight months. In other words, the abnormal behavior did not occur if the isolation was interrupted prior to eight months. Now suppose that Harlow had had access to the latest in neuroimaging technology. What would he find on PET and magnetic resonance imaging (MRI) scans of these monkeys? Would these techniques be sensitive enough to detect changes from the norm resulting from the social deprivation?

Unfortunate events in Romania gave scientists an unusual opportunity to answer these questions. Social policies and severe economic problems in that country in the 1980s caused more than 65,000 children to be placed in orphanages. Eighty-five percent of the children were younger than one month old. Conditions in the orphanages subjected a group of unfortunate children to severe social and emotional deprivation. Only one caregiver was available for every 10 infants; for children older than three, the ratio was one caregiver for 20 children. Infants spent up to 20 hours a day just lying in their cribs, unattended. Eventually, many of these children were removed from the orphanages and adopted by families in the United Kingdom and North America.

These adopted children were carefully studied by scientists, most notably Elinor Ames, Ph.D., and Michael Rutter, M.D. Not unexpectedly, they discovered that the children had cognitive, social, and physical deficits. They found that most of these children at the time of adoption showed cognitive performance in the mental retardation range. Following the children over several years, the scientists demonstrated that the children tended to show considerable recovery by four years of age; but deficits that did remain when the children were four were still present when they reached six. Interestingly, the behavioral abnormalities reported in these children are qualitatively similar to some of the behaviors seen in Harlow’s studies of socially deprived monkeys. The researchers observed repetitive and self-stimulatory behaviors such as hand flapping in the children, as well as indiscriminately friendly behavior and insecure attachment.

As a pediatric neurologist, I had seen some of these children in my clinic and was fascinated by these unusual behaviors. In order to examine changes in the brain that might underlie these behaviors, my colleagues and I performed PET scans on a group of adopted Romanian children who were older than six years at the time of the study. We were careful to exclude from our study those children suspected of having an underlying neurologic disorder such as fetal alcohol syndrome, which was not uncommon. What we discovered was generally consistent with the neurocognitive findings reported by other researchers, in that what we call “global intellectual functioning” was in the low-average range. But other researchers, because the mean scores for the group of orphans they studied were in the normal range, interpreted this to mean that the children had recovered.

When we analyzed the PET scans from these orphans and compared them with scans of children of the same age and sex who had not suffered deprivation, we were intrigued at the relatively consistent pattern of abnormality. When we conducted more extensive assessments of cognitive, language, memory, executive, and motor functioning, however, we discovered some quite specific deficits, namely, mild neurocognitive deficits in language processing, memory, and executive functioning. We also found clinically significant behavioral problems, such as attentional, thought, and social deficits.

When we analyzed the PET scans from these orphans and compared them with scans of children of the same age and sex who had not suffered deprivation, we were intrigued at the relatively consistent pattern of abnormality. We found decreased glucose metabolism in a specific group of structures in the brain, including the orbital frontal gyrus, the infralimbic cortex, the amygdala, the hippocampus, part of the temporal lobe, and the brain stem. Why was this discovery particularly intriguing? Because these brain areas, which are strongly interconnected, are integrally involved in the brain’s response to stress. Stress activates a series of pathways that involves the brain and the endocrine system and results in the release of neurochemicals called glucocorticoids. Growing evidence from the research of Bruce S. McEwen, Ph.D., shows that chronic elevations of glucocorticoids can cause permanent damage to limbic brain regions. Stress and adrenal steroids can also cause reversible impairments in episodic and spatial memory in animals and humans, and repeated stress can result in cognitive dysfunction.

LEGACY OF THE OVER-STRESSED INFANT BRAIN

Putting all of this together, it would appear that the stress of early social deprivation in the Romanian orphans acted on the brain to lead eventually to the behavioral and cognitive disturbances seen as the children grew up. In fact, there is considerable evidence from animal studies that stressful experiences early in development can affect behavior in adulthood. Similarly, early adverse experiences in humans are associated with elevated rates of severe depression and other psychiatric disorders in adulthood. Of course, one of the most potent stressors in the young is separation from the mother or other primary caregiver.

Early studies of social deprivation in monkeys involved total deprivation throughout infancy, which resulted in severe social and emotional disturbances, including aggression, motor stereotypic behavior, and reproductive problems. Depriving monkeys of their mothers but giving them access to peers resulted in less severe behavioral abnormalities, but even those monkeys become highly reactive and impulsive. Adult monkeys that have been separated from their mothers when they were infants typically rank at the bottom of the dominance hierarchy. Scientists have attempted to identify what neurochemical and neuroanatomical changes accompany social deprivation and, perhaps, might account for these abnormal behaviors.

Studies of monkeys deprived of their mothers showed that they have increased neurochemical responses to social separation, as well as changes in how they metabolize certain neurotransmitters, beginning before they are six months old and continuing through adolescence. The studies also found structural abnormalities in the cerebellum and decreases in cortical dendritic branching—a measure of the nerve connections in the brain. Similar studies in rats identified increased activity within the limbic-hypothalamic-pituitary-adrenal axis and increased reactivity to stressors during adulthood. Different strains of rats, however, showed different sensitivity to early stress, which suggests that both genetic and environmental factors are involved in the long-term effects of stress.

Nor do human infants react uniformly in terms of brain changes and behavior in response to the same stressful situations. One way this was measured is to test for the concentrations in saliva of the neurochemical cortisol, which is produced in response to stress. In 1997, Mary Carlson, Ph.D., and Felton Earls, Ph.D., measured variations of salivary cortisol in Romanian children raised at home by their families compared with orphanage-raised children at two years of age. Morning cortisol levels in the orphans were significantly lower, whereas noon and evening levels were higher. The study only reported the overall results, so there is no way to assess the variability among the children. But genetic differences in the response to stress can partly explain why some children subjected to early deprivation are more severely affected by the experience and show incomplete recovery after adoption.

As we noted, the Romanian orphans in our study showed evidence of bilateral dysfunction of brain structures including the...
It is now evident that children exposed to early social deprivation suffer long-term cognitive and behavioral deficits associated with dysfunction in brain regions known to be damaged by prolonged stress. The chronic stress endured by children who were in Romanian orphanages during infancy clearly resulted in abnormal development of the brain and altered connections in the neural circuits that underlie the persistent behavioral disturbances observed in these orphans.

The description by William T. Greenough, Ph.D., of “experience-expectant” plasticity might be relevant here. In this form of plasticity, a person’s biological system inherently expects some form of interaction with the environment; the absence of this interaction within a certain sensitive period leads to dysfunction of the system involved. We believe that the Romanian experience is an example of experience-expectant plasticity, and that the brain network that includes the amygdala, hippocampus, anterior cingulate, and orbital cortex (and probably other connected structures) must undergo socio-emotional interaction with the mother or other primary caregiver for these neural pathways to be strengthened. Failure to achieve this interaction in a timely manner leads to dysfunction of these structures, indicated by the decreased activity we saw on PET scans. Whether these dysfunctional brain regions recover with time and intervention is not known, but it is a topic of great interest to researchers and obviously to the parents who adopted such children.

THE FUTURE

We have seen how the exuberant connectivity and growth of the young brain make possible the shaping of the individual as critical brain regions come online, a process that usually proceeds successfully except in situations of extreme deprivation. The blossoming of neuroimaging technology makes ours an exciting era for those interested in brain development and the search for brain structures and pathways involved in plasticity and social impoverishment. Studies currently under way in our laboratory are using functional MRI to study activation of children’s brains by various stimuli, as well as diffusion tensor imaging techniques that allow us to measure the strength of connections between brain structures.

Some believe that neuroimaging of the developing brain is merely an academic exercise and will never play a vital role in such areas as education and social policy. I disagree. One of the powerful assets of neuroimaging is that it allows individual differences in brain function and anatomy to be dissected with great precision. For example, children with a specific learning impairment can show similar results from psychological testing but have several distinct underlying pathophysiologies. Interventions beneficial to some children might not help others. By exploring changes in brain function, we might also be able to improve treatment strategies—for instance, using neuroimaging to explore the chemical disturbances involved in attention disorders. Furthermore, only by achieving a better understanding of normal developmental changes in the brain, beginning at birth, and how these are affected by the environment in which a child grows up, can we identify patterns of abnormalities. Only then will we know when all is well and when we must intervene.

References


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