Epigenetics and Family-Centered Developmental Care for the Preterm Infant

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ABSTRACT

Adverse experiences early in life have the potential to disrupt normal brain development and create stress response channels in preterm infants that are different from those observed in term infants. Animal models show that epigenetic modifications mediate the effects of maternal separation and environmental stress on susceptibility to disease and psychobehavioral problems later in life. Epigenetic research has the potential to lead to the identification of biological markers, gene expression profiles, and profile changes that occur overtime in response to early-life experiences. Combined with knowledge gained through the use of advanced technologies, epigenetic studies have the promise to refine our understanding about how the brain matures and functions from multiple perspectives including the effect of the environment on brain growth and maturation. Such an understanding will pave the way for care practices that will allow the premature brain to develop to its full capacity and will lead to the best possible outcomes. Neonatal epigenetic research is emerging and rapidly advancing. As scientists overcome biological, technical, and cost-related challenges, such research has a great potential in determining key environmental factors that affect the preterm genome, allowing for targeted interventions. The purpose of this article is to explore existing literature related to epigenetic mechanisms that potentially mediate the effects of the environment on preterm infant brain development.

Key Words: developmental care, environment, epigenetics, genetics, neonatal intensive care, nutrition, preterm infants

Epigenetics is a field of expanding research and growing relevance and importance in today's healthcare world. For neonatal nurses in particular, it is important to understand how key environmental factors contribute to epigenetic changes in neurons and neuronal networks and how those changes affect long-term outcomes and susceptibility to disease. As the body of work related to epigenetics continues to grow, so does the realization that early-life experiences have significant effects on brain maturation, development, and long-term outcomes.

With increasing survival rates, the focus of neonatal care during the last 2 decades has shifted from a rescue model to a paradigm centered on improving quality of care and reducing morbidity.[1] Family-centered developmental care interventions aimed at reducing stress, supporting self-regulation, and promoting positive experiences for the infant as well as the family have become an essential aspect of routine care giving in the neonatal period.[2] There is no one universal definition of family-centered developmental care: it encompasses a wide range of practices from swaddling to skin-to-skin holding (kangaroo care) and infant massage to the implementation of the Newborn Individualized Developmental Care

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and Assessment Program to the bundled implementation of those strategies within the family unit.[2-4] Despite improvements in care practices and the perceived benefits of developmental care interventions, neurodevelopmental outcomes in preterm infants remain of great concern. The long-term effects of developmental care on brain development and the mechanisms that mediate its influence on neuronal responsiveness and changes in neuronal cell biology in response to stress remain unclear. The identification and characterization of key environmental factors that affect neuronal and hormonal networks in preterm infants through the alteration of genetic character may provide insights into the origins of many behavioral and developmental issues that may arise during the neonatal period and develop later in life. Focusing on the biological mechanisms of developmental care will allow for increasingly targeted interventions and will maximize the benefits gained from neonatal care practices.

THE ROLE OF EPIGENETICS

In eukaryotic organisms, the nucleus of each individual cell contains large, linear chromosomes. These chromosomes (see Table 1 for definitions throughout this section) carry the genetic blueprints for life in the form of DNA. DNA can be replicated for cell division or transcribed into messenger RNA (mRNA), which in turn is translated into amino acid sequences during protein synthesis. These processes form the basis for both the generation and development of life. Differences among individuals can often be attributed to the presence or absence of different genes, as determined by the specific sequence of base pairs within the genome. However, not all variations among individuals can be attributed to differences in DNA sequence and genotype; many phenotypic differences are a result of changes that occur above the level of nucleotides and genes—that is, epigenetic changes.

Epigenetics is defined as the study of those cellular processes that determine the function of genes.[5] Epigenetic changes typically occur at the molecular level and involve DNA or its supporting proteins. Such activity leads to alterations in activation or transcription of certain genes, while the structure and sequence of DNA remain unchanged. DNA methylation and histone changes are the most common epigenetic mechanisms. DNA methylation (addition of a methyl group to the DNA molecule), gene expression regulation (phenotype), and changes

TABLE 1. Definitions of Epigenetic Terms

Term	Definition
DNA[4]	A chain of linked nucleotides (having deoxyribose as their sugars). Two such chains in double helical form are the fundamental substance of which genes are composed.
mRNA (messenger RNA)[4]	An RNA molecule transcribed from the DNA of a gene; a protein is translated from these RNA molecules by the action of ribosomes.
Chromosome[4]	A linear end-to-end arrangement of genes and other DNA, sometimes with associated protein and RNA.
Gene[4]	The fundamental physical and functional unit of heredity, which carries information from one generation to the next; a segment of DNA composed of a transcribed region and a regulatory sequence that makes transcription possible.
Transcription[4]	The synthesis of RNA from a DNA template.
Histone	A type of basic protein that forms the unit around which DNA is coiled in the nucleosomes of eukaryotic chromosomes.
Epigenetics[4]	Cell processes that determine the function of the genes. Changes in the cell molecular composition due to environmental exposures lead to changes in the gene expression and function. Changes in the gene may be inherited transgenerationally and will affect the phenotype.
Methylation[4]	The addition of methyl groups to DNA residues after replication; methylation patterns can affect gene expression levels.
Programing known as Developmental Origins of Adult Disease Hypothesis or Barker theory[14]	Adaptations by organism to environmental exposures during critical periods of development are necessary for survival. However, those adaptations lead to dysregulated cell processes and gene modifications that increase the risk for adult disease and in specific metabolic disease. For example, early deprivation of adequate nutrition is linked to risk of metabolic syndrome later in life.

in the chromatin structure of the gene are examples of molecular changes that directly involve DNA. Changes to supporting proteins often involve histones and altered functioning of eukaryotic proteins that have roles in the packaging, ordering, and storage of the DNA. Methylation or demethylation of histones can turn on, turn off, amplify, or silence gene expression. Gene expression involves the transcription of DNA to mRNA and the translation of mRNA into protein. Protein synthesis, a continuous process, is essential for enzymatic activity and metabolism. DNA methylation patterns are inherited during cell division, and epigenetic patterns determine the different types of cells in the body during cell differentiation. Any interruptions or alterations in the enzymes that regulate DNA methylation or histone modification can lead to epigenetic pattern changes. Epigenetics can explain why identical twins can exhibit dramatically different phenotypes later in life.[6,7] Table 2 provides links to illustrations and further information on epigenetics.

The effect of epigenetics on the development and function of neuronal networks starts at conception and continues into infancy and early childhood.[8] Infants born prematurely are most often cared for in less than ideal physical and pyschosocial environments. Maternal separation and adverse experiences in children with disadvantaged backgrounds have been shown to cause early adaptations in gene expression, lead to altered protein expression across the life span, and therefore increase the risk for chronic disease and mental health problems.[9-16] On the basis of these findings, it can be assumed that similar adaptations can potentially occur in preterm infants, given that they encounter multiple early adverse experiences coupled with long periods of maternal separation while in the newborn intensive care unit (NICU). Epigenetic information may prove to be extremely relevant to care giving provided in the NICU.

Animal models have shown that sensory stimulation plays an important role in neuron function and influence neuron differentiation and neuronal pathway development through epigenetic modifications.[11-13] Infants in the NICU are often isolated from maternal care for long periods of time and are exposed to noxious sensory stimuli such as noise, light, pain, medically related touch, and medications that raise concern about environmental programing. In addition, nutritional management is not always optimal in the neonatal period even though it is essential for optimal brain development. Although it has been shown that optimal nutrition, developmental care, and maternal care early in life have a positive effect on morbidity and mortality in preterm infants, it is less known whether those effects are mediated through specific epigenetic changes.[3,15,16] Optimal brain development is a function of 3 variables: genes, appropriately supportive environment, and nutrition, and how these 3 variables interact together. The purpose of this article was to explore existing literature relevant to possible epigenetic mechanisms mediating the effects of nutrition and environment on brain maturation and development.

TABLE 2. Links and Illustrations

http://learn.genetics.utah.edu/
http://commonfund.nih.gov/epigenomics/figure.aspx
http://genome.wellcome.ac.uk/doc_WTD020756.html
http://learn.genetics.utah.edu/

METHODS

Methodology and Data Retrieval and Inclusion Criteria

In collaboration with a medical librarian who is experienced in searching computerized bibliographic databases, the authors conducted a cross-database search in EBSCO, using Expanders for search within the full text of the articles published within the last 10 years with search modes as described in Table 3. Inclusion criteria for this review included research and review articles on epigenetic mechanisms in preterm infants, environmental programing, and postnatal programing and brain development. For the purposes of this review, care environments were defined as the physical, chemical, and nutritional contexts and practices that preterm infants generally experience during the immediate perinatal period. This included maternal care and sensory stimulation such as pain and noxious stimuli (ie, noise and light).

RESULTS

The search yielded 12 articles. The articles were retrieved, examined for relevance, and searched for any previous reviews including cross-references, abstracts, conference, symposia proceedings, and dissertations. A search of the Biological Abstracts Previews was also conducted. An additional 9 articles that could potentially have some relevance to the topic were identified for inclusion in the review.

Of the 21 articles, only 1 article was a research study that met the search criteria. Three other articles met the criteria and were general review articles. Only in 1 of 3 review articles, the authors provided a description of their search strategy and study inclusion criteria. This review, which was authored by Lui et al,[3] examined care practices that support neurodevelopment in the NICU. The remaining 2 reviews by

TABLE 3. Details of Search and Key Words Used in Searching Major Databases

Boolean/Phrase Interface:

EBSCOhost Database. The search included CINAHL with Full Text; Academic Search Premier; Alt HealthWatch; America: History & Life; Bibliography of Native North Americans; Business Source Premier; Communication & Mass Media Complete; Computers & Applied Sciences Complete; EBSCO MegaFILE; Education Research Complete; ERIC; Fish, Fisheries & Aquatic Biodiversity Worldwide; Funk & Wagnalls New World Encyclopedia; GeoRef; GeoRef In Process; GreenFILE; Health Source—Consumer Edition; Health Source: Nursing/Academic Edition; Historical Abstracts; Humanities International Complete; Library, Information Science & Technology Abstracts; MAS Ultra—School Edition; MasterFILE Premier; MEDLINE; Mental Measurements Yearbook with Tests in Print; Middle Search Plus; MLA Directory of Periodicals; MLA International Bibliography; Primary Search; Professional Development Collection; PsycARTICLES; PsycINFO; Regional Business News; RILM Abstracts of Music Literature; Science Reference Center; Social Work Abstracts; SocINDEX with Full Text; SPORTDiscus; Wildlife & Ecology Studies Worldwide; Teacher Reference Center; eBook Collection (EBSCOhost); Index to Legal Periodicals & Books Full Text (H. W. Wilson); Library Literature & Information Science Full Text (H. W. Wilson); Applied Science & Technology Abstracts (H.W. Wilson).

The following key words were used: epigen* and "developmental care" and (vlbw or elbw or lbw or "low birth" or "low birthweight" or Neonat* or newborn* or nicu or preterm* or prematur*).

Wiedmeier et al[15] and Gudsnuk and Champagne[6] did not follow any specific timeframe or guidelines and recommendations for conducting integrative reviews.

The second review by Wiedmeier et al[15] examined animal studies involving diet modifications leading to postnatal programing and development of metabolic disease later in life. Mechanisms implicated in such modifications were explored and included alteration in the hypothalamic-pituitary-adrenal (HPA) axis pathways. The third review by Gudsnuk and Champagne[6] was a summary of findings on epigenetic mechanisms contributing to long-term impact of early-life adverse experiences on behavioral and psychosocial well-being. There was a significant overlap among the review articles with the same animal models being discussed and cited in more than 1 article. The research study by Guzzette et al[16] examined effects of massage on brain development and on maturation of visual functioning. Cellular and molecular mechanisms involved in visual maturation and development were explored. The following section includes a synthesis and discussion of findings presented in the 4 articles that met the review criteria.

DISCUSSION

Brain Development

Lui et al[3] provided a detailed review of brain development and how various exogenous and endogenous stimuli influence brain maturation with the focus on the role of sleep in brain development. The purpose of their study was to review current evidence supporting care practices that are believed to promote optimal brain development in newborns. The review was based on the work of the exploratory group formed by a 5-member hospital of the Vermont Oxford Network–sponsored Neonatal Intensive Care 2005. The authors provided an overview of and made recommendations on existing care practices most commonly used in the NICU including skin-to-skin holding kangaroo care, tactile stimulation, massage, nutritive suck, swaddling, and pharmacological therapies used for analgesia and sedation. The authors proposed a bundled approach to family-centered developmental care.

When an infant is born prematurely, rapid brain growth that should have taken place in utero occurs postnataly.[17] Beginning as early as 24 to 28 weeks' gestation and extending through the first 3 years of life, the human brain goes through extensive modification of its neuronal connections. This period of rapid synaptogenesis followed by synaptic pruning and restructuring is considered to be "critical" for optimal brain development.[18-20] Neurogenesis and synaptogenesis are 2 intricate processes that underlie brain development and that are regulated by endogenous and exogenous stimuli.[3] Endogenous stimulation processes are defined as those processes that are independent of factors external to the brain and are mediated by the presence of neurotransmitters such as acetylcholine and glutamate. Neurotransmitters connect brain regions together through synapses and mediate brain plasticity.[18-21]

Exogenous processes are activity-dependent and occur in response to sensory input. Endogenous processes coupled with brain plasticity, the ability of the brain to rewire and adapt, prepare the brain for the integration and interpretation of sensory input. Sensory input is essential for normal brain development, and deprivation of such stimulation during critical periods of growth will result in alterations in neuronal development.[22] Sensory systems are believed to develop in a sequential (not simultaneous) manner. Therefore, the timing, type, and level of sensory stimuli

the brain is exposed to play an important role in normal neuronal development. Excessive and early introduction of one type of stimulus may lead to gains in the sensory system that is related to that stimulus, but to a loss or alteration in the sensory systems that are related to other stimuli.[23-26] Exposure to environmental stimuli can have a significant effect on how the brain wires, fires, and connects, especially if the brain is in a vulnerable and premature state. Signals from external stressors are converted into biochemical responses triggered by a cascade of events that take place in the subcortical structures and neurotransmitter systems in the brain and that are initiated by the release of the corticotropin-releasing hormone.[10] This is the pathway that investigators normally think of being activated with stress. However, there are many others that are activated during stress, which are beyond the scope of this article.

Nutrition and Brain Development

The review by Wiedmeier et al[15] provided a summary of animal studies involving models with dietary manipulation during the neonatal period. In addition, the review discussed postnatal growth, challenges in attaining adequate nutrition, and recent dietary advances and how those advances contribute to postnatal programing in infants born prematurely. The authors supported the assumption that epigenetic modifications mediate the influence of diet on early programing, which, in turn, primes the neonate for later metabolic and health problems.

This review discussed published evidence from animal models, suggesting linkages between epigenetic modifications involving abnormal adipose tissue lipogenic gene expression, enlarged adipocytes, and adulthood metabolic disease. Animal models also show that high-fat diets in animals who suffered intrauterine growth restriction lead to accelerated growth and high levels of circulating leptin (an adipose-derived protein hormone proven to play an important role in metabolism), energy regulation and expenditure, and appetite. Animal models show that overfeeding rats in the immediate neonatal period lead to elevated levels of glucocorticoid receptor (GR) mRNA and 11β hydroxysteroid dehydrogenase type 1 in the visceral adipose tissue. Alterations in the HPA axis lead to alterations in the ability of the rat pup to regulate food intake and energy expenditure. Therefore, it is assumed that overfeeding in the immediate postnatal period can alter the function of HPA axis and lead to early obesity.[27-29]

Rat models also provide insights on epigenetic modifications associated with tube feedings, which is a common practice in preterm neonates. Gastrostomy feedings of high-protein diet in rats who were separated from their mothers have been shown to lead to short-term weight gain, insulin resistance, and modified expression of glucose transporter protein 4 and glucose transporter protein 2, which are 2 proteins encoded by the glucose transporter protein 4 and SLC2A2 genes, respectively. Glucose transporter protein 4 is an insulin-regulated glucose transporter mainly found in skeletal muscle and fat cells. Glucose transporter protein 4 facilitates the transportation of glucose across cell membranes. Rats who received high-carbohydrate diets through tube feedings had increased obesity, hexokinase activity, and increased insulin synthesis with increased pancreatic islets later in life. How these findings are relevant to how human preterm infants are fed in the NICU is unknown. Yet, they are something to consider in future research exploring factors for potential long-term outcomes for preterm infants.[27-30]

Adequate nutrition is important for optimal brain function. Despite advances in formula compositions and availability of formula fortifiers, provision of adequate protein and energy in preterm infants remains a great challenge. Meeting nutritional requirements for adequate growth and neurodevelopment that parallel those of a gestation equivalent fetus in utero is complex and requires intricate coordination between nutrition and endogenous processes, such as growth hormone synthesis and secretion. Oftentimes, nutritional goals cannot be achieved in preterm infants because of a mismatch between their nutritional needs and the immaturity of their systems and physiology. High-protein diets and the use of specialized formula have been associated with improved neurodevelopment and growth. However, those diets are believed to present an increased risk for obesity later in life. There is also growing concerns about the contribution of rapid rate of growth early in life to the development of adult disease including metabolic disease, type II diabetes, cardiovascular disease, and visceral adiposity. The mechanisms by which early diet leads to adulthood disease in preterm infants are not clear. Animal models point to the possibility of long-term epigenetic changes.[29,30]

Current evidence on the relationship between diet in the immediate postnatal period and programing and how epigenetic modification mediates programing comes from animal models. To date there is limited evidence involving human studies. Data come predominantly from retrospective epidemiologic studies and findings from those studies are consistent with animal findings.[14,31-33]

Postnatal Maternal Care, Tactile Stimulation, and Brain Development

This review yielded 2 articles involving epigenetic modifications, maternal care, and brain development in preterm infants. A study by Guzzette et al[16] examined how epigenetic modifications mediate the effect of tactile stimulation and maternal care

on the maturation of visual acuity. The investigators concurrently confirmed their findings with human infants to animal models, using rat pups. Ten medically stable infants born between 30 and 33 weeks' gestation received massage therapy, which was delivered over 2 blocks of time, 5 days each separated by a 2-day break. Infants were matched with 10 controls for age, gender, and birth weight. Massage therapy sessions started on day 10 after birth and consisted of 10-minute tactile stimulation followed by kinesthetic stimulation. Fine-tuned German music was played in the background during massage therapy. Several outcome measures were obtained pre- and postmassage and included (1) anthropometric measures of length, weight, and head circumference; (2) electrophysiological assessment including electroencephalograms (EEGs) and flash visual evoked potential to measure visual system maturation and brain auditory-evoked potentials; (3) serum levels of insulin-like growth factor (IGF), IGF binding protein 3, glucose, insulin, cortisol, and thyroid hormones; and (4) behavioral acuity was tested at 3, 7, 9, and 12 months corrected age by the same practitioner using an acuity card testing procedure.

Testing in infants was paralleled with testing in 3 groups of rat pups. One group was separated from the mother after birth and received tactile stimulation. Another group was separated from the mother but received no tactile stimulation. A third group was kept with the mother undisturbed and served as a control group. It was found that massage therapy has positive behavioral and electrophysiological outcomes. Accelerated visual maturity was observed prior to 7 months of age in infants who received massage therapy sessions. Similar observations were made in rats.

Higher levels of IGF-I, which is presumed to have a protective effect against retinopathy of prematurity, were found, and a reduction in cortisol levels was observed in massaged infants compared with their control counterparts. Rat pups who received massage therapy were found to have increased IGF-I brain levels in both the visual and auditory cortices. Electroencephalographic tracing showed brain maturation at all electrodes in the massaged rats. Injecting an IGF-I antagonist centrally in the rat pups resulted in blocking the effects of massage on IGF levels in rat pups, indicating that IGF-I plays a role in mediating the effects of massage therapy on brain development.

Evidence from animal models shows that maternal care (licking and grooming) has a significant impact on the neurobiology of brain development. Gudsnuk and Champagne[6] provided a summary on animal research involving epigenetic effects of early-life experiences on behavioral outcomes. The review provides valuable insights from animal models on how maternal care affects brain development. Effects are believed to be mediated by molecular changes involving gene transcription crucial for the synthesis and release of specific hormones and enzymes.

Animal models show that maternal care plays an important role in GR expression and HPA activity as well as attachment between the mother and her infant.[34] Rat pups who receive good maternal care through licking and grooming lose their GR methylation and as a result develop more GRs in the hippocampus. A higher number of GRs allow for better regulation of glucocorticoid hormones, which play an important role in the capacity of the pup to respond to stress. Alterations in glucocorticoids receptors are believed to persist later in life. Grooming and licking increase GR gene transcription in the hippocampus, which in turn protects rat pups from glucocorticoid hypersecretion.[35]

In addition to its effect on the HPA activity, animal models also show that grooming and licking by the mother have an effect on estrogen, growth hormone, and ornithine decarboxylase, a regulator of cell proliferation and differentiation. Female pups who were subjected to low levels of licking and grooming were found to have decreased transcription of estrogen receptor alpha (ERα) in the medial preoptic area of the hypothalamus. Estrogen's neuroprotective effect occurs through the 2 preceptors ERα and ERβ. Both receptors are present in the neocortex. Westberry and colleagues[36] found that ERα protein expression reflects changes in mRNA expression, and ERβ gene expression is regulated by DNA methylation following middle cerebral artery occlusion in rats. Gender was found to have a differential effect on DNA methylation with males having higher levels of DNA methylation. Changes at the molecular level in the neuronal system affect synthesis and secretion of various hormones that control cell differentiation, behavior, and cognitive functioning. Rat pups deprived of maternal care showed altered circadian rhythms, impaired tissue growth, and learning and memory deficits.

Implications

No doubt, evidence from animal models has expanded our knowledge and enhanced our understanding on how exogenous stimuli influence brain chemistry, maturation, wiring, pruning, and function. Currently, there is a paucity of data on epigenetic modifications in preterm infants. Lester et al[37] and Pickler et al[38] have each developed conceptual models to infer how these variables might be related to family-centered developmental care and experiences in the NICU. Results of the efficacy of these conceptual models are currently unavailable in the literature. More research is needed to understand these variables and their moderating or mediating relationships to each other. Furthermore, findings from such research with the preterm infant would support the development of targeted interventions to best support positive

short- and long-term outcomes. Inferences can be made that long-term epigenetic adaptations involving environmentally sensitive pathways similar to those observed in animals occur in premature infants, as many features of mammalian development tend to be similar. Despite significant changes to neonatal care practices and care environments, there remains a great concern about the level of maternal separation and noxious stimuli that a preterm infant experiences early in life. Brain development is dynamic with constant interaction between the brain and the environment. There are multiple pathways implicated in the neurodevelopment of preterm infants. The level, quality, and type of sensory stimulation that the brain receives play a significant role in how the brain wires, fires, and relays information from one region to another. Preterm infants are vulnerable for programed changes if their care environments are less than optimal. Epigenetic modifications occur to increase chances of survival during stressful periods of development. Survival may come at a high long-term cost; in addition, modifications could be transferred from one generation to another. Recent studies in preterm children revealed increasing rates of mild cognitive, sensory, language, attention and learning deficits, behavioral and motor problems, and low developmental scores.[39,40] Other than early gestation, there is no direct evidence to link such deficits to early-life experiences or to provide insights on the contribution of adverse early-life experiences to such outcomes.

Animal models are the basis for research in humans and at this time provide overwhelming evidence linking adverse experiences early in life to interruptions in brain maturation, which could have long-lasting effects. Even though they are built on sound scientific principles, there are still detailed differences in brain structure and neurobiology between animal and humans. Epigenetic research in humans is emerging and rapidly advancing. As scientists overcome biological, technical, and cost-related challenges, such research has a great potential in determining key environmental factors that affect the preterm genome, allowing for targeted interventions. Epigenetic research has the potential to lead to the identification of biological markers, gene expression profiles, and profile changes that occur overtime in response to early-life experiences. Combined with knowledge gained through the use of advanced technologies, epigenetic studies have the promise to refine our understanding on how the preterm brain matures and functions from multiple perspectives. Such understanding will pave the way for care practices that will allow the preterm brain to develop to its full capacity and will lead to the best possible outcome. Meanwhile, several care strategies have been identified, which are believed to protect and support brain development. A previous publication by the authors provided a discussion of such strategies.[41]

CONCLUSION

Conversion of stress signals into biochemical responses within cells triggers a cascade of events, the nature of which depends on how the signals are perceived by the cell. It is speculated that early-life experiences alter the stress response and create stress response channels in preterm infants different from those observed in term infants that disrupt normal brain growth and development. Healthcare providers must be cognizant of the implications that environmental stress has for brain development and must use every opportunity and care encounter to influence the brain plasticity in positive ways.

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