The Effect of Severe Stress on Early Brain Development, Attachment, and Emotions

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A Psychoanatomical Formulation

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KEYWORDS

• Child abuse • Child neglect • Limbic system development • Emotions • Attachment • Amygdala • Psychoanatomical formulation

KEY POINTS

- Child abuse and neglect are the most severe forms of stress experienced by children and adolescents.
- Child abuse and neglect has severe developmental consequences to the development of the amygdala, septal nucleus, and anterior cingulate gyrus, which are rapidly developing, especially in very early infancy.
- The basic emotions of joy, surprise, sadness, anger, and fear develop in the first 6 months of life. Embarrassment, envy, empathy, pride, shame, and guilt (which requires self-consciousness) develop by 3 years of age.
- Synaptic modification and consolidation is very vulnerable during the experience-expectant, sensitive developmental periods. Child maltreatment may have severe consequences, resulting in maladaptive cell assemblies and synaptic connections.
- The psychoanatomical formulation is a theoretically based explanation used to conceptualize a clinical case by correlating the disturbed neuroanatomy with behavioral and emotional symptom expression. It provides the clinician with an added dimension in understanding a clinical case.

Child neglect and abuse are the most extreme forms of stress in children, with severe effects on social, emotional, interpersonal, and neuronal development. According to the US Department of Health and Human Services, from data submitted by 49 states, the District of Columbia, and the Commonwealth of Puerto Rico, there were 3,184,000 children who received child protective services in 2012. Overall, four-fifths (78.3%) of victims were neglected, 18.3% were physically abused, 9.3% were sexually abused,

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Abbreviations	
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EBS	Electrical brain stimulation
LTP	Long-term potentiation
NIMH	National Institute of Mental Health
PAG	Periaqueductal gray matter
PTSD	Posttraumatic stress disorder

and 8.5% were psychologically maltreated.[1] Child neglect is associated with adverse psychological and educational outcomes and it is hypothesized that these outcomes may be caused by adverse brain development.[2] Early life trauma is associated with persistent developmental brain changes that mediate the increased diathesis not only to mood and anxiety disorders but also to depression, posttraumatic stress disorder (PTSD), schizophrenia, and bipolar disorder.[3]

Animal and human studies have expanded knowledge of the emotional or limbic system, and provided insight into how normal and abnormal development unfolds. This article introduces the concept of the psychoanatomical formulation, developed by the author and defined as a theoretically based explanation used to conceptualize a clinical case by correlating the disturbed neuroanatomy with behavioral and emotional symptom expression. Following the vignette of a neglected 2.5-year-old child, the development and function of limbic structures involved in emotions and attachment is discussed, with emphasis on the first year of life. Next, the emergence of basic emotions in children from birth to 3 years is reviewed, followed by a discussion of basic principles of neural and synaptic development and their implications for child abuse and neglect. In addition, the developmental neuroanatomy of child neglect is brought together in the context of the psychoanatomical formulation of the case vignette.

Clinical Vignette: A 2.5-year-old Girl with Disinhibited Social Engagement Disorder

Amy was 2.5 years old when her adoptive parents brought her to the child psychiatry clinic for evaluation and treatment of her emotional and behavioral problems, after requesting a referral from the pediatrician. The child appeared to be oblivious of danger and very accident prone. She would fall a lot; bump into furniture and walls; scream inconsolably, sometimes for an hour; and fight with her 4-year-old and 5-year-old adoptive brothers. Amy showed difficult behavior and frequent temper tantrums at the Head Start program she attended. She had out-of-control episodes, being aggressive, biting other children and, overall, being unpredictable. Her adoptive parents were appropriately concerned because Amy often went to strangers and was very friendly with them. On several occasions, she tried to leave the house with strangers who came to the door. She did not seem to show any wariness of unfamiliar people.

Past history revealed that Amy was born to Latino parents with no perinatal complications. Her biological father had been in jail since before Amy was born. Early history revealed disruptive, unstable, and chaotic child rearing. She was under the care of her biological mother from birth until 5 months of age. During that time her mother neglected taking care of her and failed to provide basic emotional needs for affection and reliable mother-child interactions. Her mother left her with multiple caregivers. She was moved consecutively to different homes of a relative and a friend before the Department of Social Services got involved when Amy was 20 months old. She was then placed with the current adoptive parents.

Medical evaluation did not show signs of physical or sexual abuse. There was no history of sexualized play. However, because language was delayed, knowing fewer than 50 intelligible words, she was referred for early intervention services. In a short period of time her speech showed improvement. She started putting 2-word phrases together and repeated phrases. She looked at people when they called her name, was affectionate with loved ones, and liked to be held often. She played appropriately with toys. However, she had trouble adjusting to change and continued to be aggressive toward other children, often hitting or biting them. She continued to have no sense of danger, banging into objects and falling from furniture she climbed, even though gross motor coordination was age appropriate. She continued to go up to unknown people indiscriminately, in spite of repeated warnings by her adoptive mother and father.

EMOTIONS, ATTACHMENT, LIMBIC NUCLEI DEVELOPMENT AND FUNCTIONS, AND TRANSITION PERIODS DURING EARLY INFANCY

In spite of controversies and open criticism by some neuroscientists,[4,5] the term limbic system, which MacLean[6] used to replace the old term rhinencephalon, has persisted in the neurologic, psychiatric, and neurobiological literature, to denote the structures that participate in generating emotions. The limbic system has become synonymous with the emotional system.[7] Five limbic structures have been posited to play a principal role in emotional expression and attachment behavior in the first year of life: hypothalamus, amygdala, septal nuclei, anterior cingulate gyrus, and hippocampus.[8] These structures form a circuit involved in the hierarchical control of emotions, with the anterior cingulate playing the role of an integrative cortical suprastructure, whereas, at the lower end, the hypothalamus (and periaqueductal gray matter [PAG]) act as a funnel through which all limbic-generated emotions are eventually expressed.[9] We argue later that child neglect and/or abuse lead to abnormal limbic development and, consequently, to severe psychological disorder. Concepts and evidence discussed here are used to provide a theoretic framework for the case using the psychoanatomical formulation.

According to Kagan and Baird[10] there are some correspondences between brain maturation and the ontogeny of human psychological competencies from birth to puberty, with significant maturational transitions that occur at specific ages. The first maturational transition period occurs at 2 to 3 months of postnatal life and is characterized by the disappearance of newborn reflexes, secondary to cortical inhibition of brain stem neurons and appearance of new synaptic contacts. There is a growth of inhibitory interneurons in the spinal cord that corresponds with the disappearance of these reflexes. There is a concomitant reduction in crying and an increase in social smiling that can probably be attributed to cortical inhibition of brain stem nuclei that mediate crying, especially in the PAG. Together with these developments, the infant shows the possibility of establishing visual expectations. This stage coincides with a great increase in the growth velocity of the mossy cells of the dentate gyrus of the hippocampus.[10]

Hypothalamus

The hypothalamus is almost fully developed at birth, and controls emotions in the newborn infant. It is the central core through which all emotions derive their motive force.[11] Endocrine, hormonal, visceral, and autonomic functions controlled by the hypothalamus are of utmost importance for the survival of the human infant. Paralleling these biological functions, and crucially important for the emotional survival, development, and attachment to the caregiver, are the emotional functions of the hypothalamus. Through this structure the newborn infant is capable of expressing aversion versus pleasure and rage versus quiescence. Vocalizations initially produced by the hypothalamus elicit maternal behaviors that attend to the basic needs of the infant, provide comfort, and are alerts to the need to be fed and cared for.

The hypothalamus consists of a complex number of nuclei, each with its subdivisions. However, in their extensive work on the neuroanatomy of the hypothalamus, Crosby and Woodbourne,[12] Crosby and Showers,[13] and Nauta and Haymaker[14] indicated that, for purposes of description, hypothalamic cell groups could be classified or subdivided into 3 longitudinal zones: periventricular, medial, and lateral.

The periventricular area is intrinsically associated with the neurohormonal control of the pituitary gland, and, as for stress, it plays a major role in the hypothalamic-pituitary-adrenal axis and is critically involved in the adaptation to stressful changes. From the point of view of the functional neuroanatomy of emotions, the medial and lateral nuclei play antagonistic but complementary functions. Electrical brain stimulation (EBS) with electrodes placed in the medial hypothalamic area in cats (and ventrolateral areas as well) resulted in what Flynn[15] called “attack with rage.” Now called affective aggression, it is manifested by rage display (eg, hissing and growling), autonomic changes (eg, pupillary dilatation, piloerection), but at the same time with an aversion component, because trained cats try to stop the apparently unpleasant stimulation. A rat sharing the cage would not be hurt, as if the aggressive display was all for show.[9,15]

In contrast with EBS to the medial hypothalamic area, electrical stimulation of the lateral hypothalamic areas (specifically the dorsolateral area) elicited what Flynn[15] called “quiet biting attacks,” which are now described in the scientific literature as predatory aggression. Cats stimulated with brain electrodes in this area move swiftly, with the nose close to the ground, stalking and going directly to the rat in the cage.

It may be useful clinically to conceptualize aggression under the subdivisions of predatory versus affective, because clinical assessment of the nature of aggression is often in one of these categories. Predatory aggression is goal oriented, planned, and controlled. The perpetrators hide their aggressive acts. The aggressors can control their aggressive acts. At the end, the predatory aggressors are proud of having been aggressive. This kind of aggression is seen in sociopathic behavior.

In contrast, affective aggression is reactive, unplanned, and uncontrolled. The aggressors may damage their own property with disregard to its value. They may be aggressive and lose control in front of other people, oblivious of shame in the heat of the moment. The aggressors expose themselves to physical harm. Children may fight with bigger, stronger children, disregarding the risk of being hurt. Aggression seems unplanned and to take place without an ultimate purpose. The aggressors may express remorse after the aggressive act.

EBS studies have the limitation that electrical stimulation may stimulate hundreds of thousands of emotions. A new, sophisticated technique developed by Karl Deisseroth and Ed Boyden at Stanford University can selectively stimulate a specially selected group of neurons (or their projection-specific dynamics) consisting of a promoter gene to an opsin (light-sensitive receptor) gene, which forms a construct that is expressed only on the specifically selected neuronal subpopulation (but not neighboring cells) when light is delivered to the brain through a fiberoptic cable (for a review see Tye and Deisseroth[16] and Fennol and colleagues[17]).

Using a variation of this technique, it has been shown that optogenetic stimulation of the ventromedial hypothalamus, ventrolateral part, causes mice to attack male and female mice and inanimate objects.[18] Optogenetic tools in the future will establish areas of dysfunction in psychiatric disease that are impossible to establish by any other means.[19]

According to Kagan and Baird's[10] ontogenetic model, the second transition occurs in most healthy infants between the ages of 7 and 12 months. During this period the infant is increasingly able to retrieve schemata (patterns of parents' physical features) and holds them along with current perceptions in a working memory circuit.[10] Separation fear occurs when the infant retrieves a schema of the mother's former presence held in a working memory circuit and tries to relate this to the discrepant perception of her current absence. Growth and development of the amygdala and prefrontal cortex are likely to be relevant to separation and stranger fear. Axonal projections from the amygdala to the anterior cingulate cortex through the capsula interna myelinize between postnatal months 7 and 10. This process coincides with the emergence of fears of strangers of separation from a caretaker.[10]

Amygdala

Experiments producing selective amygdala lesions in stressed infant monkeys, starting at 2 weeks of age, showed no difference in mother-infant interactions at 3 months of age. However, the one consistent and robust finding in both animal and human studies is that damage to the amygdala results in impairment in the danger-detection systems.[20–23]

The amygdala therefore plays a modulating role in social behaviors. The role of the amygdala as the detector of danger is to continuously evaluate the environment and surroundings for potential threats. These functions extend to social situations and generate appropriate physiologic/emotional responses.[23] Expanding on this concept, Buchanan and colleagues[24] postulated that what influences amygdala function is the unpredictable nature of social interactions. Damage to the amygdala results in inappropriate responses to ambiguous social cues.[24] Neonatal amygdala damage results in an inability to assess the degree of danger of a social situation and to modify behavior appropriately.[24]

Receiving sensory inputs from different parts of the brain, the amygdala monitors and abstracts the motivational significance from a wide array of multimodal sensory stimuli, from food to discrete social-emotional nuances.[11] It processes and funnels emotionally relevant sensory information from multiple neocortical and limbic areas and sends the processed data to the hypothalamus and brain stem, eliciting autonomic, endocrine, and emotional responses.[7] It responds mainly to danger/negative stimuli that evoke fear or defensive reactions but also responds to positive stimuli such as sexual attraction, positive emotional words, and appetizing foods.[7] It is responsive to somesthetic input and physical contact, both of which are necessary for maternal-infant bonding and the normal development of the amygdala.[8]

In general, there is a lateral-to-medial unidirectional flow and processing of information.[4,25] The lateral nucleus receives information from the neocortex and projects it to the basal and accessory basal nuclei, which in turn project it to the medial and central nuclei and form an output to visceral and autonomic regions. The centromedial amygdaloid complex forms a macrostructure with cell columns through the substantia innominata, including the bed nucleus of the stria terminalis portions of the nucleus accumbens, all of which makes up the extended amygdala.[26]

The amygdala analyzes information and transfers it back to the neocortex, with which it has extensive interconnections including the orbitofrontal and anterior cingulate gyrus. It projects to a much greater region of the neocortex than what it receives from the neocortex.[25] Hence, the normal amygdala is primarily wired to be able to adaptively sense, react, analyze, and respond to dangerous stimuli, rather than soothing and calming the individual. According to Amaral,[27] the amygdala is a protective device, designed to detect and avoid danger. It evaluates objects in the surroundings before interacting with them, and, based on this evaluation, coordinates species-typical responses.

The complexity of the small, almond-shaped amygdala cannot be overstated. It is heterogeneous in neurochemical organization, with rich intrinsic and extrinsic chemical neuroanatomy. The amygdala has the highest density of gamma-aminobutyric acid A receptors; a rich distribution of opiate receptors; and expresses as many neurotransmitters, peptides, and calcium-binding proteins as do the neurons in the neocortex.[25] Two major fiber systems, the stria terminalis and the ventral amygdalofugal pathway, connect the amygdala with the hypothalamus and other limbic structures involved in emotional expression.[28] In contrast with the hypothalamus, which can be immediately turned on and off, stimulation of the amygdala produces longer-lasting mood states after cessation of electrical stimulation.[11]

In the monkey, the amygdala receives input from area TE located in the anterior portion of the inferior temporal cortex. Area TE carries information from primary visual area V1, and comes at the end of the ventral stream of hierarchical visual processing. It is most responsive to complex visual objects like faces. It terminates in the lateral nucleus of the amygdala, which projects to the adjacent basal nucleus.[25] In the human brain, it is the fusiform gyrus that carries information of faces to the amygdala for processing. Social recognition requires the ability to recognize and remember other people before forming social relationships.[29] Lesions in the fusiform gyrus can abolish the ability to recognize faces. The right amygdala has a critical role in processing the emotional content of stimuli, including fearful facial expressions.[24,25,30]

The amygdala has a well-documented primary involvement in conditioned fear[4,31] and is prominently activated in response to fearful faces in subjects with PTSD compared with normal controls.[32]

Bilateral damage to the amygdala can result in an extreme lack of fear of dangerous stimuli and social situations. The case of S.M., a 44-year-old woman with bilateral amygdala damage as a result of lipoid proteinosis (Urbach-Wiethe disease), has been extensively studied.[33] She showed no fear of snakes and poisonous spiders when taken to an exotic pet shop. She was oblivious of danger when attacked with a knife in a park. She had an excessive degree of approach behavior and had a compulsive desire to touch and poke dangerous snakes, finding all of this interesting and amusing.[33]

Septal Nuclei

The septal nucleus attains greatest evolutionary development in humans. It is involved in emotional functioning and, like the amygdala and cingulate gyrus, it is capable of producing emotional vocalizations that may elicit care. It maintains a counterbalancing relationship with the amygdala, with antagonistic influence on the hypothalamus. The septal nucleus facilitates actions of the medial hypothalamus (whereas the amygdala mainly activates the lateral hypothalamus). It reduces extremes in emotionality and arousal and maintains a state of quiescence and readiness. It counters and inhibits aggressive behavior and suppresses expression of rage reactions following hypothalamic stimulations.[11] The septal nucleus exerts inhibitory influences on the amygdala, whereas the amygdala acts to facilitate or inhibit septal functions.[11] Development of the septal nuclei and anterior cingulate gyrus enable human infants to slowly develop a stable and selective loving attachment and, at around 6 months to 1 year of age, to show expressions of anger, joy, and fear. Normal, intact septal nuclei act to promote selective social attachments that are strengthened through positive reinforcement and caring parent-child interactions.

The septal nuclei undergo a more protracted rate of development than the cingulate gyrus. They do not reach adult levels of development until 3 years of age and continue developing into puberty.[8]

Anterior Cingulate Gyrus

The cingulum, formed by fibers from the cingulate gyrus, starts myelination in the second postnatal month, and completes its cycle of myelination about the end of the first postnatal year.[34] Through 7 to 8 months of age the septal nuclei and cingulate gyrus continue their development. The infant becomes more discriminating in interactions with others. Real and specific attachments are formed with the infant's caretaker.[8] Human attachment consequently becomes progressively more intense and stable as new synaptic connections are formed and reinforced.

From 9 to 12 months, the septal nuclei and cingulate gyrus development continues, together with that of the amygdala, which generates protective fear. About 90% of normal infants develop separation anxiety during these months. Indiscriminate social contact seeking is inhibited. Specific attachments are narrowed, strengthened, reinforced, and maintained.[8,11]

The anterior cingulate gyrus is thus of utmost importance in the formation of long-term attachments and maternal behavior. It participates with other limbic structures in the production of emotional sounds and the separation cry. Sounds generated by the infant promote intimate maternal behavior that responds, attends, and cares for the infant's needs, discomforts, or primitive emotions. A dyadic interplay seems to take place, because the sounds generated by the infant's anterior cingulate generate maternal instinctual feelings of tenderness, urgency, or care for the child. Destruction of the mother's anterior cingulate in nonhuman primates results in the loss of maternal responsiveness to the point that, if not rescued, infants may die from lack of care.[11] It is capable of processing and modulating expressions of emotional nuances, which is critical in the individual's response and adaptation in a social environment.[7]

During the first year of life, and before developing the capacity to express meaningful words, the infant develops what Joseph[8,11] calls the limbic language. Emotional sounds are initially produced by the hypothalamus, which, as mentioned previously, is fully functional at birth. The amygdala, septal nuclei, and cingulate gyrus are also capable of generating emotional sounds as they continue to mature during the first year of life. Socializations concomitantly become more complex and reflect specific mood states.[8,11]

The anterior cingulate gyrus, the largest limbic structure, functions in affective, autonomic, cognitive, social, and motor and motivational behavior.[7] It is a cortical suprastructure capable of initiating voluntary behavior and is able to produce emotional sounds that are not reflective of mood. As children grow older they develop more flexibility and increased voluntary control, and can mask a feeling state or deceptively pretend to have a different emotion.[8,11] Toddlers, aged 1 to 3 years, can whine, exaggerate feeling states, or simply imitate emotional sounds in order to manipulate a social situation, obtain a reward, or change the other person's behaviors; they can become experts at this.

Hippocampus

The hippocampus plays a major role in the storage and consolidation of information into long-term memory. It is of utmost importance in learning and memory encoding, providing long-term storage and retrieval of newly learned information.[7,11] The hippocampus has an intimate relationship with septal nuclei with which it is connected by fibers from the precommissural fornix. In concert with the medial hypothalamus and septal nuclei, it prevents extremes in arousal and maintains quiet alertness.[11] It is greatly influenced by the amygdala. It interacts with the amygdala in generating emotional imagery and is of paramount importance in learning and memory.[7,11] The amygdala and the hippocampus function in synchrony. Although the amygdala plays an important role in mediating emotional memory, the hippocampus has a major role in the organization of episodic memory.[35] Thus the hippocampus has an interdependent memory role with the amygdala. The amygdala is responsible for storing emotional aspects and personal reactions to events.[11] Functional imaging studies show that the amygdala becomes active when recalling personal and emotional memories. The hippocampus has a major role in contextual fear conditioning, contributing to the formation and retention of contextual fear associations.[4,31] There is a bidirectional neural communication between the hippocampus and the amygdala, which may provide the pathway of emotional reactions to contextual cues imparting emotional meaning to the context.[31] Projections from the amygdala to the hippocampal formation are stronger than vice versa, indicating that the amygdala provides an additional type of sensory information that is not reciprocated; perhaps the species-specific significance to an event.[25] The hippocampus interacts with the prefrontal cortex to recruit specific memories to guide planning and strategizing.[35]

In early infancy the greatest increase in the rate of growth of the hippocampus occurs between 2 and 3 months; the mossy cells of the hippocampus dentate gyrus undergo a spurt of differentiation. This differentiation probably contributes to the increased ability of a 2-month-old infant to recognize an event following a delay, and for a 3-month-old to establish expectations.[10]

EMOTIONAL ONTOGENY: FROM ZERO TO 3 YEARS

Emotions are almost fully developed by the age of 3 years, although further refinement and elaboration of emotions may take over after that time.[36] Thus, the first 3 years of life represent the major developmental leap in the emergence of human emotions.[36]

As previously discussed, the hypothalamus is almost fully developed at birth and is responsible for generating primitive emotions. At birth, children show what has been called a bipolar emotional life[36] (here, the term bipolar is not used to describe a mood disorder, but the manifestation of 2 distinct emotional poles). Although the newborn can show general distress manifested by crying and irritability (the negative pole), there is also pleasure reflected by satiation, attention, and responsivity to the environment, which represents the positive pole of this bipolar dichotomy.

The development of the social smile by the age of 3 months marks the emergence of joy in human infants. They show happiness and excitement (active and wiggling) when exposed to familiar or unfamiliar faces or even a cardboard Halloween mask when frontally presented.[37] During the same time, sadness emerges. Three-month-old infants react with sadness when their mothers stop interacting with them or on withdrawal of positive-stimulus events.[36] Infants react with joy and smiling when positioned in front of their mother's face. On the mother's presentation of a still face, 8-month-old babies first try to engage mothers by gesturing, making noises, and other maneuvers to attract the mother's attention. If the mother reengages in the interaction, the child's joy returns. However, if mothers are not available to reassume interactions with their infants, the results can severely impair the child's emotional development. Distaste, the precursor of disgust, also appears around this age and is manifested by spitting out and getting rid of unpleasant tastes in the mouth. Although some clinicians consider this to be evidence of disgust,[36] others have argued that true disgust does not appear as a separate emotion until the child is 4 to 8 years old.[38,39]

Anger emerges between 4 and 6 months of age. Anger is the adaptive action pattern that has evolved to enable humans to overcome a barrier to a goal. Anger thus results when the goal is blocked. Experiments with 4-month-old infants have shown that anger is manifested when children are frustrated (eg, when their hands are tied down and prevented from moving).[36] Anger expressions are targeted at other people by 7 months.[40]

Fearfulness emerges at around the age of 8 to 9 months. In order to develop fear, infants have to have the capacity to compare the event that frightens them with another event. For example, in the case of stranger anxiety, infants have to compare the face of the stranger with the mental representation of familiar faces. Fear results when there is a discrepancy between the new (stranger) face and the mental representations of familiar faces. Before developing this cognitive capacity, infants do not fear stranger faces, or even, as mentioned earlier, masks of human faces.

Surprise is another emotion that appears in the first 6 months. Children show a surprise response either when there is a violation of expected events or as a response to discovery. For example, when infants see a midget walking toward them, they show interest and surprise (rather than joy or fear), as a result of the discrepancy of seeing a small adult.[36]

The emergence of self-awareness during the second half of the second year of life gives rise to self-conscious emotions. These emotions include embarrassment, empathy, and envy. The emergence of embarrassment only takes place after children develop self-recognition. Embarrassment is measured by nervous touching, smiling, gaze aversion, and return behaviors.[36] Shame is closely related to embarrassment, but it is a more intense emotion accompanied by the wish to hide, disappear, or die and is a highly and painful emotional state that is difficult to dissipate.[41] Shame requires self-evaluation, which is a higher cognitive level than self-recognition or the consciousness that is required for the emotion of embarrassment. True empathy or veridical empathy develops at the end of the second year into the third year, when children become more aware that others can have their own thoughts, feelings, and desires.[42]

Self-conscious evaluative emotions require children to have the capacity to evaluate their behavior against a standard. This cognitive capacity emerges between 2 and 3 years of age. Besides shame, these complex social-evaluative emotions include pride and guilt. Evaluating self-conscious emotions of failure may result in shame, guilt, or regret, whereas self-perceived success gives rise to feelings of pride.

Therefore, by 3 years of age, normal children have formed the basis for an elaborate and complex emotional system that will expand in the years to come.[36] However, this normal development can be disrupted by excessive stress in infants or children as a result of neglect, physical or sexual abuse, or witnessing domestic violence. Individuals with poor attachment histories display empathy disorders: limited capacity to perceive the emotional state of others.[43]

PRINCIPLES OF NEURONAL DEVELOPMENT: IMPLICATIONS FOR CHILD ABUSE AND NEGLECT

The effect of child abuse and neglect on the limbic brain development at the cellular level can be conceptualized and organized under 4 closely interrelated developmental principles:

1. Hebbian synaptic modification
2. Experience-expectant learning
3. Sensitive periods of development
4. Self-organizing brain development

Influenced by the work of Spanish neurophysiologist Rafael Lorente de Nó, Canadian psychologist Donald Hebb[44] insightfully described a hypothetical mechanism of synaptic transmission that is still valid today. This hypothesis may be summarized as follows: synaptic knobs between communicating neurons develop with persistent neural activity and result in a lower synaptic resistance. The greater the contact area, the greater the chances that the action potential of the presynaptic cell will be decisive in firing another postsynaptic signal. The extent of the contact established is thus a function of joint cellular activity. As a result of the increased area of contact, firing of the efferent cell is more likely to follow the lead of the afferent cell.[44] Synaptic changes result in the consistent firing of 2 connecting neurons. Any 2-cell systems that are repeatedly active at the same time tend to become associated, forming what Hebb[44] called the cell assembly. These groups of reciprocally connected cells are simultaneously activated by the internal representation of an external event or object. If cell assemblies are repeatedly and persistently activated, consolidation occurs, making reciprocal connections more effective. Hence the observation that "neurons that fire together will wire together."[45]

The discovery of long-term potentiation (LTP) and its cellular and molecular mechanisms provided supporting scientific evidence for Hebb's[44] hypothesis. LTP results in long-lasting modifications in postsynaptic neurons, altering the synaptic structure permanently to facilitate future impulse transmission.[35] LTP has been demonstrated in the limbic system. Emotional states increase neurochemical excitation, which is essential for synaptic modification and learning. Amygdala-hippocampal synchrony mediates memory formation and consolidation.[35] LTP throughout the developing limbic system consolidates the infrastructure of intralimbic and corticolimbic circuits.

Hebbian modification of synapses resulting from the simultaneous activation of presynaptic and postsynaptic neurons enhances healthy, normal development in infants exposed to nurturing, caring environments that provide attention to basic needs, positive affections, maternal bonding, and positive sensory stimulations. However, in neglected or abused infants, this Hebbian modification can have the most detrimental and potentially long-lasting effects. These infants' brains establish, strengthen, and consolidate synaptic connections necessary for immediate survival, but, in the long run, are not adaptive or flexible enough to respond to normal environmental demands and proper learning. Moreover, development of emotions favors, strengthens, and consolidates connections that promote the expression of negative rather than positive emotions. In addition, those synapses that would provide healthy adaptation, learning, and positive emotions are not properly developed, retract, and are likely to be eliminated.

The second developmental principle is experience-expectant brain maturation. This principle is based on the theory that the neonatal brain is programmed to be stimulated by the environment in order to attain optimal development; it is experience expectant. Perinatal experiences, whether positive or adverse, play a crucial role in early brain development.[46] Experience-expectant learning implies that the developing brain expects and is primed to react to the exposure to environmental stimuli that will shape its development.[35] Rewiring and strengthening of connections and the maintenance of functional neuronal networks is achieved by epigenetic changes related to the interphase of genetic and environmental factors.[46] Experience-expectant learning takes place early in life. By contrast, experience-dependent learning refers to additional skills that the brain does not expect. It does not involve critical sensitive periods, but rather can be developed over a lifespan. Synapses are formed in response to, rather than in anticipation of, an experience.[35]

During early postnatal development, the brain expects to receive visual stimuli, including faces that are to become familiar, to develop language receptivity and the anxiety necessary for detecting danger, which will promote survival, and to establish the facial recognition necessary for bonding and so forth.

Limbic system circuit development requires extensive environmental stimulation. These circuits cannot achieve full functional potential under impoverished or adverse environmental conditions.[46] Experience-expectant emotional experiences during early infancy are crucial for interlimbic and prefrontolimbic pathway development during critical sensitive periods, and shape their function in adulthood. Neglected infants are particularly prone to this. Dysfunctional infant attachment may predispose the individuals to develop lasting, irreversibly impaired emotionality and social behavior later in life.[46]

The third developmental principle is that certain aspects of early brain development only take place during sensitive periods of development. Sensitive periods are developmental windows in which maturation and specific experiences interact to produce differential long-term effects on the brain and behavior.[47] During this time window a biological event develops more easily under the influence of an environmental stimulus. After this sensitive period has ended, learning is more difficult and less efficient. Examples of this are vision and language acquisition. Hubel and Weisel[48] performed experiments temporarily suturing the eyelids of kittens from birth to 3 months of age. These cats not only never fully developed vision through the blindfolded eye but also neurons in the occipital cortex receiving inputs from that eye greatly decreased their space compared with the increased cell growth of the cortex corresponding with the seeing eye. The deprived eye never develops normal vision later in life.

Some investigators distinguish between sensitive periods and critical periods. Sensitive periods start and end gradually and are particularly sensitive to certain types of stimuli. After the sensitive periods end, the individual can learn, but learning is more difficult, takes longer, and may require intensive interventions. An example of this is language acquisition. By contrast, critical periods are finite, compulsory, and are associated with a heightened sensitivity to a specific environmental stimulus that allows the development of a certain skill, after which acquisition is difficult or impossible. The example of vision fits this concept. Limbic and higher neocortical structures are open; that is, they change with experience during development. Lower structures like the hypothalamus and PAG are closed and change little or not at all.[9] However, limbic structures complete myelination in the second decade of life, much earlier than the neocortex.[34]

The principle of sensitive periods and critical periods has important implications for neglected or maltreated infants. Infants who do not regain adequate care after prolonged deprivation during the first year of life may be emotionally damaged for life.[37]

Finally, the fourth developmental principle conceptualizes brain development as a process of self-organization. Drawing from neurobiological research, Lewis[35] incorporated these data to formulate the principles and mechanisms of self-organization, with emphasis on the role of emotion in self-organizing neural systems.[35]

Brain development can be conceptualized as a process of self-organization, evolving in unpredictable and indeterminate ways through the repeated modification of synaptic systems.[35] Neural development organizes itself to achieve forms that were initially indeterminate. Self-organizing synaptic sculpting consists of 2 forces:

1. Synaptic elaboration (ie, proliferation and strengthening)
2. Synaptic pruning

Synaptic elaboration favors activity of some synapses rather than others. Pruning gets rid of underused synapses and consolidates synaptic stability. Neuronal substrates of emotion influence structural changes in all areas of development.[35] Emotional stress dysregulates neural activity in infancy by shutting down circuits for processing social information.[49] Self-organizing synaptic sculpting in infants exposed to neglect and abuse is expected to prune synapses promoting normal attachment and emotions, and proliferate and strengthen those maladaptive connections that express negative emotions and interpersonal difficulties.

THE PSYCHOANATOMICAL FORMULATION

Amy fulfills the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) diagnostic criteria for disinhibited social engagement disorder[50] (this corresponds with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV] diagnosis of reactive attachment disorder of infancy and early childhood, disinhibited type). This disorder is characterized by a pattern of behavior in which a child actively approaches and interacts with unfamiliar adults, and in Amy's case this was manifested by reduced or absent reticence in approaching and interacting with unfamiliar adults. She also displayed overly friendly, familiar behavior. She showed willingness to go off with an unfamiliar adult with minimal or no hesitation, as when she tried to leave the house with strangers who came to the door. Amy also experienced a pattern of extremes of insufficient care, as shown by social neglect and deprivation in the form of a persistent lack of having emotional needs met for comfort, stimulation, and affection by caregiving adults. She also had repeated changes of primary caregivers (mother, relatives, and mother's friend), which limited opportunities to form stable attachments.

However, this diagnostic formulation does not provide insight into the underlying developmental/neuroanatomic mechanisms that are playing an important part in the manifestation of emotions and behavior in the patient. This author has developed the concept of psychoanatomical formulation, which is defined as the assessment/analysis of a clinical case based on the disturbed functional neuroanatomy underlying behavioral and emotional symptom expression. The earlier discussion of limbic nuclei development and function, development of emotions, and developmental principles as they relate to child neglect and abuse serves as a background for better understanding this formulation. This psychoanatomical formulation comes closer to National Institute of Mental Health (NIMH) Director Thomas Insel and colleagues'[51] efforts to develop research domain criteria that conceptualize mental disorders as disorders of brain circuits.

Psychoanatomical Formulation of Case Vignette

Amy is a 2.5-year-old girl with a history of severe early neglect during the first 20 months of life. During the first year of life, the amygdala, followed by the septal nuclei and anterior cingulate gyrus, are rapidly developing and forming synaptic connections. Physical contact and emotional parental involvement are crucial for the development and wiring of these limbic structures. The role of the amygdala is to detect danger and continuously evaluate the environment for surrounding threats. Amy's obliviousness of danger and her accident proneness seems to have resulted in an impairment in her danger-detection system. This amygdala deficiency extends to her social situations with strangers, and impairs her amygdala's ability to generate appropriate physiologic/emotional responses. Her poorly functioning amygdala is unable to respond appropriately to social cues and the unpredictable nature of interactions with strangers. As a result she is unable to assess the degree of danger when a stranger comes to her home door, and to modify her behavior accordingly. Because of extreme neglect, Amy did not receive the somesthetic stimulation and physical contact necessary for maternal-infant bonding and the normal development of the amygdala. Her lack of fear of dangerous stimuli and in social situations is also found in individuals with bilateral damage to the amygdala.

Amy's neglect continued through the second half of her first year of life, with the changing of caregivers. It can be inferred that neglect and lack of positive reinforcement from caring parent-child interactions during this time period interfered with the normal development of the septal nuclei and anterior cingulate gyrus, which are involved in the development of stable, selective, loving attachments. Because of the lack of normal development of the anterior cingulate gyrus and its synaptic connections, she did not develop the ability to be discriminating in interactions with others and to form real, specific attachments. Although not available by history, she probably never developed stranger and separation anxiety during the ages of 7 to 12 months. She was unable to form long-term attachment because of her exposure to neglect, the change of caregivers, and the resulting poorly developed anterior cingulate gyrus.

As the result of the stress caused by neglect and social impoverishment, Amy most likely established, strengthened, and consolidated the connections necessary for her immediate survival; however, now that she has been adopted into a caring and nurturing environment, these Hebbian modifications are maladaptive. She is not able to respond appropriately to her new environment and express positive emotions. Synapses that would provide healthy adaptation, learning, and positive emotions were not properly developed, ending up retracted and most likely eliminated.

Amy was not exposed to the normal environmental stimuli that a neonatal brain is programmed to receive in order to attain optimal development. She did not receive experience-expectant emotional experiences during the 20 months of life that are crucial for limbic and prefrontolimbic circuit development. Self-organizing brain development and synaptic sculpturing most likely proliferated and strengthened maladaptive connections, with synapses promoting positive emotions and secure attachments being eliminated. In addition, all of this neglect occurred very early in life, during the sensitive periods of emotional development. Recovery from the severe consequences of this neglect will be difficult, and most probably require intensive, long-term interventions. To her advantage is that she is still at a young age in which many limbic circuits have not finished myelinating. In addition, basic research has shown that afferents and new synaptic contacts from the amygdala to the medial prefrontal cortex increase significantly during the rat age equivalent to adolescence and early adulthood.[52] The implication here is that there is a second chance during adolescence for development of increased emotional control. It is thus possible that Amy may have another opportunity to improve emotional connections.

SUMMARY

Severe stress in the form of child abuse or neglect during early infancy may have serious, long-lasting effects on a person's brain development, affecting future manifestations of negative emotions, maladaptive behaviors, and conflictual attachments. As a result, individuals thus affected operate in a survival mode, rather than learning to flexibly adapt to environmental demands. More research is needed in order to understand the genetic and developmental protective factors that enable some persons to be less vulnerable and even more resilient to these extreme stressors, and for clinicians to learn to treat these patients more effectively.

The analysis and the correlation of external traumatic events with resulting structural brain changes provide a deeper, more detailed understanding of the classic nature-versus-nurture paradigm. This article is intended to stimulate psychiatrists and other mental health professionals to expand and incorporate their knowledge of neuroanatomy to conceptualize psychoanatomical formulations for patients with a variety of psychological disorders along the lifespan.

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