NEURODEVELOPMENT AND THE PSYCHOPHYSIOLOGY OF TRAUMA I:

Conceptual Considerations for Clinical Work with Maltreated Children

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Official citation: Perry, B.D. Neurodevelopment and the neurophysiology of trauma I: Conceptual considerations for clinical work with maltreated children. APSAC Advisor, 6:1,1-18, 1993

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INTRODUCTION

A terrified 3 year old child huddles, sobbing, in a dark corner of his room after being beaten by a drunk parent for spilling milk; a 'colicky' infant cries for 8 hours, left alone, soiled and hungry, by an immature, impaired mother; a 4 year old boy watches his father beat his mother -- only the most recent of many terrorizing assaults this child has witnessed in his chaotic, violent household. Many studies, wise parents and experienced clinicians tell us that these experiences will influence dramatically how these children grow up -- but how -- how do experiences change development? What is going on in these children's heads, literally; what are they sensing, perceiving, thinking and feeling? What are the neurobiological 'correlates' of the perceptions, thoughts, feelings and actions of a child's response to a traumatic event? How does the neurochemical milieu associated with fear influence the developing brain? How does repeated exposure to a traumatizing experience alter development? What are the mechanisms by which experience, any experience, influences development?

The impact of traumatic life experiences on children and formulations regarding 'how' traumatic experiences impact development have been discussed from many perspectives, primarily using descriptive, clinical or psychological formulations (e.g., Terr, 1983: 1991; Finkelhor, 1984; ; Conte, 1985; Eth and Pynoos, 1985; Browne and Finkelhor, 1986; Alter-Reid et al., 1985; McLeer, 1988). In contrast, the purpose of this paper is to discuss the impact of traumatic life experiences on the development of the brain and, specifically, on those portions of the brain involved in mediating the 'stress' response. Knowledge of the core neurobiology of the stress response when considered in context of basic neurodevelopmental principles can lead to important insights regarding the etiology and treatment of the adverse physiological, emotional, behavioral and cognitive sequelae of childhood trauma.

TRAUMATIZED CHILDREN: THE SCOPE OF THE PROBLEM

The signficance of understanding the neurodevelopmental effects of traumatic stress cannot be overstated. Each year in the United States at least 4 million children are traumatized by physical abuse, sexual abuse, domestic violence, community violence, natural disasters or man-made disasters. The potential devastation from traumatic stress can be illustrated by examining the effects of combat on adult populations.

The neuropsychiatric sequelae of combat have been best characterized in veterans of the war in Vietnam. In the 12 year period of the Vietnam Era, 3 million Americans served in the Vietnam theater. Over the next twenty years, fully thirty percent of these young adults developed Post-traumatic Stress Disorder (PTSD, DSM III-R) following combat-related traumatic experiences (Kulka et al., 1990). The debilitating symptoms of PTSD fall into three clusters; 1) recurring intrusive recollection of the traumatic event such as dreams, 'flashbacks' and intrusive thoughts, 2) persistent avoidance of stimuli associated with the trauma or numbing of general responsiveness and 3) persistent symptoms of increased arousal characterized by hypervigilance, increased startle response, sleep difficulties, irritability, anxiety and physiological hyperreactivity, reflective of a 'hyper-reactive' autonomic nervous system (see DaCosta, 1871; Bury, 1918; Dobbs and Wilson,1960; Horowitz et al., 1980).

How much more pervasive and disruptive traumatic stress must be on young children exposed to chronic violence or abuse during the most vulnerable years of their lives, during the time in which they are developing physically, cognitively, emotionally and socially. If a similar percentage of children exposed to the 'battles of childhood' develop stress related neuropsychiatric problems, over 1 million American children each year will join the ranks of other childhood 'veterans' in need of special mental health, educational and medical services. Furthermore, these childhood problems persist; the great majority of traumatized children carry their scars into adolescence and adulthood.

Despite the scope of this serious public health problem relatively little research has been dedicated to neurodevelopmental trauma or childhood PTSD. In contrast, studies on the neurobiology of the stress response (e.g., Stone, 1975; Sapolsky et al., 1986; Murberg et al., 1990), 'sensitizing' pharmacological (Kleven et al., 1990; Farfel et al., 1992) or stress paradigms (e.g., Kalivas and Duffy, 1989; Post, 1992), and the basic neurochemical and neurophysiology of PTSD in *adults* (e.g., Perry, 1988; Krystal et al, 1989; Giller et al., 1990; Perry et al., 1990a) have led to important clinical formulations and interventions. Similar progress in understanding disorders related to childhood trauma will depend upon research advances in neurodevelopment and the impact of traumatic stress upon this process.

The development of a human being from a single cell is an amazingly complex miracle of biology. By adulthood, a single set of genetic material has been differentially expressed in a billion different ways -- each resulting in a different cell with unique structural and chemical composition and, therefore, unique functional capabilities. The most complex of all organs, the human brain, contains 100 billion neurons and 10 times as many glial cells, each of them unique. The neurons and glial cells of the human brain connect and organize into functional units with specific roles to sense, perceive, process and act on information from outside and inside the individual in a fashion that promotes, first and foremost, survival and then other actions and transactions of being human.

Understanding the traumatized child requires recognition of a key principle of developmental neurobiology, *the brain develops and organizes as a reflection of developmental experience*, organizing in response to the pattern, intensity and nature of sensory and perceptual experience. The experience of the traumatized child is fear, threat, unpredictablity, frustration,

chaos, hunger and pain and, therefore, the traumatized child's template for brain organization is the 'stress response'.

THE NEUROBIOLOGY OF SURVIVAL

When an infant, child or adult is threatened there is a set of critical, teleologically-ingrained responses which the body uses to perceive, process and act to defend itself from the threat. In 1914 Walter B. Cannon first coined the phrase "fight or flight" reaction (Cannon, 1914). This well-characterized set of adaptive physiological responses to real or perceived danger involves a series of complex, interactive neurophysiological reactions in the brain, the autonomic nervous system, the hypothalamic-pituitary adrenocortical (HPA) axis and the immune system (see Loewy and Spyer, 1990).

The neurophysiology of the 'alarm reaction' has been studied extensively in man and in animal models (see Selye, 1936; Stone ,1975; Stone, 1988; Murberg et al., 1990). Acute 'stress' is associated with a variety of physiological responses including the activation of the HPA axis with a concomitant peripheral release of hormones including ACTH, epinephrine (adrenaline) and cortisol, a significant increase in centrally-controlled peripheral sympathetic nervous system tone and the 'activation' of a variety of neurochemical systems in the central nervous systems (CNS). The major method of communication in this process is neurochemical transmission. A chemical neurotransmitter is released from one neuron and interacts with specific neurotransmitter receptors on other neurons, 'communicating' some form of chemical message to these neurons and, thereby, altering their activity and functioning.

One of the most critical neurotransmitter systems involved the stress response is the noradrenergic nucleus called the locus coeruleus (LC: Korf, 1976). This bilateral grouping of norepinephrine-containing neurons originates in the pons, a more primitive, regulatory part of the brain, and sends axonal projections throughout brain, connecting directly or indirectly with virtually all major brain regions (Moore and Bloom, 1975; Fillenz, 1990). This diverse set of connections facilitates the orchestrating role of the LC, which acts as a general regulator and 'monitor' of many important brain activities, controlling noradrenergic tone and activity throughout brainstem, midbrain, limbic and cortical areas (Foote et al., 1983). The LC plays a critical role in arousal, vigilance, regulation of affect, behavioral 'irritability', locomotion, attention, the response to stress, sleep regulation and the startle response (Korf, 1976; Redmond and Huang, 1979; Foote et al., 1983; Aston-Jones and Bloom, 1981; Svensson, 1987; Waterhouse et al., 1988; Fillenz, 1990). Another key adrenergic/noradrenergic system in the brain, is the ventral tegmental nucleus (V.T.N.) which is involved in regulation of the sympathetic nuclei in the pons/medulla (Moore and Bloom, 1975). Acute stress results in an increase in LC and VTN activity. This increases release of norepinephrine from these neurons and influences various functions throughout the brain and the rest of the body.

The neurophysiological activation seen during acute stress is usually rapid and reversible. When the stressful event is of a sufficient duration, intensity, or frequency, however, the brain is altered. Stress induced 'sensitization' may occur -- the neurochemical systems mediating the stress response (e.g., LC noradrenergic systems) change, becoming more 'sensitive' to future stressors related to the original experience. The molecular mechanisms underlying this phenomenon are not well understood but are related to the same cascade of molecular processes involved in learning and memory.

The stressful experience, via a cascade of neurochemical events, alters the microenvironmental milieu of the CNS, resulting in altered gene expression. The portion of the genome that is

expressed in a given neuron is dependent upon the local 'microenvironment' in the nucleus of the neuron. This microenvironment, in turn, is a direct reflection of a biochemical cascade which begins with 'experience'. Experience activates the neurosensory apparatus and alters the pattern and quantity of neurotransmitter release throughout the neuronal networks responsible for sensation, perception and processing of information. This change in neurotransmitter activity influences, initially, the extracellular milieu of the neurons in the system and then, by neurotransmitter receptor/effector activation, changes important intracellular chemical constituents (i.e., second and third messengers) in all of the neurons synaptically connected to these systems. It is the changes in these second (e.g., cAMP, phosphatidyl inositol) and third messengers which alter the microenvironmental milieu of the nucleus, resulting in changes in gene transcription. These new gene products may then result in 'permanent' or structural changes which are associated with sensitization, learning, memory and, in the developing brain, differentiation (see Kandel and Schwartz, 1982; Goelet and Kandel, 1986).

Stressful experiences or certain drugs, then, when they result in a certain pattern of catecholamine (norepinephrine, dopamine, epinephrine) activity trigger a neurochemical cascade which results in altered expression of proteins (including receptors) involved in catecholamine responsivity (Kalivas and Duffy, 1989; Kleven et al., 1990; Farfel et al., 1992). This altered catecholamine responsivity (sensitization) likely underlies the hypervigilance, increased startle, affective lability, anxiety, dysphoria, increased autonomic nervous system hyper-reactivity seen in adult PTSD (see Krystal et al., 1989; Perry et al., 1990a). In the adult, mature brain, increases in, or unusual patterns of, catecholamine activity may result in sensitization. In the developing brain, however, neurotransmitters, in addition to their roles in cellular communication, play an important role in the basic neurodevelopmental process (Lauder, 1988). Trauma related alterations in catecholamine activity during childhood, therefore, may alter brain development, resulting in altered functional capabilities of the 'traumatized' brain (Perry, in press).

THE DEVELOPING BRAIN

Brain development requires that a small number of cells with similar properties divide, migrate and differentiate to result in billions of cells with different physical and chemical properties. Each of these cells has the same genetic material (genotype) but they have different portions of this genetic material being actively utilized, resulting in the different expressed properties (phenotype) of each individual neuron. The expressed properties of a neuron -- the size, shape, protein makeup, chemical constituents -- confer the functional properties of the neuron. By differentially expressing portions of the genome, the remarkable structural and functional diversity of neuronal components of the human brain is possible.

Differentiation is the process by which cells become specialized, expressing those components of the genome which confer special properties associated with the functions of the neuron in the mature brain. This process takes place throughout development. While the majority of neurons have been 'born' (neurogenesis) by birth (i.e., the final number of cells in the newborn brain is roughly the same as in the mature brain), the majority of individual cell growth and specialization has not taken place. Over the three years following birth, the important processes of neuronal migration, axo-dendritic projection, myelinization, synaptogenesis, and neurochemical differentiation continue to take place. As the brain develops, neurons divide, migrate, and differentiate in response to chemical, 'microenvironmental' cues (morphogens) which confer information to, and direct specific differentiation of, the cell. Each neuron's unique structural, biochemical and functional character, then, is a function of the its unique environmental history -- the specific pattern, timing and quantity of these microenvironmental cues.

Some of the most important of these microenvironmental cues are receptor-mediated signals from neurotransmitters and hormones. Hormones, neurotransmitters and direct cell to cell contacts act as morphogens. The quantity, pattern of exposure and timing of morphogenic cues orchestrate and guide neuronal development. Indeed, catecholamine cues during development are important in determining critical functional properties of mature neurons, including the density of neurotransmitter receptors (e.g., Miller and Friedhoff, 1988; Perry et al., 1990b). Alterations in the pattern, timing and quantity of catecholamine (or any critical neurotransmitter system) activity during development might be expected to result in altered development of catecholamine receptor/effector systems and the functions mediated, in part, by these systems.

A trauma-induced prolonged stress response will result in an abnormal pattern, timing and intensity of catecholamine activity in the developing brain. The time during development that this prolonged or abnormal catecholamine activity is present determines, to some degree, the nature and severity of the disrupted development. In general, the earlier and the more pervasive the trauma, the more neurodevelopment will be disrupted. The intrauterine environment is not necessarily protective. There is some evidence to suggest that prenatal or maternal traumatic stress has significant impact on neurodevelopment -- battering the pregnant mother is also battering the developing fetus (Amaro et al., 1980). The majority of child abuse or neglect takes place after birth, however. The development of the human brain continues beyond birth and its development remains vulnerable to the abnormal patterns of neurotransmitter and hormone activity associated with traumatic stress. Young children victimized by trauma are at risk for developing permanent vulnerabilities -- changes in neuronal differentiation and organization -- changes in brain development which persist into adolescence and adulthood, with potential impact on all aspects of emotional, cognitive and behavioral functioning.

The relationships between the age of the traumatized child, vulnerability and subsequent adverse sequelae are predicted by another key principle of neurodevelopment -- critical and sensitive periods.

CRITICAL AND SENSITIVE PERIODS

As important in neurodevelopment as the pattern, quantity and quality of the neurochemical signals which neurons receive is the timing of signals. There are times in development during which a set of signals must be present for the neurons to differentiate normally. These are called critical periods. In addition, there are times when an undifferentiated neuron is specially 'receptive' or sensitive to a set of signals. At these times, termed sensitive periods, the neuron will use this set of signals to facilitate further specialization as part of a larger functional subsystem in the brain. As neurons develop, they organize into larger functional units, co-developing to specialize in a given set of brain functions. Neurons that transduce light, for example, connect with neurons that perceive light, neurons that localize the perception of light in space, neurons that process this information, others that allow 'responding' to this information and so forth. During this process of co-development, the strength of the connections in this network is dependent, first, upon the presence of the signal (e.g., the light), and then upon the pattern and intensity of this signal (see Jacobson, 1991). The times in development during which these connections are being made and these patterns of activation are taking place are 'critical' to the development of normal functional capabilities in the mature brain (see Meaney et al., 1988). Without certain patterns of activation and certain microenvironmental signals which determine differentiation and facilitate the co-development of these networks, there will be disorganized development and diminished functional capabilities in the mature system. There are many examples of disrupted neurodevelopment and function in animals following deprivation of sensory cues, primarily visual, tactile and

auditory (Jacobson, 1991). For humans, some extreme illustrations of these principles have been provided by cruel experiments of nature. Children raised with little or no exposure to verbal language never develop the neural apparatus needed for optimal speech or language development (Mason, 1942; Freedman, 1981); children raised in sensory-deprived settings have major deficits in developing integrated neurosensory processing (e.g., Davis, 1940; Freedman and Brown, 1968); children with various visual deficits (e.g., strabismus), for example, develop abnormal visual perceptual and association capabilities (e.g., Lipton, 1970; Bishop, 1987; Freedman, 1992). The length of critical and sensitive periods in animals has been documented for a variety of situations. In humans, however, there is very little information regarding these 'windows' of vulnerability; the majority of the irreversible sensory processing deficits have resulted from deprivations during the first three years of life.

The development of networks of neurons mediating a given set of important brain functions is, therefore, dependent upon the quantity, quality and pattern of activation during key time periods during development. Understanding the principles of this 'use-dependent' development is critically important for understanding the neurodevelopmental effects of childhood trauma. There are, of course, critical and sensitive periods for the development of important brain systems and functions other than neurosensory processing. There is overwhelming evidence suggesting sensitive, if not critical, periods for brain functions associated with 'mental health' including attachment, affect modulation, anxiety regulation, and behavioral impulsivity (Spitz, 1945; Spitz and Wolf, 1946; Patton and Gardner, 1963; Provence, 1983), all of which utilize to varying degrees the same neurobiological subsystems which mediate the 'stress response'. The best examples of this in humans, again, is from cruel experiments of nature. The orphans described by Spitz (1945) and the more recent Rumanian orphans illustrate the potential neurodevelopmental devastation resulting from affective, tactile and emotional undernourishment.

The sensitive periods for the stress response 'apparatus' in the brain -- developmental phases during which an individual is most vulnerable to traumatic stressors -- occur when the stress-mediating catecholamine systems are undergoing neurogenesis, migration, synaptogenesis and neurochemical differentiation. The functional capabilities of the CNS systems mediating stress in the adult are determined by the nature of the 'stress' experiences during the development of these systems, i.e., in utero, during infancy and childhood (Perry, 1988: in press; Perry et al., 1990). A number of fascinating studies in animals demonstrate the exquisite sensitivity of the developing CNS to stress (see Suoumi, 1986).

In rats exposed to perinatal handling stress major alterations in the ability of the rat to 'learn' and to mobilize a stress response are seen later in life (Weinstock et al., 1988). The most interesting aspect of these studies is that exposure to unpredictable stress resulted in deficits while exposure to consistent, daily stress resulted in 'improved' or superior behavior -- these animals were 'resilient'. The pattern of stress and the predictability are important in determining how 'traumatic' a stressor is. Elements of predictability and some elements of control make the stress much less destructive. One can speculate on equivalent 'controlled' or daily stress and uncontrollable, non-scheduled stressors in the development of a human. An infant who is allowed to have an 'optimal' degree of frustration, one who can control, during rapprochement, his own optimal degree of 'tension, anxiety' (i.e., stress) and return to mother for comfort, is one whose developing CNS is establishing an appropriate neurochemical milieu for the development of a flexible, maximally-adaptive physiological apparatus for responding to future stressors. A child who is reared in an unpredictable, abusive or neglectful environment (see Spitz and Wolfe, 1946) will likely have evoked in his developing CNS a milieu which will result in a poorly organized, 'dysregulated' CNS catecholamine system. One would hypothesize that such an individual would be susceptible to the development of more severe signs and symptoms when exposed to psychosocial stressors through the course of their life.

Studies in humans suggest this is the case. Increased psychiatric symptoms and disorders are observed in adults who have severe, unpredictable early life stressors (Brown and Harris, 1977; Lloyd, 1980; Rutter, 1984). A provocative study by Breier and co-workers (1988) reported the effects of parental loss during childhood on the development of psychopathology in adulthood. They examined a number of adults who had suffered a parental loss during childhood and found that the subjects with psychiatric disorders and symptoms had significant biological and immunological changes related to early parental loss relative to control groups. The authors concluded that early parental loss (a traumatic event) accompanied by the lack of a supportive relationship subsequent to the loss (an external stress reducing factor) is related to the development of adult psychopathology.

Other studies have documented relationships between developmental trauma and borderline personality disorders (Ogata et al., 1988; Herman et al., 1989), depressive disorders (Kaufman, 1991), dissociative disorders (Putnam, 1991; Peterson, 1991) and a variety of other medical and psychiatric conditions (Coddington, 1972a: 1972b; Garmezy, 1978; Beautris et al., 1982; Boyce, 1990; Greenwood et al., 1990; Davidson et al., 1991). Clearly, these many studies provide correlative data indicating that developmental stress is a major expressor of any underlying consitutional or genetic vulnerability and, in some cases, may be the primary etiological factor in the development of certain neuropsychiatric disorders.

The abnormal pattern of stress-mediating neurotransmitter and hormone activations during development alters the brains of traumatized children. The specific nature of these fucntional alterations is seen in all of the brain functions which are directly or tangentially related to CNS catecholamine systems. Unfortunately, the CNS catecholamines (and likely other important neurotransmitter systems altered by these experiences) are involved in almost all core regulatory activities of the brain. The brainstem and midbrain catecholamines are involved in regulation of affect, anxiety, arousal/concentration, impulse control, sleep, startle, autonomic nervous system regulation, memory and cognition. Clearly the physical signs and symptoms seen in traumatized children include dysfunction and dysregulation in these domains. Indeed, the 'core' symptoms seen in severely traumatized children may be traced back to dysregulation of these root neurophysiological regulatory functions.

CLINICAL IMPLICATIONS

The human brain and all of the functions that this amazing organ mediate, develop as a reflection of developmental experiences. This 'mirroring' quality of the developing human brain has evolved as an extention of the primary mandate of the brain to perceive, process and act on information from the environment in order to maximize survival potential. If the child is raised in an unpredictable, chaotic, violent environment, it is highly adaptive to have a hypervigilant, hyper-reactive arousal system; if primary relationships are characterized by violence, neglect and unreliability, intimacy becomes maladaptive; if a young child is frequently assaulted, it becomes adaptive to 'over interpret' non-verbal cues, to quickly act on impulses and to strike out before being struck. The 'symptoms' of hypervigilance, cognitive distortion, physiological and behavioral hyper-reactivity, intimacy avoidance and dissociation commonly seen in traumatized children were all, at some time in the lives of these children, necessary, adaptive and appropriate responses to traumatic stress.

The same remarkable qualities of the developing brain that allow the growing child to 'internalize' and rapidly learn about the world ultimately betray the traumatized child. Their brains develop as if the entire world is chaotic, unpredictable, violent, frightening and devoid of nurturance -- and unfortunately for most, the systems that our society has developed to 'help'

these children (the juvenile justice, foster care and mental health systems) often continue to fill their lives with neglect, unpredictability, fear, chaos and, most disturbing, more violence. Neurodevelopmental principles and the basic neurophysiology of the stress response would predict that the primary, baseline neurophysiological state of the traumatized child is a persisting state of 'alarm', most similar to a state of fear. Much more research in the basic neurobiology of development and the neurophysiology of traumatized children is required. Only then can the relationships between neurodevelopment and trauma-related neuropsychiatric problems be understood well enough to guide innovative therapeutic approaches and initiate social policy changes to bring an end to the war on children.

Part II of this series will address clinical implications of a neurodevelopmental conceptualization of childhood trauma, including discussions of the variable clinical outcomes following common traumatic experiences, genetic and constitutional vulnerability to trauma, diagnostic labels for maltreated children, differential effects of various traumatic events, the effects of multiple or chronic vs. single stressors, the age (chronological and developmental) of the traumatized child, the potential for reparative experiences and specific recommendations for therapeutic approaches based upon clinical work using a neurodevelopmental conceptualization of childhood trauma.

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